

PROSPECTUS

6,667,000 American Depositary Shares**Representing 6,667,000 Ordinary Shares
\$15.00 per American Depositary Share**

This is the initial public offering of our American Depositary Shares, or ADSs. We are selling 6,667,000 of our ADSs in this offering. Each ADS will represent one ordinary share, nominal value £0.04 per share. The ADSs may be evidenced by American Depositary Receipts, or ADRs.

The initial public offering price is \$15.00 per ADS. No public market has previously existed for our ADSs or ordinary shares. We have received approval to list our ADSs on the Nasdaq Global Select Market under the symbol "NCNA."

We are an "emerging growth company" as such term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements.

Investing in our ADSs involves a high degree of risk. See "[Risk Factors](#)" beginning on page 11.

Neither the U.S. Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

	<u>Per ADS</u>	<u>Total</u>
Public Offering Price	\$ 15.00	\$ 100,005,000
Underwriting Discounts and Commissions ¹	\$ 1.05	\$ 7,000,350
Proceeds to NuCana (before expenses)	\$ 13.95	\$ 93,004,650

(1) We refer you to "Underwriting" beginning on page 189 for additional information regarding underwriting compensation.

Certain of our existing shareholders have agreed to purchase an aggregate of 933,332 ADSs in this offering at the initial public offering price. See "Prospectus Summary—The Offering."

The underwriters have an option to purchase up to 1,000,050 additional ADSs from us at the public offering price, less the underwriting discounts and commissions payable by us, for 30 days after the date of this prospectus to cover over-allotments, if any.

Delivery of the ADSs will be made against payment in New York, New York on or about October 2, 2017.

Joint Book-Running Managers

Citigroup

Jefferies

Cowen

Co-Manager

William Blair

September 27, 2017

[Table of Contents](#)

You should rely only on the information contained in this prospectus and any related free-writing prospectus that we authorize to be distributed to you. We have not, and the underwriters have not, authorized any person to provide you with information different from that contained in this prospectus or any related free-writing prospectus that we authorize to be distributed to you. This prospectus is not an offer to sell, nor is it seeking an offer to buy, these securities in any jurisdiction where the offer or sale is not permitted. The information in this prospectus speaks only as of the date of this prospectus unless the information specifically indicates that another date applies, regardless of the time of delivery of this prospectus or of any sale of the securities offered hereby.

TABLE OF CONTENTS

	<u>Page</u>
About This Prospectus	ii
Presentation of Financial Information	ii
Summary	1
Risk Factors	11
Special Note Regarding Forward-Looking Statements	63
Exchange Rates	64
Use of Proceeds	65
Dividends and Dividend Policy	66
Capitalization	67
Dilution	69
Selected Consolidated Financial Data	71
Management’s Discussion and Analysis of Financial Condition and Results of Operations	72
Business	87
Management	131
Related Party Transactions	142
Principal Shareholders	144
Description of Share Capital	147
Description of American Depositary Shares	167
Shares and ADSs Eligible for Future Sale	178
Taxation	180
Underwriting	189
Expenses of the Offering	196
Legal Matters	197
Experts	197
Service of Process and Enforcement of Judgments	197
Where You Can Find More Information	197
Index to Consolidated Financial Statements	F-1

No action is being taken in any jurisdiction outside the United States to permit a public offering of the ADSs or possession or distribution of this prospectus in that jurisdiction. Persons who come into possession of this prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of the prospectus applicable to that jurisdiction.

We are incorporated under the laws of England and Wales and a majority of our outstanding securities are owned by non-U.S. residents. Under the rules of the U.S. Securities and Exchange Commission, or the SEC, we are currently eligible for treatment as a “foreign private issuer.” As a foreign private issuer, we will not be required to file periodic reports and financial statements with the SEC as frequently or as promptly as domestic registrants whose securities are registered under the Securities Exchange Act of 1934, as amended.

ABOUT THIS PROSPECTUS

On August 29, 2017, we re-registered NuCana BioMed Limited as a public limited company and changed our name from NuCana BioMed Limited to NuCana plc.

Unless otherwise indicated or the context otherwise requires, in this prospectus, “NuCana,” “NuCana BioMed Limited,” “NuCana plc,” the “Group,” the “company,” “we,” “us” and “our” refer to (i) NuCana BioMed Limited and its consolidated subsidiaries prior to the re-registration of NuCana BioMed Limited as a public limited company and (ii) NuCana plc and its consolidated subsidiaries after the re-registration of NuCana BioMed Limited as a public limited company. See “Description of Share Capital.”

PRESENTATION OF FINANCIAL INFORMATION

We report under International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or IASB. None of the financial statements were prepared in accordance with generally accepted accounting principles in the United States. We present our financial statements in pounds sterling and in accordance with IFRS. All references in this prospectus to “\$” are to U.S. dollars and all references to “£” are to pounds sterling. Unless otherwise indicated, certain U.S. dollar amounts contained in this prospectus have been translated into pounds sterling at the rate on June 30, 2017 of £1.00 to \$1.2995. These translations should not be considered representations that any such amounts have been, could have been or could be converted into pounds sterling at that or any other exchange rate as of that or any other date.

We have made rounding adjustments to some of the figures included in this prospectus. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them.

SUMMARY

This summary highlights information contained elsewhere in this prospectus. It may not contain all of the information that may be important to you. Before investing in our ADSs, you should read this entire prospectus carefully for a more complete understanding of our business and this offering, including our consolidated financial statements and the notes thereto, and the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in this prospectus.

Overview

We are a clinical-stage biopharmaceutical company focused on significantly improving treatment outcomes for cancer patients by applying our ProTide™ technology to transform some of the most widely prescribed chemotherapy agents, nucleoside analogs, into more effective and safer medicines. While these conventional agents remain part of the standard of care for the treatment of many solid tumors, their efficacy is limited by cancer cell resistance mechanisms and they are often poorly tolerated. Utilizing our proprietary technology, we are developing new medicines, ProTides, designed to overcome key cancer resistance mechanisms and generate much higher concentrations of anti-cancer metabolites in cancer cells. Our most advanced ProTide candidates, Acelarin® and NUC-3373, are new chemical entities derived from the nucleoside analogs gemcitabine and 5-fluorouracil, respectively, two widely used chemotherapy agents. Acelarin is currently being evaluated in three clinical trials across several solid tumor indications, including ovarian cancer, biliary cancer and pancreatic cancer. NUC-3373 is currently in a Phase 1 trial for the potential treatment of a wide range of advanced solid tumor cancers. We have retained worldwide rights to these lead product candidates as well as our preclinical product candidates, all of which we refer to as ProTides.

Acelarin, our most advanced product candidate, is a potential first-in-class ProTide that has been evaluated in over 140 patients. Acelarin is a ProTide transformation of gemcitabine that we believe could replace gemcitabine in certain cancer indications and have utility across a range of other cancers. In a Phase 1 dose-ranging trial in 49 evaluable patients with advanced metastatic solid tumors, Acelarin was well tolerated, achieved a 78% disease control rate and was associated with intracellular levels of active anti-cancer metabolite over 200 times higher than those reported for gemcitabine. A subset of 14 evaluable patients with relapsed/refractory gynecological cancers achieved a 93% disease control rate. In a Phase 1b dose-ranging trial in 23 evaluable patients with recurrent ovarian cancer, Acelarin was combined with carboplatin and achieved a 96% disease control rate. Based on these disease control rates and the tolerability profile, we have begun a Phase 2 trial of Acelarin in patients with platinum-resistant ovarian cancer, for which we expect to report interim data in 2018. Acelarin is also being evaluated in another Phase 1b trial in patients with biliary cancer to determine its optimal dose in combination with cisplatin. We expect to report data from this trial in 2018, after which we plan to commence a multi-national Phase 3 trial. In addition, the National Cancer Research Institute in the United Kingdom is facilitating a Phase 3 trial of Acelarin for the treatment of patients with pancreatic cancer. The disease control rates referred to above include complete responses, partial responses and stable disease, measured by radiographic assessment to determine changes in tumor size, and evaluated using the standard scoring system known as Response Evaluation Criteria in Solid Tumors, or RECIST. The disease control rates are based on investigator assessment of tumor response in a limited number of patients and may not be predictive of or consistent with the results of later trials.

NUC-3373, our second product candidate, is a ProTide transformation of the active anti-cancer metabolite of 5-fluorouracil, or 5-FU, which we believe has the potential to replace 5-FU as the standard of care in the treatment of a wide range of cancers. In preclinical studies, we observed that NUC-3373 overcame the key resistance mechanisms associated with 5-FU and generated intracellular levels of active anti-cancer metabolite over 300 times higher than that of 5-FU. NUC-3373 is currently being evaluated in a Phase 1 clinical trial of

patients with advanced solid tumors for which we reported interim data in September 2017. We expect to report final data from this trial in 2018. Contingent on regulatory guidance and other factors, we plan to initiate a number of clinical trials in 2018: a Phase 1b trial of NUC-3373 in patients with colorectal cancer together with other agents routinely used in 5-FU combination regimens; a Phase 3 trial in patients with advanced colorectal cancer; and a Phase 2 trial in patients with advanced breast cancer.

NUC-7738, our third product candidate, is a ProTide transformation of cordycepin, a novel nucleoside analog that has shown potent anti-cancer activity in preclinical studies. We are evaluating NUC-7738 in preclinical studies and we expect to initiate a Phase 1 clinical trial in 2018.

Despite the widespread use of nucleoside analogs, their efficacy is severely limited by cancer cell resistance mechanisms and they are often poorly tolerated. Harnessing the power of phosphoramidate chemistry, we convert nucleoside analogs into activated nucleotide analogs with the addition of a phosphate group, which is protected by specific combinations of aryl, ester and amino acid groupings. By adding and protecting this phosphate group, we design our ProTides to avoid or overcome key cancer resistance mechanisms in the uptake, activation and breakdown of nucleoside analogs. As a result, we believe our ProTides have the potential to generate hundreds of times higher concentrations of the active anti-cancer metabolites inside tumor cells, potentially making our ProTides more effective than the current standards of care. Because our ProTides resist breakdown, and are thus more stable, we believe they are also able to reduce or eliminate the generation of toxic byproducts that can result from the breakdown of nucleoside analogs like gemcitabine and 5-FU.

Our proprietary ProTide technology was invented in the Cardiff University laboratory of our late Chief Scientific Officer, Professor Christopher McGuigan, who conceived of, and filed the original composition of matter patents for our initial ProTides. The unique feature of his discovery was the specific combination of aryl, ester and amino acid groupings that protect the activated, or phosphorylated, nucleoside analog. This phosphoramidate chemistry approach is the key to the ProTide technology. Every ProTide grouping is distinct, and Professor McGuigan and his team synthesized and tested thousands of compounds in order to identify the optimal ProTide grouping for each underlying nucleoside analog.

We have licensed what we believe to be the foundational patent estate for the application of phosphoramidate chemistry in oncology. We have granted patents in key markets, including the United States, Europe and Japan, protecting the composition of matter of Acelarin, NUC-3373 and other of our product candidates. Professor McGuigan's work preceded and helped lead to the development of several FDA-approved anti-viral drugs containing nucleotide analogs, including: sofosbuvir, or Sovaldi®, which is also a key component of Harvoni®; and tenofovir alafenamide fumarate, or TAF, which is a key component of Genvoya®, Descovy® and Odefsey®.

We are led by Hugh S. Griffith, our founder and Chief Executive Officer, who brings over 25 years of experience in the biopharmaceutical industry, including at Abbott Laboratories (now AbbVie Inc.) and Parke-Davis Warner Lambert (now Pfizer Inc.). Before founding NuCana, he led the operations of Bioenvision, Inc. from start-up through its acquisition by Genzyme Corporation. While at Bioenvision, he was instrumental in developing and commercializing clofarabine, a nucleoside analog for the treatment of pediatric leukemia. We are backed by leading life sciences investors, including Sofinnova Partners, Sofinnova Ventures, Morningside Group and Scottish Enterprise.

Our Strategy

Our goal is to transform standards of care and improve survival for patients across a wide range of cancer indications. Our strategy includes the following key components:

- **Rapidly develop Acelarin as a first-in-class nucleotide analog for the treatment of patients with cancer.** We believe that Acelarin has the potential to replace the core chemotherapy component of treatment regimens for patients with various cancers, including:
 - *Platinum-resistant ovarian cancer.* We expect to report data from a Phase 2 trial of Acelarin in 2018. We also intend to explore the use of Acelarin in combination with Avastin, a widely used agent in the treatment of several cancers, and expect to report data from this trial in 2018.
 - *Platinum-sensitive ovarian cancer.* Contingent on regulatory guidance and other factors, we expect to commence a Phase 3 trial of Acelarin in combination with carboplatin for this indication in 2018.
 - *Biliary cancer.* We expect to report data from a Phase 1b trial of Acelarin in combination with cisplatin in 2018. Contingent on regulatory guidance and other factors, we plan to commence a Phase 3 trial of Acelarin in combination with cisplatin as a first-line treatment in 2018.
 - *Pancreatic cancer.* The National Cancer Research Institute in the United Kingdom is facilitating a Phase 3 trial of Acelarin as a first-line treatment compared to gemcitabine.
- **Rapidly develop NUC-3373 to replace 5-FU as the standard of care for the treatment of patients with various cancers.**
 - *Advanced solid tumors.* We expect to report final data from a Phase 1 trial of NUC-3373 in patients with advanced solid tumors in 2018.
 - *Colorectal cancer.* We plan to establish the optimal dose of NUC-3373 in combination with other agents in a Phase 1b trial in 2018. Contingent on regulatory guidance and other factors, we also intend to initiate a Phase 3 trial of NUC-3373 monotherapy in 2018.
 - *Breast cancer.* We intend to conduct a Phase 2 trial of NUC-3373 compared to capecitabine, the oral version of 5-FU, in patients with recurrent breast cancer and anticipate reporting interim data from this trial in 2018.
- **Rapidly advance NUC-7738 into clinical trials.** NUC-7738, a ProTide based on a novel nucleoside analog, is currently undergoing preclinical studies and we expect to initiate a Phase 1 trial in 2018 for solid tumors. In addition, we plan to develop NUC-7738 for the treatment of hematological malignancies.
- **Leverage our proprietary ProTide technology platform to develop additional product candidates.** We are pursuing both the transformation of well-established and widely used nucleoside analogs as well as novel nucleoside analogs, which we believe have the potential to address additional areas of unmet medical need in oncology.
- **Continue to strengthen our intellectual property position.** We own or have exclusive rights to the core technologies underlying our ProTide technology platform. We have granted patents in key markets, including the United States, Europe and Japan, protecting the composition of matter of Acelarin, NUC-3373 and other of our product candidates. We intend to further expand and enhance our intellectual property position.
- **Build a focused commercial organization.** We have worldwide rights to all product candidates that we are developing. We believe that many of the cancers we are initially targeting with our ProTides can be addressed by a focused sales and marketing team. We plan to commercialize any product candidates for which we receive regulatory marketing approval using a specialized sales force in the United States and Europe.

Our Pipeline

We take a scientifically driven approach to designing ProTides, which we believe have the potential to result in highly efficacious cancer therapies with improved tolerability. Our pipeline of product candidates is summarized below.

Program	IND/CTA enabling	Phase 1	Phase 2	Phase 3	Next Expected Events	Date
ACELARIN	Ovarian (Platinum resistant)	▶			Phase 2 data (interim) Phase 2 data (+Avastin)	2018 2018
	Ovarian (Platinum sensitive) + carboplatin	▶			Initiate Phase 3 study	2018
	Biliary + cisplatin	▶			Phase 1b data Initiate Phase 3 study	2018 2018
	Pancreatic (IST)	▶			Ongoing investigator sponsored study	Multi-year
NUC-3373	Solid Tumors	▶			Phase 1 data	2018
	Colorectal + combo	▶			Phase 1b data (interim)	2018
	Colorectal	▶			Initiate Phase 3 study	2018
	Breast	▶			Phase 2 data (interim) Initiate Phase 3 study	2018 2018
NUC-7738	Solid Tumors	▶			Phase 1 data (interim)	2018
	Hematology	▶			Phase 1 data (interim)	2019

Corporate Information

NuCana was incorporated under the laws of England and Wales in 1997 under the name Biomed (UK) Limited, and commenced operations in 2008. On April 28, 2008, we changed our name to NuCana BioMed Limited. On August 29, 2017, we re-registered as a public limited company and changed our name to NuCana plc. Our registered office is 77/78 Cannon Street, London EC4N 6AF, United Kingdom. Our principal executive offices are located at 3 Lochside Way, Edinburgh, EH12 9DT, United Kingdom, our general telephone number is +44 (0)131 248 3660 and our internet address is <http://www.nucana.com>. Our website and the information contained on or accessible through our website are not part of this prospectus.

NuCana, the NuCana logo and other trademarks or service marks of NuCana plc appearing in this prospectus are the property of NuCana plc. Trade names, trademarks and service marks of other companies appearing in this prospectus are the property of their respective owners. Solely for convenience, the trademarks, service marks and trade names referred to in this prospectus may be without the ® and ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights to these trademarks, service marks and trade names.

Risk Factors

Our business is subject to numerous risks that could prevent us from successfully implementing our business strategy. These and other risks are discussed more fully in “Risk Factors” immediately following this prospectus summary and include the following:

- We have incurred significant operating losses since our inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.
- We depend heavily on the success of our product candidates, Acelarin, NUC-3373 and NUC-7738. We cannot give any assurance that these product candidates will receive regulatory approval for any indication, which is necessary before any of them can be commercialized.
- Our lack of any approved products and our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.
- We will require substantial additional funding, which may not be available to us on acceptable terms, or at all.
- Drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development, and may experience delays in obtaining, or ultimately be unable to obtain, the approval, of our product candidates.
- Initial success in early-stage clinical trials may not be indicative of results obtained in later-stage trials, and the results of our clinical trials may not meet the level of statistical significance required by the Food and Drug Administration, or FDA, or comparable foreign regulatory authorities for marketing approval. In addition, the data from the Phase 1b trial are interim and may change as the data are further examined, more patient data become available and the final clinical study report is prepared and issued.
- We may not be successful in our efforts to use and expand our technology platform to build a pipeline of additional ProTide candidates.
- Our product candidates may cause undesirable side effects that could delay or prevent their marketing approval, limit the commercial profile of an approved label or result in significant negative consequences following marketing approval, if any.
- We rely on, and expect to continue to rely on, third parties to conduct our clinical trials for our product candidates.
- We contract with third parties for the manufacture and shipment of our product candidates for preclinical studies and clinical trials and expect to continue to do so for commercialization.
- We have entered into, and may in the future enter into, collaborations with third parties to discover or develop product candidates. If these collaborations are not successful, our business could be adversely affected.
- We face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than we do.
- If we are unable to obtain and maintain intellectual property protection for our technology and products, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired. In addition, if we infringe the valid patent rights of others, we may be prevented from making, using or selling our products or may be subject to damages or penalties.

- We currently have a limited number of employees, and our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

Implications of Being an Emerging Growth Company and a Foreign Private Issuer

We qualify as an “emerging growth company,” or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As such, we may take advantage of specified reduced reporting requirements and are relieved of certain other significant requirements that are otherwise generally applicable to public companies in the United States. These provisions include:

- the ability to include only two years of audited financial statements and only two years of related Management’s Discussion and Analysis of Financial Condition and Results of Operations disclosure; and
- an exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act of 2002.

We may take advantage of these provisions for up to five years or such earlier time that we are no longer an EGC. We would cease to be an EGC if we have more than \$1.07 billion in total annual gross revenue, have more than \$700 million in market value of our ordinary shares held by non-affiliates or issue more than \$1.0 billion of non-convertible debt over a three-year period.

Upon the completion of this offering, we will report under the Securities Exchange Act of 1934, as amended, or the Exchange Act, as a non-U.S. company with foreign private issuer status. Even if we no longer qualify as an EGC, as long as we qualify as a foreign private issuer under the Exchange Act we will be exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including:

- the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act;
- the sections of the Exchange Act requiring insiders to file public reports of their share ownership and trading activities, and liability for insiders who profit from trades made in a short period of time; and
- the rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specified information, or current reports on Form 8-K upon the occurrence of specified significant events.

Both foreign private issuers and EGCs are also exempt from certain more stringent executive compensation disclosure rules. Thus, even if we no longer qualify as an EGC, but remain a foreign private issuer, we will continue to be exempt from the more stringent compensation disclosures required of companies that are neither an EGC nor a foreign private issuer. As a consequence, we do not know if some investors will find our ADSs less attractive, which may result in a less active trading market for our ADSs or more volatility in the price of our ADSs.

THE OFFERING

ADSs offered by us	6,667,000 ADSs, each representing one ordinary share.
Over-allotment option	We have granted the underwriters an option for a period of 30 days from the date of this prospectus to purchase up to 1,000,050 additional ADSs from us to cover over-allotments, if any.
Ordinary shares to be outstanding immediately after this offering	30,881,641 ordinary shares (or 31,881,691 ordinary shares if the underwriters exercise in full their over-allotment option to purchase an additional 1,000,050 ADSs).
American Depositary Shares	<p>Each ADS represents one ordinary share, nominal value £0.04 per share.</p> <p>The depositary or its custodian, or a nominee of either, will hold the ordinary shares underlying your ADSs. As an ADS holder you will not be treated as one of our shareholders and you will not have shareholder rights. You will have rights as provided in the deposit agreement. You may cancel your ADSs and withdraw the underlying ordinary shares as provided in the deposit agreement. We may amend or terminate the deposit agreement without your consent. If you continue to hold your ADSs following an amendment, you agree to be bound by the terms of the deposit agreement then in effect.</p> <p>To better understand the terms of the ADSs, you should carefully read “Description of American Depositary Shares” in this prospectus. You should also read the deposit agreement, which is an exhibit to the registration statement that includes this prospectus.</p>
Depositary	Citibank, N.A.
Shareholder approval of offering	Under English law, certain steps necessary for the completion of this offering require the approval of our shareholders by way of ordinary resolutions approved by more than 50% of all voting rights and special resolutions approved by at least 75% of all voting rights. We will receive all such required approvals prior to the completion of this offering. See “Description of Share Capital” in this prospectus.
Use of proceeds	We expect to receive total estimated net proceeds from this offering of approximately \$90.7 million (or approximately \$104.7 million if the underwriters exercise in full their over-allotment option to purchase an additional 1,000,050 ADSs) after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds of this offering, together with our existing cash and cash equivalents, to fund our planned development of Acelarin, NUC-3373 and NUC-7738, other research and development activities and for working capital and other general corporate purposes. See “Use of Proceeds” in this prospectus.

Risk factors

You should carefully read the information set forth under “Risk Factors” beginning on page 11 of this prospectus before investing in our ADSs.

Nasdaq Global Select Market
Symbol

“NCNA”

The number of our ordinary shares to be outstanding immediately after this offering is calculated by reference to our entire issued share capital of 24,214,641 shares as of August 31, 2017 and gives effect to the automatic conversion, immediately prior to the completion of this offering, of all issued series A convertible participating shares, series B convertible participating shares (after giving effect to the series B conversion adjustment as described in “Description of Share Capital—Conversion of Series B Shares into Ordinary Shares”), founder ordinary 1 shares and founder ordinary 2 shares into ordinary shares on a one-for-one basis, and excludes:

- 3,233,937 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans as of August 31, 2017 at a weighted average exercise price of £0.71 per share;
- 1,261,783 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans that were granted after August 31, 2017 at a weighted average exercise price of £1.09 per share;
- 215,782 ordinary shares issuable upon exercise of options approved for grant under our equity incentive plans as of and in connection with the pricing of this offering to be issued at an exercise price equal to the initial public offering price per ADS in this offering; and
- 3,545,409 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

Unless otherwise indicated, all information in this prospectus, including information relating to the number of ordinary shares to be outstanding immediately after the completion of this offering:

- gives effect to a one-for-four reverse stock split of our ordinary shares that was effected on September 14, 2017; and
- assumes no exercise by the underwriters of their option to purchase up to 1,000,050 additional ADSs to cover over-allotments, if any.

Participation in the Offering

Certain of our existing shareholders have agreed to purchase an aggregate of 933,332 ADSs in this offering at the initial public offering price. The underwriters will receive the same underwriting discount on any securities purchased by these investors as they will on any other securities sold to the public in this offering.

SUMMARY CONSOLIDATED FINANCIAL DATA

The following tables summarize our consolidated financial data as of the dates and for the periods indicated. The consolidated financial data as of and for the years ended December 31, 2015 and 2016 have been derived from our consolidated financial statements, which have been prepared in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standard Board, or IASB, and audited in accordance with the standards of the Public Company Accounting Oversight Board (United States), and included elsewhere in this prospectus. The consolidated financial data as of and for the six months ended June 30, 2016 and 2017 have been derived from our unaudited consolidated interim financial statements included elsewhere in this prospectus. The unaudited consolidated interim financial statements have been prepared on the same basis as our audited consolidated financial statements and include all adjustments, consisting only of normal recurring adjustments, that we consider necessary for a fair statement of our financial position and operating results as of the dates and for the periods presented.

Our historical results are not necessarily indicative of the results that may be expected in the future and our results for the six months ended June 30, 2017 are not necessarily indicative of our results to be expected for the full year 2017. The following summary consolidated financial data should be read in conjunction with “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our consolidated financial statements included elsewhere in this prospectus.

	Year Ended December 31,		Six Months Ended June 30,	
	2015	2016	2016	2017
	(unaudited)			
	(in thousands, except per share data)			
Consolidated statement of comprehensive loss data:				
Research and development expenses	£ (5,655)	£ (7,904)	£ (3,784)	£ (3,689)
Administrative expenses	(1,251)	(1,143)	(908)	(637)
Initial public offering related expenses	—	—	—	(1,066)
Net foreign exchange (losses) gains	(8)	599	318	(161)
Operating loss	(6,914)	(8,448)	(4,374)	(5,553)
Finance income	406	283	167	91
Loss before tax	(6,508)	(8,165)	(4,207)	(5,462)
Income tax credit	1,176	2,116	1,090	1,077
Loss for the period	(5,332)	(6,049)	(3,117)	(4,385)
Other comprehensive (expense) income:				
Items that may be reclassified subsequently to profit or loss:				
Exchange differences on translation of foreign operations	(1)	(2)	4	(1)
Total comprehensive loss for the period	£ (5,333)	£ (6,051)	£ (3,113)	£ (4,386)
Basic and diluted loss per share	£ (0.22)	£ (0.25)	£ (0.13)	£ (0.18)

The following table presents our consolidated statement of financial position data as of June 30, 2017 on:

- an actual basis;
- a pro forma basis to give effect to the automatic conversion, immediately prior to the completion of this offering, of all issued series A convertible participating shares, series B convertible participating shares, founder ordinary 1 shares and founder ordinary 2 shares into ordinary shares on a one-for-one basis; and

[Table of Contents](#)

- a pro forma as adjusted basis to give further effect to the sale by us of 6,667,000 ADSs in this offering at the initial public offering price of \$15.00 per ADS after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

	As of June 30, 2017		
	Actual (unaudited)	Pro Forma	Pro Forma as Adjusted
			(in thousands)
Consolidated statement of financial position data:			
Cash and cash equivalents	£ 15,918	£ 15,918	£ 85,725
Total assets	23,643	23,643	93,450
Share capital	663	967	1,234
Share premium	304	—	71,303
Accumulated deficit	(26,641)	(26,641)	(28,404)
Capital reserve(1)	42,466	42,466	42,466
Total equity attributable to equity holders	21,387	21,387	91,194
Total liabilities	(2,256)	(2,256)	(2,256)

- (1) The capital reserve balance arose from the impact of the reduction of our share premium account and corresponding increase to our capital reserve account reflected as of June 30, 2017 in connection with our re-registration as a public limited company, as further described in footnote 10 to the unaudited consolidated interim financial statements.

RISK FACTORS

Investing in the ADSs involves a high degree of risk. You should carefully consider the following risk factors and all other information contained in this prospectus, including our consolidated financial statements and the related notes, before investing in the ADSs. The risks and uncertainties described below are those significant risk factors, currently known and specific to us, that we believe are relevant to an investment in the ADSs. If any of these risks materialize, our business, results of operations or financial condition could suffer, the price of the ADSs could decline and you could lose part or all of your investment. Additional risks and uncertainties not currently known to us or that we now deem immaterial may also harm us and adversely affect your investment in the ADSs.

Risks Related to Our Business and Industry

We have incurred significant operating losses since our inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

We have incurred significant operating losses since our inception. We incurred net losses of £5.3 million for the year ended December 31, 2015, £6.0 million for the year ended December 31, 2016 and £4.4 million for the six months ended June 30, 2017. As of December 31, 2016, we had an accumulated deficit of £22.3 million and, as of June 30, 2017, we had an accumulated deficit of £26.6 million. Our most advanced product candidate, Acelarin, is currently being evaluated in four clinical trials: two Phase 1b trials, one Phase 2 trial, and one multi-year investigator-sponsored Phase 3 trial. Our other clinical-stage product candidate, NUC-3373, is currently in a Phase 1 trial. It may be several years, if ever, before we have a product candidate ready for commercialization. To date, we have financed our operations primarily through private placements of our equity securities. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- continue development of our ProTides, including initiating additional clinical trials of Acelarin and NUC-3373;
- complete preclinical studies and potentially initiate clinical trials of our preclinical-stage product candidates, including our product candidate NUC-7738;
- identify and develop new product candidates;
- establish a robust supply chain for the manufacture of our product candidates in accordance with current good manufacturing practice, or cGMP;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we obtain marketing approval;
- pursue market acceptance of our product candidates in the medical community and with third-party payors;
- maintain, expand and protect our intellectual property portfolio;
- expand our headcount by recruiting personnel to drive our clinical development programs and effectively manage out-sourced development activities;
- enter into collaboration arrangements, if any, for the development of our product candidates or in-license other products and technologies;
- achieve milestones which will trigger payments under our license agreements;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and
- incur increased administrative and other costs as a result of operating as a public company.

[Table of Contents](#)

Because of the numerous risks and uncertainties associated with developing new pharmaceutical drugs, we are unable to predict the extent of any future losses or when we will become profitable, if at all. In addition, our expenses could increase beyond expectations if we are required by the European Medicines Agency, or EMA, the Food and Drug Administration, or FDA, or other foreign regulatory agencies, to perform studies and clinical trials in addition to those that we currently anticipate, or if there are any delays in the completion of planned clinical trials or the development of any of our ProTides.

To become and remain profitable, we must develop and eventually commercialize products with significant market potential. This will require us to be successful in a range of challenging activities, including the following:

- completing clinical trials of our product candidates that achieve their clinical endpoints;
- obtaining marketing approval for our product candidates;
- manufacturing, marketing and selling those products for which we may obtain marketing approval; and
- achieving market acceptance of our product candidates in the medical community and with third-party payors.

We may never succeed in these activities and, even if we do, may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain our discovery and preclinical development efforts, expand our business or continue our operations and may require us to raise additional capital that may dilute your ownership interest. A decline in the value of our company could also cause you to lose all or part of your investment.

We depend heavily on the success of our product candidates, Acelarin, NUC-3373 and NUC-7738. We cannot give any assurance that these product candidates will receive regulatory approval for any indication, which is necessary before any of them can be commercialized. If we, and any collaborators with whom we may enter into agreements for the development and commercialization of any of these product candidates, are unable to commercialize them, or experience significant delays in doing so, our ability to generate revenue and our financial condition will be adversely affected.

We do not currently generate any revenues from sales of any products, and we may never be able to develop or commercialize a marketable product. We have invested substantially all of our efforts and financial resources to date in the development of Acelarin, NUC-3373 and NUC-7738. Our ability to generate product revenues, which we do not expect will occur for at least the next several years, if ever, will depend heavily on the successful development and eventual commercialization of these product candidates, if approved, which may never occur. Each of Acelarin, NUC-3373 and NUC-7738 will require additional clinical development, management of clinical, preclinical and manufacturing activities, regulatory approval in multiple jurisdictions, procurement of manufacturing supply, commercialization, substantial additional investment and significant marketing efforts before we generate any revenues from product sales, if at all. We are not permitted to market or promote any product candidates in the United States, Europe or other countries before we receive regulatory approval from the FDA, the EMA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for Acelarin, NUC-3373 or NUC-7738 or any future product candidate. We have not submitted a New Drug Application, or NDA, to the FDA, a Marketing Authorization Application, or MAA, to the EMA or comparable applications to other regulatory authorities for any of our product candidates and do not expect to be in a position to do so in the foreseeable future. The success of our product candidates will depend on many factors, including the following with respect to each of Acelarin, NUC-3373 and NUC-7738, specifically:

- we may not be able to demonstrate that the product candidate is safe and effective as a treatment for our targeted indications to the satisfaction of the applicable regulatory authorities;

[Table of Contents](#)

- the applicable regulatory authorities may require additional preclinical or clinical trials of the product candidate, including additional toxicology trials, which would increase our costs and prolong our development;
- the results of clinical trials of our product candidates may not meet the level of statistical or clinical significance required by the applicable regulatory authorities for marketing approval;
- the applicable regulatory authorities may disagree with the number, design, size, conduct or implementation of our planned clinical trials;
- the contract research organizations, or CROs, that we retain to conduct clinical trials may take actions outside of our control that adversely impact our clinical trials;
- the applicable regulatory authorities may not find the data from preclinical studies and clinical trials sufficient to demonstrate that the clinical and other benefits of the product candidate outweigh its safety risks;
- the applicable regulatory authorities may disagree with our interpretation of data from preclinical studies and clinical trials or may require that we conduct additional studies;
- the applicable regulatory authorities may not accept data generated at our clinical trial sites;
- if we submit an NDA to the FDA or an MAA to the EMA, and it is reviewed by an advisory committee, the advisory committee may recommend against approval of our application or may recommend that the FDA or the EMA require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the applicable regulatory authorities may require development of a risk evaluation and mitigation strategy, or REMS, as a condition of approval;
- the applicable regulatory authorities may change its approval policies or adopt new regulations;
- the applicable regulatory authorities may identify deficiencies in our formulation and manufacturing processes or facilities of our third-party manufacturers;
- we may face delays in our formulation and manufacturing process as a result of having not yet optimized formulations or due to lack of availability of starting materials;
- we may be unable to scale up the manufacture process for some of our product candidates;
- we may face challenges on the safe and appropriate administration of our drugs in the clinic, including with respect to the conversion of our product candidates from a dry powder formulation to a liquid formulation prior to intravenous, or IV, administration, precipitation or other blockages in IV infusion lines, and the handling and storage of the IV infusion bags containing our product candidates, any of which may result in the need to carry out additional studies on the administration and compatibility of our product candidates with infusion sets and pumps;
- we may be faced with challenges from third parties on our right to use certain processes used in the formulation and process development of our product candidates;
- we may have to defend our patents against infringement by third parties;
- we may unknowingly infringe third-party patents;
- we may face a “freedom to operate” issue;
- we will be dependent on the efforts of third parties in completing clinical trials of, receiving regulatory approval for and commercializing, any product candidate we license to such third parties;
- through our clinical trials, we may discover factors that limit the commercial viability of the product candidate or make their commercialization unfeasible;

[Table of Contents](#)

- we may not be successful in completing preclinical studies and clinical trials of, receiving marketing approvals for, establishing commercial manufacturing capabilities for and commercializing, any product candidate to which we retain rights under a collaboration agreement; and
- we may not be successful in gaining acceptance of any product candidate by patients, the medical community and third-party payors, effectively competing with other therapies, maintaining a continued acceptable safety profile following approval and qualifying for, maintaining, enforcing and defending our intellectual property rights and claims.

With respect to each of Acelarin, NUC-3373 and NUC-7738, if we or our suppliers, as applicable, do not overcome one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize that product candidate.

We cannot be certain that Acelarin, NUC-3373 or NUC-7738 or any future product candidates will be successful in clinical trials or receive regulatory approval. Further, Acelarin, NUC-3373 or NUC-7738 or any future product candidates may not receive regulatory approval even if they are successful in clinical trials. If we do not receive regulatory approvals for Acelarin, NUC-3373 or NUC-7738 or any future product candidates, we may not be able to continue our operations. Even if we successfully obtain regulatory approvals to manufacture and market Acelarin, NUC-3373 or NUC-7738 or any future product candidates, our revenues will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval and have commercial rights. If the markets for patient groups that we are targeting are not as significant as we estimate, we may not generate significant revenues from sales of such products, if approved.

We plan to seek regulatory approval to commercialize Acelarin, NUC-3373 and NUC-7738 in the United States and the European Union, and potentially in additional foreign countries. While the scope of regulatory approval is similar in many countries, to obtain separate regulatory approval in multiple countries requires us to comply with the numerous and varying regulatory requirements of such countries regarding safety and efficacy and governing, among other things, clinical trials, commercial sales, pricing and distribution of Acelarin, NUC-3373 and NUC-7738, and we cannot predict success in these jurisdictions.

Our lack of any approved products and our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

Biopharmaceutical drug development is a highly speculative undertaking and involves a substantial degree of risk. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, undertaking preclinical studies, and conducting early-stage, non-comparative clinical trials of Acelarin and NUC-3373. We have not yet demonstrated our ability to successfully complete large-scale, randomized, pivotal clinical trials compared to standards of care, obtain marketing approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Typically, it takes several years to develop one new drug from the time it is discovered to when it is available for treating patients. In addition, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We will require substantial additional funding which may not be available to us on acceptable terms, or at all. If we fail to obtain additional financing, we may be unable to complete the development and commercialization of our product candidates or continue our development programs.

The development of pharmaceutical drugs is capital-intensive. We expect our expenses to increase with our ongoing activities, particularly as we conduct larger-scale clinical trials of, and seek marketing approval for, our

[Table of Contents](#)

product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. We may also need to raise additional funds sooner if we choose to pursue additional indications or geographies for our product candidates or otherwise expand more rapidly than we presently anticipate. Furthermore, upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations.

As of June 30, 2017, we had £15.9 million in cash and cash equivalents. We believe, based upon our current operating plan, that, our cash and cash equivalents on hand, together with the anticipated net proceeds from this offering, will be sufficient to fund our anticipated operations at least through the first quarter of 2020. Our future capital requirements and the period for which we expect our existing resources to support our operations may vary significantly from what we expect. Our monthly spending levels vary based on new and ongoing research and development and other corporate activities. Because the length of time and activities associated with successful research and development of our product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. In addition, our future capital requirements will depend on many factors, and could increase significantly as a result of many factors, including:

- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our product candidates;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our product candidates;
- the extent to which we enter into non-exclusive, jointly funded clinical research collaboration arrangements, if any, for the development of our product candidates in combination with other companies' products;
- our ability to establish collaboration arrangements for the development of our product candidates on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under our license agreements and any collaboration agreements into which we may enter, if any;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the extent to which we acquire or in-license product candidates and technologies, and the terms of such in-licenses;
- the costs of future commercialization activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that can take years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that may not be commercially available for several years, if ever. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. Volatility in the financial

[Table of Contents](#)

markets has generally made equity and debt financing more difficult to obtain, and may compromise our ability to meet our fundraising needs. We cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidate or be unable to expand our operations or otherwise capitalize on our business opportunities.

Raising additional capital may cause dilution to our shareholders, including purchasers of ADSs in this offering, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity and debt financings. The sale of additional equity or convertible debt securities would dilute all of our shareholders, including purchasers of ADSs in this offering. The incurrence of indebtedness could result in increased fixed payment obligations, and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights, limitations on declaring dividends and other operating restrictions that could adversely impact our ability to conduct our business. Moreover, the terms of any financing may adversely affect the holdings or the rights of our shareholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our ADSs to decline.

We could decide to seek funds through collaborations, strategic alliances or licensing arrangements with third parties, and we could be required to do so at an earlier stage than otherwise would be desirable. In connection with any such collaborations, strategic alliances or licensing arrangements, we may be required to relinquish valuable rights to our intellectual property, future revenue streams, research programs or product candidates, grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves, or otherwise agree to terms unfavorable to us.

We may be unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable United Kingdom tax legislation.

As a United Kingdom resident company, we are subject to U.K. corporate taxation. We have generated losses since inception. As of June 30, 2017, we had cumulative carry forward tax losses of £8.5 million. Subject to any relevant restrictions, we expect these to be available to carry forward and offset against future operating profits. As a company that carries out extensive research and development activities, we benefit from the United Kingdom research and development tax credit regime for small and medium-sized companies, whereby we are able to surrender the trading losses that arise from our qualifying research and development activities for a payable tax credit of up to 33.35% of eligible research and development expenditures. Qualifying expenditures largely comprise employment costs for research staff, consumables and subcontract costs incurred as part of research projects. Certain subcontracted qualifying research expenditures are eligible for a cash rebate of up to 21.68%. The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these tax credit cash rebate claims. We may not be able to continue to claim payable research and development tax credits in the future as we become a public company because we may no longer qualify as a small or medium-sized company.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products to be taxed at an effective rate of 10%. As we have many different patents covering our products, future upfront fees, milestone fees, product revenues and royalties could be taxed at this favorably low tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the United Kingdom research and development tax credit

[Table of Contents](#)

regime or the “patent box” regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

Our business may become subject to economic, political, regulatory and other risks associated with international operations.

As a company based in the United Kingdom, our business is subject to risks associated with conducting business internationally. Many of our suppliers and collaborative and clinical trial relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for drug approvals in non-U.S. countries;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with non-U.S. laws and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, the euro and currency controls;
- changes in a specific country’s or region’s political or economic environment, including the implications of the 2016 decision of the eligible members of the U.K. electorate for the United Kingdom to withdraw from the European Union or any potential future referendum regarding the independence of Scotland;
- trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or non-U.S. governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

Exchange rate fluctuations may adversely affect our results of operations and financial condition.

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. Since the vote of a majority of the eligible members of the electorate in the United Kingdom to withdraw from the European Union in a national referendum held on June 23, 2016, referred to as “BREXIT,” there has been a significant increase in the volatility of the exchange rate between the pound sterling and the U.S. dollar and an overall weakening of the pound sterling. Although we are based in the United Kingdom, we source our active pharmaceutical ingredient, or API, and other raw

[Table of Contents](#)

materials and our research and development, manufacturing, consulting and other services worldwide, including from the United States, the European Union and India. Any weakening of the pound sterling against the currencies of such other jurisdictions makes the purchase of such goods and services more expensive for us. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the currencies of other countries, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

Risks Related to Development of Our Product Candidates

Initial success in the completed and ongoing early-stage clinical trials may not be indicative of results obtained when these trials are completed or in later stage trials.

Acelarin is currently being evaluated in three clinical trials across numerous solid tumor indications: one Phase 1b trial in combination with cisplatin in patients with biliary cancer, one Phase 2 trial in patients with recurrent ovarian cancer, and one multi-year investigator-sponsored Phase 3 trial in patients with pancreatic cancer. While Acelarin has shown high disease control rates and a favorable tolerability profile in early-stage trials, including in two first-in-human dose-ranging Phase 1 trials, we may not see such favorable data in future clinical trials involving Acelarin. Similarly, favorable results obtained from preclinical studies of NUC-3373 and in the ongoing Phase 1 trial in patients with advanced solid tumors may not be replicated in any future clinical trials. In addition, data generated in these early stage Phase 1 trials are not the basis on which marketing approval by the FDA or a comparable foreign regulatory authority would be sought. Furthermore, the results of our clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for marketing approval. Statistical significance means that an effect is unlikely to have occurred by chance. Clinical trial results are considered statistically significant when the probability of the results occurring by chance, rather than from the efficacy of the product candidate, is sufficiently low. There can be no assurance that any of our clinical trials will ultimately be successful or support further clinical development of any of our product candidates. There is a high failure rate for drugs proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies.

Preliminary and interim data from our clinical trials may change as patient enrollment continues, patient data are further examined and more patient data become available.

Preliminary or interim data from our clinical trials, including those from the Phase 1b trial of Acelarin in combination with cisplatin in patients with biliary cancer, the Phase 2 trial of Acelarin in patients with recurrent ovarian cancer, the multi-year investigator-sponsored Phase 3 trial of Acelarin in patients with pancreatic cancer, the Phase 1 trial of NUC-3373 in patients with advanced solid tumors, and any future clinical trials of any of product candidates, are not necessarily predictive of final results and may change. Preliminary and interim data are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues, patient data are further examined, more patient data become available, and we prepare and issue our final clinical study report. As a result, preliminary and interim data should be viewed with caution until the final data are available. Material adverse changes in the final data compared to the preliminary or interim data could significantly harm our business prospects.

We are very early in our development efforts. If we are unable to successfully develop and commercialize our product candidates or experience significant delays in doing so, our business will be harmed.

We currently do not have any products that have gained marketing approval. We have invested substantially all of our efforts and financial resources identifying and developing our ProTides, such as Acelarin, NUC-3373 and NUC-7738. Our ability to generate product revenues, which may not occur for several years, if ever, will

[Table of Contents](#)

depend on the successful development and eventual commercialization of Acelarin, for which one Phase 1b trial, one Phase 2 trial and one multi-year investigator-sponsored Phase 3 trial are ongoing, NUC-3373, for which one Phase 1 trial is ongoing, and NUC-7738, which is currently in preclinical development. We currently do not generate any revenues from sales of any products, and we may never be able to develop or commercialize a marketable drug. Each of our product candidates will require development, management of development and manufacturing activities, marketing approval in multiple jurisdictions, obtaining manufacturing supply, building of a commercial organization, substantial investment and significant marketing efforts before we generate any revenues from drug sales.

We have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute development activities for our product candidates, including successful enrollment in and completion of clinical trials;
- manage our spending as costs and expenses increase due to preclinical development, clinical trials, marketing approvals and commercialization;
- obtain required marketing approvals for the development and commercialization of our product candidates;
- obtain and maintain patent and trade secret protection and regulatory exclusivity for our product candidates and ensure that we do not infringe the valid patent rights of third parties;
- protect, leverage and expand our intellectual property portfolio;
- establish and maintain clinical and commercial manufacturing capabilities or make arrangements with third-party manufacturers for clinical and commercial manufacturing;
- build and maintain robust sales, distribution and marketing capabilities, either on our own or in collaboration with strategic partners, if our product candidates are approved;
- gain acceptance for our product candidates, if approved, by patients, the medical community and third-party payors;
- compete effectively with other therapies;
- obtain and maintain healthcare coverage and adequate reimbursement;
- maintain a continued acceptable safety profile for our product candidates following approval, if approved; and
- develop and maintain any strategic relationships we elect to enter into, if any.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would harm our business. If we do not receive marketing approvals for our product candidates, we may not be able to continue our operations.

If we experience delays or difficulties in the enrollment of patients in clinical trials, development of our product candidates may be delayed or prevented.

Identifying and qualifying patients to participate in clinical trials for our product candidates is critical to our success. We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials. Patient enrollment may be affected by many factors including:

- the severity of the disease under investigation;

Table of Contents

- the size of the patient population for a product indication;
- the eligibility criteria for the clinical trial in question;
- the perceived risks and benefits of the product candidate under study;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the availability of competing therapies and clinical trials; and
- the proximity and availability of clinical trial sites for prospective patients.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our clinical trials may be delayed or terminated. Any delays in completing our clinical trials will increase our costs, delay or prevent our product candidate development and approval process, and jeopardize our ability to commence product sales and generate revenue.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and may experience delays in obtaining, or ultimately be unable to obtain, the approval of our product candidates.

The risk of failure in drug development is high. Acelarin is currently being studied in one Phase 1b trial, one Phase 2 trial and one multi-year investigator-sponsored Phase 3 trial, NUC-3373 is currently being studied in one Phase 1 trial, and NUC-7738 is in preclinical development. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in patients. Clinical trials are expensive, difficult to design and implement and can take several years to complete, and their outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Further, the results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates. Clinical trials may be delayed, suspended or prematurely terminated because costs are greater than we anticipate or for a variety of reasons, such as:

- delay or failure in reaching agreement with the FDA, the EMA or a comparable foreign regulatory authority on a trial design that we are able to execute;
- delay or failure in obtaining authorization to commence a trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical trial;
- delays in reaching, or failure to reach, agreement on acceptable terms with prospective trial sites and prospective CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inability, delay, or failure in identifying and maintaining a sufficient number of trial sites, many of which may already be engaged in other clinical programs;
- delay or failure in recruiting and enrolling suitable subjects to participate in a trial;

Table of Contents

- delay or failure in having subjects complete a trial or return for post-treatment follow-up;
- clinical sites and investigators deviating from the clinical protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial;
- failure to initiate or delay of or failure to complete a clinical trial as a result of an Investigational New Drug Application, or IND, being placed on clinical hold by the FDA, or for other reasons;
- lack of adequate funding to continue a clinical trial, including unforeseen costs due to enrollment delays, requirements to conduct additional clinical trials and increased expenses associated with the services of our CROs and other third parties;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators, or a Data Safety Monitoring Board, or DSMB, if one is used for our clinical trials, may require that we suspend or terminate our clinical trials for various reasons, including noncompliance with regulatory requirements, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, or a finding that the participants are being exposed to unacceptable health risks;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient;
- the FDA or other regulatory authorities may require us to submit additional data or impose other requirements before permitting us to initiate a clinical trial; or
- there may be changes in governmental regulations or administrative actions.

Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of marketing approval for our product candidates. The FDA may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials. Even though Acelarin and NUC-3373 are transformations of chemotherapeutic agents that have been widely used for many years and there is a clear unmet medical need in each of the indications that we are currently pursuing in the clinic, there can be no assurance that the FDA will permit us to move more quickly to the initiation of pivotal clinical trials in large patient populations. Furthermore, NUC-7738 is a transformation of cordycepin, a nucleoside analog that has never been successfully developed or approved as a chemotherapy, which may result in the need for more preclinical studies or clinical trials than would be the case for transformations of approved chemotherapeutic agents.

If we are required to conduct additional clinical trials or other studies of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other studies, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval for our product candidates at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;

[Table of Contents](#)

- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings that would reduce the potential market for our products or inhibit our ability to successfully commercialize our products;
- be subject to additional post-marketing restrictions or requirements, including confirmatory trials; or
- have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in preclinical and clinical development or receiving the requisite marketing approvals. We do not know whether any of our preclinical studies or clinical trials will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Due to our limited resources and access to capital, we must, and have in the past decided to, prioritize development of certain ProTide candidates over other potential candidates. These decisions may prove to have been wrong and may adversely affect our performance.

Because we have limited resources and access to capital to fund our operations, we must decide which ProTides to pursue and the amount of resources to allocate to each. Our decisions concerning the allocation of research, collaboration, management and financial resources toward particular ProTides or therapeutic areas may not lead to the development of viable commercial products and may divert resources away from better opportunities. Similarly, our decisions to delay, terminate or collaborate with third parties in respect of product development programs may also prove not to be optimal and could cause us to miss valuable opportunities. If we make incorrect determinations regarding the market potential of our ProTides or misread trends in the biopharmaceutical industry, in particular for our lead ProTides, then our business may be adversely affected.

We may not be successful in our efforts to use and expand our technology platform to build a pipeline of additional ProTide candidates.

A key element of our strategy is to use and expand our proprietary ProTide technology to build a pipeline of additional ProTide candidates and progress these ProTide candidates through clinical development for the treatment of cancer. Although our research and development efforts to date have resulted in a pipeline of ProTide candidates directed at the treatment of many solid tumors and hematological malignancies, we may not be able to develop ProTide candidates that are safe and effective. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance.

Risks Related to Marketing Approval of Our Product Candidates

If we are not able to obtain, or if there are delays in obtaining, required marketing approvals, we will not be able to commercialize our product candidates and our ability to generate revenue will be impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, distribution, import and export are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other countries.

These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, current good manufacturing practice, or cGMP, requirements relating to

[Table of Contents](#)

manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, including periodic inspections by FDA and other regulatory authorities, requirements regarding the distribution of samples to physicians and recordkeeping. Before we can commercialize any of our product candidates, each such product candidate must be approved by the FDA pursuant to an NDA in the United States, by the EMA pursuant to a MAA in the European Union, and by similar regulatory authorities outside the United States prior to commercialization.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive and takes several years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have limited experience in planning and conducting the clinical trials required for marketing approvals, and we expect to rely on third-party contract research organizations, or CROs, to assist us in this process. Obtaining marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process, and in many cases the inspection of manufacturing facilities by the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. Because a number of our clinical trials will be in combination with other approved therapies, there may also be undesirable or unintended side effects, toxicities or other characteristics resulting from the other therapy or from its combination with our product candidate. In addition, because our product candidates are transformations of nucleoside analogs, including those that are approved chemotherapeutic agents and those that have never been approved as chemotherapeutic agents, our product candidates could be negatively impacted by the identification of any new undesirable or unintended side effects, toxicities or other characteristics in such existing nucleoside analogs, in particular in those that have never been approved as chemotherapeutic agents. Although we use the proprietary name Acelarin for our product candidate NUC-1031, we have not obtained any conditional approval of this proprietary name and any goodwill or recognition that we accrue during development of the product candidate may be lost if we are required to select a different proprietary name in the course of obtaining regulatory approval, if such approval occurs at all.

Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies or clinical trials. Our product candidates could be delayed in receiving, or fail to receive, marketing approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials or require that we perform additional clinical trials, including toxicology trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication;
- the results of our clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for marketing approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA or other submission to obtain marketing approval in the United States or elsewhere;

Table of Contents

- third-party manufacturers or our clinical or commercial product candidates may be unable to meet the FDA’s cGMP requirements or similar requirements of foreign regulatory authorities; and
- the approval requirements or policies of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

In addition, even if we were to obtain approval, regulatory authorities may approve our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could harm the commercial prospects for our product candidates.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be impaired.

Our product candidates may cause undesirable side effects that could delay or prevent their marketing approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could cause us or the FDA or other regulatory authorities to interrupt, delay or halt our clinical trials and could result in more restrictive labels or the delay or denial of marketing approval by the FDA or other regulatory authorities of our product candidates. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our product candidates for any or all targeted indications. The drug-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims.

Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates or any other similar drugs after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such product candidates;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way such product candidates are distributed or administered, conduct additional clinical trials or change the labeling of the product candidates;
- regulatory authorities may require a REMS plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to remove such product candidates from the marketplace after they are approved;
- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and
- our reputation may suffer.

[Table of Contents](#)

In addition, the patient profile in the indications for which we are currently developing our product candidates, with many patients already seriously ill at the time of initiation of treatment, may result in an increased risk of claims that undesirable side effects or poor prognoses or outcomes are related to our product candidates. Regardless of whether or not such side effects or prognoses or outcomes are ultimately determined to be related to our product candidates, the claims themselves could result in some or all of the foregoing negative consequences.

We believe that any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates and could substantially increase the costs of commercializing our product candidates, if approved, and significantly impact our ability to successfully commercialize our product candidates and generate revenues.

A Fast Track Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

We do not currently have Fast Track Designation for any of our product candidates but may seek such designation. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether to grant this designation. Even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many drugs that have received Fast Track Designation have failed to obtain drug approval.

We may be unable to obtain orphan drug designation from the FDA for any of our product candidates, and even if we do obtain such designations, we may be unable to obtain or maintain the benefits associated with orphan drug designation, including the potential for orphan drug exclusivity.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, defined as one occurring in a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product or where there is no satisfactory method of diagnosis, prevention or treatment, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax credits for qualified clinical testing and user-fee waivers. In addition, if a product receives the first FDA approval of that drug for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the rare disease or condition. Under the FDA's regulations, the FDA will deny orphan drug exclusivity to a designated drug upon approval if the FDA has already approved another drug with the same

[Table of Contents](#)

active ingredient for the same indication, unless the drug is demonstrated to be clinically superior to the previously approved drug. In the European Union, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

We do not currently have orphan drug designation for any of our product candidates but may seek such designation. Even if we are able to obtain orphan designation for one or more of our product candidates in the United States or the European Union, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products, which could prevent us from marketing such product candidate if another company is able to obtain orphan drug exclusivity before we do. In addition, exclusive marketing rights in the United States may be unavailable if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition following approval. Further, even if we obtain orphan drug exclusivity for one or more of our ProTides, that exclusivity may not effectively protect them from competition because different drugs with different active moieties can be approved for the same condition. In addition, the FDA or the EMA can subsequently approve products with the same active moiety for the same condition if the FDA or the EMA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, while we may seek orphan drug designation for one or more of our product candidates, we may never receive such designations.

There have been legal challenges to aspects of the FDA's regulations and policies concerning the exclusivity provisions of the Orphan Drug Act, and future challenges could lead to changes that affect the protections afforded our products in ways that are difficult to predict. In 2014, a U.S. district court invalidated the FDA's denial of orphan exclusivity to an orphan designated drug, which the FDA had based on its determination that the drug was not proven to be clinically superior to a previously approved "same drug." In response to the decision, the FDA released a policy statement stating that the court's decision is limited just to the facts of that particular case and that the FDA will continue to deny orphan drug exclusivity to a designated drug upon approval if the drug is the "same" as a previously approved drug, unless the drug is demonstrated to be clinically superior to that previously approved drug. In April 2016, another similar legal challenge was initiated against the FDA for its denial of orphan drug exclusivity to another designated drug. In the future, there is the potential for additional legal challenges to the FDA's orphan drug regulations and policies, and it is uncertain how ongoing and future challenges might affect our business.

Any product candidate for which we obtain marketing approval will be subject to extensive post-marketing regulatory requirements and could be subject to post-marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

If the FDA or a comparable foreign regulatory authority approves any of our product candidates, activities such as the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. The FDA or a comparable foreign regulatory authority may also impose requirements for costly post-marketing preclinical studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding use of their products, and if we promote our products beyond their approved indications, we may be subject to enforcement actions or prosecution arising from that off-label promotion. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse and other laws, as well as state consumer protection laws.

[Table of Contents](#)

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance can also result in significant financial penalties. Similarly, failure to comply with the European Union's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay marketing approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Although we do not currently have any drugs on the market, once we begin commercializing our product candidates, we will be subject to additional healthcare statutory and regulatory requirements and enforcement by the U.S. federal and state governments and the foreign governments in the jurisdictions in which we conduct our business. Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable U.S. federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under a federal healthcare program such as Medicare and Medicaid; a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

Table of Contents

- the federal false claims laws, including, without limitation, the civil False Claims Act (which can be enforced by private citizens through qui tam actions), impose criminal and civil penalties against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; in addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the federal physician payment transparency requirements under the Physician Payments Sunshine Act, created under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report to the Centers for Medicare & Medicaid Services, or CMS, information related to payments and other transfers of value to physicians and teaching hospitals and the ownership and investment interests of physicians and their immediate family members in such manufacturers;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which also imposes obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouses as well as their business associates that perform certain services involving the use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- some state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and
- state and foreign laws that govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion of our products from government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm, and the curtailment or restructuring of our operations. In addition, if any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Current and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and certain disabled people by establishing the Medicare Part D Program and introduced a reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this law provided authority for Medicare Part D plans to limit the number of drugs covered in any therapeutic class. Cost reduction initiatives and other provisions of this law and future laws could decrease the coverage and price that we will receive for any approved products. While the MMA only applies to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Therefore, any limitations in reimbursement that results from the MMA may result in reductions in payments from private payors.

In March 2010, the ACA became law. The ACA is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Among the provisions of the ACA of importance to our potential product candidates are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service Act's pharmaceutical pricing program;
- new requirements to report financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

The current administration supports a repeal of the ACA and an Executive Order has been signed commanding federal agencies to try to waive or delay requirements of the ACA that impose economic or regulatory burdens on states, families, the health-care industry and others. The Executive Order also declares that the administration will seek the "prompt repeal" of the law and that the government should prepare to "afford the States more flexibility and control to create a more free and open healthcare market." In addition, following the

passage of the budget resolution for fiscal year 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act, which, if enacted, would have amended or repealed significant portions of the ACA. More recently, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a “skinny” version of the Better Care Reconciliation Act of 2017. Each of these measures was rejected by the full Senate. Congress will likely consider other legislation to replace elements of the ACA. At this time, we cannot know how any legislation that may be passed to amend or replace the ACA will impact our business in the United States.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These new laws may result in additional reductions in Medicare and other healthcare funding. For example, as a result of the Budget Control Act of 2011, providers are subject to Medicare payment reductions of 2% per fiscal year through 2025 unless additional Congressional action is taken. In addition, the American Taxpayer Relief Act of 2012 reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments from providers from three to five years. Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to product pricing, contain the cost of drugs, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we will receive for any approved product. Any reduction in payments from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize any of our products for which we receive marketing approval.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed or what the impact of such changes on the marketing approvals, if any, of our product candidates, may be. In addition, increased scrutiny by the U.S. Congress of the FDA’s approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing conditions and other requirements.

Our future growth may depend, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability may depend, in part, on our ability to commercialize our product candidates in foreign markets. In order to market and sell our products in the European Union and many other jurisdictions, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and economic areas and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. Additionally, a failure or delay in obtaining marketing approval in one jurisdiction may have a negative effect on the marketing approval process in others.

Table of Contents

Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials. Obtaining foreign marketing approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market. If we obtain approval of our product candidates and ultimately commercialize our product candidates in foreign markets, we would be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for our product candidates in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced or no protection on pharmaceutical products or their use in some foreign countries;
- the unwillingness of courts in some foreign jurisdictions to enforce patents even when valid and infringed in that country;
- the possibility of pre-grant or post-grant review proceedings in certain foreign countries that allow a petitioner to hold up patent rights for an extended period or permanently by challenging the patent filing at the patent office of that country;
- the possibility of a compulsory license issued by a foreign country that allows a third-party entity or a government to manufacture, use or sell our products with a government-set low royalty to us;
- the existence of additional potentially relevant third-party intellectual property rights;
- foreign currency exchange rate fluctuations;
- an increase in restrictions on trade or other protectionist measures; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of our product candidates could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that

[Table of Contents](#)

compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our financial results would suffer.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and the amount of the liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against other potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our discovery, preclinical development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Our Dependence on Third Parties

We rely on, and expect to continue to rely on, third parties to conduct our clinical trials for our product candidates. If these third parties do not successfully carry out their contractual duties, comply with regulatory requirements or meet expected deadlines, we may not be able to obtain marketing approval for or commercialize our product candidates, and our business could be substantially harmed.

We do not have the ability to independently conduct clinical trials. We rely on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct or otherwise support clinical trials for our product candidates. We expect to rely heavily on these parties for performance of clinical trials for our product candidates. Nevertheless, we will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards.

We, our investigators, and our CROs will be required to comply with regulations, including good clinical practice, or GCP, and other related requirements for conducting, monitoring, recording and reporting the results of clinical trials to ensure that the data and results are scientifically credible and accurate, and that the trial patients are adequately informed of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any drugs in clinical development. The FDA enforces GCPs through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we, our investigators or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be called into question and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before considering our marketing applications for approval. We cannot assure you that, upon inspection, the FDA will determine that any of our future clinical trials will comply with GCPs.

[Table of Contents](#)

In addition, our clinical trials must be conducted with product candidates produced under cGMPs. Our failure or the failure of our investigators or CROs to comply with these requirements may require us to repeat clinical trials, which would delay the marketing approval process and could also subject us to enforcement action. We also are required to register certain clinical trials and post the results of such completed clinical trials involving product candidates for which we receive marketing approval on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Although we intend to design the clinical trials for our product candidates, CROs will administer all of the clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct future clinical trials will also result in less direct control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed;
- make errors in the design, management or retention of our data or data systems; or
- form relationships with other entities, some of which may be our competitors.

These factors may adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. If the CROs do not perform clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development, marketing approval and commercialization of our product candidates may be delayed, we may not be able to obtain marketing approval and commercialize our product candidates, or our development program may be irreversibly harmed. If we are unable to rely on clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of any clinical trials we conduct and this could significantly delay commercialization and require significantly greater expenditures.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any clinical trials such CROs are associated with may be extended, delayed or terminated and we may not be able to obtain marketing approval for or successfully commercialize our product candidates. As a result, we believe that our financial results and the commercial prospects for our product candidates in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We contract with third parties for the manufacture and shipment of our product candidates for preclinical studies and clinical trials and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or drugs or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not currently own or operate, nor do we have any plans to establish in the future, any manufacturing facilities or personnel. We rely, and expect to continue to rely, on third parties for the manufacture and shipment of our product candidates for preclinical studies and clinical trials, as well as for the commercial manufacture of our drugs if any of our product candidates receive marketing approval. This reliance on third parties increases the

[Table of Contents](#)

risk that we will not have sufficient quantities of our product candidates or drugs or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

The facilities used to manufacture our product candidates must be evaluated by the FDA pursuant to inspections that will be conducted after we submit our marketing applications to the FDA to ensure compliance with cGMP. We do not control the manufacturing and shipment process of, and will be completely dependent on, our contract manufacturers for compliance with cGMPs in connection with the manufacture and shipment of our product candidates. If our contract manufacturers cannot successfully manufacture and ship material that conforms to our specifications and the regulatory requirements of the FDA or others, we will not be able to use the products produced at their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority finds that these facilities do not comply with cGMP, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain marketing approval for or market our product candidates, if approved. Further, our failure, or the failure of our third-party manufacturers, to comply with these or other applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, if approved, operating restrictions and criminal prosecutions.

We may be unable to establish any agreements with third-party manufacturers or do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Our product candidates and any other drugs that we may develop may compete with other product candidates and approved drugs for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture and shipment of our product candidates or drugs may adversely affect our future profit margins and our ability to commercialize any drugs that receive marketing approval on a timely and competitive basis.

We, or our third-party manufacturers, may be unable to successfully scale-up manufacturing of our product candidates in sufficient quality and quantity, which would delay or prevent us from developing our product candidates and commercializing approved products, if any.

In order to conduct large-scale clinical trials of our product candidates, we will need to manufacture them in large quantities. We, or any of our manufacturing partners, may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In

[Table of Contents](#)

addition, quality issues may arise during scale-up activities. If we, or any manufacturing partners, are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing, and clinical trials of that product candidate may be delayed or infeasible, and regulatory approval or commercial launch of any resulting product may be delayed or not obtained, which could significantly harm our business.

The third parties upon which we rely for the supply of the active pharmaceutical ingredients, formulations, and drug products are our sole sources of supply and have limited capacity, and the loss of any of these suppliers could harm our business.

The API, formulations and drug products for our product candidates are supplied to us from single-source suppliers with limited capacity. Our ability to successfully develop our product candidates, and to ultimately supply our commercial drugs in quantities sufficient to meet the market demand, depends in part on our ability to obtain the API, formulations and drug products in accordance with cGMP requirements and in sufficient quantities for commercialization and clinical trials. We do not currently have arrangements in place for a redundant or second-source supply of any such API, formulation or drug product in the event any of our current suppliers cease their operations for any reason.

We do not know whether our suppliers will be able to meet our demand, either because of the nature of our agreements with those suppliers, our limited experience with those suppliers or our relative importance as a customer to those suppliers. It may be difficult for us to assess their ability to timely meet our demand in the future based on past performance. While our suppliers have generally met our demand for their products on a timely basis in the past, they may subordinate our needs in the future to their other customers.

For all of our product candidates, we intend to identify and qualify additional manufacturers to provide API, formulations and drug products prior to submission of an NDA to the FDA or an MAA to the EMA. Establishing additional or replacement suppliers for the API, formulations and drug products for our product candidates, if required, may not be accomplished quickly. If we are able to find a replacement supplier, such replacement supplier would need to be qualified, or we may have to perform comparative studies comparing the drug product from a new manufacturer to the product used in any completed clinical trials. All of this may require additional marketing approval, which could result in further delay. While we seek to maintain adequate inventory of the API, formulations and drug products for our product candidates, any interruption or delay in the supply of components or materials, or our inability to obtain such API, formulation and drug product from alternate sources at acceptable prices in a timely manner could impede, delay, limit or prevent our development efforts.

We have entered into, and may in the future enter into, collaborations with third parties to discover or develop product candidates. If these collaborations are not successful, our business could be adversely affected.

We have entered into a research, collaboration and license agreement with Cardiff University and University College Cardiff Consultants Ltd., or Cardiff Consultants, for the design, synthesis, characterization and evaluation of ProTides, with the results of such research assigned to us and other intellectual property of Cardiff University and Cardiff Consultants exclusively licensed to us for use for all purposes related to selected ProTides and the nucleoside family of the selected ProTides. We are significantly reliant on this collaboration for the generation of additional potential product candidates and on the scientists employed by Cardiff University and Cardiff Consultants to perform such research. We have limited control over the amount and timing of resources that our collaborators dedicate to the development of ProTides and our ability to generate potential additional ProTides from these arrangements will depend on our and our collaborators' abilities to successfully perform the functions assigned to each of us in these arrangements. In addition, our collaborators have the ability to abandon research or development projects and terminate applicable agreements. If we breach any of our obligations under this agreement, Cardiff University and Cardiff Consultants may have the right to terminate the agreement, which would result in a significant reduction in our ability to develop additional ProTides, and in our being unable to

[Table of Contents](#)

develop, manufacture and sell products that are covered by the licensed intellectual property, or in a competitor's gaining access to the licensed intellectual property. Our agreement will expire at the end of 2017. Although we anticipate extending the agreement beyond its expiration, there can be no assurance that we will be successful in doing so. Any expiration of this agreement could also result in a significant reduction in our ability to develop additional ProTides.

We may potentially enter into additional collaborations with third parties in the future. Our collaboration with Cardiff University and Cardiff Consultants, and any future collaborations we enter into in the future, may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- the clinical trials conducted as part of, or as a result of, these collaborations may not be successful;
- collaborators may not pursue development or commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our shareholders about the status of such product candidates;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates developed in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

[Table of Contents](#)

- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our collaborations do not result in the successful development and commercialization of products, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this prospectus also apply to the activities of our collaborators.

We may in the future decide to collaborate with pharmaceutical and biotechnology companies and other organizations for the development and potential commercialization of our product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing shareholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement will depend, among other things, upon our assessment of the collaborator's resources and expertise and the terms and conditions of the proposed collaboration. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and strategy.

If we fail to comply with our obligations under our license and collaboration agreement with Cardiff ProTides Ltd., we could lose rights to licensed and assigned intellectual property that are necessary for developing and commercializing Acelarin and other potential product candidates.

We entered into an exclusive, worldwide assignment, license and collaboration agreement with Cardiff ProTides Ltd., or Cardiff ProTides, for certain of the patents related to Acelarin and other potential ProTides. This agreement imposes various development, commercialization, royalty payment, diligence and other obligations on us. Among other obligations, we are specifically required to: pay Cardiff ProTides potential milestone payments; pay Cardiff ProTides royalties equal to mid- to high-single digit percentages of sales of such products, including sales by sublicensees; use commercially reasonable efforts to bring products to market; provide development and financial reports to Cardiff ProTides; file, prosecute, defend and maintain patent rights; indemnify Cardiff ProTides against certain claims and maintain insurance coverage; and direct future medicinal chemistry work related to certain compounds to Cardiff ProTides on a preferential basis.

If we breach any of these obligations, Cardiff ProTides may have the right to terminate the license and require us to assign back to Cardiff ProTides the intellectual property which was assigned to us under this agreement, which would result in our being unable to develop, manufacture and sell products that are covered by the licensed intellectual property or the assigned intellectual property, including Acelarin, or in a competitor's gaining access to the licensed intellectual property or the assigned intellectual property.

Risks Related to the Commercialization of Our Product Candidates

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If our

Table of Contents

product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the timing of our receipt of any marketing approvals;
- the terms of any approvals and the countries in which approvals are obtained;
- the efficacy and safety and potential advantages and disadvantages compared to alternative treatments;
- the prevalence and severity of any side effects associated with our products or with any product that is used in combination with our product;
- the indications for which our products are approved;
- adverse publicity about our products or favorable publicity about competing products;
- the approval of other products for the same indications as our products;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the success of our physician education programs;
- the strength of our marketing and distribution;
- the availability of third-party coverage and adequate reimbursement, including patient cost-sharing programs such as copays and deductibles; and
- any restrictions on the use of our products together with other medications.

We face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as, or similar to, our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Specifically, there are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. If Acelarin is approved, it would compete with (a) existing chemotherapies, including gemcitabine, (b) existing targeted therapies or immunotherapies and, if approved, targeted therapies or immunotherapies in clinical trials for the treatment of patients with cancer and (c) multiple approved drugs or drugs that may be approved in the future for indications for which we may develop Acelarin. If NUC-3373 is approved, it would compete with (a) existing chemotherapies, including 5-FU, (b) existing targeted therapies or immunotherapies and, if approved, targeted therapies or immunotherapies in clinical trials for the treatment of patients with cancer and (c) multiple approved drugs or drugs that may be approved in the future for indications for which we may develop NUC-3373. If NUC-7738 is approved, it would

Table of Contents

compete with existing chemotherapies and multiple approved drugs or drugs that may be approved in the future for indications for which we may develop NUC-7738. Existing chemotherapies with which we may compete, including gemcitabine and 5-FU, are no longer under patent and are produced by numerous generic pharmaceutical manufacturers. As a result, these chemotherapies are and will continue to be substantially less expensive to patients than many other potential therapies, including our ProTide candidates, if approved.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, more convenient or less expensive or have fewer or less severe side effects than any products that we may develop. Our competitors also may obtain FDA or other marketing approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market or slow our marketing approval. Some of the important competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price and the availability of reimbursement from government and other third-party payors.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining marketing approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel and in establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Even if we are able to commercialize any product candidates, such drugs may become subject to unfavorable pricing regulations or third-party coverage and reimbursement policies.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product candidate in a particular country but then be subject to price regulations that delay our commercial launch of the product candidate, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product candidate in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize any product candidates, if approved, successfully will depend in part on the extent to which coverage and adequate reimbursement for these product candidates and related treatments will be available from government authorities, private health insurers and other organizations. In the United States, the principal decisions about coverage and reimbursement for new medicines under Medicare are made by CMS, an agency within the U.S. Department of Health and Human Services. Private payors ultimately determine which drugs they will cover and the amount of reimbursement they will provide for a covered drug. While there is no uniform system among payors for making coverage and reimbursement decisions, private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs are generally covered and paid for in the United States, but have not been approved for reimbursement in certain European countries. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of payments for particular drugs. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for drugs. We

[Table of Contents](#)

may also need to conduct expensive pharmacoeconomic studies, in addition to the costly studies required to obtain FDA or other comparable regulatory approvals, in order to demonstrate the medical necessity and cost-effectiveness of the product in order to secure coverage and reimbursement. We cannot be sure that coverage will be available for any product candidate that we commercialize and, if coverage is available, the level of payments. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

In addition to CMS and private payors, professional organizations such as the National Comprehensive Cancer Network and the American Society of Clinical Oncology can influence decisions about reimbursement for new medicines by determining standards of care. In addition, many private payors contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our products.

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could compromise our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

We currently have no marketing capability or sales force. If we are unable to establish effective sales or marketing capabilities or enter into agreements with third parties to sell or market our product candidates, we may not be able to effectively sell or market our product candidates, if approved, or generate product revenues.

We currently have no marketing capability or sales force, but we plan to commercialize any product candidates for which we receive regulatory marketing approval using a specialized sales force in the United States and Europe. To achieve commercial success for any approved product candidate for which we retain sales and marketing responsibilities, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any drug launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future drugs;

Table of Contents

- the lack of complementary drugs to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our drug revenues or the profitability of these drug revenues to us are likely to be lower than if we were to market and sell any product candidates that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so when needed or on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates that receive marketing approval or any such commercialization may experience delays or limitations.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the evaluation of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to successfully commercialize any products that we may develop.

Our product liability insurance may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain intellectual property protection for our technology and products, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired. In addition, if we infringe the valid patent rights of others, we may be prevented from making, using or selling our products or may be subject to damages or penalties.

Our success depends in large part on our ability to obtain and maintain patents in the United States and other countries that adequately protect our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and in foreign countries that cover our novel product candidates and their uses, pharmaceutical formulations and dosages, and processes for the manufacture of them. Our patent portfolio currently includes both patents and patent applications.

[Table of Contents](#)

The patent prosecution process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. We may choose not to seek patent protection for certain innovations and may choose not to pursue patent protection in certain jurisdictions. Under the laws of certain jurisdictions, patents or other intellectual property rights may be unavailable or limited in scope. It is also possible that we will fail to identify patentable aspects of our research and development before it is too late to obtain patent protection.

We currently solely own or exclusively license our patents and patent applications and we have the right to control the prosecution of the in-licensed patent applications. In the future, we may choose to in-license additional patents or patent applications from third parties that we conclude are useful or necessary for our business goals. We may not have the right to control the preparation, filing, prosecution or maintenance of such patent applications. Therefore, if we do license additional patents or patent applications in the future, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or, in some cases, not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The U.S. Patent and Trademark Office, or USPTO, recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, became effective on March 16, 2013. The Leahy-Smith Act also created certain new administrative adversarial proceedings, discussed below. It is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

The U.S. Supreme Court has issued opinions in patent cases in the last few years that many consider may weaken patent protection in the United States, either by narrowing the scope of patent protection available in certain circumstances, holding that certain kinds of innovations are not patentable or generally otherwise making it easier to invalidate patents in court. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and in other countries. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In particular, third parties, such as generics companies, may seek to develop or acquire intellectual property rights proximate to our patents, including with respect to formulation and process matters, and may be able to do so in a non-infringing manner. Additionally, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Likewise, a court could uphold and enforce a third-party patent that it rules we have infringed, which would subject us to damages or prevent us from making, using or selling our products.

During patent prosecution in the United States and in most foreign countries, a third party can submit prior art or arguments to the reviewing patent office to attempt to prevent the issuance of a competitor's patent. For example, our pending patent applications may be subject to a third-party preissuance submission of prior art to the USPTO or an Observation in Europe. Such submission may convince the receiving patent office not to issue the patent. In addition, if the breadth or strength of protection provided by our patents and patent applications is reduced by such third-party submission, it could affect the value of our resulting patent or dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. We may also seek to have issued patents re-issued for purposes of strengthening our patent position; however, such requests for reissuance may not result in the issuance of the new patent and could result in loss of the originally issued patent.

The risks described here pertaining to our patents and other intellectual property rights also apply to any intellectual property rights that we currently license or may license in the future. In some cases we may not have control over the prosecution, maintenance or enforcement of the patents that we license, and our licensors may fail to take the steps that we believe are necessary or desirable in order to obtain, maintain and enforce the licensed patents.

We may become involved in administrative adversarial proceedings in the USPTO or in the patent offices of foreign countries brought by a third party to attempt to cancel or invalidate our patent rights, which could be expensive, time consuming and cause a loss of patent rights.

The Leahy-Smith Act created for the first time new procedures to challenge issued patents in the United States, including post-grant review and inter partes review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with a priority date of March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for inter partes review can be filed immediately following the issuance of a patent if the patent was filed prior to March 16, 2013. A petition for inter partes review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with a priority date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of challenge, whereas inter partes review proceedings can only be brought to raise a challenge based on published prior art. These administrative adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts, use a lower burden of proof than used by U.S. federal courts and interpret patent claims using a "broadest reasonable construction" instead of "plain and ordinary

meaning,” which is used in court litigation. Because of these differences between U.S. administrative and judicial adversarial patent proceedings, it is generally considered easier for a competitor or third party to have a U.S. patent cancelled in a patent office post-grant review or inter partes review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third party in such a U.S. patent office proceeding, there is no guarantee that we will be successful in defending the patent, which would result in a loss of the challenged patent right to us.

Opposition or invalidation procedures are also available in most foreign countries. Many foreign authorities, such as the authorities at the European Patent Office, have only post-grant opposition proceedings. However, certain countries, such as India, have both pre-grant and post-grant opposition proceedings. These procedures have been used frequently against pharmaceutical patents in foreign countries. For example, in some foreign countries, these procedures are used by generic companies to hold up an innovator’s patent rights as a means to allow the generic company to enter the market. This activity is particularly prevalent in India, China and South America and may become more prevalent in Africa and other parts of Asia as certain countries reach more established economies. If any of our patents are challenged in a foreign opposition or invalidation proceeding, we could face significant costs to defend our patents and may not be successful. Further, in many foreign jurisdictions, the losing party must pay the attorneys’ fees of the winning party, which can be substantial.

We may have to file one or more lawsuits in court to prevent a third party from selling a product or using a product in a manner that infringes our patent, which could be expensive, time consuming and unsuccessful, and ultimately result in the loss of our proprietary market.

Because competition in our industry is intense, competitors may infringe or otherwise violate our issued patents, patents of our licensors or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement lawsuits, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent’s claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. We may also elect to enter into license agreements in order to settle patent infringement claims or to resolve disputes prior to litigation, and any such license agreements may require us to pay royalties and other fees that could be significant. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure.

Because our ProTides are small molecules, after commercialization they will be subject to the patent litigation process of the Hatch-Waxman Act, which allows a generic company to submit an Abbreviated New Drug Application, or ANDA, to the FDA to obtain approval to sell our drug using bioequivalence data only. Under the Hatch-Waxman Act, since our candidates will be considered new chemical entities, we will have the opportunity to list all of our patents that cover our drug product or its method of use in the FDA’s compendium of “Approved Drug Products with Therapeutic Equivalence Evaluation,” sometimes referred to as the FDA’s Orange Book. A generic company can submit an ANDA to the FDA four years after our drug approval. The submission of the ANDA by a generic company is considered a technical act of patent infringement. The generic company can certify that it will wait until the natural expiration date of our listed patents to sell a generic version of our product or can certify that one or more of our listed patents are invalid, unenforceable, or not infringed. If the latter, we will have 45 days to bring a patent infringement lawsuit against the generic company. This will initiate a challenge to one or more of our Orange Book-listed patents based on arguments from the generic company that either our patent is invalid, unenforceable or not infringed. Under the Hatch-Waxman Act, if a lawsuit is brought, the FDA is prevented from issuing a final approval on the generic drug until the earlier of seven-and-a-half years from our drug approval or a final decision of a court holding that our asserted patent claims are invalid, unenforceable or not infringed. If we do not properly list our relevant patents in the Orange

[Table of Contents](#)

Book, timely file a lawsuit in response to a certification from a generic company under an ANDA or prevail in the resulting patent litigation, we can lose our proprietary market, which can rapidly become generic. Further, even if we do correctly list our relevant patents in the Orange Book, bring a lawsuit in a timely manner and prevail in that lawsuit, it may be at a very significant cost to us of attorneys' fees and employee time and distraction over a long period. Further, it is common for more than one generic company to try to sell an innovator drug at the same time, so we may be faced with the cost and distraction of multiple lawsuits. We may also determine it is necessary to settle the lawsuit in a manner that allows the generic company to enter our market prior to the expiration of our patent or otherwise in a manner that adversely affects the strength, validity or enforceability of our patent.

A number of pharmaceutical companies have been the subject of intense review by the U.S. Federal Trade Commission, or FTC, or a corresponding agency in another country based on how they have conducted or settled drug patent litigation, and certain reviews have led to an allegation of an antitrust violation, sometimes resulting in a fine or loss of rights. We cannot be sure that we would not also be subject to such a review or that the result of the review would be favorable to us, which could result in a fine or penalty.

The FTC has brought a number of lawsuits in federal court in the past few years to challenge Hatch-Waxman ANDA litigation settlements between innovator companies and generic companies as anti-competitive. The FTC has taken an aggressive position that anything of value is a payment, whether money is paid or not. Under their approach, if an innovator as part of a patent settlement agrees not to launch or delay launch of an authorized generic during the 180-day period granted to the first generic company to challenge an Orange Book-listed patent covering an innovator drug, or negotiates a delay in entry without payment, the FTC may consider it an unacceptable reverse payment. The biopharmaceutical industry argues that such agreements are rational business decisions to dismiss risk and are immune from antitrust attack if the terms of the settlement are within the scope of the exclusionary potential of the patent. In 2013, the U.S. Supreme Court, in a five-to-three decision in *FTC v. Actavis, Inc.*, rejected both the biopharmaceutical industry's and FTC's arguments with regard to so-called reverse payments, and held that whether a "reverse payment" settlement involving the exchange of consideration for a delay in entry is subject to an anticompetitive analysis depends on five considerations: (a) the potential for genuine adverse effects on competition; (b) the justification of payment; (c) the patentee's ability to bring about anticompetitive harm; (d) whether the size of the payment is a workable surrogate for the patent's weakness; and (e) that antitrust liability for large unjustified payments does not prevent litigating parties from settling their lawsuits, for example, by allowing the generic to enter the market before the patent expires without the patentee's paying the generic. Furthermore, whether a reverse payment is justified depends upon its size, its scale in relation to the patentee's anticipated future litigation costs, its independence from other services for which it might represent payment, as was the case in *Actavis*, and the lack of any other convincing justification. The Court held that reverse payment settlements can potentially violate antitrust laws and are subject to the standard antitrust rule-of-reason analysis, with the burden of proving that an agreement is unlawful on the FTC and leaving to lower courts the structuring of such rule of reason analysis. If we are faced with drug patent litigation, including Hatch-Waxman litigation with a generic company, we could be faced with such an FTC challenge based on that activity, including how or whether we settle the case, and even if we strongly disagree with the FTC's position, we could face a significant expense or penalty.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could hurt our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell Acelarin, NUC-3373 and our other product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. While our product candidates are in preclinical studies and clinical trials, we believe that the use of our product candidates in these preclinical studies and clinical trials falls within the scope of the exemptions provided by 35 U.S.C. Section 271(e) in the United States, which exempts from patent infringement liability activities reasonably related to the development and submission of information to the FDA. As Acelarin, NUC-3373 and our other product candidates progress toward commercialization, the possibility of a

[Table of Contents](#)

patent infringement claims against us increases. There can be no assurance that our product candidates do not infringe other parties' patents or other proprietary rights, however, and competitors or other parties may assert that we infringe their proprietary rights in any event.

We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights covering our products and technology, including interference or derivation proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, including against our product candidates themselves, our formulation and manufacturing processes or our drug administration methods. In particular, because Acelarin and NUC-3373 are transformations of widely used approved chemotherapeutic agents, there is significant intellectual property held by third parties with respect to the formulation and manufacturing of those existing agents, which may increase the risk that such third parties allege infringement by us in the formulation and manufacture processes of our product candidates. Furthermore, if any of our future ProTides are transformations of an existing chemotherapeutic agent that remains on patent, we could be subject to claims of infringement by the holder of such patents.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. Alternatively, we may need to redesign infringing products, which may be impossible or require substantial time and monetary expenditure. Under certain circumstances, we could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may not be able to effectively enforce our intellectual property rights throughout the world.

We generally file our first patent application, or priority filing, at the United Kingdom Intellectual Property Office. International applications under the Patent Cooperation Treaty, or PCT, are usually filed within 12 months after the priority filing. Based on the PCT filing, national and regional patent applications may be filed in additional jurisdictions where we believe our product candidates may be marketed or manufactured. Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive, and therefore we only file for patent protection in selected countries. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws.

The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, Europe, India, China and certain other countries do not allow patents for methods of treating the human body. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions that do not favor patent protection on drugs. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drugs and, further, may export otherwise infringing drugs to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These drugs may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Furthermore, while we

intend to protect our intellectual property rights in the major markets for our product candidates, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

A number of foreign countries have stated that they are willing to issue compulsory licenses to patents held by innovator companies on approved drugs to allow the government or one or more third-party companies to sell the approved drug without the permission of the innovator patentee where the foreign government concludes it is in the public interest. India, for example, has used such a procedure to allow domestic companies to make and sell patented drugs without innovator approval. There is no guarantee that patents covering any of our drugs will not be subject to a compulsory license in a foreign country, or that we will have any influence over if or how such a compulsory license is granted. Further, Brazil allows its regulatory agency, ANVISA, to participate in deciding whether to grant a drug patent in Brazil, and patent grant decisions are made based on several factors, including whether the patent meets the requirements for a patent and whether such a patent is deemed in the country's interest. In addition, several other countries have created laws that make it more difficult to enforce drug patents than patents on other kinds of technologies. Further, under the treaty on the Trade-Related Aspects of Intellectual Property, or TRIPS, as interpreted by the Doha Declaration, countries in which drugs are manufactured are required to allow exportation of the drug to a developing country that lacks adequate manufacturing capability. Therefore, our drug markets in the United States or foreign countries may be affected by the influence of current public policy on patent issuance, enforcement or involuntary licensing in the healthcare area.

In November 2015, members of the World Trade Organization, or the WTO, which administers TRIPS, voted to extend the exemption against enforcing pharmaceutical drug patents in least developed countries until 2033. We currently have no patent applications filed in least developed countries, and our current intent is not to file in these countries in the future, at least in part due to this WTO pharmaceutical patent exemption.

In addition, some countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. Further, some countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market, which could compromise our competitive position.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable, generally expensive and time consuming and is likely to divert significant resources from our core

[Table of Contents](#)

business, including distracting our technical and management personnel from their normal responsibilities. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and, if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our ADSs. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon, misappropriating or successfully challenging our intellectual property rights.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors. The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement.

If any of our licenses or material relationships or any in-licenses upon which our licenses are based are terminated or breached, we may:

- lose our rights to develop and market our product candidates;
- lose patent protection for our product candidates;
- experience significant delays in the development or commercialization of our product candidates;
- not be able to obtain any other licenses on acceptable terms, if at all; or
- incur liability for damages.

These risks apply to any agreements that we may enter into in the future for our current or any future product candidates. If we experience any of the foregoing, it could have a negative impact on our business, financial condition, results or operations and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We have entered into license agreements with third parties and may need to obtain additional licenses from one or more of these same third parties or from others to advance our research or allow commercialization of our product candidates. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize our product candidates, which would harm our business. We cannot provide any

[Table of Contents](#)

assurances that third-party patents or other intellectual property rights do not exist which might be enforced against our current manufacturing methods, product candidates or future methods, resulting in either an injunction prohibiting our manufacture or sales, or, with respect to our sales, an obligation on our part to pay royalties or other forms of compensation to third parties.

It is possible that in any future license agreements, patent prosecution of our licensed technology may be controlled solely by the licensor, and we may be required to reimburse the licensor for their costs of patent prosecution. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship or ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize our product candidates.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our

[Table of Contents](#)

competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We seek to protect our confidential proprietary information but enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

Our proprietary information, or that of our suppliers and any future collaborators, may be lost or we may suffer security breaches.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, clinical trial data, proprietary business information, personally identifiable information of our employees and, potentially in the future, personally identifiable information of our clinical trial subjects, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Although to our knowledge we have not experienced any such material security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, regulatory penalties, disrupt our operations, damage our reputation, and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay the clinical development of our product candidates.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to make, use or sell compounds that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We, our licensors or strategic partners might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We, our licensors or strategic partners, or future licensors or strategic partners, might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies, or duplicate any of our technologies without infringing our intellectual property rights.
- It is possible that our pending patent applications will not lead to issued patents.
- Issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable as a result of legal challenges by our competitors.
- Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.
- We may not develop additional proprietary technologies that are patentable.
- The patents of others may have an adverse effect on our business.

Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business

We currently have a limited number of employees, and our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are a clinical-stage company, and, as of September 18, 2017, had 16 employees, including three executive officers. We are highly dependent on the research and development, clinical and business development expertise of Hugh S. Griffith, our Chief Executive Officer, as well as the other principal members of our management team and our collaborators' scientific and clinical team. Although we have entered into employment agreements with our executive officers, each of them may at any time serve notice to terminate their employment with us. Other than for Mr. Griffith, we do not maintain "key person" insurance for any of our executives or other employees. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we or our collaborators are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Recruiting and retaining qualified scientific, clinical, manufacturing, finance, sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, obtain marketing approval of and commercialize products. Competition to hire from this limited pool is intense and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel. If we or our collaborators are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

To manage our anticipated development and expansion, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business, which could reduce the price of our ADSs.

Following the BREXIT referendum held on June 23, 2016, the United Kingdom government served notice under Article 50 of the Treaty of the European Union on March 29, 2017 to formally initiate the process of withdrawing from the European Union. The United Kingdom and the European Union have a two-year period under Article 50 to negotiate the terms of withdrawal. Any extension of the negotiation period for withdrawal will require the consent of all of the remaining 27 member states.

The referendum and withdrawal have created significant uncertainty about the future relationship between the United Kingdom and the European Union. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which E.U.-derived laws and regulations to replace or replicate as part of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. If the United Kingdom and the European Union are unable to negotiate acceptable terms for the United Kingdom's withdrawal from the European Union, or if other E.U. member states pursue withdrawal from the European Union, barrier-free access between the United Kingdom and other E.U. member states or across the European Economic Area overall could be diminished or eliminated. In addition, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members. These developments, or the perception that any of them could occur, have had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Asset valuations, currency exchange rates and credit ratings may be especially subject to increased market volatility. These developments, or the perception that any of them could occur, may also have a significant effect on our ability to attract and retain employees, including scientists and other employees who are important for our and our collaborators' research and development efforts.

If Scotland decides to secede from the United Kingdom, our business may be adversely affected.

A referendum on Scottish independence from the United Kingdom took place on September 18, 2014, the result of which was that Scotland remained part of the United Kingdom. There may in the future be a second referendum on Scottish independence from the United Kingdom. Any such referendum, even if it again ultimately resulted in Scotland remaining part of the United Kingdom, could lead to uncertainty and disrupt the markets in which we operate, and might cause us to lose potential customers, suppliers, collaborators and employees, including scientists and other key employees employed by us or our collaborators.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The 2008 global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as resulted from the 2008 global financial crisis, could result in a variety of risks to our business, including our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption.

Our business and operations could suffer in the event of information technology and other internal infrastructure system failures.

Despite the implementation of security measures, our information technology and other internal infrastructure systems and those of our third-party CROs and other contractors and consultants, including

[Table of Contents](#)

corporate firewalls, servers, leased lines and connections to the Internet, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Furthermore, we have little or no control over the security measures and computer systems of our third-party CROs and other contractors and consultants. While we have not experienced any such system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for our product candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed.

Our employees, principal investigators, CROs and consultants may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk that our employees, principal investigators, CROs and consultants may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless or negligent conduct or disclosure of unauthorized activities to us that violate the regulations of the FDA and other regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities; healthcare fraud and abuse laws and regulations in the United States and abroad; or laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, disgorgement, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and oversight if we become subject to a corporate integrity agreement to resolve allegations of non-compliance with these laws, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We may expend our limited resources to pursue a particular product candidate and fail to capitalize on product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on specific product candidates. As a result, we may forgo or delay pursuit of opportunities with other product candidates that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We may acquire businesses or drugs, or form strategic alliances in the future and we may not realize the benefits of such acquisitions.

We may acquire additional businesses or drugs, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and strategy. We may encounter numerous difficulties in developing, manufacturing and marketing any new drugs resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

We or the third parties upon which we depend may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Natural disasters could severely disrupt our operations and hurt our financial condition. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans.

We are subject to certain U.K., U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations, violations of which can have a negative impact on our business.

We are subject to certain U.K., U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations. Among other matters, these laws and regulations prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors and other partners from authorizing, promising, offering, providing, soliciting or receiving, directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of these laws and regulations can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We also expect our international activities to increase over time. We engage third parties to obtain necessary permits, licenses, patent registrations and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of our personnel, agents or other partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Risks Related to the ADSs and This Offering

The price of our ADSs may be volatile and may fluctuate due to factors beyond our control.

The trading market for publicly traded emerging biopharmaceutical and drug discovery and development companies has been highly volatile and is likely to remain highly volatile in the future. The market price of our ADSs may fluctuate significantly due to a variety of factors, including:

- positive or negative results from, or delays in, testing and clinical trials by us, collaborators or competitors;
- technological innovations or commercial product introductions by us or competitors;
- changes in government regulations;

Table of Contents

- developments concerning proprietary rights, including patents and litigation matters;
- public concern relating to the commercial value or safety of Acelarin, NUC-3373 or NUC-7738;
- financing, collaborations or other corporate transactions;
- publication of research reports or comments by securities or industry analysts;
- general market conditions in the pharmaceutical industry or in the economy as a whole;
- the loss of any of our key scientific or senior management personnel;
- sales of our ADSs or ordinary shares by us, our senior management and board members, holders of our ADSs or our ordinary shares in the future; or
- other events and factors, many of which are beyond our control.

These and other market and industry factors may cause the market price and demand for our ADSs to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from readily selling their ADSs and may otherwise negatively affect the liquidity of our ADSs. In addition, the stock market in general, and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, when the market price of a stock has been volatile, holders of that stock have sometimes instituted securities class action litigation against the issuer. If any of the holders of our ADSs were to bring such a lawsuit against us, we could incur substantial costs defending the lawsuit and the attention of our senior management would be diverted from the operation of our business. Any adverse determination in litigation could also subject us to significant liabilities.

We will incur increased costs as a result of operating as a public company in the United States, and our senior management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we no longer qualify as an “emerging growth company”, or EGC, we will incur significant legal, accounting and other expenses that we did not incur previously. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market, or Nasdaq, and other applicable securities rules and regulations impose various requirements on non-U.S. reporting public companies, including the establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our senior management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified senior management personnel or members for our board of directors.

However, these rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we will be required to furnish a report by our senior management on our internal control over financial reporting. However, while we remain an EGC we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To prepare for eventual compliance with Section 404, once we no longer qualify as an EGC, we will be engaged in a process to document and evaluate our internal control

[Table of Contents](#)

over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants, adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

There has been no public market for our ADSs prior to this offering, and an active market may not develop in which investors can resell our ADSs.

Prior this offering, there has been no public market for our ADSs or our ordinary shares and, subsequent to this offering, there will continue not to be a public market for our ordinary shares. We cannot predict the extent to which an active market for our ADSs will develop or be sustained after this offering, or how the development of such a market might affect the market price for our ADSs. The initial public offering price of our ADSs in this offering has been agreed upon between us and the underwriters based on a number of factors, including market conditions in effect at the time of this offering, which may not be indicative of the price at which our ADSs will trade following completion of this offering. Investors may not be able to sell their ADSs at or above the initial public offering price.

Certain of our existing shareholders, members of our board of directors and senior management will maintain the ability to exercise significant control over us. Your interests may conflict with the interests of these existing shareholders.

As of September 15, 2017, after giving effect to the closing of this offering, including the purchase by certain of our existing shareholders of 933,332 ADSs that they have agreed to purchase in this offering, our senior management, board of directors and greater than 5% shareholders and their respective affiliates, in the aggregate, will own 64.8% of our ordinary shares (including ordinary shares in the form of ADSs), assuming that we sell the number of ADSs set forth on the cover page of this prospectus. These shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such general meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our general meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, the approval of certain significant corporate transactions and amendments to our Articles of Association. Among other consequences, this concentration of ownership may have the effect of delaying or preventing a change in control and might therefore negatively affect the market price of our ADSs.

Future sales, or the possibility of future sales, of a substantial number of our ADSs or ordinary shares could adversely affect the price of our ADSs.

Future sales of a substantial number of our ADSs or ordinary shares, or the perception that such sales will occur, could cause a decline in the market price of our ADSs. Based upon the number of shares outstanding as of August 31, 2017, after giving effect to the closing of this offering, we will have 30,881,641 ordinary shares (including ordinary shares in the form of ADSs) outstanding, assuming that we sell the number of ADSs set forth on the cover page of this prospectus. ADSs issued and sold in this offering may be resold in the public market immediately without restriction, unless purchased by our affiliates. A significant portion of our ordinary shares outstanding prior to the completion of this offering will be subject to the lock-up agreements described in “Shares and ADSs Eligible for Future Sale” and “Underwriting.” If, after the end of such lock-up agreements, these shareholders sell substantial amounts of our securities in the public market, or the market perceives that such sales may occur, the market price of our ADSs and our ability to raise capital through an issue of equity

[Table of Contents](#)

securities in the future could be adversely affected. We have also entered into a registration rights agreement to be effective upon the completion of this offering and pursuant to which we have agreed under specified circumstances to file a registration statement to register the resale of the ordinary shares (which may be converted to ADSs) held by some of our existing shareholders, as well as to cooperate in specified public offerings of such shares.

If you purchase ADSs in this offering, you will suffer immediate dilution of your investment.

We expect the initial public offering price of our ADSs in this offering to be substantially higher than the pro forma as adjusted net tangible book value per ADS, and per underlying ordinary share, prior to this offering. Therefore, if you purchase ADSs in this offering, you will pay a price per ADSs, and per underlying ordinary share, that substantially exceeds our net tangible book value per ADS, and per underlying ordinary share, after this offering. To the extent outstanding options are exercised for ordinary shares, you may experience further dilution. Based on the initial public offering price of \$15.00 per ADS, you will experience immediate dilution of \$11.24 per ADS, representing the difference between our pro forma as adjusted net tangible book value per ADS after giving effect to this offering and the offering price. See “Dilution.”

Because we do not anticipate paying any cash dividends on our ADSs or ordinary shares in the foreseeable future, capital appreciation, if any, will be your sole source of potential gains and you may never receive a return on your investment.

Under current English law, a company’s accumulated realized profits must exceed its accumulated realized losses on a non-consolidated basis before dividends can be paid. Therefore, we must have distributable profits before issuing a dividend. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. As a result, capital appreciation, if any, on our ADSs or ordinary shares will be your sole source of potential gains for the foreseeable future, and you will suffer a loss on your investment if you are unable to sell your ADSs at or above the public offering price. Investors seeking cash dividends should not purchase our ADSs in this offering.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our senior management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our ADSs. The failure by our senior management to apply these funds effectively could result in financial losses, cause the price of our ADSs to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

Purchasers of our ADSs may not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise their right to vote.

Except as described in this prospectus, holders of our ADSs will not be able to exercise voting rights attaching to the ordinary shares evidenced by our ADSs on an individual basis. Holders of our ADSs will appoint the depositary or its nominee as their representative to exercise the voting rights attaching to the ordinary shares in the form of ADSs in accordance with the deposit agreement. Purchasers of ADSs in this offering may not receive voting materials in time to instruct the depositary to vote, and it is possible that they, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote. In certain cases, the shares represented by your ADSs may be voted contrary to your instructions and you may be deemed to have instructed the depositary to give a discretionary proxy to a person we designate to vote shares represented by your ADSs in such person’s discretion. Furthermore, the depositary will not be liable for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, purchasers of ADSs in this offering may not be able to exercise voting rights and may lack

[Table of Contents](#)

recourse if their ADSs are not voted as requested. In addition, in their capacity as ADS holders, purchasers of our ADSs will not be able to call a shareholders' meeting.

Purchasers of our ADSs may not receive distributions on our ordinary shares in the form of ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

The depository for our ADSs has agreed to pay to purchasers of our ADSs the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses and certain taxes. Purchasers of our ADSs will receive these distributions in proportion to the number of our ordinary shares their ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders of ADSs. We have no obligation to take any other action to permit the distribution of our ADSs, ordinary shares, rights or anything else to holders of our ADSs. This means that purchasers of our ADSs may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to them. These restrictions may have a negative impact on the market value of our ADSs.

Purchasers of our ADSs may be subject to limitations on transfer of their ADSs.

ADSs are transferable on the books of the depository. However, the depository may close its transfer books at any time or from time to time when it deems expedient in connection with the performance of its duties. In addition, the depository may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depository are closed, or at any time if we or the depository deems it advisable to do so because of any requirement of law or of any government or governmental body, or under any provision of the deposit agreement, or for any other reason in accordance with the terms of the deposit agreement.

The rights of our shareholders may differ from the rights typically offered to shareholders of a U.S. corporation.

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the Companies Act 2006, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. See "Description of Share Capital—Differences in Corporate Law" in this prospectus for a description of the principal differences between the provisions of the Companies Act 2006 applicable to us and, for example, the Delaware General Corporation Law relating to shareholders' rights and protections.

Shareholder protections found in provisions under the U.K. City Code on Takeovers and Mergers, or the Takeover Code, will not apply if our place of management and control is considered to change to outside the United Kingdom.

We are a public limited company incorporated in England and Wales and have our place of central management and control in the United Kingdom. Accordingly, we are currently subject to the Takeover Code and, as a result, our shareholders are entitled to the benefit of certain takeover offer protections provided under the Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted. If, at the time of a takeover offer, the Panel on Takeovers and Mergers determines that we do not have our place of central management and control in the United Kingdom, then the Takeover Code would not apply to us and our shareholders would not be entitled to the benefit of the various protections that the Takeover Code affords. In particular, we would not be subject to the rules regarding mandatory takeover bids. The following is a brief summary of some of the most important rules of the Takeover Code:

- When a person or group acquires interests in shares carrying 30% or more of the voting rights of a company (which percentage is treated by the Takeover Code as the level at which effective control is obtained), they must make a cash offer to all other shareholders at the highest price paid by them in the 12 months before the offer was announced.

Table of Contents

- When interests in shares carrying 10% or more of the voting rights of a class have been acquired by an offeror (i.e. a bidder) in the offer period and the previous 12 months, the offer must include a cash alternative for all shareholders of that class at the highest price paid by the offeror in that period. Further, if an offeror acquires for cash any interest in shares during the offer period, a cash alternative must be made available at a price at least equal to the price paid for such shares.
- If the offeror acquires an interest in shares in an offeree company (i.e. a target) at a price higher than the value of the offer, the offer must be increased accordingly.
- The offeree company must appoint a competent independent adviser whose advice on the financial terms of the offer must be made known to all the shareholders, together with the opinion of the board of directors of the offeree company.
- Favorable deals for selected shareholders are banned.
- All shareholders must be given the same information.
- Those issuing takeover circulars must include statements taking responsibility for the contents.
- Profit forecasts, quantified financial benefits statements and asset valuations must be made to specified standards and must be reported on by professional advisers.
- Misleading, inaccurate or unsubstantiated statements made in documents or to the media must be publicly corrected immediately.
- Actions during the course of an offer by the offeree company, which might frustrate the offer are generally prohibited unless shareholders approve these plans.
- Stringent requirements are laid down for the disclosure of dealings in relevant securities during an offer.
- Employees of both the offeror and the offeree company and the trustees of the offeree company's pension scheme must be informed about an offer. In addition, the offeree company's employee representatives and pension scheme trustees have the right to have a separate opinion on the effects of the offer on employment appended to the offeree board of directors' circular or published on a website.

Claims of U.S. civil liabilities may not be enforceable against us.

We are incorporated under English law. Substantially all of our assets are located outside the United States. The majority of our senior management and board of directors reside outside the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

The United States and the United Kingdom do not currently have a treaty providing for the reciprocal recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in England and Wales. In addition, uncertainty exists as to whether the English and Welsh courts would entertain original actions brought in England and Wales against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of England and Wales as a cause of action in itself and sued upon as a debt so that no retrial of the issues would be necessary, provided that certain requirements are met consistent with English law and public policy. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws is an issue for the English court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose.

[Table of Contents](#)

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

We qualify as a foreign private issuer and, as a result, we will not be subject to U.S. proxy rules and will be subject to Exchange Act reporting obligations that, to some extent, are more lenient and less frequent than those of a U.S. domestic public company.

Upon the closing of this offering, we will report under the Securities Exchange Act of 1934, as amended, or the Exchange Act, as a non-U.S. company with foreign private issuer status. Because we qualify as a foreign private issuer under the Exchange Act, we are exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including (i) the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act; (ii) the sections of the Exchange Act requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades made in a short period of time; and (iii) the rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specified information, or current reports on Form 8-K upon the occurrence of specified significant events. In addition, foreign private issuers are not required to file their annual report on Form 20-F until 120 days after the end of each fiscal year, while U.S. domestic issuers that are accelerated filers are required to file their annual report on Form 10-K within 75 days after the end of each fiscal year. Foreign private issuers also are exempt from Regulation Fair Disclosure, aimed at preventing issuers from making selective disclosures of material information. As a result of the above, you may not have the same protections afforded to shareholders of companies that are not foreign private issuers.

As a foreign private issuer, we are permitted to adopt certain home country practices in relation to corporate governance matters that differ significantly from Nasdaq corporate governance listing standards. These practices may afford less protection to shareholders than they would enjoy if we complied fully with Nasdaq corporate governance listing standards.

As a foreign private issuer listed on Nasdaq, we will be subject to corporate governance listing standards. However, Nasdaq rules permit a foreign private issuer like us to follow the corporate governance practices of its home country in lieu of certain Nasdaq corporate governance listing standards. Certain corporate governance practices in the United Kingdom, which is our home country, may differ significantly from Nasdaq corporate governance listing standards. For example, neither the corporate laws of the United Kingdom nor our Articles of Association require a majority of our directors to be independent; we can and intend to include non-independent directors as members of our nominations and remuneration committees; and our independent directors would not necessarily hold regularly scheduled meetings at which only independent directors are present. Therefore, our shareholders may be afforded less protection than they otherwise would have under Nasdaq corporate governance listing standards applicable to U.S. domestic issuers. See “Management—Foreign Private Issuer Exemption.”

We may lose our foreign private issuer status, which would then require us to comply with the Exchange Act’s domestic reporting regime and cause us to incur significant legal, accounting and other expenses.

As a foreign private issuer, we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. We may no longer be a foreign private issuer as of June 30, 2018 (the end of our second fiscal quarter in the fiscal year after this offering), which would require us to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers as of January 1, 2019. In order to maintain our current status as a foreign private issuer, either (a) a majority of our voting securities must be either directly or indirectly owned of record by non-residents of the United States or (b)(i) a majority of our executive officers or directors cannot be

Table of Contents

U.S. citizens or residents, (ii) more than 50% of our assets must be located outside the United States and (iii) our business must be administered principally outside the United States. If we lose our status as a foreign private issuer, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We may also be required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the cost we would incur as a foreign private issuer. As a result, we expect that a loss of foreign private issuer status would increase our legal and financial compliance costs and would make some activities highly time consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

We are an “emerging growth company,” and we cannot be certain if the reduced reporting requirements applicable to “emerging growth companies” will make our ADSs less attractive to investors.

We are an EGC as defined in the JOBS Act. For as long as we continue to be an EGC, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not EGCs, including not being required to comply with the auditor attestation requirements of Section 404, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. As an EGC, we are able to report only two years of financial results and selected financial data compared to three and five years, respectively, for comparable data reported by other public companies. We may take advantage of these exemptions until we are no longer an EGC. We could be an EGC for up to five years, although circumstances could cause us to lose that status earlier, including if the aggregate market value of our ADSs and ordinary shares held by non-affiliates exceeds \$700 million as of the end of our second fiscal quarter before that time, in which case we would no longer be an EGC as of the following December 31st (the last day of our fiscal year). We cannot predict if investors will find our ADSs less attractive because we may rely on these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and the price of our ADSs may be more volatile.

If we fail to maintain an effective system of internal controls over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ADSs.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inadequate internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

Management will be required to assess the effectiveness of our internal controls annually. However, for as long as we are an EGC under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. An independent assessment of the effectiveness of our internal controls could detect problems that our

management's assessment might not. Undetected material weaknesses in our internal controls could lead to financial statement restatements requiring us to incur the expense of remediation and could also result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If securities or industry analysts do not publish research, or publish inaccurate or unfavorable research, about our business, the price of our ADSs and our trading volume could decline.

The trading market for our ADSs will depend in part on the research and reports that securities or industry analysts publish about us or our business. Securities and industry analysts do not currently, and may never, publish research on us. If no or too few securities or industry analysts commence coverage on us, the trading price for our ADSs would likely be negatively affected. In the event securities or industry analysts initiate coverage, if one or more of the analysts who cover us downgrade our ADSs or publish inaccurate or unfavorable research about our business, the price of our ADSs would likely decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, demand for our ADSs could decrease, which might cause the price of our ADSs and trading volume to decline.

We may be classified as a passive foreign investment company, or a PFIC, in any taxable year and U.S. holders of our ADSs could be subject to adverse U.S. federal income tax consequences.

Generally, if for any taxable year, at least 75% of our gross income is passive income, or at least 50% of the value of our assets is attributable to assets that produce passive income or are held for the production of passive income, including cash, we would be characterized as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes. The determination of whether we are a PFIC depends on the particular facts and circumstances (such as the valuation of our assets, including goodwill and other intangible assets, and the characterization of our income, including whether certain research and development tax credits received from the government of the United Kingdom will constitute gross income, and if they do, whether they will constitute passive income for purposes of the PFIC income test) and may also be affected by the application of the PFIC rules, which are subject to differing interpretations. Based on our estimated gross income, the average value of our assets, including goodwill and the nature of our active business, we do not expect to be treated as a PFIC for U.S. federal income tax purposes for the taxable year ending December 31, 2017.

If we are a PFIC, U.S. holders of our ADSs may be subject to adverse U.S. federal income tax consequences, such as the ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends for individuals who are U.S. holders, having interest apply to distributions by us and the proceeds of sales of the ADSs, and additional reporting requirements under U.S. federal income tax laws and regulations. Investors should consult their own tax advisors regarding all aspects of the application of the PFIC rules to our ADSs. For more information related to classification as a PFIC, see "Taxation—Material U.S. Federal Income Tax Consideration—Passive Foreign Investment Company Considerations."

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains estimates and forward-looking statements, principally in the sections titled “Risk Factors,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and “Business.” Some of the matters discussed concerning our operations and financial performance include forward-looking statements and estimates within the meaning of the Securities Act of 1933, as amended, and the Securities Exchange Act of 1934, as amended. The words “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “expect” and similar words are intended to identify forward-looking statements and estimates. Forward-looking statements include, but are not limited to, statements about:

- the development of Acelarin, NUC-3373 and NUC-7738, including statements regarding the expected initiation, timing, progress and availability of data from our clinical trials;
- the potential attributes and benefit of our ProTides and their competitive positions;
- our ability to successfully commercialize our ProTides, if approved;
- our expectations regarding the use of proceeds from this offering;
- our estimates regarding expenses, capital requirements and our need for additional financing;
- our ability to acquire or in-license new product candidates;
- potential collaborations; and
- the duration of our patent portfolio.

These forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors that could cause our actual results of operations, financial condition, liquidity, performance, prospects, opportunities, achievements or industry results, as well as those of the markets we serve or intend to serve, to differ materially from those expressed in, or suggested by, these forward-looking statements. Factors that could cause actual results, financial condition, liquidity, performance, prospects, opportunities, achievements or industry results to differ materially include, but are not limited to, those discussed under “Risk Factors” in this prospectus. Additional risks that we may currently deem immaterial or that are not presently known to us could also cause the forward-looking events discussed in this prospectus not to occur. These forward-looking statements are based on assumptions regarding our present and future business strategies and the environment in which we expect to operate in the future.

Forward-looking statements and estimates speak only at the date they were made, and we undertake no obligation to update or to review any forward-looking statement or estimate because of new information, future events or other factors. Forward-looking statements and estimates involve risks and uncertainties and are not guarantees of future performance. Our future results may differ materially from those expressed in these forward-looking statements and estimates.

In light of the risks and uncertainties described above, the forward-looking statements and estimates discussed in this prospectus might not occur and our future results and our performance may differ materially from those expressed in these forward-looking statements and estimates due to, inclusive of, but not limited to, the factors mentioned above. Because of these uncertainties, you should not make any investment decision based on these forward-looking statements and estimates.

EXCHANGE RATES

Fluctuations in the exchange rate between the pound sterling and the U.S. dollar will affect the U.S. dollar amounts received by owners of the ADSs on conversion of dividends, if any, paid in pound sterling on the ordinary shares and will affect the U.S. dollar price of the ADSs on Nasdaq. The table below shows the period end, average, high and low exchange rates of U.S. dollars per pound sterling for the periods shown. Average rates are computed by using the noon buying rate of the Federal Reserve Bank of New York for the U.S. dollar on the last business day of each month during the relevant year indicated or each business day during the relevant month indicated. The rates set forth below are provided solely for your convenience and may differ from the actual rates used in the preparation of our consolidated financial statements included in this prospectus and other financial data appearing in this prospectus.

Period:	Noon Buying Rate			
	Period End	Average(1)	High	Low
	(\$ per £ 1.00)			
2012	1.6262	1.5924	1.6275	1.5301
2013	1.6574	1.5668	1.6574	1.4837
2014	1.5578	1.6461	1.7165	1.5517
2015	1.4746	1.5250	1.2155	1.4800
2016	1.2337	1.3444	1.4648	1.5882
2017 (through September 8)	1.2888	1.2854	1.3236	1.2118
January 2017	1.2585	1.2355	1.2620	1.2118
February 2017	1.2427	1.2495	1.2643	1.2427
March 2017	1.2537	1.2347	1.2583	1.2152
April 2017	1.2938	1.2639	1.2938	1.2398
May 2017	1.2905	1.2929	1.3018	1.2795
June 2017	1.2995	1.2810	1.2995	1.2628
July 2017	1.3196	1.2996	1.3196	1.2851
August 2017	1.2888	1.2952	1.3236	1.2787
September 2017 (through September 8)	1.3211	1.3073	1.3211	1.2972

- (1) The average of the noon buying rate for pounds sterling on the last day of each full month during the relevant year or each business day during the relevant month indicated.

On September 8, 2017, the noon buying rate of the Federal Reserve Bank of New York for the U.S. dollar was £1.00 to \$1.3211.

USE OF PROCEEDS

We estimate that we will receive total estimated net proceeds from this offering of approximately \$90.7 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their over-allotment option in full, we estimate that the net proceeds to us from this offering will be approximately \$104.7 million.

We intend to use the net proceeds we receive from this offering, together with our existing cash and cash equivalents, as follows:

- approximately \$38.0 to \$50.0 million to further the development of Acelarin, including (i) completing an ongoing Phase 2 trial, completing a planned Phase 2 trial in combination with Avastin, and initiating a planned Phase 3 trial in combination with carboplatin, each in patients with ovarian cancer, (ii) completing an ongoing Phase 1b trial in combination with cisplatin and initiating a planned Phase 3 trial in combination with cisplatin, each in patients with biliary cancer, and (iii) funding the ongoing Phase III trial in pancreatic cancer that is being facilitated by The National Cancer Research Institute in the United Kingdom;
- approximately \$28.0 to \$35.0 million to further the development of NUC-3373, including (i) completing a Phase 1 trial in patients with advanced solid tumors, (ii) completing a Phase 1b trial and initiating a Phase 3 trial, each in patients with colorectal cancer, and (iii) completing a Phase 2 trial in patients with breast cancer;
- approximately \$3.0 to \$4.0 million to further the development of NUC-7738, including completing a Phase 1 trial in patients with solid tumors and a Phase 1 trial in patients with hematological malignancies; and
- the remaining proceeds to fund other research and development activities, working capital and other general corporate purposes, including costs and expenses of being a public company.

This expected use of the net proceeds from this offering and our existing cash and cash equivalents represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development and commercialization efforts, the status of and results from clinical trials, any collaborations that we may enter into with third parties for our product candidates and any unforeseen cash needs. Moreover, our estimates of the costs to fund our trials are based on the current designs of the trials. If we were to modify the design of any of these trials, for instance, to increase the number of patients in the trials, our costs to fund the trials could increase. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Based on our planned use of the net proceeds of this offering and our current cash and cash equivalents, we estimate that such funds will be sufficient to enable us to fund our operating expenses and capital expenditure requirements at least through the first quarter of 2020. We have based this estimate on assumptions that may prove to be incorrect, and we could use our available capital resources sooner than we currently expect.

Pending specific utilization of the net proceeds as described above, we intend to invest the net proceeds from this offering in short- and intermediate-term interest-bearing obligations and certificates of deposit.

DIVIDENDS AND DIVIDEND POLICY

Since our incorporation, we have not declared or paid any dividends on any class of our issued share capital. We intend to retain any earnings for use in our business and do not currently intend to pay dividends on our ordinary shares. The declaration and payment of any future dividends will be at the discretion of our board of directors and will depend upon our results of operations, cash requirements, financial condition, contractual restrictions, any future debt agreements or applicable laws and other factors that our board of directors may deem relevant.

CAPITALIZATION

The following table presents our total capitalization and cash and cash equivalents as of June 30, 2017 on:

- an actual basis;
- a pro forma basis to give effect to the automatic conversion, immediately prior to the completion of this offering, of all issued series A convertible participating shares, series B convertible participating shares, founder ordinary 1 shares and founder ordinary 2 shares into ordinary shares on a one-for-one basis; and
- a pro forma as adjusted basis to give further effect to the sale by us of 6,667,000 ADSs in this offering at the initial public offering price of \$15.00 per ADS after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table in conjunction with our unaudited consolidated financial statements, audited consolidated financial statements and related notes appearing elsewhere in this prospectus and “Exchange Rate Information,” “Use of Proceeds,” “Selected Consolidated Financial Data” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations.”

	As of June 30, 2017		
	Actual (unaudited)	Pro Forma (in thousands)	Pro Forma as Adjusted
Cash and cash equivalents	£ 15,918	£ 15,918	£ 85,725
Total equity attributable to equity holders:			
Founder ordinary 1 shares, nominal value £0.04 per share, 1,000,000 shares issued and outstanding, actual; no shares issued and outstanding, pro forma and pro forma as adjusted	£ 40	£ —	£ —
Founder ordinary 2 shares, nominal value £0.04 per share, 1,000,000 shares issued and outstanding, actual; no shares issued and outstanding, pro forma and pro forma as adjusted	40	—	—
Series A convertible participating shares, nominal value £0.04 per share, 7,483,334 shares issued and outstanding, actual; no shares issued and outstanding, pro forma and pro forma as adjusted	299	—	—
Series B convertible participating shares, nominal value £0.004 per share, 8,462,500 shares issued and outstanding, actual; no shares issued and outstanding, pro forma and pro forma as adjusted	34	—	—
Ordinary shares, nominal value £0.04 per share, 6,238,807 shares issued and outstanding, actual; 24,184,641 shares issued and outstanding, pro forma; and 30,881,641 shares issued and outstanding, pro forma as adjusted	250	967	1,234
Share premium	304	—	71,303
Share option reserve	4,938	4,938	4,938
Accumulated deficit	(26,641)	(26,641)	(28,404)
Capital reserve(1)	42,466	42,466	42,466
Own share reserve	(339)	(339)	(339)
Foreign currency translation reserve	(4)	(4)	(4)
Total equity	21,387	21,387	91,194
Total capitalization	£ 21,387	£ 21,387	£ 91,194

(1) The capital reserve balance arose from the reduction of our share premium account and corresponding increase to our capital reserve account reflected as of June 30, 2017 in connection with our re-registration as a public limited company, as further described in footnote 10 to the unaudited consolidated interim financial statements.

The number of our ordinary shares to be outstanding immediately after this offering is based on 24,184,641 of our shares outstanding as of June 30, 2017, and gives effect to the automatic conversion, immediately prior to the completion of this offering, of all issued series A convertible participating shares, series B convertible participating shares, founder ordinary 1 shares and founder ordinary 2 shares into ordinary shares on a one-for-one basis.

The outstanding share information excludes:

- 3,233,937 ordinary shares issuable upon exercise of outstanding options under our equity compensation plans as of June 30, 2017 at a weighted average exercise price of £0.71 per share;
- 30,000 ordinary shares issued upon exercise of options under our equity incentive plans subsequent to June 30, 2017 at an exercise price of £4.00 per share;
- 1,261,783 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans that were granted after June 30, 2017 at a weighted average exercise price of £1.09 per share;
- 215,782 ordinary shares issuable upon exercise of options approved for grant under our equity incentive plans as of and in connection with the pricing of this offering to be issued at an exercise price equal to the initial public offering price per ADS in this offering; and
- 3,545,409 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

DILUTION

If you invest in the ADSs, your interest will be diluted to the extent of the difference between the initial public offering price per ADS and our pro forma net tangible book value per ADS after this offering. Our net tangible book value as of June 30, 2017 was £19.6 million, or £3.14 per ordinary share, equivalent to \$4.08 per ordinary share and \$4.08 per ADS. Net tangible book value represents the amount of total assets minus intangible assets and total liabilities. Net tangible book value per share represents net tangible book value divided by the total number of ordinary shares outstanding.

After giving effect to the automatic conversion, immediately prior to the completion of this offering, of all issued series A convertible participating shares, series B convertible participating shares, founder ordinary 1 shares and founder ordinary 2 shares into ordinary shares on a one-for-one basis, our pro forma net tangible book value as of June 30, 2017 would have been £0.81 per ordinary share, equivalent to \$1.05 per ordinary share and \$1.05 per ADS.

After giving further effect to the sale by us of 6,667,000 ADSs in this offering at the initial public offering price of \$15.00 per ADS after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of June 30, 2017 would have been £2.90 per ordinary share, equivalent to \$3.77 per ordinary share and \$3.77 per ADS. This represents an immediate increase in pro forma net tangible book value of \$2.72 per ordinary share and ADS to existing shareholders and an immediate dilution in pro forma net tangible book value of \$11.23 per ordinary share and ADS to purchasers of ADSs in this offering. The following table presents this dilution to new investors purchasing ADSs in the offering:

Initial public offering price per ADS		\$ 15.00
Net tangible book value per ADS as of June 30, 2017	\$ 4.08	
Decrease per ADS attributable to the pro forma adjustments described above	<u>(3.03)</u>	
Pro forma net tangible book value per ADS as of June 30, 2017	1.05	
Increase in pro forma net tangible book value per ADS attributable to this offering	<u>2.72</u>	
Pro forma as adjusted net tangible book value per ordinary share and ADS after this offering		<u>3.77</u>
Dilution per ADS to new investors in this offering		<u>\$ 11.23</u>

If the underwriters exercise their over-allotment option in full, the pro forma as adjusted net tangible book value per ADS after the offering would be \$4.08, the increase in net tangible book value per ordinary share and ADS to existing shareholders would be \$3.03 and the immediate dilution in net tangible book value per ordinary share and ADS to new investors in this offering would be \$10.92.

Table of Contents

The following table summarizes, on the pro forma as adjusted basis described above as of June 30, 2017, the differences between the existing shareholders and the new investors in this offering with respect to the number of ordinary shares purchased from us (including ordinary shares underlying ADSs), the total consideration paid to us and the average price per ordinary share (including ordinary shares underlying ADSs), based on the initial public offering price of \$15.00 per ADS before deducting underwriting discounts and commissions and estimated offering expenses payable by us.

	Ordinary Shares Purchased(1)		Total Consideration		Average Price per Ordinary Share(1)
	Number	%	Amount	%	
Existing shareholders	24,184,641	78.4%	\$ 56,441,020 (2)	36.1%	\$ 2.33
New investors	6,667,000	21.6	100,005,000	63.9	15.00
Total	30,851,641	100.0%	\$156,446,020	100.0%	

(1) Including ordinary shares underlying ADSs.

(2) Reflects £43,432,874 translated into U.S. dollars at the noon buying rate of the Federal Reserve Bank of New York on June 30, 2017 of £1.00 to \$1.2995.

If the underwriters exercise their over-allotment option in full, the percentage of ordinary shares held by existing shareholders will decrease to 76.0% of the total number of ordinary shares outstanding after the offering, and the number of shares held by new investors will be increased to 7,667,050, or 24.0% of the total number of ordinary shares outstanding after this offering.

The share information above excludes:

- 3,233,937 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans, as of June 30, 2017 at a weighted average exercise price of £0.71 per share;
- 30,000 ordinary shares issued upon exercise of options under our equity incentive plans subsequent to June 30, 2017 at a weighted average exercise price of £4.00 per share;
- 1,261,783 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans that were granted after June 30, 2017 at a weighted average exercise price of £1.09 per share;
- 215,782 ordinary shares issuable upon exercise of options approved for grant under our equity incentive plans as of and in connection with the pricing of this offering to be issued at an exercise price equal to the initial public offering price per ADS in this offering; and
- 3,545,409 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

To the extent these outstanding options or any newly issued options are exercised, there will be further dilution to the new investors purchasing ADSs in this offering.

SELECTED CONSOLIDATED FINANCIAL DATA

The following tables summarize our consolidated financial data as of the dates and for the periods indicated. The selected consolidated financial data as of and for the years ended December 31, 2015 and 2016 have been derived from our consolidated financial statements, which have been prepared in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or IASB, and audited in accordance with the standards of the Public Company Accounting Oversight Board (United States) and included elsewhere in this prospectus. The consolidated financial data as of and for the six months ended June 30, 2016 and 2017 have been derived from our unaudited consolidated interim financial statements included elsewhere in this prospectus. The unaudited consolidated interim financial statements have been prepared on the same basis as our audited consolidated financial statements and include all normal recurring adjustments that we consider necessary for a fair statement of our financial position and operating results as of the dates and for the periods presented.

Our historical results are not necessarily indicative of the results that may be expected in the future. The following selected consolidated financial data should be read in conjunction with “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our consolidated financial statements included elsewhere in this prospectus.

	<u>Year Ended December 31,</u>		<u>Six Months Ended June 30,</u>	
	<u>2015</u>	<u>2016</u>	<u>2016</u>	<u>2017</u>
	(unaudited)			
	(in thousands, except per share data)			
Consolidated statement of comprehensive loss data:				
Research and development expenses	£ (5,655)	£ (7,904)	£ (3,784)	£ (3,689)
Administrative expenses	(1,251)	(1,143)	(908)	(637)
Initial public offering related expenses	—	—	—	(1,066)
Net foreign exchange (losses) gains	(8)	599	318	(161)
Operating loss	(6,914)	(8,448)	(4,374)	(5,553)
Finance income	406	283	167	91
Loss before tax	(6,508)	(8,165)	(4,207)	(5,462)
Income tax credit	1,176	2,116	1,090	1,077
Loss for the period	(5,332)	(6,049)	(3,117)	(4,385)
Other comprehensive (expense) income:				
Items that may be reclassified subsequently to profit or loss:				
Exchange differences on translation of foreign operations	(1)	(2)	4	(1)
Total comprehensive loss for the period	<u>£ (5,333)</u>	<u>£ (6,051)</u>	<u>£ (3,113)</u>	<u>£ (4,386)</u>
Basic and diluted loss per share	<u>£ (0.22)</u>	<u>£ (0.25)</u>	<u>£ (0.13)</u>	<u>£ (0.18)</u>

	<u>As of December 31,</u>		<u>As of</u>
	<u>2015</u>	<u>2016</u>	<u>June 30,</u>
	(in thousands)		
	(unaudited)		
Consolidated statement of financial position data:			
Cash, cash equivalents and short-term deposits	£ 29,187	£ 19,990	£ 15,918
Total assets	31,685	27,214	23,643
Share capital	659	663	663
Share premium	42,574	42,770	304
Accumulated deficit	(16,224)	(22,256)	(26,641)
Capital reserve(1)	—	—	42,466
Total equity attributable to equity holders	29,960	25,241	21,387
Total liabilities	(1,725)	(1,973)	(2,256)

(1) The capital reserve balance arose from the reduction of our share premium account and corresponding increase to our capital reserve account reflected as of June 30, 2017 in connection with our re-registration as a public limited company, as further described in footnote 10 to the unaudited consolidated interim financial statements.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of financial condition and operating results together with the information in "Selected Consolidated Financial Data" and our consolidated financial statements and the related notes to those statements included elsewhere in this prospectus. We present our consolidated financial statements in pounds sterling and in accordance with International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or IASB, which may differ in material respects from generally accepted accounting principles in other jurisdictions, including generally accepted accounting principles in the United States, or U.S. GAAP.

The statements in this discussion regarding industry outlook, our expectations regarding our future performance, liquidity and capital resources and other non-historical statements are forward-looking statements. These forward-looking statements are subject to numerous risks and uncertainties, including the risks and uncertainties described in the sections titled "Risk Factors." Our actual results may differ materially from those contained in or implied by any forward-looking statements.

Overview

We are a clinical-stage biopharmaceutical company focused on significantly improving treatment outcomes for cancer patients by applying our ProTide technology to transform some of the most widely prescribed chemotherapy agents, nucleoside analogs, into more effective and safer medicines. While these conventional agents remain part of the standard of care for the treatment of many solid tumors, their efficacy is limited by cancer cell resistance mechanisms and they are often poorly tolerated. Utilizing our proprietary technology, we are developing new medicines, ProTides, designed to overcome key cancer resistance mechanisms and generate much higher concentrations of anti-cancer metabolites in cancer cells. Our most advanced ProTide candidates, Acelarin and NUC-3373, are new chemical entities derived from the nucleoside analogs gemcitabine and 5-fluorouracil, respectively, two widely used chemotherapy agents. Acelarin is currently being evaluated in three clinical trials across several solid tumor indications, including ovarian cancer, biliary cancer and pancreatic cancer. NUC-3373 is currently in a Phase 1 trial for the potential treatment of a wide range of advanced solid tumor cancers. We have retained worldwide rights to these lead product candidates as well as our preclinical product candidates, all of which we refer to as ProTides.

Acelarin, our most advanced product candidate, is a ProTide transformation of gemcitabine. We have begun a Phase 2 trial of Acelarin in patients with platinum-resistant ovarian cancer for which we expect to report interim data in 2018. Acelarin is also being evaluated in another Phase 1b trial in patients with biliary cancer to determine its optimal dose in combination with cisplatin. We expect to report data from this trial in 2018, after which we plan to commence a multi-national Phase 3 trial. In addition, the National Cancer Research Institute in the United Kingdom is facilitating a Phase 3 trial of Acelarin for the treatment of patients with pancreatic cancer.

NUC-3373, our second product candidate, is a ProTide transformation of the active anti-cancer metabolite of 5-fluorouracil, or 5-FU. NUC-3373 is currently being evaluated in a Phase 1 clinical trial of patients with advanced solid tumors for which we reported interim data in September 2017. We expect to report final data from this trial in 2018. Contingent on regulatory guidance and other factors, we plan to initiate a number of clinical trials in 2018: a Phase 1b trial of NUC-3373 in patients with colorectal cancer together with other agents routinely used in 5-FU combination regimens; a Phase 3 trial in patients with advanced colorectal cancer; and a Phase 2 trial in patients with advanced breast cancer.

NUC-7738, our third product candidate, is a ProTide transformation of cordycepin, a novel nucleoside analog that has shown potent anti-cancer activity in preclinical studies. We are evaluating NUC-7738 in preclinical studies and we expect to initiate a Phase 1 clinical trial in 2018.

We do not have any approved products and, as a result, have not generated any revenue from product sales or otherwise. Our ability to generate revenue sufficient to achieve profitability will depend on our successful

[Table of Contents](#)

development and eventual commercialization of our product candidates, if approved, for one or more of their targeted indications. Since our inception, we have incurred significant operating losses. For the years ended December 31, 2015 and 2016, we incurred net losses of £5.3 million and £6.0 million, respectively. For the six months ended June 30, 2016 and 2017, we incurred net losses of £3.1 million and £4.4 million, respectively. As of June 30, 2017, we had an accumulated deficit of £26.6 million.

We expect to incur significant expenses and operating losses for the foreseeable future as we advance the clinical development of our ProTides, and seek regulatory approval and pursue commercialization of our product candidates, if approved. In addition, if we obtain regulatory approval for our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. In addition, we may incur expenses in connection with the in-license or acquisition of additional product candidates and the potential clinical development of any such product candidates. Furthermore, after the closing of this offering, we expect to incur additional costs associated with operating as a foreign private issuer listed on the Nasdaq Global Select Market, or Nasdaq, including significant legal, accounting, investor relations and other expenses that we did not previously incur as a private company.

As a result of these anticipated expenditures, we will need additional financing to support our continuing operations. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of public or private equity or debt financings or other sources, which may include collaborations with third parties. Adequate additional financing may not be available to us on acceptable terms, or at all. Our inability to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

We were incorporated under the laws of England and Wales in 1997 and commenced business operations in 2008. On August 29, 2017, we re-registered as a public limited company and changed our name from NuCana BioMed Limited to NuCana plc. Our principal executive offices are located in Edinburgh, United Kingdom. We have raised £43.4 million in gross proceeds from investors since our incorporation, of which £33.9 million was raised in our most recent equity financing in 2014, primarily with a number of European and U.S.-based institutional investors.

Strategic Licensing Agreements

In August 2009, we entered into a research, collaboration and license agreement with Cardiff University and University College Cardiff Consultants Ltd., or Cardiff Consultants, which we refer to as the Cardiff Agreement. Under the Cardiff Agreement, we collaborate with Cardiff University in the design, synthesis, characterization and evaluation of phosphoramidate prodrugs, which we refer to as ProTides, based on certain nucleosides. We are responsible for funding certain work performed by Cardiff University and making other payments, which we expect will total approximately £141,350 in aggregate in 2017. On our filing, or that of a sublicensee, of patent applications resulting from research under the Cardiff Agreement, we will owe Cardiff Consultants certain immaterial payments. If we or our sublicensees develop and commercialize a product resulting from such research, we will owe Cardiff Consultants clinical development milestone payments of up to £1,875,000; provided, that such milestone payments are due only with respect to the first product within each nucleoside family to achieve the milestone. We will also owe Cardiff Consultants royalties equal to a low-single digit percentage on our sales of a product resulting from such research. Should we sublicense our right to commercialize a product resulting from the research, we will owe Cardiff Consultants a high-single digit percentage of payments received in consideration of the sublicense.

In October 2009, we entered into a license and collaboration agreement with Cardiff ProTides Ltd., or Cardiff ProTides, which agreement was subsequently amended and restated as an assignment, license and collaboration agreement in March 2012 and was further amended in May 2012, which we refer to as the ProTides Agreement. Under the ProTides Agreement, we collaborated with Cardiff ProTides in the discovery, drug design

[Table of Contents](#)

and in vitro screening of purine and pyrimidine based nucleosides as potential drug candidates. If we or a sublicensee develop one or more products covered by a valid claim of an assigned patent or patent resulting from Cardiff ProTides' research, such as Acelarin, we will owe Cardiff ProTides up to approximately \$4.5 million in development and approval milestone payments in the aggregate for the first such product. Additional development and approval milestones would be payable for the first additional product in a new nucleoside series covered by a valid claim of an assigned patent or a patent resulting from Cardiff ProTides' research, although the maximum potential value of such milestone payments is approximately half the value of the milestone payments associated with the first product. We will also owe Cardiff ProTides royalties equal to a percentage in mid- to high-single digits on sales of such products, subject to reduction under certain circumstances. Royalties on sales by sublicensees are set by formula, which formula would be likely to result in a royalty in the mid-single digits.

Financial Operations Overview

Revenues

We do not have any approved products. Accordingly, we have not generated any revenue, and we do not expect to generate any revenue from the sale of any products unless and until we obtain regulatory approvals for, and commercialize any of, our product candidates. In the future, we will seek to generate revenue primarily from product sales and, potentially, regional or global collaborations with strategic partners.

Operating Expenses

We classify our operating expenses into two categories: research and development expenses and administrative expenses. Personnel costs, including salaries, benefits, bonuses and share-based payment expense, comprise a significant component of each of these expense categories. We allocate expenses associated with personnel costs based on the function performed by the respective employees.

Research and Development Expenses. The largest component of our total operating expenses since inception has been costs related to our research and development activities, including the preclinical and clinical development of our product candidates.

Research and development costs are expensed as incurred. Our research and development expense primarily consists of:

- costs incurred under agreements with contract research organizations, or CROs, and investigative sites that conduct preclinical studies and clinical trials;
- costs related to manufacturing active pharmaceutical ingredients and drug products for preclinical studies and clinical trials;
- salaries and personnel-related costs, including bonuses, benefits and any share-based payment expense, for our personnel performing research and development activities or managing those activities that have been out-sourced;
- fees paid to consultants and other third parties who support our product candidate development;
- other costs incurred in seeking regulatory approval of our product candidates;
- costs of related office space allocated to our research and development function, materials and equipment; and
- payments under our license agreements.

The successful development of our product candidates is highly uncertain. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. Accordingly, we

Table of Contents

expect research and development costs to increase significantly for the foreseeable future as programs progress. However, we do not believe that it is possible at this time to accurately project total program-specific expenses through commercialization. We are also unable to predict when, if ever, material net cash inflows will commence from our product candidates to offset these expenses. Our expenditures on current and future preclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion.

The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors including:

- the scope, rate of progress, results and expenses of our ongoing and future clinical trials, preclinical studies and research and development activities;
- the potential need for additional clinical trials or preclinical studies requested by regulatory agencies;
- potential uncertainties in clinical trial enrollment rates or drop-out or discontinuation rates of patients;
- competition with other drug development companies in, and the related expense of, identifying and enrolling patients in our clinical trials and contracting with third-party manufacturers for the production of the drug product needed for our clinical trials;
- the achievement of milestones requiring payments under in-licensing agreements;
- any significant changes in government regulation;
- the terms and timing of any regulatory approvals;
- the expense of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights; and
- the ability to market, commercialize and achieve market acceptance for any of our product candidates, if approved.

We track research and development expenses on a program-by-program basis for both clinical-stage and preclinical product candidates. Manufacturing and nonclinical research and development expenses are assigned or allocated to individual product candidates.

Administrative Expenses. Administrative expenses consist of personnel costs, allocated expenses and other expenses for outside professional services, including legal, audit and accounting services. Personnel costs consist of salaries, bonuses, benefits and share-based payment expense. Other administrative expenses include office space-related costs not otherwise allocated to research and development expense, professional fees and costs of our information systems. We anticipate that our administrative expenses will continue to increase in the future as we increase our headcount to support our continued research and development and potential commercialization of our product candidates. We also expect to incur additional expenses as a public company, including expenses related to compliance with the rules and regulations of the SEC and Nasdaq, additional insurance expenses, and expenses related to investor relations activities and other administrative and professional services.

Initial Public Offering Related Expenses

Initial public offering, or IPO, related expenses primarily relates to legal, accounting and other advisors' fees in relation to our anticipated IPO.

Net Foreign Exchange Gains (Losses)

Net foreign exchange gains (losses) primarily includes gains or losses on cash held in U.S. dollars and on advances paid to suppliers.

Finance Income

Finance income relates to interest earned on our cash, cash equivalents and short-term deposits.

Income Tax Credit

We are subject to corporate taxation in the United Kingdom. Our wholly owned U.S. subsidiary, NuCana, Inc., is subject to corporate taxation in the United States. Due to the nature of our business, we have generated losses since inception. Our income tax credit recognized represents the sum of the research and development tax credits recoverable in the United Kingdom and income tax payable in the United States.

As a company that carries out extensive research and development activities, we benefit from the U.K. research and development tax credit regime and are able to surrender some of our losses for a cash rebate of up to 33.35% of expenditures related to eligible research and development projects. Qualifying expenditures largely comprise clinical trial and manufacturing costs, employment costs for relevant staff and consumables incurred as part of research and development projects. Certain subcontracted qualifying research and development expenditures are eligible for a cash rebate of up to 21.68%. A large portion of costs relating to our research and development, clinical trials and manufacturing activities are eligible for inclusion within these tax credit cash rebate claims.

We may not be able to continue to claim research and development tax credits in the future under the current research and development tax credit scheme when we become a public company because we may no longer qualify as a small or medium-sized company. However, we may be able to file under a large company scheme.

Unsurrendered tax losses are carried forward to be offset against future taxable profits. After accounting for tax credits receivable, there were accumulated tax losses for carry forward in the United Kingdom of £8.5 million as of June 30, 2017. There were also temporary differences on share-based compensation arrangements of £31.4 million. No deferred tax asset is recognized in respect of accumulated tax losses or temporary differences on share-based compensation arrangements because future profits are not sufficiently certain.

In the event we generate revenues in the future, we may benefit from the new “patent box” initiative that allows profits attributable to revenues from patents or patented products to be taxed at a lower rate than other revenue. The rate of tax for relevant streams of revenue for companies receiving this relief will be 10%.

Value Added Tax, or VAT, is charged on all qualifying goods and services by VAT-registered businesses. An amount of 20% of goods and services is added to all sales invoices and is payable to the U.K. tax authorities. Similarly, VAT paid on purchase invoices is reclaimable from the U.K. tax authorities.

[Table of Contents](#)

Results of Operations

Comparison of Six Months Ended June 30, 2016 and 2017

The following table summarizes the results of our operations for the six month periods ended June 30, 2016 and 2017.

	<u>Six Months Ended June 30,</u>	
	<u>2016</u>	<u>2017</u>
	<u>(unaudited)</u>	
	<u>(in thousands)</u>	
Research and development expenses	£ (3,784)	£ (3,689)
Administrative expenses	(908)	(637)
Initial public offering related expenses	—	(1,066)
Net foreign exchange (losses) gains	318	(161)
Operating loss	(4,374)	(5,553)
Finance income	167	91
Loss before tax	(4,207)	(5,462)
Income tax credit	1,090	1,077
Loss for the period	(3,117)	(4,385)
Other comprehensive (expense) income:		
Items that may be reclassified subsequently to profit or loss:		
Exchange differences on translation of foreign operations	4	(1)
Total comprehensive loss for the period	£ (3,113)	£ (4,386)

Research and Development Expenses

Research and development expenses were £3.7 million for the six months ended June 30, 2017 as compared to £3.8 million for the six month period ended June 30, 2016, a decrease of £0.1 million, which decrease resulted from differences in the phases of our ongoing research projects. The following table summarizes the costs incurred for each of our research and development programs for the six month periods ended June 30, 2016 and 2017:

	<u>Six Months Ended June 30,</u>	
	<u>2016</u>	<u>2017</u>
	<u>(unaudited)</u>	
	<u>(in thousands)</u>	
Acelarin	£ 2,361	£ 2,248
NUC-3373	537	816
NUC-7738	78	267
Other	808	358
	£ 3,784	£ 3,689

Administrative Expenses

Administrative expenses were £0.6 million for the six months ended June 30, 2017 as compared to £0.9 million for the six months ended June 30, 2016. The decrease was largely attributable to higher legal fees in 2016.

[Table of Contents](#)

Initial Public Offering Expenses

In the six months ended June 30, 2017, costs of £1.1 million were incurred, primarily related to legal, accounting and other advisors' fees in connection with our anticipated IPO. There were no such costs in the six months ended June 30, 2016.

Net Foreign Exchange Gains (Losses)

For the six months ended June 30, 2017, we reported a net foreign exchange loss of £0.2 million as compared to a net foreign exchange gain of £0.3 million for the six months ended June 30, 2016. In the six months ended June 30, 2017, the loss arose from revaluation of cash balances and advance supplier payments made in U.S. dollars, which depreciated during the first six months of 2017 relative to the U.K. pound sterling. In the six months ended June 30, 2016, the gain arose primarily from higher average cash balances held in U.S. dollars, which appreciated during 2016 relative to the U.K. pound sterling.

Finance Income

Finance income represents bank interest and was £0.1 million for the six months ended June 30, 2017 and £0.2 million for the six months ended June 30, 2016. The decrease in bank interest for the six month ended June 30, 2017 was primarily due to lower average cash balances as compared to the same period in 2016 as well as lower rates of interest on bank balances.

Income Tax Credit

Our consolidated effective tax rate for the full year 2017 is estimated to be 19.7%, which is consistently applied to the 2017 interim period. In 2016, our consolidated effective tax rate was 25.9% which is consistently applied to the 2016 interim period. The income tax credit, which is largely comprised of research and development tax credits, amounted to £1.1 million for both the six months ended June 30, 2016 and 2017. Research and development credits are obtained at a maximum rate of 33.35% of our qualifying research and development expenses.

Comparison of Years Ended December 31, 2015 and 2016

The following table summarizes the results of our operations for the years ended December 31, 2015 and 2016.

	Year Ended December 31,	
	2015	2016
	(in thousands)	
Research and development expenses	£ (5,655)	£ (7,904)
Administrative expenses	(1,251)	(1,143)
Net foreign exchange gains (losses)	(8)	599
Operating loss	(6,914)	(8,448)
Finance income	406	283
Loss before tax	(6,508)	(8,165)
Income tax credit	1,176	2,116
Loss for the year	(5,332)	(6,049)
Other comprehensive expense:		
Items that may be reclassified subsequently to profit or loss:		
Exchange differences on translation of foreign operations	(1)	(2)
Total comprehensive loss for the year	<u>£ (5,333)</u>	<u>£ (6,051)</u>

[Table of Contents](#)

Research and Development Expenses

Research and development expenses for the year ended December 31, 2016 were £7.9 million as compared to £5.7 million for the year ended December 31, 2015, an increase of £2.2 million. The increase was attributable to the number and size of clinical trials being performed in 2016 as compared to 2015 as well as an increase in the number of research and development personnel. The following table summarizes the costs incurred for each of our research and development programs for the years ended December 31, 2015 and 2016:

	Year Ended December 31,	
	2015	2016
	(in thousands)	
Acelarin	£ 3,408	£ 4,729
NUC-3373	1,122	1,413
NUC-7738	252	587
Other	873	1,175
	<u>£ 5,655</u>	<u>£ 7,904</u>

Administrative Expenses

Administrative expenses were £1.1 million for the year ended December 31, 2016 as compared to £1.3 million for the year ended December 31, 2015. This decrease was largely attributable to lower recruitment expenses in 2016 as compared to 2015.

Net Foreign Exchange Gains (Losses)

For the year ended December 31, 2016, we reported a net foreign exchange gain of £0.6 million as compared to a net foreign exchange loss of £8,000 for the year ended December 31, 2015. This was primarily from a higher average cash balance being held in U.S. dollars, which appreciated during 2016 relative to the U.K. pound sterling.

Finance Income

Finance income represents bank interest and was £0.3 million for the year ended December 31, 2016 and £0.4 million for the year ended December 31, 2015. The decrease in bank interest for 2016 was primarily due to lower average cash balances in 2016 as compared to 2015.

Income Tax Credit

The income tax credit, which is largely comprised of research and development credits, amounted to £2.1 million for the year ended December 31, 2016 as compared to £1.2 million for the year ended December 31, 2015, an increase in the net credit amount of £0.9 million. Research and development credits are obtained at a maximum rate of 33.35% of our qualifying research and development expenses, and the increase in the net credit was primarily attributable to an increase in our eligible research and development expenses.

Liquidity and Capital Resources

Overview

Since our inception, we have incurred significant operating losses and negative cash flows. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and administrative expenses will increase in connection with conducting clinical trials and seeking marketing approval for our product candidates, as well as costs associated with operating as a public company. As a result, we will need additional capital to fund our operations, which we may obtain from additional equity financings, debt financings, research funding, collaborations, contract and grant revenue or other sources.

[Table of Contents](#)

As of December 31, 2016 and June 30, 2017, we had cash and cash equivalents of £20.0 million and £15.9 million, respectively. As of December 31, 2015, we had cash, cash equivalents and short-term deposits of £29.2 million. We do not currently have any approved products and have never generated any revenue from product sales or otherwise. To date, we have financed our operations primarily through the issuances of our equity securities.

We have no ongoing material financing commitments, such as lines of credit or guarantees, that are expected to affect our liquidity over the next five years, other than operating leases.

Cash Flows

The following table summarizes the results of our cash flows for the six months ended June 30, 2016 and 2017.

	Six Months Ended June 30,	
	2016	2017
	(unaudited) (in thousands)	
Net cash used in operating activities	£(4,380)	£(3,670)
Net cash (used in) provided by investing activities	5,210	(399)
Net cash from financing activities	—	—
Net (decrease) increase in cash and cash equivalents	<u>£ 830</u>	<u>£(4,069)</u>

Operating activities. The decrease in net cash used in operating activities to £3.7 million for the six months ended June 30, 2017 from £4.4 million for the six months ended June 30, 2016 was primarily due to the utilization of advance payments made during 2016 to two vendors to manufacture drug substance and to manage our clinical trials, and the receipt of a research and development tax credit.

Investing activities. The decrease in cash relating to investing activities of £5.6 million from the six months ended June 30, 2016 to June 30, 2017 is primarily due to proceeds from maturing deposits of £5.1 million, received in the six months ended June 30, 2016. The six months ended June 30, 2017 also included higher acquisition payments in respect of intangible assets.

The following table summarizes the results of our cash flows for the years ended December 31, 2015 and 2016.

	Year Ended December 31,	
	2015	2016
	(in thousands)	
Net cash used in operating activities	£ (4,467)	£ (9,264)
Net cash (used in) provided by investing activities	(181)	14,931
Net cash from financing activities	—	200
Net (decrease) increase in cash and cash equivalents	<u>£ (4,648)</u>	<u>£ 5,867</u>

Operating activities. The increase in net cash used in operating activities to £9.3 million for the year ended December 31, 2016 from £4.5 million for the year ended December 31, 2015 was primarily due to advance payments made during 2016 to two vendors to manufacture drug substance and to manage our clinical trials and an increase in the research and development tax credit receivable.

Investing activities. Net cash used in investing activities was £0.2 million for the year ended December 31, 2015. Net cash provided by investing activities was £14.9 million for the year ended December 31, 2016. This change was primarily due to an increase in proceeds from maturing deposits.

[Table of Contents](#)

Financing activities. The increase in net cash from financing activities to £0.2 million for the year ended December 31, 2016 from zero for the year ended December 31, 2015 was due to proceeds received from the issuance of ordinary shares upon the exercise of share options.

Operating and Capital Expenditure Requirements

We have not achieved profitability on a quarterly or annual basis since our inception, and we expect to incur net losses in the future. We expect that our operating expenses will increase as we continue to invest to grow our ProTide pipeline, hire additional employees and increase research and development expenses.

Additionally, as a public company, we will incur significant audit, legal and other expenses that we did not incur as a private company. We believe that our existing capital resources, including the net proceeds from this offering, will be sufficient to fund our operations, including currently anticipated research and development activities and planned capital spending, at least through the first quarter of 2020.

Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress and cost of our clinical trials, preclinical programs and other related activities;
- the extent of success in our early preclinical and clinical stage research programs, which will determine the amount of funding required to further the development of our product candidates;
- the progress that we make in developing new product candidates based on our proprietary ProTide technology;
- the cost of manufacturing clinical supplies and establishing commercial supplies of our product candidates and any products that we may develop;
- the costs involved in filing and prosecuting patent applications and enforcing and defending potential patent claims;
- the outcome, timing and cost of regulatory approvals of our ProTide product candidates;
- the cost and timing of establishing sales, marketing and distribution capabilities; and
- the costs of hiring additional skilled employees to support our continued growth and the related costs of leasing additional office space.

Contractual Obligations and Commitments

The following table summarizes our contractual commitments and obligations as of December 31, 2016.

	Payments Due by Period				
	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
Operating lease obligations	£ 254	£ 192	£ 62	£ —	£ —
Total	£ 254	£ 192	£ 62	£ —	£ —

Operating lease obligations relate to rental of office space. As of June 30, 2017, we had operating lease obligations of £50,140, which are due in less than one year. On August 11, 2017 and August 31, 2017, we entered into new lease obligations for office space. The lease obligations are for a period of five years with a break clause after three years.

We have agreed to make milestone payments and pay royalties and annual maintenance fees to third parties under various licensing and related agreements and we have agreed to make payments to CROs and

[Table of Contents](#)

manufacturers under various CRO and manufacturing agreements. We have not included any such contingent payment obligations in the table above as the amount, timing and likelihood of such payments are not fixed or determinable.

Off-Balance Sheet Arrangements

We do not have variable interests in variable interest entities or any off-balance sheet arrangements.

Quantitative and Qualitative Disclosures about Market Risk

Market risk arises from our exposure to fluctuation in interest rates and currency exchange rates. These risks are managed by maintaining an appropriate mix of cash deposits in the two main currencies we operate in, placed with a variety of financial institutions for varying periods according to expected liquidity requirements.

Interest Rate Risk

As of June 30, 2017, we had cash and cash equivalents of £15.9 million. As of December 31, 2016, we had cash and cash equivalents of £20.0 million. Our exposure to interest rate sensitivity is impacted primarily by changes in the underlying U.K. bank interest rates. Our surplus cash and cash equivalents are invested in interest-bearing savings accounts and certificates of deposit from time to time. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, an immediate one percentage point change in interest rates would not have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

Currency Risk

Our functional currency is U.K. pounds sterling, and our transactions are commonly denominated in that currency. However, we incur a portion of expenses in other currencies, primarily U.S. dollars, and are exposed to the effects of this exchange rate. Since mid-2016, there has been significantly increased volatility in the exchange rate between the pound sterling and the U.S. dollar and an overall weakening of the pound sterling related to Britain's exit from the European Union. Although we are based in the United Kingdom, we source our active pharmaceutical ingredient, or API, and other raw materials and our research and development, manufacturing, consulting and other services worldwide, including from the United States, the European Union and India.

Any weakening of the pound sterling against the currencies of such other jurisdictions makes the purchase of such goods and services more expensive for us. We seek to minimize this exposure by maintaining currency cash balances at levels appropriate to meet foreseeable short to mid-term expenses in these other currencies. We do not use forward exchange contracts to manage exchange rate exposure. A 1% increase in the value of the pound sterling relative to the U.S. dollar would not have had a material effect on the carrying value of our net financial assets and liabilities in foreign currencies at December 31, 2016 or at June 30, 2017.

Critical Accounting Policies, Judgments and Estimates

In the application of our accounting policies, we are required to make judgments, estimates, and assumptions about the value of assets and liabilities for which there is no definitive third-party reference. The estimates and associated assumptions are based on historical experience and other factors that are considered to be relevant. Actual results may differ from these estimates. We review our estimates and assumptions on an ongoing basis. Revisions to accounting estimates are recognized in the period in which the estimate is revised if the revision affects only that period or in the period of the revisions and future periods if the revision affects both current and future periods.

The following are our critical judgments that we have made in the process of applying our accounting policies and that have the most significant effect on the amounts recognized in our consolidated financial statements included elsewhere in this prospectus.

Recognition of Clinical Trial Expenses

As part of the process of preparing our consolidated financial statements, we may be required to estimate accrued expenses related to our clinical trials. In order to obtain reasonable estimates, we review open contracts and purchase orders. In addition, we communicate with applicable personnel in order to identify services that have been performed, but for which we have not yet been invoiced. In most cases, our vendors provide us with monthly invoices in arrears for services performed. We confirm our estimates with these vendors and make adjustments as needed. The following are examples of our accrued expenses:

- fees paid to CROs for services performed on preclinical studies and clinical trials; and
- fees paid for professional services.

Share-Based Payments

We award share options to certain of our employees, directors and consultants as part of their compensation. All of these compensation arrangements are settled in equity at a predetermined price and generally vest over a period of three to four years. All share options have a term of 10 years before expiration. We measure share-based awards at the grant date based on the fair value of the award and we recognize it as a compensation expense over the vesting period with a corresponding increase in reserves. We determine the fair value of our share options using the Black-Scholes option-pricing model.

In future periods, we expect our share-based payment expense to increase due in part to our existing unrecognized share-based payment expenses and the grant of additional share-based awards to continue to attract, incent and retain our employees, directors and consultants.

Valuation of Share Options. The Black-Scholes option pricing model requires the input of subjective assumptions, including assumptions about the expected life of share-based awards and share price volatility. In addition, as a privately held company, one of the most subjective inputs into the Black-Scholes option pricing model is the estimated fair value of our ordinary shares.

As a privately held company, our share price does not have sufficient historical volatility for us to adequately assess the fair value of the share option grants. As a result, our management considered the historical volatility of other comparable publicly traded companies and, based on this analysis, concluded that a volatility range of 60.92% to 69.05% was appropriate for the valuation of our share options. We intend to continue to consistently apply this methodology using the same comparable companies until a sufficient amount of historical information regarding the volatility of our own share price as a public company becomes available.

The expected life of the option, beginning with the option grant date, was used in valuing our share options. The expected life used in the calculation of share-based payment expense is the time from the grant date to the expected exercise date. The life of the options depends on the option expiration date, volatility of the underlying shares and vesting features.

IFRS 2, *Share-based Payment*, requires the use of the risk-free interest rate of the country in which the entity's shares are principally traded, with a remaining term equal to the expected life of the option. The third-party valuation firm applied the appropriate risk-free rate using the Bank of England's estimates of gilt zero-coupon yield curve as at the respective share option grant dates.

Valuation of Ordinary Shares. There are significant judgments and estimates inherent in the determination of the fair value of our ordinary shares. These judgments and estimates include assumptions regarding our future operating performance, the likelihood and time to complete an IPO or other liquidity event, the related company valuations associated with such events, and the determinations of the appropriate valuation methods. If we had made different assumptions, our share-based payment expense, loss for the year and total comprehensive loss, on both an absolute and per-share basis, could have been significantly different.

[Table of Contents](#)

In conducting our valuations, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including our best estimate of our business condition, prospects, and operating performance at each valuation date. Within the valuations performed, a range of factors, assumptions, and methodologies were used. The significant factors considered included:

- the lack of an active public market for our ordinary shares, as well as our series A and series B convertible participating preferred shares;
- the prices of our series A and series B convertible participating preferred shares that we had sold to outside investors in arm's length transactions, and the rights, preferences and privileges of the series A and series B convertible participating preferred shares relative to our ordinary shares;
- the data generated from our research and development programs and financial condition;
- the material risks related to our business and industry;
- our business strategy;
- the market performance of publicly traded companies in the life sciences and biotechnology sectors; and
- the likelihood of achieving a liquidity event for the holders of our ordinary shares, such as an IPO, given prevailing market conditions.

During 2016, we issued share options on June 30, August 22, October 28 and December 12. These share options were awarded based on the underlying share price of £4.00 per ordinary share. We made contemporaneous estimates of the valuation of the share price, which for share options issued in 2016 was retrospectively revalued upon contemplation of this offering. After considering the market approach, the income approach and the asset-based approach, we utilized the market approach to determine the estimated fair value of our ordinary shares based on its determination that this approach was most appropriate for a clinical-stage biopharmaceutical company at this point in its development. Consideration was given to the American Institute of Certified Public Accountants' Practice Aid: "Valuation of Privately-Held Company Equity Securities Issued as Compensation," or the Practice Aid, in addition to input from management, the likelihood of completing an IPO and recent transactions with investors. Once a public trading market for our ordinary shares (in the form of ADSs) has been established in connection with the completion of this offering, it will no longer be necessary to estimate the fair value of our ordinary shares in connection with our accounting for share-based payment expenses, as the fair value of our ordinary shares will be determinable by reference to the trading price of our ADSs on Nasdaq. The retrospective valuation dates for June 30, 2016, August 22, 2016, October 28, 2016 and December 12, 2016 resulted in valuations of our ordinary shares of £6.97, £8.61, £8.76 and £9.19 per share, respectively, as of those dates.

Our ordinary share valuations were prepared using the guideline public company, or GPC, method under the market approach. In the application of the GPC method, we considered the pricing of IPOs completed by clinical-stage oncology companies between April 2015 and May 2016. We converted prospective IPO value to present value by applying a discount rate of 25%. The discount rate was derived from studies of rates of return required by venture investors in IPO-stage companies. In addition to the IPO GPCs, we considered the enterprise values indicated by a group of eight trading GPCs. The trading prices of these clinical-stage GPCs provided contemporaneous indications of value as of each appraisal date. We applied a discount for lack of marketability to the ordinary shares to account for the lack of access to an active public market. We estimated the discount for lack of marketability using an Asian put model.

During the six months ended June 30, 2017, we issued share options on May 16. These share options were awarded based on the underlying share price of £11.08 per ordinary share. We made contemporaneous estimates of the valuation of the share price using the same methodology described above and updated for pricing of initial public offerings completed by clinical stage oncology companies between April 2015 and May 2017.

The following table summarizes by grant date the number of ordinary shares subject to options granted between January 1, 2016 and June 30, 2017, the per share purchase or exercise prices, the fair value of the

[Table of Contents](#)

ordinary shares on the dates of grant, the re-assessed fair value of the ordinary shares on the dates of grant, if applicable, and the estimated fair value per option utilized to calculate share-based payment expense.

Grant date	Number of options granted	Exercise price per share	Fair value of ordinary share at grant date	Re-assessed fair value of ordinary share at grant date	Estimated fair value per option
June 30, 2016	270,690	£ 4.00	£ 4.00	£ 6.97	£ 4.02
Aug. 22, 2016	12,500	£ 2.80	£ 4.00	£ 8.61	£ 6.15
Aug. 22, 2016	37,500	£ 3.00	£ 4.00	£ 8.61	£ 6.01
Aug. 22, 2016	25,000	£ 3.40	£ 4.00	£ 8.61	£ 5.74
Aug. 22, 2016	11,250	£ 3.60	£ 4.00	£ 8.61	£ 5.62
Aug. 22, 2016	5,000	£ 3.60	£ 4.00	£ 8.61	£ 5.62
Aug. 22, 2016	37,500	£ 3.60	£ 4.00	£ 8.61	£ 5.62
Oct. 28, 2016	12,500	£ 3.40	£ 4.00	£ 8.76	£ 5.85
Oct. 28, 2016	50,000	£ 4.00	£ 4.00	£ 8.76	£ 5.46
Dec. 12, 2016	45,750	£ 4.00	£ 4.00	£ 9.19	£ 5.22
May 16, 2017	23,250	£ 4.00	£ 11.08	n/a	£ 7.70

Subsequent to June 30, 2017 and prior to the date of this prospectus, we granted options under our equity incentive plans for 1,261,783 ordinary shares at a weighted average exercise price of £1.09 per share. We intend to assess the fair value of these options grants for financial reporting purposes, and the associated share-based expense to be recorded, by reference to the initial public offering price per ADS in this offering. We have also approved for grant as of and in connection with this offering options under our equity incentive plans for 215,782 ordinary shares to be issued at an exercise price equal to the initial public offering price per ADS in this offering.

The initial public offering price set forth on the cover of this prospectus, \$15.00 per ADS, was determined as a result of negotiations between us and the underwriters. As is typical in initial public offerings, the initial public offering price was not derived using a formal determination of fair value, but was determined by negotiation between us and the underwriters. Among the factors that were considered in setting this price were the following: (i) the history and prospects for the industry in which we compete; (ii) our financial information; (iii) the ability of our management and our business potential and earning prospects; (iv) the prevailing securities markets at the time of this offering; and (v) the recent market prices of, and the demand for, publicly traded shares of generally comparable companies.

Deferred Tax and Current Tax Credits

Tax on the profit or loss for the year comprises current and deferred tax. Tax is recognized in the statement of operations, except to the extent that it relates to items recognized directly in equity, in which case it is recognized in equity. Current tax is the expected tax payable on the taxable income or loss for the year, using tax rates enacted or substantively enacted at the balance sheet date, and any adjustment to tax payable in respect of previous years. Tax credits are accrued for the year based on calculations that conform to the U.K. research and development tax credit regime applicable to small and medium-sized companies. We may not be able to continue to claim research and development tax credits in the future under the current research and development tax credit scheme, when we become a U.S. public company because we may no longer qualify as a small or medium-sized company. However, we may be able to file under a large company scheme. Deferred tax is recognized on temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for taxation purposes. The amount of deferred tax is based on the expected manner of realization or settlement of the carrying amount of assets and liabilities, using tax rates enacted or substantively enacted at the balance sheet date. A deferred tax asset is recognized only to the extent that it is probable that future taxable profits will be available against which the asset can be utilized. No deferred tax assets are recognized on our losses carried forward because there is currently no indication that we will make sufficient profits to utilize these tax losses.

[Table of Contents](#)

Recent Accounting Pronouncements

The International Accounting Standards Board, or IASB, and International Financial Reporting Interpretations Committee, or IFRIC, have issued the following standards and interpretations, which are considered relevant to us, with an effective date after December 31, 2017.

	<u>Effective Date</u>
IFRS 9: Financial Instruments	January 1, 2018
IFRS 16: Leases	January 1, 2019
Amendments to IFRS 2: Classification and Measurement of Share-based Payment Transactions	January 1, 2018
Annual Improvements to IFRSs 2014-2016 Cycle	January 1, 2018
IFRIC Interpretation 22 Foreign Currency Transactions and Advance Consideration	January 1, 2018

We will adopt these standards and interpretations in accordance with their effective dates. See Note 2 “Significant Accounting Policies—Accounting Standards” of the notes to our audited consolidated financial statements for the year ended December 31, 2016 included elsewhere in this prospectus for more information.

Jumpstart Our Business Startups Act of 2012

In April 2012, the U.S. Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107(b) of the JOBS Act provides that an “emerging growth company,” or EGC, can take advantage of an extended transition period for complying with new or revised accounting standards. Thus, an EGC can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. Given that we currently report and expect to continue to report under IFRS as issued by the IASB, we have irrevocably elected not to avail ourselves of this extended transition period, and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

We intend to rely on other exemptions and reduced reporting requirements under the JOBS Act. Subject to certain conditions, as an EGC, we may rely on certain of these exemptions, including exemptions from (1) providing an auditor’s attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act and (2) complying with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis. We will remain an EGC until the earliest of (a) the last day of our fiscal year during which we have total annual gross revenue of at least \$1.07 billion; (b) the last day of our fiscal year following the fifth anniversary of the completion of this offering; (c) the date on which we have, during the previous three-year period, issued more than \$1.0 billion in non-convertible debt; or (d) the date on which we are deemed to be a “large accelerated filer” under the Securities Exchange Act of 1934, as amended, which would occur if the market value of our equity securities that are held by non-affiliates exceeds \$700 million as of the last business day of our most recently completed second fiscal quarter. Once we cease to be an EGC, we will not be entitled to the exemptions provided in the JOBS Act.

We have taken advantage of reduced reporting requirements in this prospectus. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold equity securities.

BUSINESS

Overview

We are a clinical-stage biopharmaceutical company focused on significantly improving treatment outcomes for cancer patients by applying our ProTide technology to transform some of the most widely prescribed chemotherapy agents, nucleoside analogs, into more effective and safer medicines. While these conventional agents remain part of the standard of care for the treatment of many solid tumors, their efficacy is limited by cancer cell resistance mechanisms and they are often poorly tolerated. Utilizing our proprietary technology, we are developing new medicines, ProTides, designed to overcome key cancer resistance mechanisms and generate much higher concentrations of anti-cancer metabolites in cancer cells. Our most advanced ProTide candidates, Acelarin and NUC-3373, are new chemical entities derived from the nucleoside analogs gemcitabine and 5-fluorouracil, respectively, two widely used chemotherapy agents. Acelarin is currently being evaluated in three clinical trials across several solid tumor indications, including ovarian cancer, biliary cancer and pancreatic cancer. NUC-3373 is currently in a Phase 1 trial for the potential treatment of a wide range of advanced solid tumor cancers. We have retained worldwide rights to these lead product candidates as well as our preclinical product candidates, all of which we refer to as ProTides.

Acelarin, our most advanced product candidate, is a potential first-in-class ProTide that has been evaluated in over 140 patients. Acelarin is a ProTide transformation of gemcitabine that we believe could replace gemcitabine in certain cancer indications and have utility across a range of other cancers. In a Phase 1 dose-ranging trial in 49 evaluable patients with advanced metastatic solid tumors, Acelarin was well tolerated, achieved a 78% disease control rate and was associated with intracellular levels of active anti-cancer metabolite over 200 times higher than those reported for gemcitabine. A subset of 14 evaluable patients with relapsed/refractory gynecological cancers achieved a 93% disease control rate. In a Phase 1b dose-ranging trial in 23 evaluable patients with recurrent ovarian cancer, Acelarin was combined with carboplatin and achieved a 96% disease control rate. Based on these disease control rates and the tolerability profile, we have begun a Phase 2 trial of Acelarin in patients with platinum-resistant ovarian cancer for which we expect to report interim data in 2018. Acelarin is also being evaluated in another Phase 1b trial in patients with biliary cancer to determine its optimal dose in combination with cisplatin. We expect to report data from this trial in 2018, after which we plan to commence a multi-national Phase 3 trial. In addition, the National Cancer Research Institute in the United Kingdom is facilitating a Phase 3 trial of Acelarin for the treatment of patients with pancreatic cancer.

NUC-3373, our second product candidate, is a ProTide transformation of the active anti-cancer metabolite of 5-fluorouracil, or 5-FU, which we believe has the potential to replace 5-FU as the standard of care in the treatment of a wide range of cancers. In preclinical studies, we observed that NUC-3373 overcame the key resistance mechanisms associated with 5-FU and generated intracellular levels of active anti-cancer metabolite over 300 times higher than that of 5-FU. NUC-3373 is currently being evaluated in a Phase 1 clinical trial of patients with advanced solid tumors for which we reported interim data in September 2017. We expect to report final data from this trial in 2018. Contingent on regulatory guidance and other factors, we plan to initiate a number of clinical trials in 2018: a Phase 1b trial of NUC-3373 in patients with colorectal cancer together with other agents routinely used in 5-FU combination regimens; a Phase 3 trial in patients with advanced colorectal cancer; and a Phase 2 trial in patients with advanced breast cancer.

NUC-7738, our third product candidate, is a ProTide transformation of cordycepin, a novel nucleoside analog that has shown potent anti-cancer activity in preclinical studies. We are evaluating NUC-7738 in preclinical studies and we expect to initiate a Phase 1 clinical trial in 2018.

Despite the widespread use of nucleoside analogs, their efficacy is severely limited by cancer cell resistance mechanisms and they are often poorly tolerated. Harnessing the power of phosphoramidate chemistry, we convert nucleoside analogs into activated nucleotide analogs with the addition of a phosphate group, which is protected by specific combinations of aryl, ester and amino acid groupings. By adding and protecting this

[Table of Contents](#)

phosphate group, we design our ProTides to avoid or overcome key cancer resistance mechanisms in the uptake, activation and breakdown of nucleoside analogs. As a result, we believe our ProTides have the potential to generate hundreds of times higher concentrations of the active anti-cancer metabolites inside tumor cells, potentially making our ProTides more effective than the current standards of care. Because our ProTides resist breakdown, and are thus more stable, we believe they are also able to reduce or eliminate the generation of toxic byproducts that can result from the breakdown of nucleoside analogs like gemcitabine and 5-FU.

Our proprietary ProTide technology was invented in the Cardiff University laboratory of our late Chief Scientific Officer, Professor Christopher McGuigan, who conceived of, and filed the original composition of matter patents for our initial ProTides. The unique feature of his discovery was the specific combination of aryl, ester and amino acid groupings that protect the activated, or phosphorylated, nucleoside analog. This phosphoramidate chemistry approach is the key to the ProTide technology. Every ProTide grouping is distinct, and Professor McGuigan and his team synthesized and tested thousands of compounds in order to identify the optimal ProTide grouping for each underlying nucleoside analog.

We have licensed what we believe to be the foundational patent estate for the application of phosphoramidate chemistry in oncology. We have granted patents in key markets, including the United States, Europe and Japan, protecting the composition of matter of Acelarin, NUC-3373 and other of our product candidates. Professor McGuigan's work preceded and helped lead to the development of several FDA-approved anti-viral drugs containing nucleotide analogs, including: sofosbuvir, or Sovaldi®, which is also a key component of Harvoni®; and tenofovir alafenamide fumarate, or TAF, which is a key component of Genvoya®, Descovy® and Odefsey®.

We are led by Hugh S. Griffith, our founder and Chief Executive Officer, who brings over 25 years of experience in the biopharmaceutical industry including at Abbott Laboratories (now AbbVie Inc.) and Parke-Davis Warner Lambert (now Pfizer Inc.). Before founding NuCana, he led the operations of Bioenvision, Inc. from start-up through its acquisition by Genzyme Corporation. While at Bioenvision, he was instrumental in developing and commercializing clofarabine, a nucleoside analog for the treatment of pediatric leukemia. We are backed by leading life sciences investors, including Sofinnova Partners, Sofinnova Ventures, Morningside Group and Scottish Enterprise.

Our Strategy

Our goal is to transform standards of care and improve survival for patients across a wide range of cancer indications. Our strategy includes the following key components:

- **Rapidly develop Acelarin as a first-in-class nucleotide analog for the treatment of patients with cancer.** We believe that Acelarin has the potential to replace the core chemotherapy component of treatment regimens for patients with various cancers, including:
 - *Platinum-resistant ovarian cancer.* We expect to report data from a Phase 2 trial of Acelarin in 2018. We also intend to explore the use of Acelarin in combination with Avastin, a widely used agent in the treatment of several cancers, and expect to report data from this trial in 2018.
 - *Platinum-sensitive ovarian cancer.* Contingent on regulatory guidance and other factors, we expect to commence a Phase 3 trial of Acelarin in combination with carboplatin for this indication in 2018.
 - *Biliary cancer.* We expect to report data from a Phase 1b trial of Acelarin in combination with cisplatin in 2018. Contingent on regulatory guidance and other factors, we plan to commence a Phase 3 trial of Acelarin in combination with cisplatin as a first-line treatment in 2018.
 - *Pancreatic cancer.* The National Cancer Research Institute in the United Kingdom is facilitating a Phase 3 trial of Acelarin as a first-line treatment compared to gemcitabine.

- **Rapidly develop NUC-3373 to replace 5-FU as the standard of care for the treatment of patients with various cancers.**
 - *Advanced solid tumors.* We expect to report final data from a Phase 1 trial of NUC-3373 in patients with advanced solid tumors in 2018.
 - *Colorectal cancer.* We plan to establish the optimal dose of NUC-3373 in combination with other agents in a Phase 1b trial in 2018. Contingent on regulatory guidance and other factors, we also intend to initiate a Phase 3 trial of NUC-3373 monotherapy in 2018.
 - *Breast cancer.* We intend to conduct a Phase 2 trial of NUC-3373 compared to capecitabine, the oral version of 5-FU, in patients with recurrent breast cancer and anticipate reporting interim data from this trial in 2018.
- **Rapidly advance NUC-7738 into clinical trials.** NUC-7738, a ProTide based on a novel nucleoside analog, is currently undergoing preclinical studies and we expect to initiate a Phase 1 trial in 2018 for solid tumors. In addition, we plan to develop NUC-7738 for the treatment of hematological malignancies.
- **Leverage our proprietary ProTide technology platform to develop additional product candidates.** We are pursuing both the transformation of well-established and widely used nucleoside analogs as well as novel nucleoside analogs, which we believe have the potential to address additional areas of unmet medical need in oncology.
- **Continue to strengthen our intellectual property position.** We own or have exclusive rights to the core technologies underlying our ProTide technology platform. We have granted patents in key markets, including the United States, Europe and Japan, protecting the composition of matter of Acelarin, NUC-3373 and other of our product candidates. We intend to further expand and enhance our intellectual property position.
- **Build a focused commercial organization.** We have worldwide rights to all product candidates that we are developing. We believe that many of the cancers we are initially targeting with our ProTides can be addressed by a focused sales and marketing team. We plan to commercialize any product candidates for which we receive regulatory marketing approval using a specialized sales force in the United States and Europe.

Our Pipeline

We take a scientifically driven approach to designing ProTides, which we believe have the potential to result in highly efficacious cancer therapies with improved tolerability. Our pipeline of product candidates is summarized below.

Program	IND/CTA enabling	Phase 1	Phase 2	Phase 3	Next Expected Events	Date
ACELARIN	Ovarian (Platinum resistant)	[Progress bar]			Phase 2 data (interim) Phase 2 data (+Avastin)	2018 2018
	Ovarian (Platinum sensitive) + carboplatin	[Progress bar]			Initiate Phase 3 study	2018
	Biliary + cisplatin	[Progress bar]			Phase 1b data Initiate Phase 3 study	2018 2018
	Pancreatic (IST)	[Progress bar]			Ongoing investigator sponsored study	Multi-year
NUC-3373	Solid Tumors	[Progress bar]			Phase 1 data	2018
	Colorectal + combo	[Progress bar]			Phase 1b data (interim)	2018
	Colorectal	[Progress bar]			Initiate Phase 3 study	2018
	Breast	[Progress bar]			Phase 2 data (interim) Initiate Phase 3 study	2018 2018
NUC-7738	Solid Tumors	[Progress bar]			Phase 1 data (interim)	2018
	Hematology	[Progress bar]			Phase 1 data (interim)	2019

Cancer and the Need for Improved Treatment Options

Cancer is the second leading cause of death in the United States, with approximately 1.7 million new cases and 600,000 deaths expected in 2017 according to the American Cancer Society.

The medical treatment of cancer can be divided into three major categories: surgery, radiotherapy and therapeutics. Therapeutics include chemotherapy, immunotherapy, and targeted and hormonal agents.

The backbone of treatment for patients with cancer consists of chemotherapeutics, which generated sales of \$20.6 billion worldwide in 2016. These therapies exert their effects by killing cancer cells or preventing them from replicating. Within the larger universe of chemotherapy, nucleoside analogs, such as gemcitabine and 5-FU, play a significant role. Nucleoside analogs have been in clinical use for over 50 years and have become cornerstones of treatment for patients with cancer. The FDA has approved 16 nucleoside analogs for the treatment of cancer and many of these have become the standard of care globally for patients. FDA-approved anti-cancer nucleoside analogs are: gemcitabine; 5-FU; capecitabine; floxuridine; clofarabine; fludarabine; cytarabine; azacytidine; decitabine; nelarabine; cladribine; pentostatin; 6-mercaptopurine; tipiracil; 6-thioguanine; and trifluorothymidine. The World Health Organization has classified seven of these nucleoside analogs, including gemcitabine and 5-FU, as Essential Medicines, which they define as medicines that satisfy the priority healthcare needs of the population and should be available at all times.

Many on-patent chemotherapies have generated significant sales, including, for example, gemcitabine, marketed as Gemzar®, which had peak annual sales of \$1.7 billion before losing patent protection in 2010. Gemcitabine is still used extensively and remains an important part of the standard of care for many cancers,

including pancreatic, ovarian, biliary, non-small cell lung, bladder and breast cancers. In addition, approximately 500,000 patients per year in North America receive 5-FU, which is widely used for the treatment of many cancers, including colorectal, breast, stomach, head and neck, and pancreatic cancers. The oral version of a derivative of 5-FU, known as capecitabine and marketed as Xeloda® for the treatment of colorectal, breast and stomach cancer, had worldwide sales of \$1.5 billion in 2012, before the market launch of generic competitors. We believe the number of patients receiving capecitabine represents a small proportion of the overall number of patients treated with 5-FU and its derivatives.

Shortcomings of Existing Nucleoside Analog Drugs

Despite the widespread use of nucleoside analogs, their efficacy is severely limited by cancer cell resistance and they are often poorly tolerated.

Nucleoside analogs are based on the principle of blocking the replication of cancer cells by providing faulty DNA and RNA building blocks during the cell replication process, thus leading to cancer cell death, known as apoptosis. Some nucleoside analogs exert their effect by blocking enzymes necessary for the production of these DNA and RNA building blocks. However, there are critical barriers and cellular defenses that limit the efficacy of existing nucleoside analogs. The three critical shortcomings of nucleoside analogs are: (1) the need for uptake into cells by way of membrane proteins known as transporters; (2) the need for activation by the addition of one or more phosphate groups; and (3) the potential for enzymatic breakdown.

1. Uptake by transporters. Nucleoside analogs require specific active-transport proteins in the cell membrane to enter cancer cells. If these proteins are missing or down-regulated, nucleoside analogs cannot enter the cancer cell to exert their anti-cancer effect. Transport proteins, such as the human equilibrative nucleoside transporter 1, or hENT1, are often not expressed at sufficient levels in many solid tumor cancers. For example, based on the published results of multiple studies assessing the correlation of hENT1 expression to survival outcomes in pancreatic cancer patients treated with gemcitabine, approximately 40% to 50% of pancreatic patients express low levels of hENT1, and thus derive little or no benefit from gemcitabine therapy.

2. Conversion to the active form. Nucleoside analogs are all dosed as inactive precursors, or prodrugs, because their active forms are unstable and their negative charge further prevents them from entering cells. Naturally occurring enzymes in cells must add at least one chemical entity known as a phosphate group to activate these prodrugs and enable them to be incorporated into nucleic-acid chains or to bind to their target enzymes and thereby exert their anti-cancer effect. This process of activation by adding a phosphate group is known as phosphorylation. However, the addition of phosphate groups often occurs at such an insufficient rate in cancer cells that it limits or prevents the generation of active anti-cancer metabolites, and in some cases phosphorylation does not occur at all.

3. Breakdown. Multiple enzymatic processes can break down nucleoside analogs, resulting in their degradation prior to phosphorylation, as well as the release of toxic byproducts that can lead to off-target toxicity. Breakdown can take place either inside or outside the cancer cell.

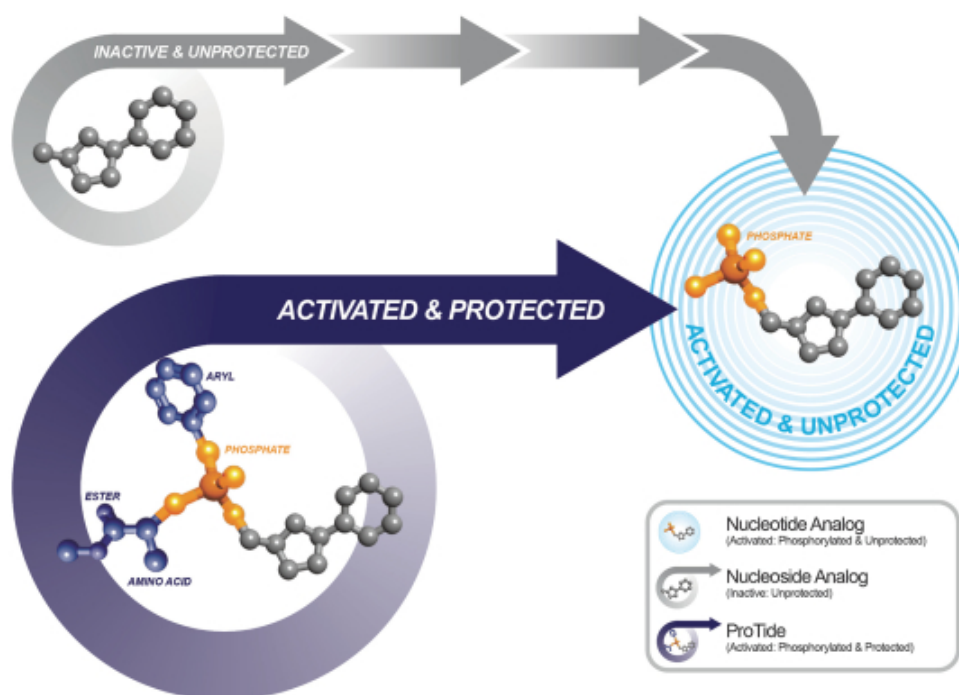
Our ProTide Technology and its Key Advantages

We use our ProTide technology to design new chemical entities to overcome the three key challenges associated with existing nucleoside analogs: uptake, activation and breakdown as shown below:

Problem	Nucleoside Analog Limitations	ProTide Solution
Uptake: Insufficient expression of membrane transporters	Dependent on membrane transporters to enter cancer cells	Enters cancer cells independent of membrane transporters
Activation: Rate limiting phosphorylation	Requires phosphorylation within cancer cells to exert anti-cancer activity	Pre-activated, thus bypassing rate-limiting phosphorylation
Breakdown: High levels of metabolizing enzymes	Subject to breakdown and generation of toxic byproducts	Resistant to breakdown

Harnessing the power of phosphoramidate chemistry, we transform nucleoside analogs into activated nucleotide analogs with the addition of a phosphate group, which is protected by specific combinations of aryl, ester and amino acid groupings. We refer to these compounds as ProTides. We are applying our ProTide technology both to nucleoside analogs currently approved for use as a chemotherapy and to nucleoside analogs that have not, to date, been successfully developed.

A graphical representation of the chemical structure of nucleoside analogs, nucleotide analogs and ProTides is set forth below:



Our researchers have invested over a decade of work in designing, synthesizing and screening ProTides, which we believe are optimally designed to overcome cancer cell resistance mechanisms. We have gained considerable insight from our scientific founders and executives in understanding phosphoramidate chemistry and the biology of how nucleotide analogs are able to exert their anti-cancer effects. Based on these learnings, we are able to efficiently create hundreds of target candidates from the millions of potential candidates. We then perform biological testing on these target candidates to select our lead ProTides.

Acelarin: A Transformation of Gemcitabine

Our lead product candidate, Acelarin, was designed to overcome the key cancer resistance mechanisms associated with the nucleoside analog, gemcitabine. We are rapidly advancing Acelarin in the clinic and exploring its use as a therapy against platinum-resistant and platinum-sensitive ovarian cancer, biliary cancer and pancreatic cancer.

Gemcitabine and its Limitations

Gemcitabine is a nucleoside analog that is used as a chemotherapeutic to treat a wide range of tumors and has been investigated in over 1,900 clinical trials. It is approved as a single agent for the treatment of pancreatic cancer and in combination with other chemotherapeutic drugs for the treatment of advanced ovarian, metastatic breast, and non-small cell lung cancers. Gemcitabine is also used to treat many other types of tumors, including biliary cancer, both as monotherapy and in combination with other therapeutics.

Gemcitabine is a conventional nucleoside analog which, like all nucleoside analogs, is an inactive prodrug. There are three key cancer resistance mechanisms that have been associated with a poor survival prognosis for gemcitabine therapy: transport, activation and breakdown. While there have been attempts to address the requirement for active transport of gemcitabine into cancer cells, we believe we are the first to address all three limitations at once.

1. Requires active transport. Gemcitabine requires the membrane transporter hENT1 to enter the cancer cell. Patients with a low level of hENT1 who receive gemcitabine have lower overall survival as compared to patients with a high level of hENT1. In a study published in 2004 in the journal *Clinical Cancer Research*, it was reported that pancreatic cancer patients with a high level of hENT1 expression had a median overall survival of 13 months compared to four months for those patients with a low level of hENT1 expression.

In a study published in 2009 in the *Journal of Clinical Oncology*, non-small cell lung cancer patients with low levels of hENT1 who were treated with therapies that included gemcitabine survived for less than half as long as those with high levels of hENT1, specifically, 316 days in the case of low levels of hENT1, and 714 days in the case of high levels of hENT1.

Some previous product candidates that have been tested clinically by others were designed to address the challenge of membrane transport but these efforts failed even when the transport of these candidates across the cell membrane appeared to succeed. We believe that this was due to the failure of those candidates to address the other cancer resistance mechanisms of activation and breakdown.

2. Requires activation within the cancer cell. Once gemcitabine enters cells, it must be activated by the addition of phosphate groups before it can exert its cell-killing effect. The rate-limiting addition of the first phosphate group is rapidly followed by the addition of a second and third phosphate group. The end result of this phosphorylation is the creation of the active anti-cancer metabolite, which is known as dFdCTP. A specific enzyme, deoxycytidine kinase, or dCK, is responsible for the first rate-limiting phosphorylation step. Initially, about one-third of cancer cells have reduced levels of dCK, which has negative consequences for the efficacy of gemcitabine. A study published in the journal *Gastroenterology* in 2012 reported that decreased expression of dCK led to resistance to gemcitabine treatment in cellular assays. In another published study, low levels of dCK in the pancreatic cancer cells of patients who were treated with gemcitabine were associated with a median

overall survival that was seven months shorter than that observed in patients with medium to high levels of dCK. dCK is also associated with acquired resistance and studies have shown that cancer cells can downregulate the production of dCK in the presence of gemcitabine leading to reduced efficacy.

Because gemcitabine has a short half-life, ranging from 42 to 94 minutes, even with dCK present in the cancer cell, much of the gemcitabine will have broken down before it can be converted to its active anti-cancer metabolite, dFdCTP.

3. Subject to breakdown. Gemcitabine, prior to being phosphorylated to its active form, is susceptible to being broken down chemically by metabolic enzymes, such as cytidine deaminase, or CDA, which irreversibly degrades up to 90% of gemcitabine to an inactive form in less than three hours. A study published in the *British Journal of Cancer* in 2005 showed that increased levels of CDA were associated with an approximate five-month reduction in median overall survival in gemcitabine-treated pancreatic cancer patients. CDA is also expressed by various microorganisms in the body, such as mycoplasma that have been found to be associated with 30% to 50% of solid tumors, which further exacerbates the breakdown of gemcitabine.

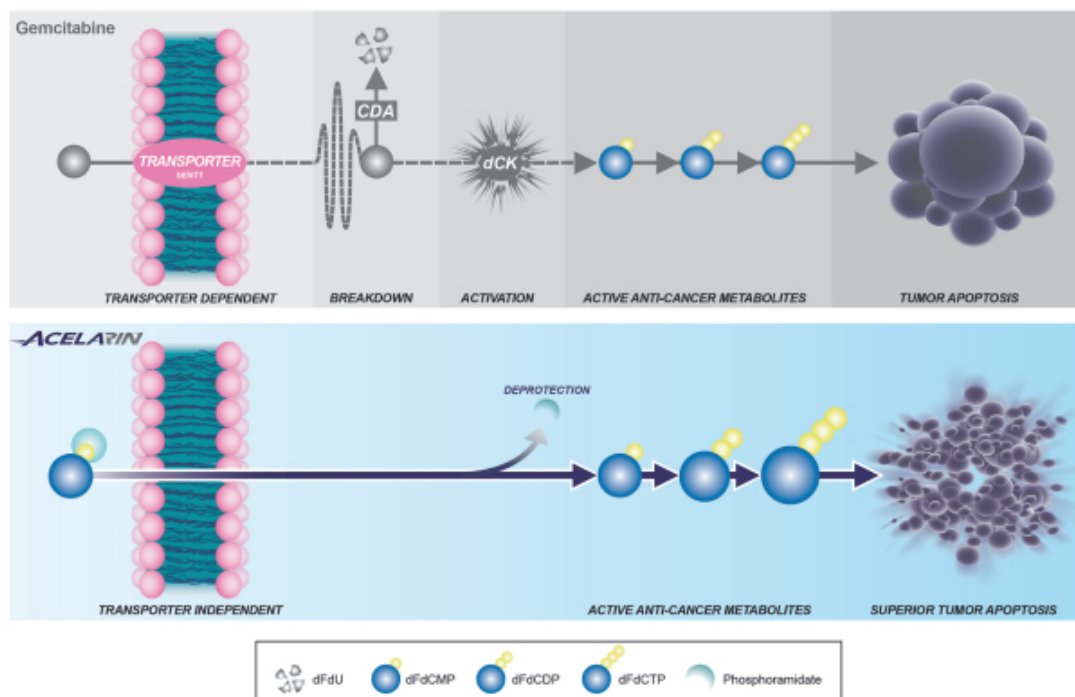
Contribution of resistance mechanisms to survival

Each of these resistance mechanisms on its own negatively impacts the survival of cancer patients receiving gemcitabine therapy by at least five months. While studies have not been done on the effect of the combination of all three of these resistance mechanisms, one study in pancreatic cancer patients who had undergone resection found that two of these resistance mechanisms had a cumulative effect. Specifically, patients with low levels of hENT1 and any level of dCK experienced a median overall survival of 16.2 months, while patients with high levels of hENT1 and low levels of dCK had a median overall survival of 33.6 months and patients with high levels of hENT1 and moderate to high levels of dCK had a median overall survival of 61.4 months.

Our Solution: Acelarin

Our lead product candidate, Acelarin, was designed to overcome the key cancer resistance mechanisms associated with gemcitabine. Acelarin is designed to generate and maintain higher concentrations of the anti-cancer metabolite inside the tumor compared to gemcitabine. This ProTide is comprised of gemcitabine, a phosphate group and a specific combination of aryl, ester and amino acid, also referred to as the phosphoramidate moiety. Acelarin's distinctive feature is this proprietary moiety, which protects the phosphate group. The moiety also changes the chemical properties of the molecule, enabling Acelarin to enter the cancer cell independent of the presence of the hENT1 transporter. Once Acelarin has entered the cell, the moiety is optimally cleaved off, resulting in "deprotection" and the release of an activated, phosphorylated form of gemcitabine in the cell. Accordingly, the activating enzyme, dCK, which drives the rate-limiting phosphorylation of gemcitabine, is no longer required and the cancer cells' deficiency of dCK does not result in resistance to Acelarin, as it does with gemcitabine. This activated nucleotide analog, dFdCMP, is then rapidly converted to dFdCDP and then the key anti-cancer metabolite, dFdCTP. Moreover, Acelarin, like the phosphorylated forms of gemcitabine, is not subject to breakdown by CDA, thus bypassing another key resistance mechanism. As a result, Acelarin achieves much higher levels of dFdCTP than does gemcitabine.

The metabolism of Acelarin compared to gemcitabine as described above is illustrated in the following graphic.



Clinical Data

Acelarin has been evaluated in one Phase 1 dose-ranging clinical trial and one Phase 1b clinical trial for recurrent ovarian cancer and is being evaluated in three clinical trials across numerous solid tumor cancer indications: Phase 2 for platinum-resistant ovarian cancer; Phase 1b for biliary cancer; and Phase 3 for pancreatic cancer.

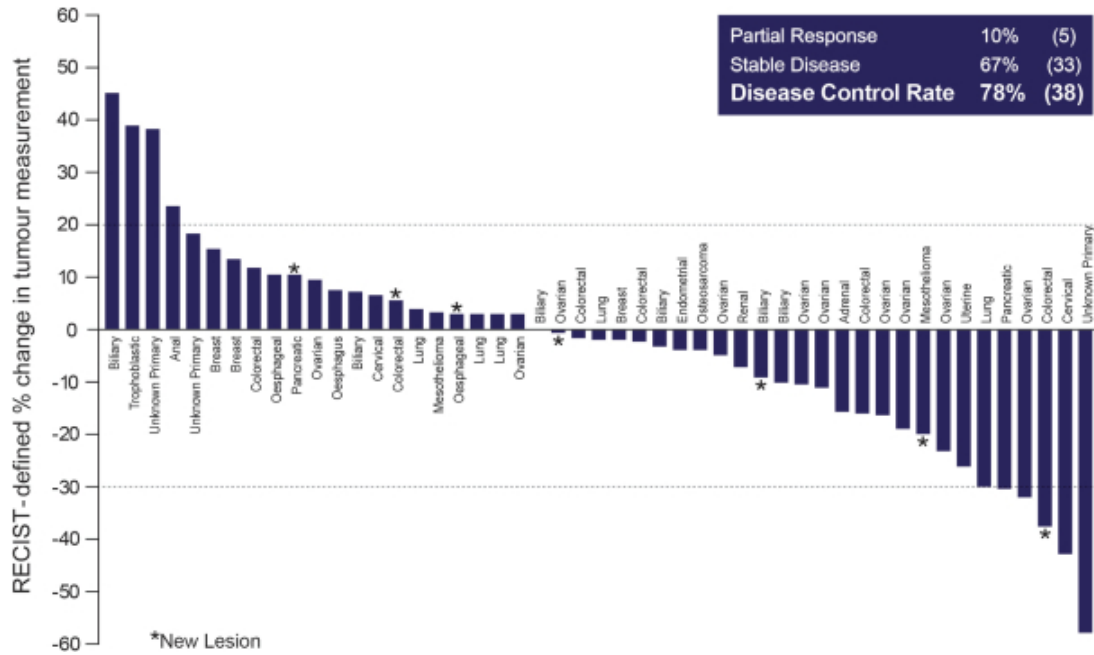
The vast majority of patients in the completed Phase 1 and Phase 1b trials were resistant or refractory to all existing standards of care and yet a high proportion obtained significant tumor regression or stable disease when treated with Acelarin. Both of these investigator-sponsored trials were conducted in the United Kingdom under a clinical trial authorization, or CTA, by the Medicines and Healthcare products Regulatory Agency, or MHRA. These trials were designed to assess the safety, pharmacokinetics and clinical activity of Acelarin as monotherapy or in combination with carboplatin.

Acelarin: Phase 1 clinical trial (PRO-001). In the completed Phase 1 trial, 68 patients with advanced solid tumors and metastatic disease that had previously been treated with other systemic anti-cancer therapies received Acelarin as monotherapy at doses ranging from 375 mg/m² to 1,000 mg/m². All of these patients had rapidly progressing recurrent disease, had received on average 2.7 prior lines of chemotherapy, and had exhausted all other standard treatment options. Initial signs of efficacy were evaluated using the standard scoring system known as Response Evaluation Criteria In Solid Tumors, or RECIST. A subset of 49 patients received two or more cycles of Acelarin, equivalent to two or more months of therapy, and had at least one follow-up radiographic assessment to measure changes in tumor size. Of these patients, five achieved a partial response, with at least a 30% decrease in tumor size, although not all of these five patients received a final confirmatory

[Table of Contents](#)

scan as technically required by the RECIST criteria for classification as a partial response. Another 33 patients had tumors that either decreased by up to 30% or increased by less than 20% and were scored as having stable disease. This resulted in an overall disease control rate, the combination of both partial response and stable disease, of 78% in the total 49-patient evaluable population.

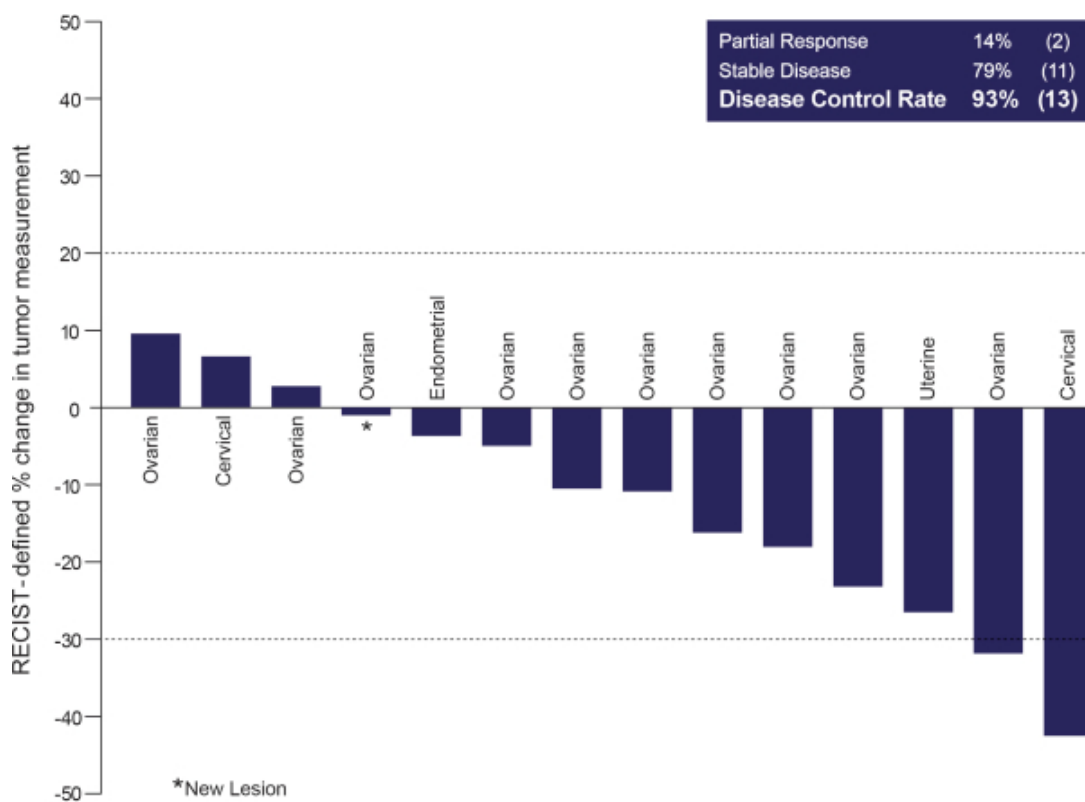
The following graph illustrates the best percentage change from baseline tumor size in the 49 evaluable patients. Asterisks in the graph below indicate patients who had disease progression as a result of a new lesion rather than an increase in size of any existing measurable tumors. These patients are accordingly not included in the partial response or stable disease classifications. The median progression-free survival in the 49 evaluable patients was 4.0 months with a range of two to 25 months. Of the 33 patients who achieved stable disease, 32 maintained stable disease for at least 12 weeks.



An analysis was performed on a subset of 18 patients from the same trial who had some form of gynecological cancer: ovarian, endometrial, cervical or uterine cancers. This patient subset had received on average 3.5 prior lines of chemotherapy. Of these patients, 14 were evaluable. Two of these 14 heavily pre-treated patients with gynecological cancer achieved a partial response and an additional 11 achieved stable disease, resulting in a disease control rate of 93% with a median progression-free survival duration of 8.0 months. In the seven evaluable patients with platinum-refractory or platinum-resistant ovarian cancer, the median progression-free survival duration was also 8.0 months.

[Table of Contents](#)

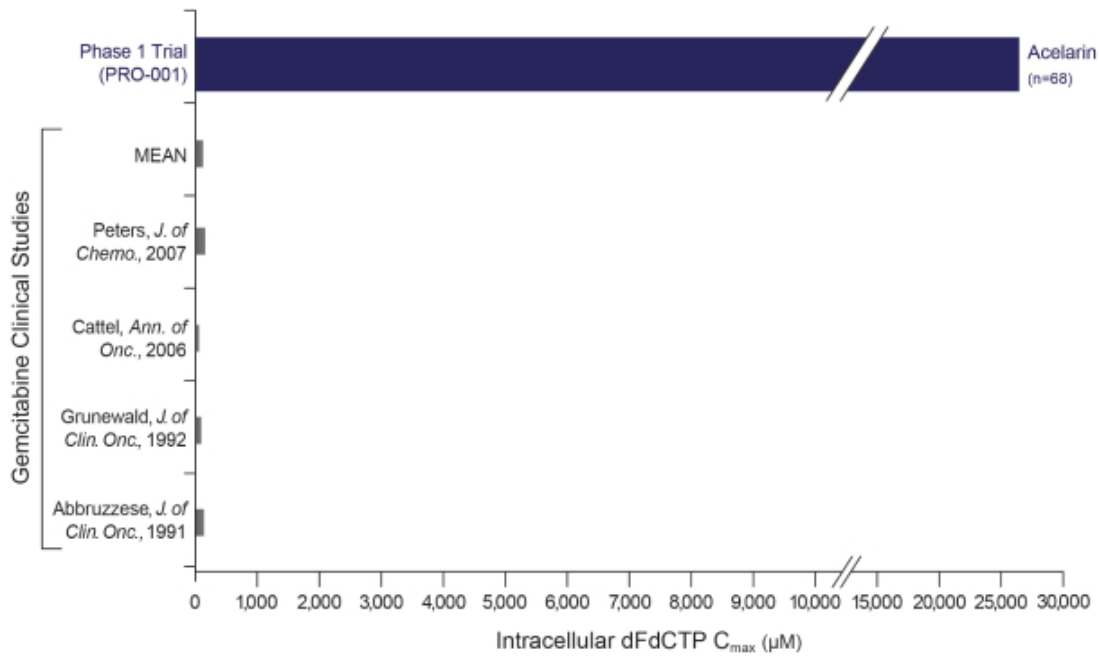
The following graph illustrates the best percentage change from baseline tumor size in the 14 evaluable patients with gynecological cancer. The asterisk in the graph below indicates the one patient who experienced progressive disease as a result of a new lesion rather than an increase in size of any existing measurable tumor. This patient is therefore not included in the partial response or stable disease classifications.



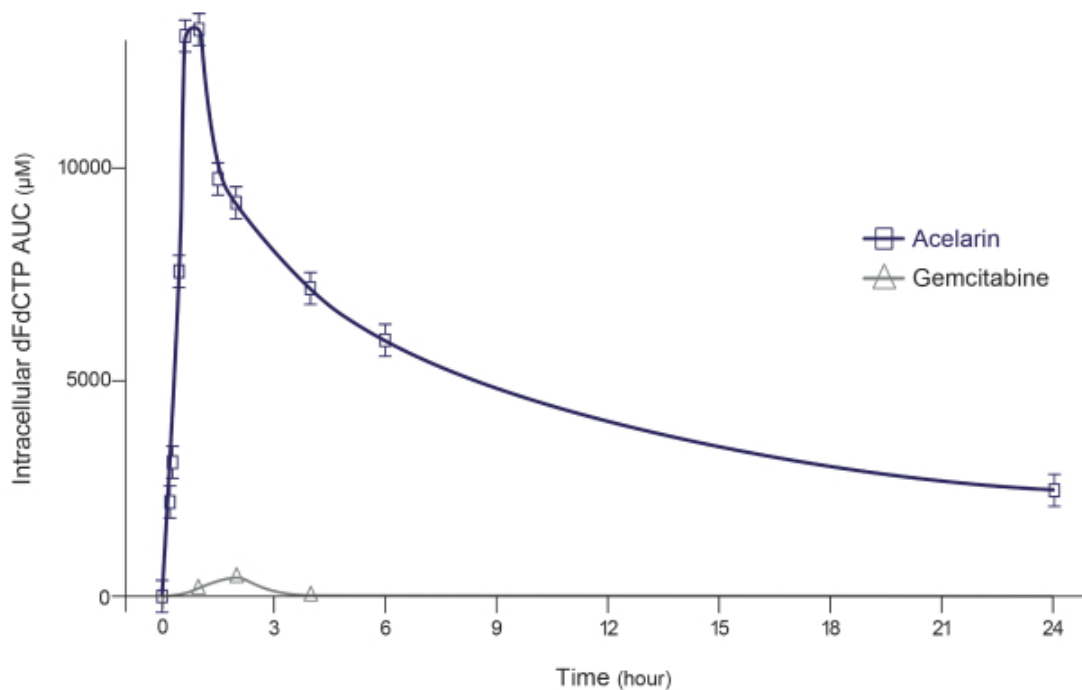
While not directly comparable to Acelarin, Doxil, or pegylated liposomal doxorubicin, a standard of care for patients with recurrent ovarian cancer, was assessed in the AURELIA clinical trial in patients who had received no more than two prior lines of chemotherapy. Doxil was associated with an overall response rate of 8% and a median progression-free survival duration of 3.5 months.

[Table of Contents](#)

In the Phase 1 trial, Acelarin had a plasma half-life of 8.3 hours, as compared to the plasma half-life of gemcitabine, which ranges from 42 minutes to 94 minutes. The median intracellular levels of the active anti-cancer metabolite, dFdCTP, achieved with Acelarin were over 200 times higher than those reported in the literature for gemcitabine on an equimolar dose comparison, as shown in the graphic below. Equimolar means that all of the doses being compared contained the same number of molecules of Acelarin or gemcitabine.



We observed levels of dFdCTP that were still higher 24 hours after dosing with Acelarin than the maximum reported concentration generated with gemcitabine at its peak level two hours after dosing. Furthermore, the concentration of intracellular dFdCTP over a 24-hour period, as measured by the area under the curve, or AUC, a measure of drug exposure over time, was 139 times higher for Acelarin on an equimolar dose comparison compared to the levels reported for gemcitabine in the literature referenced above. We have combined the data from those four studies in order to derive the curve shown in the graphic below.



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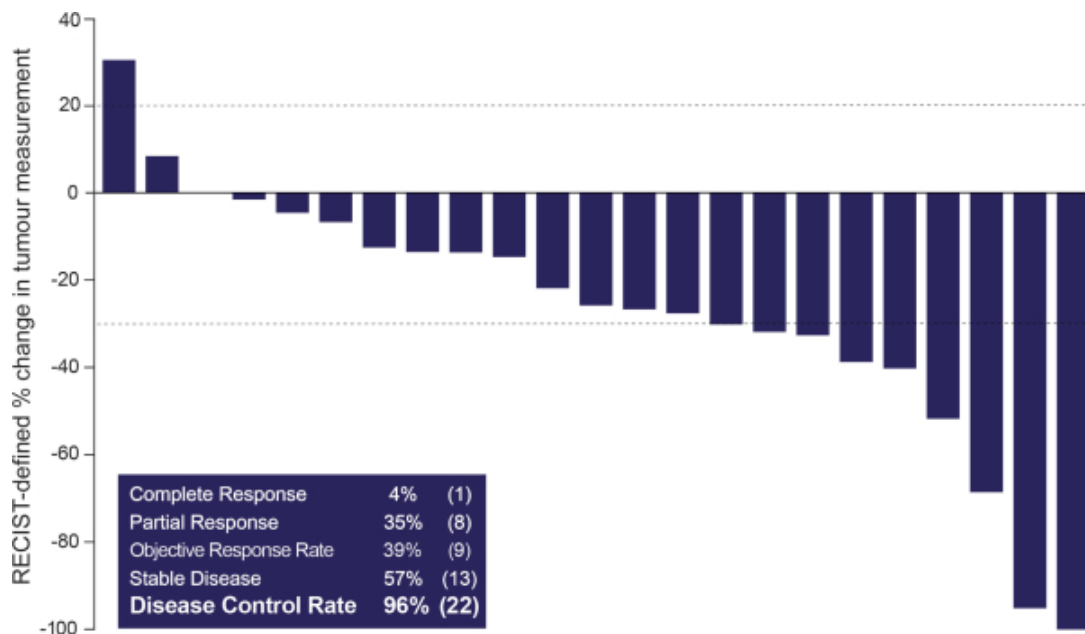
We believe that the higher concentrations of dFdCTP results from Acelarin's ability to bypass the key cancer resistance mechanisms and its favorable pharmacokinetics, or the process by which Acelarin is distributed and metabolized in the body.

Acelarin was generally well-tolerated. The most common Grade 3 and Grade 4 treatment-related adverse events, which occurred in 10% to 20% of patients, were fatigue and decreased counts of blood cells, including neutrophils, lymphocytes and platelets. A total of eight dose-limiting toxicities were observed in four patients at doses of 725 mg/m² and above. These included Grade 3 increases in liver enzymes known as transaminases, and Grade 4 decreases in platelets and neutrophils. All of these adverse events were transient and all patients recovered. To date, we have not observed any treatment-related adverse events that have not previously been associated with gemcitabine.

Acelarin: Phase 1b clinical trial in combination with carboplatin (PRO-002). In the Phase 1b trial, 25 patients with recurrent ovarian cancer received Acelarin at doses from 500 mg/m² to 750 mg/m² in combination with carboplatin for a maximum of six treatment cycles lasting three weeks each. Patients had received on average three prior lines of chemotherapy and had a median age of 64. Of the 25 patients enrolled, 23 were evaluable and these patients were characterized by their platinum status: seven were platinum-refractory, 10

were platinum-resistant, four were partially platinum-sensitive and two were platinum-sensitive. Efficacy was evaluated using the RECIST standard scoring system. The 23 evaluable patients had received one or more cycles of Acelarin in combination with carboplatin and had at least one follow-up radiographic assessment to measure changes in tumor size. Of these patients, one achieved a complete response, with a complete disappearance of all target lesions, and eight achieved a partial response, with at least a 30% decrease in tumor size, although not all of these patients have received a confirmatory scan. This resulted in an overall response rate of 39%. Another 13 patients had tumors that either decreased by up to 30% or increased by less than 20% and were scored as having stable disease. This resulted in a disease control rate of 96%. The median progression-free survival duration for all 25 patients recruited was 7.3 months and for the evaluable population was 7.4 months.

The following graph illustrates the best percentage change from baseline tumor size in the 23 evaluable patients.



Although gemcitabine has never been approved as a single agent for patients with ovarian cancer, it is approved in combination with carboplatin in patients who have relapsed at least six months after completion of platinum-based therapy. These patients are platinum-sensitive or partially platinum-sensitive. In this population, as a second line treatment, the combination of gemcitabine and carboplatin achieved an overall response rate of 47% and a disease control rate of 85%. Due to the toxicity burden of gemcitabine, carboplatin is limited to a suboptimal dose. Even at the suboptimal dose of carboplatin, the incidence of Grade 3 and Grade 4 neutropenia, or low neutrophils, and thrombocytopenia, or low platelets, was 71% and 35%, respectively, with this combination.

The results of the Phase 1b Acelarin trial suggest that Acelarin can be combined with carboplatin at a higher, more optimal carboplatin dose. In the seven patients with platinum partially sensitive and sensitive disease, the incidence of Grade 3 and Grade 4 neutropenia and thrombocytopenia was 43% and 0%, respectively. In all 25 patients, the incidence of Grade 3 and Grade 4 neutropenia and thrombocytopenia was 52% and 32%, respectively.

[Table of Contents](#)

The data from the Phase 1b trials are interim because the Phase 1b trial is still ongoing. Interim data are not necessarily predictive of final results and may change as the data are further examined, more patient data become available and the final clinical study report is prepared and issued. As a result, interim data should be viewed with caution until the final data are available. Initial success with either interim or final data in early-stage clinical trials may not be indicative of results obtained in later-stage trials, and the results of our clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for marketing approval. Statistical significance means that an effect is unlikely to have occurred by chance. Clinical trial results are considered statistically significant when the probability of the results occurring by chance, rather than from the efficacy of the product candidate, is sufficiently low. We plan to design our later stage trials to establish the statistical significance of the efficacy of our ProTides.

Acelarin development strategy and ongoing clinical trials

Acelarin has been administered to over 140 patients with a wide range of advanced cancers. We are developing Acelarin for multiple indications: in both platinum-resistant and platinum-sensitive ovarian cancer; as first-line treatment in biliary cancer, an indication in which no drug has ever been approved; and as first-line treatment in pancreatic cancer.

Our ongoing clinical trials are:

- a Phase 2 trial, in up to 64 patients with platinum-resistant ovarian cancer, to establish the optimal dose of Acelarin as monotherapy, with the expectation of interim data in 2018;
- a Phase 1b trial, in up to 24 patients with biliary cancer, to establish the optimal dose of Acelarin in combination with cisplatin as a first-line treatment, with the expectation of interim results in 2018; and
- a Phase 3 trial expected to enroll 328 patients with metastatic pancreatic cancer to compare Acelarin to gemcitabine as a first-line treatment, facilitated by the National Cancer Research Institute in the United Kingdom.

The Phase 2 trial in platinum-resistant ovarian cancer is being conducted under an Investigational New Drug application, or IND, in the United States and a CTA in the United Kingdom.

The Phase 1b trial in biliary cancer and the Phase 3 trial in pancreatic cancer are investigator-sponsored trials and being conducted under a CTA in the United Kingdom.

Ovarian cancer

Overview. Ovarian cancer is the fifth-leading cause of cancer death in women in the United States. According to the U.S. National Cancer Institute, there are approximately 22,000 new cases and 14,000 cancer-related deaths each year from ovarian cancer in the United States. Worldwide, there are approximately 225,000 new cases of ovarian cancer and 140,000 deaths yearly. Surgery and cytotoxic chemotherapies are widely used to treat ovarian cancer; however, the outcomes have changed little over several decades. The five-year survival rate for ovarian cancer patients in the United States has improved only marginally from 42.2% in 1995 to 46.6% in 2009.

Limitations of current treatment options in ovarian cancer. First-line therapy for patients with advanced ovarian cancer is typically a combination of a platinum drug, such as carboplatin, and a taxane drug such as paclitaxel. Due to toxicities, most patients undergo a maximum of six cycles, equivalent to four and a half months, of this therapy. Between 62% and 85% of patients will relapse depending on the stage of the disease, and these patients can be divided into four groups depending on length of time between the end of treatment and the relapse. Those with disease progression while receiving platinum-based therapy or who relapse within four weeks of the last platinum dose are defined as platinum-refractory. Those relapsing after more than one month

[Table of Contents](#)

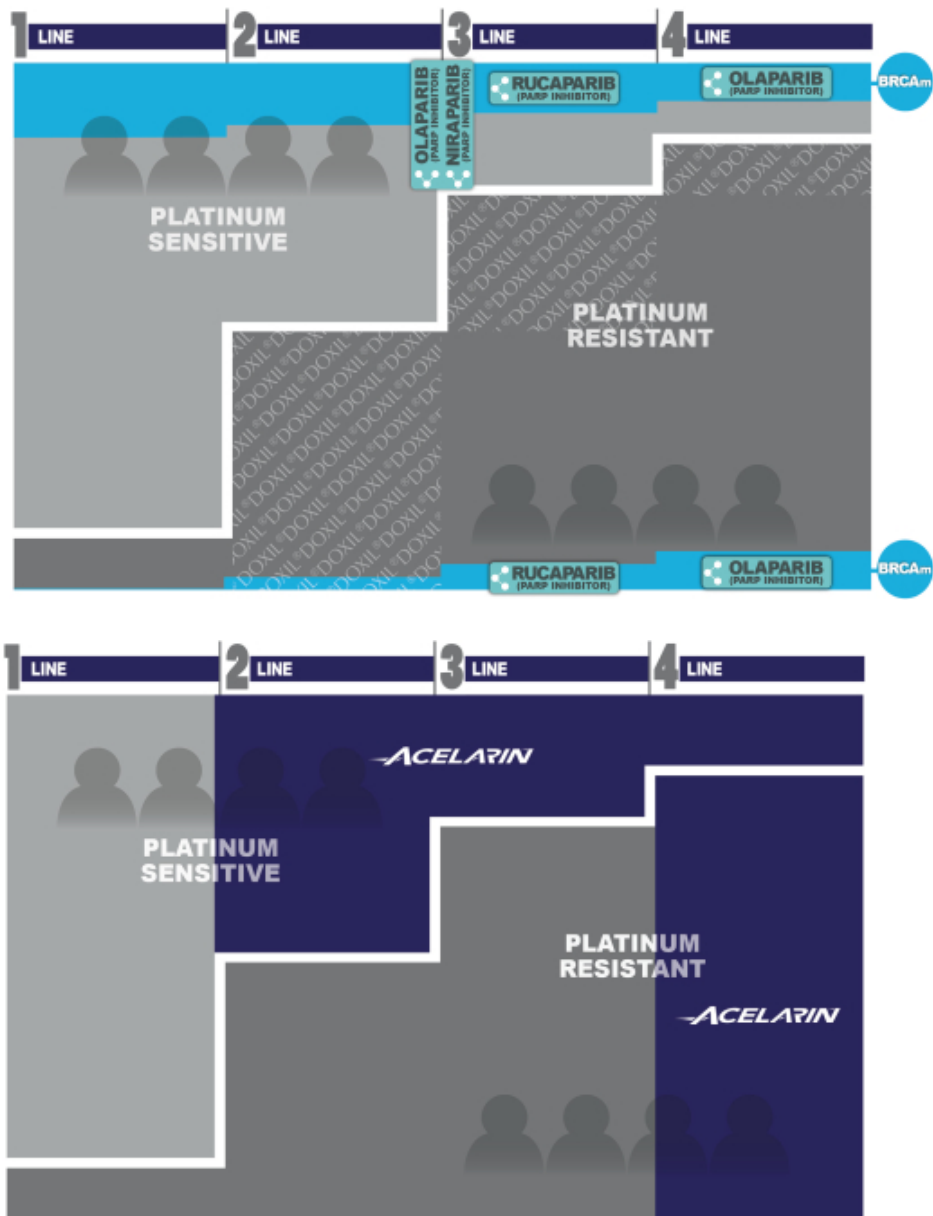
but less than six months are deemed platinum-resistant and have a worse prognosis than partial platinum-sensitive patients, who relapse between six and 12 months, and platinum-sensitive patients, who relapse after more than 12 months.

Relapsed platinum-sensitive patients typically receive a platinum-containing agent such as carboplatin or cisplatin in combination with other therapies such as gemcitabine. The addition of gemcitabine to carboplatin in these patients increased the progression-free survival to 8.6 months from 5.8 months with carboplatin alone but had no significant effect on overall survival. Gemcitabine as monotherapy, although not approved, is used in relapsed, platinum-resistant ovarian cancer patients resulting in progression-free survival of approximately four months.

Recently, a new class of anti-cancer drugs, known as PARP inhibitors, has been approved for the third- or fourth-line treatment of a subset of ovarian cancers, specifically those containing mutations in BRCA genes, or BRCAm, which constitute approximately 15% of ovarian cancer patients. PARP inhibitors have also been approved as maintenance therapy in patients with recurrent ovarian cancer with a complete or partial response to platinum-based chemotherapy.

[Table of Contents](#)

The market can be simplified into platinum-resistant and platinum-sensitive (including partially platinum-sensitive) ovarian cancer patients. The following illustrations show how platinum-resistance increases with line of therapy and highlights where some existing therapies are being utilized and the ovarian cancer indications we are targeting with Acelarin.



Biliary cancer

Overview. Biliary cancers, including cholangiocarcinoma, gallbladder and ampullary carcinoma, are cancers originating in the bile duct, a vessel that transports bile from the liver to the gall bladder and small intestine. Approximately 178,000 new cases of biliary cancer are diagnosed each year worldwide, with approximately 9,000 of those diagnoses in the United States.

Limitations of current treatment options in biliary cancer. There are currently no agents approved for the treatment of biliary cancer; however, the worldwide standard of care in biliary cancer patients with advanced or metastatic disease is the combination of gemcitabine and cisplatin. Patients receiving this regimen have a median overall survival of 11.7 months compared to 8.1 months for patients receiving gemcitabine as monotherapy.

Pancreatic cancer

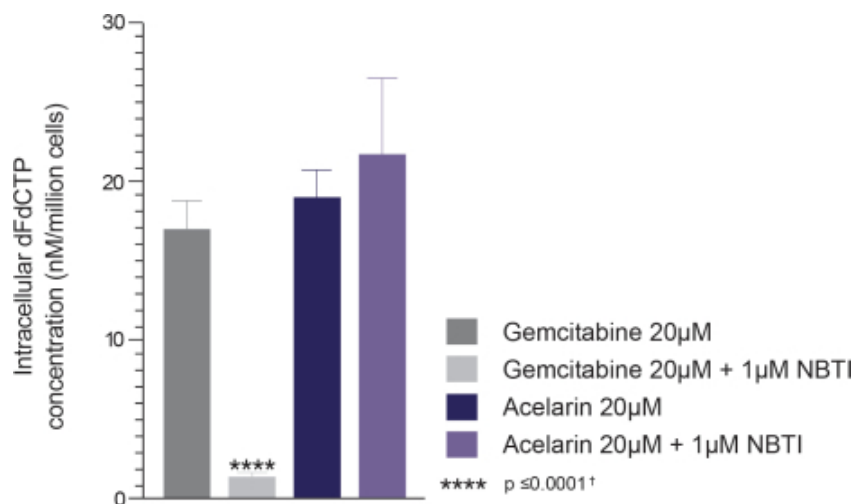
Overview. Pancreatic cancer is the third-leading cause of cancer deaths in the United States with approximately 53,000 new diagnoses and 41,800 deaths in 2016. Worldwide, there were approximately 338,000 new pancreatic cancer diagnoses in 2012. Approximately 85% of patients diagnosed with pancreatic cancer have advanced disease at the time of diagnosis, are ineligible for surgery and are treated with chemotherapy. Patients with pancreatic cancer have a poor prognosis, with a five-year survival rate of only 7.7%.

Limitations of current treatment options in pancreatic cancer. First-line treatment in pancreatic cancer for patients with a good performance score, which is a standard measure of general well-being, is a combination of 5-FU, oxaliplatin, leucovorin and irinotecan, a treatment regimen known as FOLFIRINOX. Treatment with FOLFIRINOX is, however, associated with high levels of toxicity, so it is generally not recommended for patients without good performance scores. For patients with a less robust performance score, a common first-line treatment is a combination of gemcitabine and nab-paclitaxel, or Abraxane®. For patients who are less fit or who have co-morbidities, the standard of care is single-agent gemcitabine. In separate clinical trials, patients treated with FOLFIRINOX had a median overall survival of 11.1 months and patients treated with the combination of gemcitabine and nab-paclitaxel had a median overall survival of 8.5 months. The addition of nab-paclitaxel to gemcitabine resulted in a seven-week improvement in median overall survival compared to gemcitabine alone.

Acelarin preclinical data

Prior to progressing our product candidates into clinical trials, we wanted to evaluate in preclinical studies whether Acelarin would: (1) be able to enter cells independent of transporters, including hENT1; (2) generate the active anti-cancer metabolite, dFdCTP, inside cancer cells without the need for the phosphorylating enzyme dCK; and (3) not be susceptible to breakdown by enzymes like CDA. The results of these preclinical studies are summarized below:

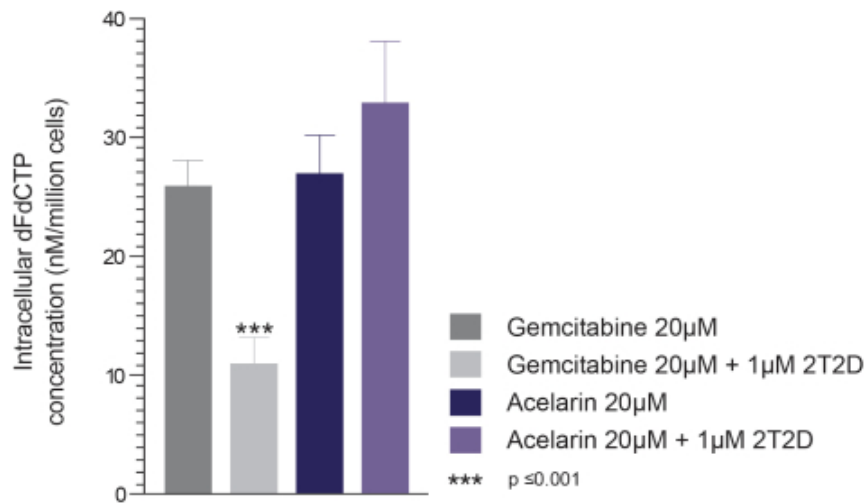
1. Acelarin is not dependent on transporters to enter cancer cells. Gemcitabine requires the hENT1 transporter to cross the cell membrane. Evidence of this can be seen in cellular assays we completed in which hENT1 was specifically blocked by an inhibitor known as NBTI in human cancer cells. A group including our researchers published a study in the *Journal of Medicinal Chemistry* in which we observed that Acelarin did not require hENT1 in order to enter cells and that NBTI had no effect on intracellular levels of dFdCTP. These results are illustrated below.



(†) p-value is a conventional statistical method for measuring the statistical significance of preclinical study and clinical trial results. A p-value of 0.05 or less represents statistical significance, meaning that there is a 1-in-20 or less likelihood that the observed results occurred by chance. A p-value of 0.0001 or less means that there is a 1-in-10,000 or less likelihood that the observed results occurred by chance.

This finding was confirmed in a separate study where hENT1 was blocked by dipyridamole, a commonly used nucleoside transporter inhibitor, with the result that gemcitabine's ability to kill the cancer cells was significantly reduced while Acelarin retained its activity.

2. Acelarin does not require rate-limiting activation step. Gemcitabine must be phosphorylated, or activated, inside the cell by the addition of a phosphate group to the molecule in order to exert a cytotoxic effect. This phosphorylation requires the enzyme dCK. In our preclinical studies, inhibition of dCK by a specific inhibitor, known as 2T2D, significantly reduced the phosphorylation step to generate dFdCTP within human cancer cells while Acelarin was unaffected by 2T2D and was still able to generate the same level of the key active anti-cancer metabolite, dFdCTP. These results are illustrated below.



This observation is consistent with the fact that Acelarin already includes the first phosphate group and thus does not require the action of dCK for activation. Furthermore, we confirmed these findings in a separate study in which we blocked the action of dCK with the inhibitor deoxycytidine, which significantly reduced the ability of gemcitabine to kill the cancer cells while Acelarin retained its activity.

3. Acelarin not susceptible to breakdown by CDA. Nucleoside analogs such as gemcitabine are susceptible to breakdown by enzymes such as CDA. The presence of the phosphate on Acelarin protects it from breakdown by CDA. In our preclinical studies, incubation of Acelarin with purified CDA resulted in no degradation of Acelarin over the full 30-minute assay while gemcitabine under these same conditions was almost completely degraded in two minutes.

We believe that the ability of Acelarin to generate the active anti-cancer metabolites within the cancer cells in higher concentrations than gemcitabine gives Acelarin the potential to have greater efficacy and to overcome the key cancer cell resistance mechanisms, while avoiding breakdown and release of toxic byproducts.

NUC-3373: A Transformation of 5-FU

We have designed our second ProTide, NUC-3373, to overcome the key cancer resistance mechanisms, improve upon the safety profile and reduce the dosing administration burdens associated with the nucleoside analog, 5-FU. We are advancing NUC-3373 in the clinic and developing this new chemical entity as a therapy for colorectal cancer, breast cancer and other solid tumors.

5-FU and its Limitations

First introduced in 1957, 5-FU is still widely used for the treatment of many cancers, including colorectal, breast, stomach, head and neck, and pancreatic cancers. Approximately 500,000 patients per year in North America receive 5-FU.

5-FU requires conversion to the phosphorylated anti-cancer metabolite, fluorodeoxyuridine monophosphate, or FUDR-MP, before it can exert its primary cytotoxic activity through the inhibition of an intracellular enzyme, thymidylate synthase, or TS. TS is required to convert uridine, specifically deoxy-uridine monophosphate, or dUMP, to thymidine, specifically deoxy-thymidine monophosphate, or dTMP, one of the four nucleotides that comprise DNA. The inhibition of TS therefore results in an imbalance in the ratio of the nucleotides dUMP and dTMP, disrupting DNA synthesis and repair, which leads to cancer cell death.

Two other drugs have been approved that aim to generate the same active anti-cancer metabolite as 5-FU: fluorodeoxyuridine, or Floxuridine, marketed as FUDR®, and capecitabine, marketed as Xeloda®. Like 5-FU, both of these drugs must be converted to FUDR-MP inside the cancer cell in order to exert their primary cytotoxic activity. Capecitabine is a derivative of 5-FU containing a chemical modification of the nucleoside ring, which allows oral dosing of capecitabine.

Similar to gemcitabine, the key cancer resistance mechanisms of breakdown, activation and transport have been associated with a poor prognosis to a 5-FU therapeutic regimen. We believe our ProTide, NUC-3373, overcomes these specific key resistance mechanisms as well as dosing administration challenges associated with 5-FU.

1. Subject to breakdown. More than 85% of an injected dose of 5-FU is degraded by dihydropyrimidine dehydrogenase, or DPD, an enzyme largely expressed in the liver. This breakdown destroys most of the drug before it has an opportunity to enter the cancer cell, become activated and exert any therapeutic effect. Furthermore, this breakdown results in the generation of a toxic byproduct, F-BAL, which has been associated with off-target toxicity, such as “hand-foot syndrome,” which is reported in various sources as affecting at least half of patients treated with 5-FU. Hand-foot syndrome is a reddening, swelling, numbness and skin sloughing or peeling on the palms of the hands and soles of the feet. In addition, levels of DPD have also been found to be elevated in tumors that are resistant to 5-FU.

2. Requires activation within the cancer cell. Once 5-FU enters cells, it must be processed by a series of enzymes to generate the active anti-cancer metabolite, FUDR-MP. FUDR-MP binds to and inhibits TS, leading to decreased levels of thymidine and resulting in cancer cell death. There are several key enzymes involved in the conversion of 5-FU to the active anti-cancer metabolite, FUDR-MP. One of these is orotate phosphoribosyl transferase, or OPRT. Lower levels of OPRT in tumor cells are associated with resistance to 5-FU. Another intracellular enzyme, thymidine phosphorylase, or TP, can reversibly convert 5-FU to fluorodeoxyuridine, or FUDR, an intermediate to the formation of FUDR-MP. Low expression of TP in human cancer cells is associated with resistance to 5-FU. In addition, thymidine kinase, or TK, is the enzyme that converts FUDR to the active anti-cancer metabolite, FUDR-MP. Low expression of TK in human cancer cells is associated with resistance to 5-FU.

3. Requires active transport. Similar to gemcitabine and all nucleoside analogs, 5-FU relies on specific transporters in order to cross the cellular membrane. If these transporters are not present or are expressed in low

[Table of Contents](#)

levels, 5-FU's ability to enter into the cancer cell will be limited. For example, low expression of the nucleoside transporter, hENT1, has been associated with cancer cell resistance to 5-FU.

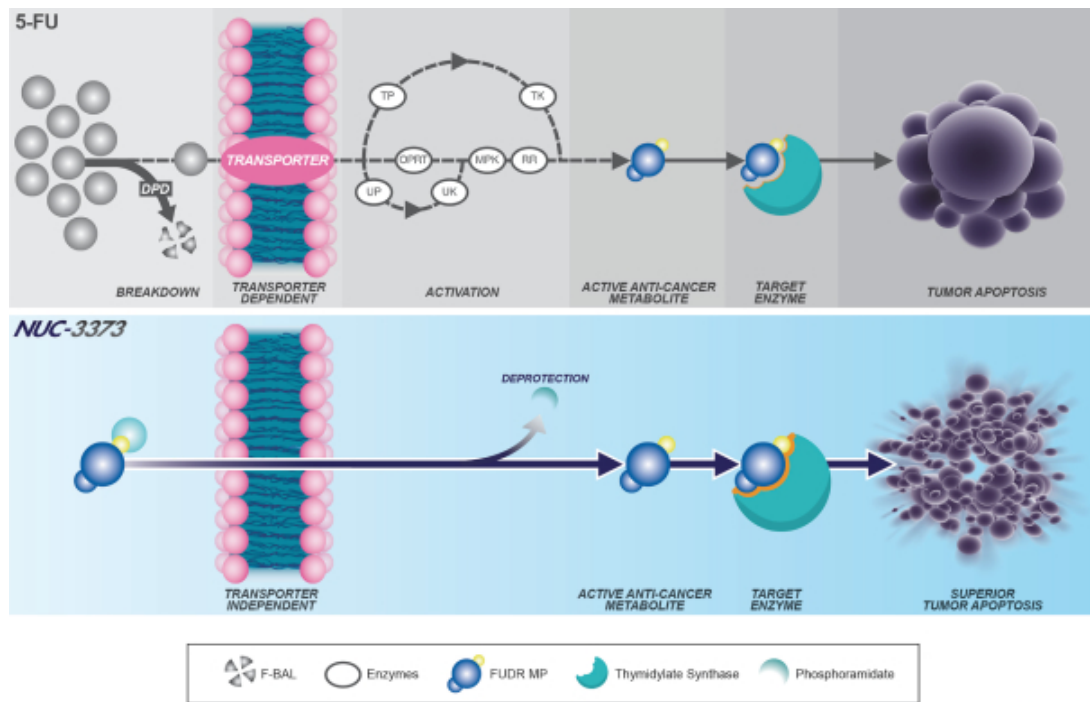
4. Dosing administration challenges. The pharmacokinetic and pharmacodynamic properties of 5-FU also lead to dosing administration challenges. Pharmacodynamic properties refer to the biochemical and physiological effects of a drug on the human body. 5-FU has a half-life between eight and 14 minutes in plasma. In an effort to counter this short time period, healthcare providers often administer 5-FU as a continuous infusion over extended periods of time, often days. For example, patients being treated for colorectal or pancreatic cancer typically receive their first dose, or loading dose, of 5-FU over 46 hours using a portable infusion pump. This dosing regimen creates burdens for providers, inconveniences patients and contributes additional costs to the healthcare system.

Our Solution: NUC-3373

We designed our second ProTide, NUC-3373, to overcome the key cancer resistance mechanisms, improve upon the safety profile and reduce the dosing administration burdens associated with the nucleoside analog, 5-FU. NUC-3373 is a nucleotide analog that delivers the same active anti-cancer metabolite, FUDR-MP, that 5-FU aims to generate within a cancer cell, but at far higher concentrations. NUC-3373 is in a Phase 1 clinical trial in patients with advanced solid tumors.

Unlike 5-FU, NUC-3373 consists of the active anti-cancer metabolite, FUDR-MP, and a protective phosphoramidate moiety. This moiety allows NUC-3373 to enter the cell without the need for any membrane transporters. Once inside the cancer cell, the phosphoramidate moiety is optimally cleaved off, resulting in deprotection and the release of FUDR-MP. This bypasses the need for any activating enzymes, resulting in significantly higher levels of the active anti-cancer metabolite, which we believe may lead to improved efficacy as compared to 5-FU. In addition, because NUC-3373 avoids breakdown by the enzyme DPD, certain toxic byproducts such as F-BAL are not released, which we believe may lead to an improved tolerability profile as compared to 5-FU. Lastly, we believe that the improved pharmacokinetic and pharmacodynamic profile, including the significantly longer half-life of NUC-3373, may result in a more favorable dosing regimen relative to 5-FU.

The metabolism of NUC-3373 compared to 5-FU as described above is illustrated in the following graphic.



Clinical Data

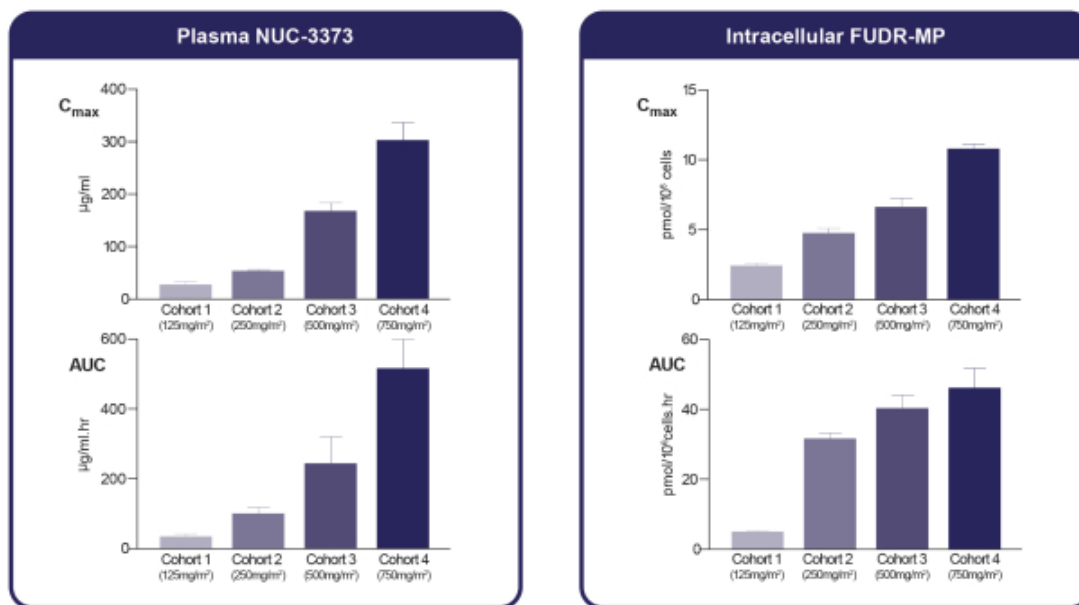
NUC-3373 is currently being evaluated in a Phase 1 trial in patients with advanced solid tumors. We are planning further clinical trials across a number of indications, including colorectal cancer and metastatic breast cancer.

NUC-3373: Phase 1 clinical trial. We have initiated a Phase 1 clinical trial of NUC-3373 in which we are planning to enroll approximately 76 patients. We have currently enrolled over 20 patients with ten different advanced solid tumor types. We have completed four dose cohorts and we are continuing with dose-escalation cohorts to establish the optimal dose and frequency of administration. Patients are being dosed with a short infusion of NUC-3373, initially once per week.

In this trial, we are measuring various pharmacokinetic and pharmacodynamic parameters, including plasma concentration of NUC-3373, intracellular concentrations of the active anti-cancer metabolite, FUDR-MP, the ability of NUC-3373 to bind to its target enzyme, TS, and the downstream effects on the levels of dTMP.

Table of Contents

We have interim data from 21 of the patients currently enrolled in the trial. The following graphs on the left labeled “Plasma NUC-3373” illustrate the maximum plasma concentrations, or C_{max} , of NUC-3373 among the four cohorts as measured after one administration and the plasma concentrations of NUC-3373 over time, as measured by AUC. The following graphs on the right labeled “Intracellular FUDR-MP” illustrate the corresponding data for intracellular levels of the active anti-cancer metabolite, FUDR-MP.



The interim data from these 21 patients also showed:

- pharmacokinetics were consistent across patients and showed a linear dose response;
- NUC-3373 had a plasma half-life of 9.7 hours compared with the half-life of 8 to 14 minutes for 5-FU reported in the literature;
- intracellular FUDR-MP was detected within five minutes after infusion with a half-life of 14.9 hours while the literature reports that 5-FU does not generate detectable levels of intracellular FUDR-MP;
- intracellular FUDR-MP was still detectable up to 48 hours after dosing;
- within one hour after infusion, FUDR-MP had bound to the target enzyme, TS, leading to depletion of intracellular dTMP two to four hours after administration; and
- the toxic byproducts, FBAL and dhFU, were undetectable both intracellularly and in the patient’s plasma.

These interim pharmacokinetic and pharmacodynamic data support our belief that NUC-3373 may have greater anti-cancer activity, an improved safety profile and a lower dosing administration burden than 5-FU. We expect final data from this Phase 1 trial in 2018.

NUC-3373 Development Strategy and Planned Clinical Trials

We are rapidly developing NUC-3373 for multiple indications and initially targeting advanced colorectal cancer and metastatic breast cancer. We intend to initiate the following clinical trials in 2018:

- a Phase 1b trial in approximately 36 patients with recurrent metastatic colorectal cancer in combination with standard agents that are routinely used in combination with 5-FU, including leucovorin, oxaliplatin

and irinotecan. The FDA recently provided authorization, following review of our IND, for this study to proceed;

- a Phase 3 trial in 400 patients with end-stage metastatic colorectal cancer; and
- a Phase 2 trial in 50 metastatic breast cancer patients who have been previously treated with post-anthracycline and taxane therapy.

The Phase 1 trial in advanced solid tumors is investigator-sponsored and being conducted under a CTA.

Colorectal Cancer Overview

In the United States, approximately 135,000 new cases of colorectal cancer and 50,000 deaths due to the disease are expected in 2017. Worldwide, there were an estimated 1.4 million new colorectal cancer cases and 694,000 deaths in 2012, and the global burden is expected to increase to more than 2.2 million new cases and 1.1 million deaths annually by 2030. Most systemic therapies for colorectal cancer include 5-FU, either as monotherapy or in combination with another chemotherapeutic, typically oxaliplatin or irinotecan. Both alone and in combination, 5-FU is the single most effective compound against these tumors. Nevertheless, despite being the standard of care, the effectiveness of 5-FU is modest. Overall response rates are in the range of 10% to 15%.

Breast Cancer Overview

Approximately one in eight women will be diagnosed with breast cancer at some point in their lifetime. In the United States alone, approximately 253,000 women are expected to be diagnosed with the disease and over 40,000 women are projected to die from it in 2017. On a worldwide basis, approximately 1.7 million women were diagnosed with breast cancer in 2012.

An estimated 30% of all breast cancers become metastatic and require systemic treatment. There are many available agents to treat metastatic breast cancer and the choice of therapy depends on factors such as tumor burden, the patient's overall health, prior history of cancer treatment, the importance to the patient of minimizing toxicity, dosing convenience, and the physician's preferences. Physicians often prefer to treat patients with limited metastatic disease with these agents used as monotherapy in a sequential fashion. Initially, taxanes, such as docetaxel, paclitaxel and nabpaclitaxel, and anthracyclines, such as doxorubicin and epirubicin, are frequently prescribed. However, these categories of therapeutics must be administered intravenously and are commonly associated with neutropenia, or low neutrophils, and gastrointestinal toxicities. The nucleoside analog, capecitabine, which is a prodrug of 5-FU, has advantages over taxanes and anthracyclines and has become a standard of care for patients with metastatic breast cancer. Recently, the PARP inhibitor olaparib has shown a clinical benefit for metastatic breast cancer patients with a BRCA mutation, who represent approximately 5% of this population.

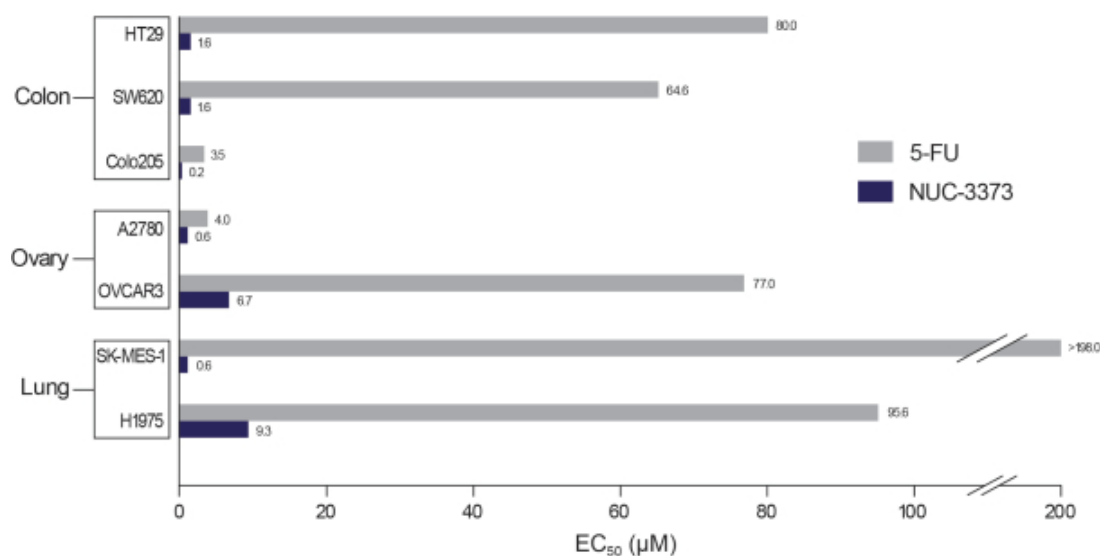
NUC-3373 Preclinical Data

NUC-3373 avoids breakdown. In our preclinical studies, NUC-3373, unlike 5-FU, was not susceptible to breakdown by the enzyme DPD, which is a major factor in limiting the efficacy of 5-FU. Therefore, the ability of NUC-3373 to generate the active anti-cancer metabolite, FUDR-MP, should be unaffected by DPD activity and result in much higher intracellular concentrations of FUDR-MP. Furthermore, in patients receiving NUC-3373, the toxic byproduct, FBAL, produced by DPD's breakdown of 5-FU has not been observed.

In addition, a study published in the *World Journal of Gastroenterology* in 2001 indicated that approximately half of patients with colorectal cancer had tumors that were infected with a type of bacteria called mycoplasma. A 2008 study published in the *International Journal of Cancer Research and Treatment* highlighted that 5-FU's activity was reduced by up to 100 times in cancer cell lines infected with mycoplasma. In our preclinical studies, the anti-cancer activity of NUC-3373 was unaffected by the presence of mycoplasma infection.

Table of Contents

NUC-3373 has greater anti-cancer activity than 5-FU. In preclinical studies, NUC-3373 was not reliant on activating enzymes, including OPRT, TP and TK, all of which are essential for activating the prodrug, 5-FU. For example, we measured the anti-cancer activity of NUC-3373 and 5-FU across a range of human tumor cell lines, including colorectal, ovarian and lung cancers. NUC-3373 had up to 330 times greater activity than 5-FU. The following figure shows the levels of NUC-3373 or 5-FU required, in various tumor cell lines, to kill half of the cancer cells, with the shorter bars representing more potent activity.



Studies in human colorectal cancer cells showed that NUC-3373 generated levels of the active anti-cancer metabolite, FUDR-MP, 366 times higher than those achieved by administering equivalent amounts of 5-FU. We believe that these increased levels of FUDR-MP could translate into the ability of NUC-3373 to kill various cancer cells at much lower doses than those of 5-FU. Moreover, in a preclinical colorectal cancer xenograft study, NUC-3373 showed a greater ability to reduce tumor weight and volume than 5-FU.

NUC-7738: A Transformation of Cordycepin

NUC-7738 is a ProTide transformation of cordycepin, a nucleoside analog that was isolated from the fungus *cordyceps militaris* in 1950. Since that time, cordycepin has not been successfully developed or approved as a chemotherapy, but has shown potent anti-cancer activity in preclinical studies conducted by other companies and research institutions. Similar to our other ProTide products, NUC-7738 is designed to generate the active anti-cancer metabolite of cordycepin directly inside cells, bypassing the resistance mechanisms of transportation, activation and breakdown. In a preclinical study, we examined the *in vitro* cytotoxic activity of NUC-7738 across a range of different human cancer cell lines, including leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, T-cell leukemia, multiple myeloma, pancreas, colon, liver and breast cancers, as compared with cordycepin. NUC-7738 was found, in 16 of the 20 cell lines examined in this study, to be more potent than cordycepin when comparing the concentrations of the respective compounds required to kill 50% of the cancer cells. In three leukemia cell lines, NUC-7738 was found to be more than 50-times more potent than cordycepin based on the method of comparison described above.

Cordycepin and its limitations

Cordycepin must be converted to its active form once inside the cancer cell. Similar to other nucleoside analogs such as gemcitabine, the rate-limiting step of activation requires the addition of a phosphate group, in

[Table of Contents](#)

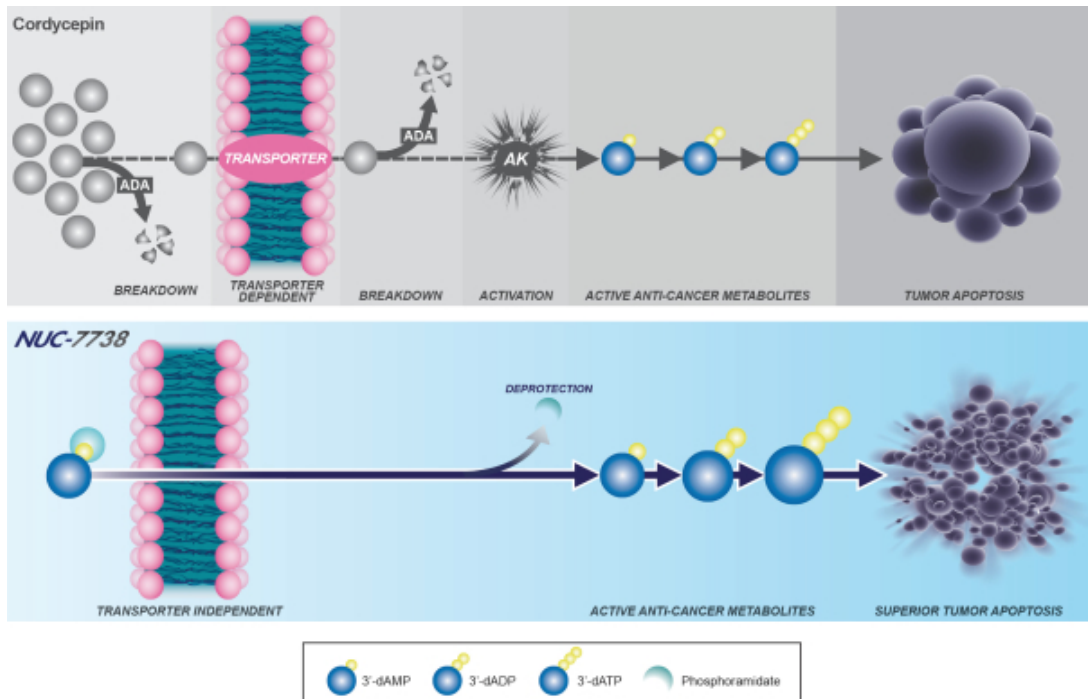
this case by an enzyme called adenosine kinase, or AK. This phosphorylated form of cordycepin is subsequently converted into its active metabolite, 3' deoxyadenosine triphosphate, or 3' dATP. This metabolite interferes with multiple pathways in cancer cells, including purine biosynthesis, RNA synthesis and growth factor signalling pathways, such as mTOR, and therefore inhibits the proliferation of cancer cells.

Until cordycepin is converted to its phosphorylated form, it is subject to breakdown by adenosine deaminase, or ADA. Because of this potential for breakdown of cordycepin by ADA, cordycepin must be administered together with inhibitors of ADA. Given the critical role of ADA in multiple human metabolic pathways, we believe the need to inhibit ADA when administering cordycepin represents a significant obstacle to the clinical development of cordycepin. Therefore, we designed NUC-7738 to generate 3' dATP inside cancer cells while avoiding breakdown by ADA and the requirement for AK.

Our Solution: NUC-7738

As a ProTide of cordycepin, NUC-7738, once inside the cancer cell, is rapidly converted into 3' dATP. There is no need for AK to act on it, a process that has been shown to be rate-limiting. There is also no breakdown by ADA. This results in significantly higher levels of 3' dATP in cells. We have observed in our preclinical studies that NUC-7738 enters into cancer cells independent of any nucleoside transporters and is converted to 3' dATP regardless of ADA or AK levels.

The metabolism of NUC-7738 compared to cordycepin as described above is illustrated in the following graphic.



We are targeting NUC-7738 for development in both solid and hematological tumors based on the broad activity seen with cordycepin in preclinical studies. We are currently evaluating NUC-7738 in preclinical toxicology studies and we expect to initiate a Phase 1 clinical trial in 2018 in patients with solid tumors, with a second Phase 1 clinical trial planned for 2019 in patients with hematological tumors.

Molecular Profiling

Healthcare professionals often use molecular-profiling tools to help choose the optimal therapy for patients with cancer. Therapeutic responses vary among patients because cancers are heterogeneous, even for tumors arising from the same site in the body. Molecular diagnostics assays that detect specific biomarkers can provide a framework to classify tumors according to their molecular signature. In turn, the cancer profile can guide the choice of therapy for a particular patient.

As part of our clinical development strategy, we are building a molecular profiling tool with the aim of identifying patients who may receive the greatest benefit from our ProTides compared with the current nucleoside analog standards of care. We are working to identify and quantify key biomarkers relevant to Acelarin and NUC-3373, as well as to assess their predictive nature with regard to treatment. In addition, such assays may become relevant to our eventual commercial and reimbursement strategy by helping to pre-identify those patients for whom existing nucleoside analogs are unlikely to provide a significant benefit due to the existence in these patients of one or more cancer-resistance mechanisms.

Manufacturing

We currently rely, and expect to continue to rely, on third-party contract manufacturing organizations, or CMOs, for the supply of clinical trial materials of Acelarin, NUC-3373, NUC-7738 and any future product candidates under the current good manufacturing practices, or cGMP, specified by the FDA. cGMP is a regulatory standard for the production of pharmaceuticals to be used in humans. In the future, we intend to also rely on our CMOs to produce sufficient commercial quantities of Acelarin, NUC-3373, NUC-7738 and any future product candidates, if approved. We source key materials from third parties, either directly from suppliers or indirectly through our CMOs. These raw materials are generally available from multiple vendors, which provides us with a robust and cost-effective supply chain.

Manufacturing of any product candidate is subject to extensive regulations that impose various procedural and documentation requirements governing recordkeeping, manufacturing processes and controls, personnel, quality control and quality assurance, among others. We expect that all of our CMOs will manufacture Acelarin, NUC-3373 and NUC-7738 under cGMP conditions and in compliance with any similar regulatory requirements outside the United States.

Competition

The development and commercialization of new drug therapies is highly competitive. While we believe that our scientific knowledge, proprietary ProTide technology and development experience provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, biotechnology and specialty pharmaceutical companies, academic institutions, governmental agencies and public and private research institutions. Any ProTide candidates that we successfully develop and commercialize will compete with existing products and new products that may become available in the future. Key product features that would affect our ability to effectively compete with other therapeutics include efficacy, safety profile, price, convenience of administration and level of promotional activity.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy, immunotherapy and targeted drug therapy. There are a variety of available drug therapies marketed for cancer, including many which are administered in combination to enhance efficacy. We believe that our product candidates, if approved, will principally face competition from other chemotherapies, immunotherapy and targeted drug therapies. In the field of chemotherapy, our competitors include companies that manufacture off-patent chemotherapies, including gemcitabine and 5-FU, as well as companies that have developed new or improved chemotherapies.

[Table of Contents](#)

In addition, our product candidates, if approved, may face competition from cancer therapies developed by other companies using phosphoramidate chemistry, as well as other approved drugs or drugs that may be approved in the future for indications for which we may develop our product candidates.

The availability of reimbursement from government and other third-party payors will also significantly affect the pricing and competitiveness of our products. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Many of the companies against which we may compete have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Intellectual Property

We actively seek to protect the intellectual property and proprietary technology that we believe is important to our business, including seeking, maintaining, enforcing and defending patent rights for our therapeutics and processes, whether developed internally or licensed from third parties. Our success will depend on our ability to obtain and maintain patent and other protection including data/market exclusivity for our product candidates and platform technology, preserve the confidentiality of our know-how and operate without infringing the valid and enforceable patents and proprietary rights of third parties. See “*Risk Factors—Risks Related to Our Intellectual Property.*”

Our policy is to seek to protect our proprietary position, generally by filing an initial priority filing at the U.K. Intellectual Property Office. This is followed by the filing of a patent application under the Patent Co-operation Treaty claiming priority from the initial application(s) and then filing applications for patent grant in territories including, for example, the United States, Europe and Japan. In each case, we determine the strategy and territories required after discussion with our patent attorneys so that we obtain relevant coverage in territories that are commercially important to us and our product candidates. We additionally rely on data exclusivity, market exclusivity and patent term extensions when available. We also rely on trade secrets and know-how relating to our underlying platform technology and product candidates. Prior to making any decision on filing any patent application, we consider with our patent attorneys whether patent protection is the most sensible strategy for protecting the invention concerned or whether the invention should be maintained as confidential.

As of September 5, 2017, we owned 176 granted patents (of which five are U.S.-issued patents) and 142 pending patent applications (of which eight are U.S. pending patent applications). Commercially or strategically important non-U.S. jurisdictions in which we hold issued or pending patent applications include: Australia, Canada, China, Eurasia (in the form of a regional patent), Europe (in the form of a regional patent), Hong Kong, Israel, Japan, South Korea, Malaysia, Mexico, Philippines, Singapore and South Africa. Not included in the patent count is one U.S. patent that is currently in reissue proceedings which were initiated by us for purposes of narrowing the claims covered by such patent.

Acelarin

We own 33 granted patents covering the composition of matter of our Acelarin product candidate which is a mixture of two diastereoisomers, both of which are therapeutically active. The patent claims are directed to the Acelarin product candidate and to a genus around that candidate. The patent has been granted in major territories, including Europe and Japan. These granted patents are expected to expire in 2024, excluding any patent term adjustments and any patent term extensions. As disclosed above, there is also one patent in the United States for Acelarin that is currently under reissue.

[Table of Contents](#)

We own 37 granted patents, as well as 46 pending patent applications, directed towards Acelarin in single diastereoisomer form. A patent claiming the more soluble single diastereoisomer of Acelarin has been granted in Europe and corresponding patent applications are pending in other major territories, including the United States and Japan. These granted patents and patents arising from the pending applications, if issued, are expected to expire in 2033 and 2035, excluding any patent term adjustments and any patent term extensions.

We own patent applications covering formulations of Acelarin (including those used in the clinical trials), methods of making Acelarin (including as a single diastereoisomer), and specific uses of Acelarin, including the use of Acelarin in combination with carboplatin. Patents arising from these pending applications have been filed in all major territories, including the United States, Europe and Japan and are expected to expire in 2035, 2036 and 2038 excluding any patent term adjustments and any patent term extensions.

NUC-3373

We own 54 granted patents and 9 pending applications covering the composition of matter of NUC-3373, a genus around NUC-3373 and specific uses of NUC-3373. Those patents were granted in major territories, including the United States, Europe and Japan. These granted patents and patents arising from the pending applications, if issued, are expected to expire in 2032, excluding any patent term adjustments and any patent term extensions.

NUC-7738

We own 19 pending applications covering the composition of matter of NUC-7738, a genus around NUC-7738 and specific uses of NUC-7738. The patent applications are pending in major territories, including the United States, Europe and Japan. Patents arising from these pending applications, if issued, are expected to expire in 2035 excluding any patent term adjustments and any patent term extensions.

Laws and Regulations Regarding Patent Terms

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent term may be shortened if a patent is terminally disclaimed over another patent or as a result of delays in patent prosecution by the patentee. A patent's term may be lengthened by a patent term adjustment, which compensates a patentee for administrative delays by the USPTO in granting a patent. The patent term of a European patent is 20 years from its effective filing date, which, unlike in the United States, is not subject to patent term adjustments in the same way as U.S. patents.

The term of a patent that covers an FDA-approved drug or biologic may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug or biologic is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other jurisdictions to extend the term of a patent that covers an approved drug, for example Supplementary Protection Certificates. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We anticipate that some of our issued patents may be eligible for patent term extensions but such extensions may not be available and therefore our commercial monopoly may be restricted.

Collaboration and License Agreements

Cardiff University License

In August 2009, we entered into a research, collaboration and license agreement with Cardiff University and University College Cardiff Consultants Ltd., or Cardiff Consultants, which we refer to as the Cardiff Agreement. Under the Cardiff Agreement, we collaborate with Cardiff University in the design, synthesis, characterization and evaluation of phosphoramidate prodrugs, which we refer to as ProTides, based on certain nucleosides. We are responsible for funding certain work performed by Cardiff University and making other payments, which we expect will total approximately £141,350 in aggregate in 2017. Cardiff University and Cardiff Consultants, which is a holder of intellectual property developed by Cardiff University, have assigned to us all rights in the results of the research under the Cardiff Agreement, and agreed not to undertake any research for any competing third party on nucleoside families of interest to us where such research would make use of ProTide-related intellectual property owned or controlled by Cardiff University as of the date of the Cardiff Agreement or which at any time thereafter becomes owned or controlled by Cardiff University, which we refer to as the Cardiff intellectual property, or to grant rights in the Cardiff intellectual property to any third party for use in connection with nucleosides of interest to us.

Upon our completion of the evaluation of the ProTides, we have the right to select one or more of the evaluated ProTides as candidates for potential development of a commercial product. Cardiff University and Cardiff Consultants have granted us an exclusive worldwide license to use for all purposes the Cardiff intellectual property in respect of the nucleoside family of our selected ProTides. The exclusive dealing obligations of Cardiff University and Cardiff Consultants will continue for these nucleoside families.

On our filing, or that of a sublicensee, of patent applications resulting from research under the Cardiff Agreement, we will owe Cardiff Consultants certain immaterial payments. If we or our sublicensees develop and commercialize a product resulting from such research, we will owe Cardiff Consultants clinical development milestone payments of up to £1,875,000; provided that such milestone payments are due only with respect to the first product within each nucleoside family to achieve the milestone. We will also owe Cardiff Consultants royalties equal to a low-single digit percentage on our sales of a product resulting from such research. Should we sublicense our right to commercialize a product resulting from the research, we will owe Cardiff Consultants a high-single digit percentage of payments received in consideration of the sublicense.

The Cardiff Agreement currently expires on December 31, 2017, although prior expiration dates have been repeatedly extended through the agreement of the parties. Upon expiration, we have the right to extend the period in which we may evaluate products for three months, and for a further three months in exchange for an additional payment. The Cardiff Agreement may also be terminated for an uncured material breach. Licenses to use the Cardiff intellectual property in the development and commercialization of products we have selected for commercialization, and related payment obligations, will survive expiration of the Cardiff Agreement, but not on termination for an uncured material breach.

Cardiff ProTides Agreement

In October 2009, we entered into a license and collaboration agreement with Cardiff ProTides Ltd., or Cardiff ProTides, which agreement was subsequently amended and restated as an assignment, license and collaboration agreement in March 2012 and was further amended in May 2012, which we refer to as the ProTides Agreement. Under the ProTides Agreement, we collaborated with Cardiff ProTides in the discovery, drug design and in vitro screening of purine and pyrimidine based nucleosides as potential drug candidates. We funded certain work at Cardiff ProTides, and Cardiff ProTides has assigned to us all rights in the results of its research under the ProTides Agreement. Cardiff ProTides also assigned to us patents related to certain compounds of interest, including with respect to Acelarin, and granted us an exclusive, worldwide license, including the right to grant sublicenses, to rights in and technical information related to certain unpatented compounds for all therapeutic, diagnostic, prognostic and prophylactic applications.

[Table of Contents](#)

If we or a sublicensee develop one or more products covered by a valid claim of an assigned patent or patent resulting from Cardiff ProTides' research, such as Acelarin, we will owe Cardiff ProTides up to approximately \$4.5 million in development and approval milestone payments in the aggregate for the first such product. Additional development and approval milestones would be payable for the first additional product in a new nucleoside series covered by a valid claim of an assigned patent or a patent resulting from Cardiff ProTides' research, although the maximum potential value of such milestone payments is approximately half the value of the milestone payments associated with the first product. We will also owe Cardiff ProTides royalties equal to a percentage in mid- to high-single digits on sales of such products, subject to reduction under certain circumstances. Royalties on sales by sublicensees are set by formula, which formula would be likely to result in a royalty in the mid-single digits.

The ProTides Agreement expires, on a country by country basis, on the later of the expiration, invalidity, abandonment, lapsing or rejection of the last valid claim of an assigned patent or patent resulting from Cardiff ProTides' research, or, if certain technical information licensed from Cardiff ProTides remains confidential or the product is covered by a period of data exclusivity, ten years from the date of first commercial sale of a product in such country. The ProTides Agreement may be sooner terminated on an uncured material breach, bankruptcy of a party or, by Cardiff ProTides, if we challenge, or assist in a challenge, of the validity or ownership of an assigned patent or patent resulting from Cardiff ProTides' research, or fail to pay amounts payable under the ProTides Agreement. It may also be sooner terminated where sums payable by us remain unpaid for 45 days after we receive a notice from Cardiff ProTides that the relevant sums are overdue. Upon a termination of the ProTides Agreement, our license rights will terminate except where the breach results from certain breaches by Cardiff ProTides, in which case our license rights continue on a non-exclusive basis, subject to reduced payment obligations. Upon termination of the ProTides Agreement, including as a result of our breach, we will be under an obligation to assign back to Cardiff ProTides the patents which Cardiff ProTides originally assigned to us.

Government Regulation and Product Approval

FDA Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending new drug applications, or NDAs, warning letters, voluntary product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Pharmaceutical product development in the United States typically involves the performance of nonclinical laboratory and animal tests, the submission to the FDA of an IND which must become effective before clinical testing may commence, and adequate, well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical and other nonclinical tests must comply with certain federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long term nonclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

[Table of Contents](#)

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations, (ii) in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors, and (iii) under protocols detailing the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The clinical trial protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board, or IRB, at each site where a clinical trial will be performed for approval. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements or it may impose other conditions.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves clinical trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance, and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 clinical trial with other confirmatory evidence may be sufficient in rare instances where the clinical trial is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and confirmation of the result in a second clinical trial would be practically or ethically impossible.

After completion of the required clinical testing, a new drug application, or NDA, is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include the results of all nonclinical, clinical, and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an NDA is substantial. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee and the manufacturer or sponsor under an approved NDA is also subject to annual product and establishment user fees. These fees are typically increased annually.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Most such applications for standard review drug products are reviewed within ten to twelve months, while most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment, or provide a treatment where no adequate therapy exists. For biologics, priority review is further limited only for

[Table of Contents](#)

drugs intended to treat a serious or life-threatening disease relative to the currently approved products. The review process for both standard and priority review may be extended by FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an advisory committee, which is typically a panel that includes clinicians and other experts, for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with current good manufacturing practice requirements, or cGMP, is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for health care professionals, and elements to assure safe and effective use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory requirements is not maintained or problems are identified following initial marketing or any time thereafter.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of certain FDA-regulated products, including prescription drugs, are required to register and disclose certain clinical trial information on a public website maintained by the U.S. National Institutes of Health. Information related to the product, patient population, phase of investigation, clinical trial sites and investigator, and other aspects of the clinical trial is made public as part of the registration. Sponsors are also obligated to disclose the results of these clinical trials after completion if the product candidate is ultimately approved, and disclosure of the results of these clinical trials will be delayed until such approval. Competitors may use this publicly-available information to gain knowledge regarding the design and progress of our development programs.

The Hatch-Waxman Act

Orange Book Listing. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant's product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths

[Table of Contents](#)

and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, nonclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as “generic equivalents” to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA’s Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA applicant may also elect to submit a section viii statement, certifying that its proposed ANDA label does not contain or carve out any language regarding the patented method-of-use, rather than certify to a listed method-of-use patent.

If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. A certification that the new product will not infringe the already approved product’s listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA applicant.

The ANDA application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Exclusivity. Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which time the FDA cannot receive any ANDA seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which the FDA cannot approval an ANDA for a generic drug that includes the change.

An ANDA may be submitted one year before NCE exclusivity expires if a Paragraph IV certification is filed. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA may be filed before the expiration of the exclusivity period.

Patent Term Extension. After NDA approval, owners of relevant drug patents may apply for up to a five-year patent term extension. The allowable patent term extension is calculated as half of the drug’s testing phase—the time between IND submission and NDA submission—and all of the review phase—the time between NDA submission and approval up to a maximum of five years. The time can be shortened if FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the PTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

Advertising and Promotion

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Changes to some of the conditions established in an approved application, including changes in indications, labeling, or certain manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Adverse Event Reporting and cGMP Compliance

Adverse event reporting and submission of periodic reports is required following FDA approval of an NDA. The FDA also may require post-marketing testing, sometimes called Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or the FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality-control, drug manufacture, packaging, and labeling procedures, among other things, must continue to conform to cGMP after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects manufacturing facilities to assess compliance with cGMP. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production, quality control and record keeping to maintain compliance with cGMP. Regulatory authorities may impose a range of enforcement actions, including bringing a seizure and injunction in court, withdraw product approvals or request a product recall if a company fails to comply with cGMP requirements.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The sponsor must submit an initial Pediatric Study Plan, or PSP, within 60 days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials or other clinical development programs. The FDA may grant full or partial waivers, or deferrals, for submission of data.

The Best Pharmaceuticals for Children Act, or BPCA, provides NDA holders a six-month extension of any exclusivity—patent or non-patent—for a drug if certain conditions are met, including satisfaction of a pediatric trial as described above. Conditions for exclusivity include the FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric clinical trials, and the applicant agreeing to perform, and reporting on, the requested clinical trials within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

Special Protocol Assessment

A company may reach an agreement with FDA under the Special Protocol Assessment, or SPA, process as to the required design and size of clinical trials intended to form the primary basis of an efficacy claim. Under the FDC Act and FDA guidance implementing the statutory requirement, an SPA is generally binding upon the FDA except in limited circumstances, such as if the FDA identifies a substantial scientific issue essential to determining safety or efficacy after the clinical trial begins, public health concerns emerge that were unrecognized at the time of the protocol assessment, the sponsor and FDA agree to the change in writing, or if the clinical trial sponsor fails to follow the protocol that was agreed upon with the FDA.

Expedited Review and Approval

The FDA has various programs, including Fast Track, priority review, accelerated approval and breakthrough designation which are intended to expedite or simplify the process for reviewing drugs or provide for approval on the basis of surrogate endpoints. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened. Generally, drugs that may be eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, or those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development, and expedite the review, of drugs to treat serious diseases and fill an unmet medical need. The request may be made at the time of IND submission and generally no later than the pre-NDA meeting. The FDA will respond within 60 calendar days of receipt of the request. Priority review, which is requested at the time of NDA submission, is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists an initial review within six months as compared to a standard review time of ten months. Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review. Accelerated approval provides an earlier approval of drugs to treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint, which is a laboratory measurement or physical sign used as an indirect or substitute measurement representing a clinically meaningful outcome. Discussions with the FDA about the feasibility of an accelerated approval typically begin early in the development of the drug in order to identify, among other things, an appropriate endpoint. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform post-marketing clinical trials to confirm the appropriateness of the surrogate marker clinical trial.

Another expedited program is that for Breakthrough Therapy. A Breakthrough Therapy designation is designed to expedite the development and review of drugs that are intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). A sponsor may request Breakthrough Therapy designation at the time that the IND is submitted, or no later than at the end-of-Phase 2 meeting. The FDA will respond to a Breakthrough Therapy designation request within 60 days of receipt of the request. A drug that receives Breakthrough Therapy designation is eligible for all fast track designation features, intensive guidance on an efficient drug development program, beginning as early as Phase 1 and commitment from the FDA involving senior managers.

Regulation of Companion Diagnostic Devices

If we decide that a diagnostic test would provide useful information for patient selection or if the FDA requires us to develop such a test, we may work with a collaborator to develop an *in vitro* diagnostic, or companion test. The FDA regulates *in vitro* diagnostic tests as medical devices, and the type of regulation to which such a test will be subjected will depend in part on a risk assessment by the FDA as well as a determination of whether the test is intended to yield results that would be helpful to know versus one that the FDA or we believe is necessary to know for the safe and effective use of our drugs under development.

[Table of Contents](#)

The FDA issued Guidance on In-Vitro Companion Diagnostic Devices in August 2014, which is intended to assist companies developing *in vitro* companion diagnostic devices and companies developing therapeutic products that depend on the use of a specific *in vitro* companion diagnostic for the safe and effective use of the product. The FDA defined an *in vitro* companion diagnostic device, or IVD companion diagnostic device, as a device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a therapeutic product will be stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product. The FDA expects that the therapeutic sponsor will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan and that, in most cases, the therapeutic product and its corresponding companion diagnostic will be developed contemporaneously.

Europe/Rest of World Government Regulation

In addition to regulations in the United States, we are and will be subject, either directly or through our distribution partners, to a variety of regulations in other jurisdictions governing, among other things, clinical trials and commercial sales and distribution of our products, if approved.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in non-U.S. countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a process that requires the submission of a clinical trial application much like an IND prior to the commencement of human clinical trials. In Europe, for example, a clinical trial authorization, or CTA, must be submitted to the competent national health authority and to independent ethics committees in each country in which a company plans to conduct clinical trials. Once the CTA is approved in accordance with a country's requirements, clinical trials may proceed in that country.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country, even though there is already some degree of legal harmonization in the E.U. member states resulting from the national implementation of underlying E.U. legislation. In all cases, the clinical trials are conducted in accordance with GCP and other applicable regulatory requirements.

To obtain regulatory approval of a new drug, or medicinal product, in the European Union a sponsor must obtain approval of a marketing authorization application, or MAA. The way in which a medicinal product can be approved in the European Union depends on the nature of the medicinal product.

The centralized procedure results in a single MAA granted by the European Commission that is valid across the European Union, as well as in Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for human drugs that are: (i) derived from biotechnology processes, such as genetic engineering, (ii) contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions and viral diseases, (iii) officially designated "orphan drugs" (drugs used for rare human diseases) and (iv) advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines. The centralized procedure may at the request of the applicant also be used for human drugs which do not fall within the above mentioned categories if the human drug (a) contains a new active substance which, on the date of entry into force of this Regulation, was not authorized in the Community; or (b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorization in the centralized procedure is in the interests of patients or animal health at European Community level.

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of a MAA by the EMA is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human

[Table of Contents](#)

Use, or CHMP), with adoption of the actual marketing authorization by the European Commission thereafter. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest from the point of view of therapeutic innovation, defined by three cumulative criteria: the seriousness of the disease to be treated; the absence of an appropriate alternative therapeutic approach, and anticipation of exceptional high therapeutic benefit. In this circumstance, EMA ensures that the evaluation for the opinion of the CHMP is completed within 150 days and the opinion issued thereafter.

The mutual recognition procedure, or MRP, for the approval of human drugs is an alternative approach to facilitate individual national marketing authorizations within the European Union. Basically, the MRP may be applied for all human drugs for which the centralized procedure is not obligatory. The MRP is applicable to the majority of conventional medicinal products, and is based on the principle of recognition of an already existing national marketing authorization by one or more member states.

The characteristic of the MRP is that the procedure builds on an already existing marketing authorization in a member state of the European Union that is used as reference in order to obtain marketing authorizations in other E.U. member states. In the MRP, a marketing authorization for a drug already exists in one or more E.U. member states and subsequently marketing authorization applications are made in other E.U. member states by referring to the initial marketing authorization. The member state in which the marketing authorization was first granted will then act as the reference member state. The member states where the marketing authorization is subsequently applied for act as concerned member states.

The MRP is based on the principle of the mutual recognition by E.U. member states of their respective national marketing authorizations. Based on a marketing authorization in the reference member state, the applicant may apply for marketing authorizations in other member states. In such case, the reference member state shall update its existing assessment report about the drug in 90 days. After the assessment is completed, copies of the report are sent to all member states, together with the approved summary of product characteristics, labeling and package leaflet. The concerned member states then have 90 days to recognize the decision of the reference member state and the summary of product characteristics, labeling and package leaflet. National marketing authorizations shall be granted within 30 days after acknowledgement of the agreement.

Should any Member State refuse to recognize the marketing authorization by the reference member state, on the grounds of potential serious risk to public health, the issue will be referred to a coordination group. Within a timeframe of 60 days, member states shall, within the coordination group, make all efforts to reach a consensus. If this fails, the procedure is submitted to an EMA scientific committee for arbitration. The opinion of this EMA Committee is then forwarded to the Commission, for the start of the decision making process. As in the centralized procedure, this process entails consulting various European Commission Directorates General and the Standing Committee on Human Medicinal Products or Veterinary Medicinal Products, as appropriate.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the other applicable regulatory requirements.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Healthcare Reform

There have been and continue to be legislative and regulatory changes to the healthcare system in the United States that could affect our future results of operations. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the ACA,

[Table of Contents](#)

includes measures that have significantly changed health care financing by both governmental and private insurers. The provisions of the ACA of importance to the pharmaceutical and biotechnology industry are, among others, the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs agents and biologic agents, which is apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, unless the drug is subject to discounts under the 340B drug discount program;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Physician Payments Sunshine Act for drug manufacturers to report information related to payments and other transfers of value made to physicians and teaching hospitals as well as ownership or investment interests held by physicians and their immediate family members;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- creation of the Independent Payment Advisory Board, which, if and when impaneled, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs; and
- establishment of a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

There have been judicial and Congressional challenges to certain aspects of the ACA, and we expect the current administration and Congress will likely continue to seek legislative and regulatory changes, including repeal and replacement of certain provisions of the ACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The U.S. House of Representatives passed legislation known as the American Health Care Act of 2017 in May 2017. More recently, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a "skinny" version of the Better Care Reconciliation Act of 2017. Each of these measures was rejected by the full Senate. Congress

[Table of Contents](#)

will likely consider other legislation to replace elements of the ACA. It is uncertain whether the American Health Care Act or similar legislation will become law or how any future healthcare reform legislation will impact our business.

In addition, other federal health reform measures have been proposed and adopted in the United States since the ACA was enacted. For example, as a result of the Budget Control Act of 2011, providers are subject to Medicare payment reductions of 2% per fiscal year through 2025 unless additional Congressional action is taken. Further, the American Taxpayer Relief Act of 2012 reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments from providers from three to five years. Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to product pricing, contain the cost of drugs, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models. The U.S. Department of Health and Human Services, or HHS, set a goal of moving 30% of Medicare payments to alternative payment models tied to the quality or value of services by 2016 and 50% of Medicare payments into these alternative payment models by the end of 2018. In March 2017, HHS announced that it has achieved its goal for 2016. In addition, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. We expect that additional U.S. federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Individual states in the United States have also become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could compromise our ability to profitably commercialize any of our product candidates, if approved. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our products or put pressure on our product pricing, which could negatively affect our business, results of operations, financial condition and prospects.

In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize any of our product candidates, if approved. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or member state level may result in significant additional requirements or obstacles that may increase our operating costs. The delivery of healthcare in the European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than European Union, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with increasing European Union and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize any products for which we obtain marketing approval. In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies.

Other Healthcare Laws

Physicians, other healthcare providers, and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Although we currently do not have any products on the market, our current and future business operations are and will be subject to various U.S. federal and state and other foreign fraud and abuse laws and other healthcare laws and regulations. These laws and regulations may impact, among other things, our arrangements with third-party payors, healthcare professionals who participate in our clinical research programs, healthcare professionals and others who purchase, recommend or prescribe our approved products, and our proposed sales, marketing, distribution, and education programs. The U.S. federal and state healthcare laws and regulations that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits persons from, among other things, knowingly and willfully soliciting, receiving, offering or paying anything of value, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federally funded healthcare programs, such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including, without limitation, the federal civil monetary penalties law and the civil False Claims Act (which can be enforced by private citizens through *qui tam* actions), prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment of federal funds, and knowingly making, or causing to be made, a false record or statement material to a false or fraudulent claim to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal liability for executing or attempting to execute a scheme to defraud any healthcare benefit program and creates federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and its implementing regulations, which imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without the appropriate authorization by entities subject to the law, such as healthcare providers, health plans, and healthcare clearinghouses and their respective business associates that perform certain functions or activities that involve the use or disclosure of protected health information on their behalf;
- the federal transparency requirements under the Physician Payments Sunshine Act, created under the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies reimbursed under Medicare, Medicaid, or CHIP to report to HHS information related to payments and other transfers of value provided to physicians and teaching hospitals and physician ownership and investment interests; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, that impose similar restrictions and may apply to items or services reimbursed by non-governmental third-party payors, including private insurers; state laws that require pharmaceutical companies to implement compliance programs, comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or to track and report gifts, compensation and other remuneration provided to physicians and other health care providers; and state health information privacy and data breach notification laws, which govern the collection, use, disclosure, and protection of health-related and other personal information, many of which differ from each other in significant ways and often are not pre-empted by HIPAA, thus complicating compliance efforts.

[Table of Contents](#)

We will be required to spend substantial time and money to ensure that our business arrangements with third parties comply with applicable healthcare laws and regulations. In the United States, healthcare reform legislation has strengthened these federal and state healthcare laws. For example, the ACA amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes to clarify that liability under these statutes does not require a person or entity to have actual knowledge of the statutes or a specific intent to violate them. Moreover, the ACA provides that the government may assert that a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of these laws can subject us to criminal, civil and administrative sanctions including monetary penalties, damages, fines, disgorgement, individual imprisonment, and exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm, and we may be required to curtail or restructure our operations. Moreover, we expect that there will continue to be federal and state laws and regulations, proposed and implemented, that could impact our future operations and business.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. Sales of any of our product candidates, if approved, will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government healthcare programs such as Medicare and Medicaid, and private payors, such as commercial health insurers and managed care organizations. Third-party payors determine which drugs they will cover and the amount of reimbursement they will provide for a covered drug. In the United States, there is no uniform system among payors for making coverage and reimbursement decisions. In addition, the process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication.

In order to secure coverage and reimbursement for our products, if approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costly studies required to obtain FDA or other comparable regulatory approvals. Even if we conduct pharmacoeconomic studies, our product candidates may not be considered medically necessary or cost-effective by payors. Further, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures, and foreign governments have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement, and requirements for substitution of generic products for branded prescription drugs. For example, in the United States, the ACA contains provisions that may reduce the profitability of products, including, for example, increased rebates for products sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. CMS may develop new payment and delivery models, such as bundled payment models. For example, HHS set a goal of moving 30% of Medicare payments to alternative payment models tied to the quality or value of services by 2016 and 50% of Medicare payments into these alternative payment models by the end of 2018. Adoption of government controls and measures, and

[Table of Contents](#)

tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for our products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. The focus on cost containment measures in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if we attain favorable coverage and reimbursement status for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Employees

As of September 18, 2017, we had 16 full-time employees. We have never had a work stoppage and none of our employees are covered by collective bargaining agreements or represented by a labor union. We believe our employee relations are good.

Facilities

Our corporate headquarters and most of our operations, are located at 3 Lochside Way, Edinburgh, EH12 9DT, United Kingdom, which has a total leasable area of 5,632 square feet. We believe that our office facilities in the United Kingdom are sufficient to meet our current needs.

Legal Proceedings

From time to time, we may be party to litigation that arises in the ordinary course of our business. We do not have any pending litigation that, separately or in the aggregate, would, in the opinion of management, have a material adverse effect on our results of operations, financial condition or cash flows.

MANAGEMENT

The following table sets forth the names, ages and positions of our executive officers and directors:

<u>Name</u>	<u>Age</u>	<u>Position</u>
<i>Executive Officers</i>		
Hugh Griffith	49	Chief Executive Officer and Director
Christopher Wood	71	Chairman and Chief Medical Officer
Donald Munoz	48	Chief Financial Officer
<i>Non-Executive Directors</i>		
Isaac Cheng	42	Non-Executive Director
James Healy	52	Non-Executive Director
Martin Mellish	60	Non-Executive Director
Rafaële Tordjman	48	Non-Executive Director

Executive Officers

Hugh Griffith is our co-founder and has served as our Chief Executive Officer and as a member of our board of directors since our operations began in March 2008. In addition, he currently serves as a non-executive director of EdixoMed Limited and MedAnnex Limited, biotech companies which he co-founded in 2009. He also serves as director of Alida Capital International, a biotech business angel syndicate that he formed in 2009. Prior to founding NuCana, Mr. Griffith was Chief Operating Officer of Bioenvision, Inc., a biopharmaceutical company, from July 2004 until December 2007, when it was acquired by Genzyme Corporation (now Sanofi). He previously served as Commercial Director of Bioenvision, Inc. from September 2002 to June 2004. Before that, Mr. Griffith held several senior commercial positions at Quantanova Limited, a biopharmaceutical company, from January 2002 to July 2002, Abbott Laboratories (now AbbVie Inc.) from October 1995 to December 2001 and Warner-Lambert Company (now Pfizer Inc.) from April 1992 to October 1995. He currently serves on the advisory board of the Scottish Lifesciences Association. Mr. Griffith received an M.B.A. from Cardiff Business School and a B.Sc. Honours in Biology from the University of Stirling. We believe that Mr. Griffith possesses specific attributes that qualify him to serve as a member of our board of directors, including the perspective and experience he brings as our Chief Executive Officer, which provides historic knowledge of our company, operational expertise and continuity to our board of directors, and his significant experience in the biopharmaceutical industry in positions including chief executive officer, chief operating officer and executive director.

Christopher Wood is our co-founder and has served as a member of our board of directors since our founding, as our Chairman since 2008 and as our Chief Medical Officer since July 2017. Dr. Wood also currently serves as chairman of several biopharmaceutical or biotechnology companies including: Edixomed Limited, MedAnnex Limited and OncoBioPharm Limited. In addition, he is a director of MiNA Therapeutics Limited, a biotechnology company. Prior to joining our board of directors, Dr. Wood was a co-founder of Bioenvision, Inc., a biopharmaceutical company, and served as its Chairman and Chief Executive Officer from 2000 until 2007, when it was acquired by Genzyme Corporation (now Sanofi). From 1995 through 1999, Dr. Wood was chairman of the board and Chief Executive of Eurobiotech, Inc. From 1989 through 1990, Dr. Wood was co-founder and director of Genethics Ltd until it was acquired by Proteus International plc. Dr. Wood co-founded and served as chairman from 1986 to 1992 of Medirace Ltd., a biotechnology company, which later became Medeva PLC and was acquired by Celltech Group PLC (now UCB). From 1979 to 1991, Dr. Wood was a surgical oncologist at The Royal Postgraduate Medical School and a consultant surgeon at Hammersmith Hospital, both in London, England. Dr. Wood is an honorary Professor at Imperial College London, a Fellow of the Royal College of Surgeons of Edinburgh and a Fellow of the Learned Society of Wales. Dr. Wood received an M.D. from the University of Wales School of Medicine. We believe that Dr. Wood possesses specific attributes that qualify him to serve as a member of our board of directors, including his extensive experience in the biotechnology sector and his having founded and managed four companies, including our company.

[Table of Contents](#)

Donald Munoz has served as our Chief Financial Officer since October 2015. Prior to joining NuCana, Mr. Munoz served as Group Chief Financial Officer of NOXXON Pharma AG (now NOXXON Pharma N.V.), a biopharmaceutical company, from September 2014 to September 2015. Before that, he was Head of Investment Banking at Summer Street Research Partners, an investment banking and institutional securities firm focused exclusively on healthcare, from August 2012 to September 2014. Mr. Munoz previously served as a Managing Director leading the medical technology investment banking franchises at Cowen and Company, LLC from 2009 to 2011 and Leerink Partners LLC from 2005 to 2009. Prior to that, he spent approximately ten years in the healthcare investment banking group at Alex. Brown & Sons and its successor, Deutsche Bank Securities. Mr. Munoz received an M.B.A. in Finance and Accounting from Columbia Business School and a B.A. from Dartmouth College.

Non-Executive Directors

Rafaèle Tordjman has served as a member of our board of directors since November 2011. From February 2017 to August 2017, Dr. Tordjman was a Special Advisor at Sofinnova Partners, an independent venture capital firm based in Paris, where she specialized in life sciences investments. She joined Sofinnova Partners in 2001 and served as a Managing Partner from January 2011 to February 2017. Dr. Tordjman currently serves as a director of ObsEva SA, a Nasdaq-listed biopharmaceutical company, and Lysogene, a Euronext-listed biotechnology company, and has previously served as a director of several biopharmaceutical or biotechnology companies, including: Ascendis Pharma A/S, DBV Technologies S.A., Medtronic CoreValve LLC and Flexion Therapeutics, Inc. Previously, Dr. Tordjman was a research scientist at the Institut National de la Santé et de la Recherche Médicale (INSERM) in Cochin Hospital, Paris, France. Before joining INSERM, Dr. Tordjman was a medical doctor specializing in clinical hematology and internal medicine. Dr. Tordjman received a Ph.D. with high honors in hematopoiesis and angiogenesis, and a post-doctoral fellowship in immunology, from the University Paris VII. Dr. Tordjman received an M.D. and fellowship in hematology and internal medicine from the Paris University Hospitals. We believe that Dr. Tordjman possesses specific attributes that qualify her to serve as a member of our board of directors, including her medical background, clinical and research experience, and industry knowledge.

James Healy has served as a member of our board of directors since March 2014. Dr. Healy has also been a General Partner of Sofinnova Ventures since 2000, and currently serves as a director of Ascendis Pharma A/S, Coherus BioSciences, Inc., Edge Therapeutics, Inc., Natera, Inc., ObsEva SA and several private companies. Dr. Healy has previously served as a board member of Amarin Corporation, Auris Medical Holding AG, Hyperion Therapeutics, Inc., InterMune, Inc., Anthera Pharmaceuticals, Inc., Durata Therapeutics, Inc., CoTherix, Inc., Movetis NV and several private companies. Prior to 2000, Dr. Healy held various positions at Sanderling Ventures, Bayer Healthcare Pharmaceuticals (as successor to Miles Laboratories) and ISTA Pharmaceuticals, Inc. Dr. Healy also currently serves on the board of directors of the U.S. National Venture Capital Association and the Biotechnology Industry Organization. Dr. Healy holds an M.D. and a Ph.D. in Immunology from Stanford University School of Medicine and a B.A. in Molecular Biology and Scandinavian Studies from the University of California, Berkeley. We believe that Dr. Healy possesses specific attributes that qualify him to serve as a member of our board of directors, including extensive experience in biomedical research, development and finance.

Isaac Cheng has served as a member of our board of directors since May 2017. Dr. Cheng is currently an investment advisor at Morningside Technology Advisory LLC, a venture capital firm, which he joined in 2006, and is also a director of Cognoa, Inc., a digital health company, and several biopharmaceutical or biotechnology companies, including: Liquidia Technologies, Inc., Artugen Therapeutics Limited, Amylyx Pharmaceuticals, Inc. and K-Gen, Inc. Previously, he was a board member of Advanced Cell Diagnostics, Inc., a biotechnology company, and a board observer of both Chimerix, Inc., a biotechnology company, and Argos Therapeutics, Inc., a biotechnology company. From 2004 to 2005, Dr. Cheng was Director of Research and Development at Serica Technologies, Inc., a Morningside portfolio company. Prior to that, Dr. Cheng was an Associate Director at

[Table of Contents](#)

Novartis Pharmaceuticals Corporation in Clinical Development and Medical Affairs. Dr. Cheng received his M.D. from Tufts University School of Medicine. We believe that Dr. Cheng possesses specific attributes that qualify him to serve as a member of our board of directors, including his medical background, clinical and research experience and industry knowledge.

Martin Mellish has served as a member of our board of directors since December 2009. Since 1994, Mr. Mellish has served as the Executive Director of Aspen Advisory Services Ltd., a London-based private investment office overseeing private and publicly traded investments in North America, Europe and Asia. Mr. Mellish also currently serves as a non-executive director of Kensington Green (Management) Limited, a real estate management company, Levitronix Technologies LLC, a technology company, Alturki Holding, an industrial investment and development holding company, Livercyte Limited, a biotechnology company, and Omnicyte Limited, a biotechnology company. From 1992 to 1994, Mr. Mellish pursued studies at the Massachusetts Institute of Technology. From 1984 to 1992, he was controller and subsequently Chief Financial Officer of Alturki Holding. Prior to that, Mr. Mellish trained at Price Waterhouse Coopers. He was awarded an SM (Management) from the Massachusetts Institute of Technology and an M.Sc. (Accounting) from Northeastern University. We believe that Mr. Mellish possesses specific attributes that qualify him to serve as a member of our board of directors, including his significant experience in accounting and finance.

Foreign Private Issuer Exemption

As a “foreign private issuer,” as defined by the SEC, although we are permitted to follow certain corporate governance practices of England and Wales, instead of those otherwise required under The Nasdaq Stock Market, or Nasdaq, for domestic issuers, we intend to follow the Nasdaq corporate governance rules applicable to foreign private issuers. While we voluntarily follow most Nasdaq corporate governance rules, we intend to take advantage of the following limited exemptions:

- Exemption from filing quarterly reports on Form 10-Q or provide current reports on Form 8-K disclosing significant events within four days of their occurrence.
- Exemption from Section 16 rules regarding sales of ordinary shares by insiders, which will provide less data in this regard than shareholders of U.S. companies that are subject to the Exchange Act.
- Exemption from the Nasdaq rules applicable to domestic issuers requiring disclosure within four business days of any determination to grant a waiver of the code of business conduct and ethics to directors and officers. Although we will require board approval of any such waiver, we may choose not to disclose the waiver in the manner set forth in the Nasdaq rules, as permitted by the foreign private issuer exemption.
- Exemption from the requirements that director nominees are selected, or recommended for selection by our board of directors, either by (1) independent directors constituting a majority of our board of directors’ independent directors in a vote in which only independent directors participate, or (2) a committee comprised solely of independent directors, and that a formal written charter or board resolution, as applicable, addressing the nominations process is adopted.

Furthermore, Nasdaq Rule 5615(a)(3) provides that a foreign private issuer, such as us, may rely on home country corporate governance practices in lieu of certain of the rules in the Nasdaq Rule 5600 Series and Rule 5250(d), provided that we nevertheless comply with Nasdaq’s Notification of Noncompliance requirement (Rule 5625), the Voting Rights requirement (Rule 5640) and that we have an audit committee that satisfies Rule 5605(c)(3), consisting of committee members that meet the independence requirements of Rule 5605(c)(2)(A)(ii). Although we are permitted to follow certain corporate governance rules that conform to U.K. requirements in lieu of many of the Nasdaq corporate governance rules, we intend to comply with the Nasdaq corporate governance rules applicable to foreign private issuers as set forth in the prior sentence. Accordingly, our shareholders will not have the same protections afforded to stockholders of companies that are subject to all of the corporate governance requirements of Nasdaq. We may utilize these exemptions for as long as we continue to qualify as a foreign private issuer.

Board Composition and Director Independence

Our business affairs are managed under the direction of our board of directors, which is currently composed of six members. Under the rules and regulations of Nasdaq a director will qualify as “independent” if our board of directors affirmatively determines that he or she has no material relationship with us (either directly or as a partner, stockholder or officer of an organization that has a relationship with us). Our board of directors will establish guidelines to assist it in determining whether a director has such a material relationship. Ownership of a significant amount of our shares, by itself, does not constitute a material relationship.

Pursuant to Nasdaq rules, a director employed by us cannot be deemed to be an “independent director,” and consequently Mr. Griffith and Dr. Wood do not qualify as independent directors.

Our board of directors has reviewed the materiality of any relationship that each of our directors has with us, either directly or indirectly. Based on this review, our board of directors has determined that the following directors are “independent directors” as defined by the applicable rules and regulations of Nasdaq: Rafaèle Tordjman, James Healy, Isaac Cheng and Martin Mellish.

Committees of the Board of Directors and Corporate Governance

Subject to certain exceptions, the rules of the Nasdaq permit a foreign private issuer to follow its home country practice in lieu of the listing requirements of Nasdaq.

The committees of our board of directors will consist of an audit committee, a remuneration committee and a nominations committee. As permitted by home country practice, our remuneration and nominations committees may include non-independent directors. Each of these committees has the responsibilities described below. Our board of directors may also establish other committees from time to time to assist in the discharge of its responsibilities.

Audit Committee

Immediately upon completion of the offering, the members of our audit committee will be three of our non-executive directors, Martin Mellish, James Healy and Isaac Cheng, and each of these members is an “independent director” as such term is defined in Rule 10A-3 under the Exchange Act. Martin Mellish will serve as chair of the audit committee. Our board of directors has determined that Martin Mellish is a financial expert as contemplated by the rules of the SEC implementing Section 407 of the Sarbanes Oxley Act of 2002. Our audit committee will meet at least four times per year and oversee the monitoring of our internal controls, accounting policies and financial reporting and provide a forum through which our external auditors and independent registered public accounting firm reports. Our audit committee will meet at least once a year with the external auditors and our independent registered public accounting firm without executive board members present. The audit committee will also be responsible for overseeing the activities of the external auditors and our independent registered public accounting firm, including their appointment, reappointment, or removal as well as monitoring their objectivity and independence. The audit committee will also review and approve the fees paid to our external auditors and independent registered public accounting firm and determine whether the fee levels for non-audit services, individually and in aggregate, relative to the audit fee are appropriate so as not to undermine their independence.

Remuneration Committee

Immediately upon the completion of this offering, the members of the remuneration committee will be Hugh Griffith and two of our non-executive directors, Rafaèle Tordjman and James Healy. Each of these non-executive director members is a non-employee director as defined in Rule 166-3 under the Exchange Act and an outside director as defined in Section 162(m) of the Internal Revenue Code of 1986, as amended. Rafaèle Tordjman will serve as chair of the remuneration committee. Our remuneration committee will review, among other things, the performance of the executive officers and sets the scale and structure of their remuneration and the basis of their

[Table of Contents](#)

service agreements with due regard to the interests of the shareholders. It will be a policy of the remuneration committee that no individual participates in discussions or decisions concerning his or her own remuneration.

Nominations Committee

Immediately upon completion of this offering, the members of the nominations committee will be Hugh Griffith and Christopher Wood and one of our non-executive directors, Rafaèle Tordjman. Hugh Griffith will serve as chair of the nominations committee and oversee the evaluation of the board of directors' performance. The nominations committee will meet at least twice a year and review the structure, size and composition of the board of directors, supervise the selection and appointment process of directors, making recommendations to the board of directors with regard to any changes and using an external search consultancy if considered appropriate. For new appointments, the nominations committee will make a final recommendation to the board of directors, and the board of directors will have the opportunity to meet the candidate prior to approving the appointment. Once appointed, the nominations committee will oversee the induction of new directors and provide the appropriate training to the board of directors during the course of the year in order to ensure that they have the knowledge and skills necessary to operate effectively. The nominations committee will also be responsible for annually evaluating the performance of the board of directors, both on an individual basis and for the board of directors as a whole, taking into account such factors as attendance record, contribution during board of directors meetings and the amount of time that has been dedicated to board matters during the course of the year.

Code of Business Conduct and Ethics

Upon the completion of this offering, we will adopt a Code of Business Conduct and Ethics that will cover a broad range of matters including the handling of conflicts of interest, compliance issues and other corporate policies such as equal opportunity and non-discrimination standards.

Compensation

The following discussion provides the amount of compensation paid, and benefits in kind granted, by us and our subsidiaries to our directors and members of management for services in all capacities to us and our subsidiaries for the year ended December 31, 2016, as well as the amount contributed by us or our subsidiaries into money purchase plans for the year ended December 31, 2016 to provide pension, retirement or similar benefits to, our directors and members of the executive management board.

Directors' and Executive Officers' Compensation

For the year ended December 31, 2016, we paid an aggregate of £1.3 million in cash and benefits to our executive officers and directors.

Bonus Plans

The summary set forth below describes the bonus plan pursuant to which compensation was paid to our executive officers and directors for the year ended December 31, 2016.

Our executive officers and directors are eligible for an annual bonus at the discretion of the Remuneration Committee. Bonus awards are reviewed at the end of each calendar year and any such awards are determined by the performance of the individual and our company as a whole based upon the achievement of strategic objectives set at the beginning of the year.

Outstanding Equity Awards, Grants and Option Exercises

During the year ended December 31, 2016, options to purchase 366,440 ordinary shares were awarded to our executive officers and directors. As of December 31, 2016, our executive officers and directors held options

[Table of Contents](#)

to purchase 2,655,687 ordinary shares. Our executive officers and directors exercised options to purchase 45,750 ordinary shares during the year ended December 31, 2016.

We periodically grant share options to employees, directors and consultants to enable them to share in our successes and to reinforce a corporate culture that aligns their interests with that of our shareholders. From December 31, 2014 through August 31, 2017, we have granted options to purchase 389,690 ordinary shares to our executive officers and directors. Subsequent to August 31, 2017, we have granted options to purchase 1,074,283 ordinary shares to our executive officers and directors and we have approved for grant, as of and in connection with this offering, options to purchase 178,282 ordinary shares to our executive officers and directors. From December 31, 2014 through August 31, 2017, we have granted options to purchase 191,250 ordinary shares to 12 employees and consultants who are not directors or executive officers. Of these, options to purchase 50,000 shares were cancelled in 2016. Subsequent to August 31, 2017, we have granted options to purchase 187,500 ordinary shares to five employees who are not executive officers or directors and we have approved for grant, as of and in connection with this offering, options to purchase 37,500 ordinary shares to one employee who is not an executive officer or director.

Pension, Retirement and Similar Benefits

For the year ended December 31, 2016, we and our subsidiaries contributed a total of £33,722 into money purchase plans to provide pension, retirement or similar benefits to our executive officers and directors.

Insurance and Indemnification

To the extent permitted by the Companies Act 2006, we are permitted to indemnify our directors against any liability they incur by reason of their directorship. We maintain directors' and officers' insurance to insure such persons against certain liabilities. In connection with this offering, we expect to enter into a deed of indemnity with each of our directors and executive officers prior to completion of this offering.

Insofar as indemnification of liabilities arising under the Securities Act may be permitted to our directors, executive officers or persons controlling us pursuant to the foregoing provisions, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Equity Compensation Plans

We have granted options to purchase our shares under three share option schemes, which are summarized in this section.

2009 Share Option Scheme

On August 1, 2009, we adopted a share option scheme, or the 2009 Share Option Scheme, for the purpose of enabling the grant of share options to incentivize our employees, consultants and directors and those employees, consultants and directors of our subsidiary companies. The 2009 Share Option Scheme was subsequently amended and approved by our board of directors and by our shareholders on November 15, 2011 and November 17, 2011, respectively.

The 2009 Share Option Scheme permits grants of (i) enterprise management incentive options which are potentially tax-advantaged in the United Kingdom under the terms of Schedule 5 to the United Kingdom Income Tax (Earnings and Pensions) Act 2003 (subject to the relevant conditions being met by the company and the grantee) and (ii) "unapproved" options (which do not attract tax advantages as they have not been "approved" by the U.K. tax authority, HMRC).

[Table of Contents](#)

As of August 31, 2017, we had granted options to purchase 1,032,500 ordinary shares to directors, employees and consultants under the 2009 Share Option Scheme. 7,500 of these options lapsed in 2017. The remainder of these options have vested and are exercisable.

Class of Share. An option granted under the 2009 Share Option Scheme entitles the option holder, subject to the satisfaction, waiver or acceleration of specific exercise conditions, to subscribe for ordinary shares.

Exercise Conditions. Options granted under our 2009 Share Option Scheme may be granted subject to vesting schedules, performance targets or other conditions which must be satisfied or waived before exercise. Exercise conditions may be removed or varied by our board of directors, provided that any variation shall be (in the reasonable opinion of our board of directors) no more difficult to satisfy than the original exercise condition.

Each option grant is documented through an option agreement. Most of the option agreements entered into under the 2009 Share Option Scheme provide that all unexercised options are exercisable upon one or more of the following events: (i) the admission of part of or the entirety of issued share capital (or of any holding company) to listing on the Official List of the U.K. Listing Authority and to trading on the market for listed securities of London Stock Exchange plc, or to trading on AIM, a market of the London Stock Exchange, or to trading on any recognized investment exchange (as that term was defined in Section 841 of Income and Corporate Taxes Act 1988, or ICTA, and as now contained in Section 1137 of the Corporation Tax Act 2010, or CTA); (ii) a change of control; or (iii) a sale of our company.

Takeovers and Corporate Events. If (a) any person or group of persons acting in concert obtains control (as defined in section 840 of ICTA and as now contained in section 995 Income Tax Act, or ITA) of the company, as a result of making either (i) an offer to acquire shares amounting to more than 50% of the issued share capital of the company on a condition such that if it is satisfied the person or group of persons will have control of the company, or (ii) a general offer to acquire all of the issued share capital of the company (or all of the ordinary shares of the company in issue); or (b) any person becomes entitled or bound to acquire shares in the company under sections 428 to 430F of the Companies Act 1985 (since repealed and replaced by sections 974 to 991 of the Companies Act 2006); or (c) under section 425 of the Companies Act 1985 (since repealed and replaced by sections 895 to 901 of the Companies Act 2006) the courts of England and Wales sanction a compromise or arrangement proposed for the purpose of or in connection with a scheme for the reconstruction of the company or its amalgamation with any other company or companies, and, in each case an option holder's option agreement expressly so provides, an option holder may at any time exercise his or her options or any part thereof which has not lapsed within a specified period. To the extent they are not exercised, such options will lapse at the end of the specified period for exercise.

Lapse of Options. If not otherwise lapsed in accordance with the provisions of the 2009 Share Option Scheme, an option granted under the 2009 Share Option Scheme shall lapse at 5p.m. on the day before the 10th anniversary of the grant of the option.

If an option holder dies, his or her personal representatives may exercise his or her options within a period ending on the earlier of (i) the expiry of 12 months after the date of death, and (ii) 5 p.m. on the day before the 10th anniversary of the grant of the option, only to the extent that any exercise conditions have been met at the time of death. Failing such exercise the deceased option holder's options shall lapse.

Adjustment of Awards. In the event that there is any variation in our share capital that affects the value of the options, our board of directors will make such adjustments to the number and exercise price of shares subject to each option or the option price as our board of directors considers appropriate in accordance with the rules of the 2009 Share Option Scheme.

Transferability. No options under the 2009 Share Option Scheme may be transferred, assigned or have any created over them and will lapse immediately upon an attempt to do so.

[Table of Contents](#)

Amendment. Our board of directors may, with the approval of the shareholders of the company at a general meeting, amend the 2009 Share Option Scheme, provided that any amendment shall not, without the consent of an option holder, materially increase his or her liabilities or materially decrease the value of his or her subsisting rights under an outstanding option.

With effect from closing of this offering, the rules of the 2009 Share Option Scheme shall be amended such that any amendment to the scheme shall take effect without the requirement for the prior approval of our shareholders, except as otherwise required by applicable laws or the rules of any securities exchange on which our securities are listed.

2012 Share Option Scheme

On July 3, 2012, we adopted a share option scheme, or the 2012 Share Option Scheme, for the purpose of enabling the grant of share options to incentivize our employees and directors and those employees and directors of our subsidiary companies.

The 2012 Share Option Scheme permits grants of (i) enterprise management incentive options, which are potentially tax advantaged in the United Kingdom, and (ii) “unapproved” options, which do not attract tax advantages as they have not been “approved” by HMRC.

As of August 31, 2017, we had granted options to purchase 1,908,935 ordinary shares to directors and employees under the 2012 Share Option Scheme. Of these, options to purchase 105,188 shares have been cancelled and options to purchase 37,500 shares were exercised in 2016. The remaining options to purchase 1,766,247 shares have vested and are exercisable.

Class of Share. An option granted under the 2012 Share Option Scheme entitles the option holder, subject to the satisfaction, waiver or acceleration of specific exercise conditions, to subscribe for ordinary shares.

Exercise Conditions. Options granted under our 2012 Share Option Scheme may be granted subject to vesting schedules, performance targets or other conditions which must be satisfied or waived before exercise. Exercise conditions may be removed or varied by our board of directors, provided that any variation shall be (in the reasonable opinion of our board of directors) no more difficult to satisfy than the original exercise condition. Each option grant is documented through an option agreement.

Leaver Provisions. Absent summary dismissal with just cause, options will be retained by an option holder once they have ceased to be an employee or director of us or a subsidiary. Where an option holder has been summarily dismissed for cause, such option holder’s unexercised options shall immediately cease to be exercisable and shall lapse after 90 days unless our board of directors determines within such 90 day period that the option holder may exercise all or part of his options within a specified period.

Lapse of Options. If not otherwise lapsed in accordance with the provisions of the 2012 Share Option Scheme, an option granted under the 2012 Share Option Scheme shall lapse at 5 p.m. on the day before the 10th anniversary of the grant of the option.

If an option holder dies, his personal representatives may exercise his options within a period ending on the earlier of (i) the expiry of 12 months after the date of death, and (ii) 5 p.m. on the day before the 10th anniversary of the grant of the option, only to the extent that any exercise conditions have been met at the time of death. Failing such exercise the deceased option holder’s options shall lapse.

Takeovers and Corporate Events. If (a) any person or group of persons acting in concert obtains control (as defined in section 840 of ICTA and as now contained in section 995 of ITA) of the company, as a result of making either (i) an offer to acquire shares amounting to more than 50% of the issued share capital of the

[Table of Contents](#)

company on a condition such that if it is satisfied the person or group of persons will have control of the company, or (ii) a general offer to acquire all of the issued share capital of the company (or all of the ordinary shares of the company in issue); or (b) any person becomes entitled or bound to acquire shares in the company under sections 428 to 430F of the Companies Act 1985 (since repealed and replaced by sections 974 to 991 of the Companies Act 2006); or (c) under section 425 of the Companies Act 1985 (since repealed and replaced by sections 895 to 901 of the Companies Act 2006) the courts of England and Wales sanction a compromise or arrangement proposed for the purpose of or in connection with a scheme for the reconstruction of the company or its amalgamation with any other company or companies, and, in each case an option holder's option agreement expressly so provides, an option holder may at any time exercise his or her options or any part thereof which has not lapsed within a specified period. To the extent they are not exercised, such options will lapse at the end of the specified period for exercise.

Adjustment of Awards. In the event that there is any variation in our share capital that affects the value of the options, our board of directors will make such adjustments to the number and exercise price of shares subject to each option or the option price as our board of directors considers appropriate in accordance with the rules of the 2012 Share Option Scheme.

Transferability. No options under the 2012 Share Option Scheme may be transferred, assigned or have any charge created over them and will lapse immediately upon an attempt to do so.

Amendment. Our board of directors may, with the approval of the shareholders of the company at a general meeting, amend the 2012 Share Option Scheme, provided that any amendment shall not, without the consent of an option holder, materially increase his or her liabilities or materially decrease the value of his or her subsisting rights under an outstanding option.

With effect from closing of this offering, the rules of the 2012 Share Option Scheme shall be amended such that any amendment to the scheme shall take effect without the requirement for the prior approval of our shareholders, except as otherwise required by applicable laws or the rules of any securities exchange on which our securities are listed.

2016 Share Option Scheme

On January 14, 2016 we adopted a share option scheme, or the 2016 Share Option Scheme, for the purpose of enabling the grant of share options to incentivize our employees and directors and those employees and directors of our subsidiary companies. The 2016 Share Option Scheme incorporates a sub-plan for option holders subject to taxation in the United States, or the 2016 U.S. Sub-Plan.

The 2016 Share Option Scheme permits grants of (i) enterprise management incentive options, (ii) "unapproved" options, and (iii) incentive stock options and non-qualified stock options under the 2016 U.S. Sub-Plan.

As of August 31, 2017, we had granted options to purchase 518,440 ordinary shares to directors and employees under the 2016 Share Option Scheme. Of these, options to purchase 45,750 shares were exercised in 2016 and options to purchase 30,000 shares were exercised in 2017.

Class of Share. An option granted under the 2016 Share Option Scheme entitles the option holder, subject to the satisfaction, waiver or acceleration of specific exercise conditions, to subscribe for ordinary shares.

Exercise Conditions. Options granted under our 2016 Share Option Scheme may be granted subject to vesting schedules, performance targets or other conditions which must be satisfied or waived before exercise. Exercise conditions may be removed or varied by our board of directors, provided that any variation shall be (in the reasonable opinion of our board of directors) no more difficult to satisfy than the original exercise condition.

Table of Contents

Each option grant is documented through an option agreement. Most of option agreements entered into under the 2016 Share Option Scheme provide that all unvested options shall immediately vest if, following one of the Takeover and Corporate Events listed below, the option holder (i) remains an eligible employee for the purpose of the plan; and (ii) has experienced a material reduction in base compensation that was payable as at the date of grant or has otherwise experienced a material change or reduction in authority, duties, reporting or responsibilities.

Leaver Provisions. If an option holder ceases to be an employee or director of the company or a subsidiary for a variety of specified reasons (including ill health, retirement, sale of a subsidiary company or part of the business to a third party, or if his employment/directorship ceases for any reason part from summary dismissal from fraud or gross misconduct) then the option holder may exercise his options during the 12 months after the date of such cessation of employment/directorship only to the extent that any exercise conditions have been met at the time of such cessation of employment/directorship. Any part of an option in respect of which the relevant exercise conditions have not been met at the point at which the option holder ceases his employment/directorship shall lapse.

Lapse of Options. If not otherwise lapsed in accordance with the provisions of the 2016 Share Option Scheme, an option granted under the 2016 Share Option Scheme shall lapse at 5 p.m. on the day before the 10th anniversary of the grant of the option.

If an option holder dies, his personal representatives may exercise his options within a period ending on the earlier of (i) the expiry of 12 months after the date of death, and (ii) 5 p.m. on the day before the 10th anniversary of the grant of the option, only to the extent that any exercise conditions have been met at the time of death. Failing such exercise the deceased option holder's options shall lapse.

Takeovers and Corporate Events. If (a) any person or group of persons acting in concert obtains control (as defined in section 840 of ICTA and as now contained in section 995 of ITA) of the company, as a result of making either (i) an offer to acquire shares amounting to more than 50% of the issued share capital of the company on a condition such that if it is satisfied the person or group of persons will have control of the company, or (ii) a general offer to acquire all of the issued share capital of the company (or all of the ordinary shares of the company in issue); or (b) any person becomes entitled or bound to acquire shares in the company under sections 974 to 991 of the Companies Act 2006; or (c) under sections 895 to 901 of the Companies Act 2006 the courts of England and Wales sanction a compromise or arrangement proposed for the purpose of or in connection with a scheme for the reconstruction of the company or its amalgamation with any other company or companies, and, in each case an option holder's option agreement expressly so provides, an option holder may at any time exercise his or her options or any part thereof which has not lapsed within a specified period. To the extent they are not exercised, such options will lapse at the end of the specified period for exercise.

Adjustment of Awards. In the event that there is any variation in our share capital that affects the value of the options, our board of directors will make such adjustments to the number and exercise price of shares subject to each option or the option price as our board of directors considers appropriate in accordance with the rules of the 2016 Share Option Scheme.

Transferability. No options under the 2016 Share Option Scheme may be transferred, assigned or have any charge created over them and will lapse immediately upon an attempt to do so.

Amendment. Our board of directors may, with the approval of the shareholders of the company at a general meeting, amend the 2016 Share Option Scheme, provided that any amendment shall not, without the consent of an option holder, materially increase his or her liabilities or materially decrease the value of his or her subsisting rights under an outstanding option.

With effect from closing of this offering, the rules of the 2016 Share Option Scheme shall be amended such that any amendment to the scheme shall take effect without the requirement for the prior approval of our

shareholders, except as otherwise required by applicable laws or the rules of any securities exchange on which our securities are listed.

2016 U.S. Sub-Plan

The 2016 U.S. Sub-Plan applies to grantees that are subject to U.S. federal income tax. The 2016 U.S. Sub-Plan provides that options granted to the U.S. grantees will either be incentive stock options pursuant to Section 422 of the Internal Revenue Code or nonqualified stock options. Options, other than certain incentive stock options described below, must have an exercise price not less than 100% of the fair market value of an underlying share on the date of grant. Incentive stock options that are not exercised within 10 years from the grant date expire, provided that incentive stock options granted to a person holding more than 10% of our voting power will expire within five years from the date of the grant date and must have an exercise price at least equal to 110% of the fair market value of an underlying share on the date of grant. The number of shares available under the 2016 Share Option Scheme for grants of incentive stock options shall not exceed 5,008,284 ordinary shares, subject to any applicable adjustment pursuant to the 2016 Share Option Scheme due to a variation of capital. With respect to grantees that are subject to U.S. federal income tax, the 2016 Share Option Scheme, the 2016 U.S. Sub-Plan and all options issued thereunder are intended to comply with, or be exempt from, Section 409A of the Internal Revenue Code, and they are to be interpreted accordingly. In the event that any option is subject to Section 409A of the Internal Revenue Code, our board of directors or our general counsel may, in their sole discretion, amend the 2016 Share Option Scheme, the 2016 U.S. Sub-Plan and any option issued thereunder, adopt policies and procedures or take such other actions as our board of directors or our general counsel deem appropriate, to exempt the 2016 Share Option Scheme, the 2016 U.S. Sub-Plan or any option from Section 409A of the Internal Revenue Code, preserve the intended tax treatment of such option or comply with the requirements of Section 409A of the Internal Revenue Code.

Employee Benefit Trust

On December 19, 2011, we established a discretionary employee benefit trust under the terms of a trust deed, or the Employee Benefit Trust, to operate in conjunction with our share option schemes. The beneficiaries of the Employee Benefit Trust are our employees and former employees (including executive directors) and their spouses, civil partners, surviving spouses and civil partners, children and step-children under the age of 18. The trustee of the Employee Benefit Trust is NuCana BioMed Trustee Company Limited, or the Trustee, our wholly owned subsidiary. As of August 31, 2017, the Trustee holds 500,000 of our ordinary shares in trust under the terms of the trust deed, which, pursuant to the terms of our three option schemes, and at the election of the Trustee, may be used to satisfy awards under our share option schemes. Under the terms of the trust deed, unless we direct otherwise, the Trustee must abstain from voting at a general meeting any of our shares held in the trust fund for which the Trustee holds the whole of the beneficial interest.

RELATED PARTY TRANSACTIONS

The following is a description of related party transactions we have entered into since January 1, 2014 with any members of our board of directors or executive officers or the holders of more than 5% of our share capital.

Participation in this Offering

Certain of our existing shareholders have agreed to purchase an aggregate of 933,332 ADSs in this offering at the initial public offering price. The underwriters will receive the same underwriting discount on any securities purchased by these investors as they will on any other securities sold to the public in this offering.

Series B Share Placement

In March 2014, we issued an aggregate of 8,462,500 series B convertible participating shares, or Series B Shares, to new and existing institutional and other investors at a price of £4.00 per share for an aggregate subscription price of £33.85 million, or the Series B Placement.

The following table sets forth the aggregate number of our Series B Shares issued to our 5% or greater shareholders and their affiliates and one of our former executive officers in the Series B Placement.

<u>Participants(1)</u>	<u>Series B Shares</u>
Sofinnova Capital VI FCPR (2)	2,500,000
Sofinnova Venture Partners VIII, L.P. (3)	4,000,000
Morningside Venture Investments Limited (4)	1,800,000
Scottish Enterprise	125,000
Christopher McGuigan (5)	37,500

(1) For further information, see “Principal Shareholders.”

(2) Rafaèle Tordjman, a member of our board of directors, was a Managing Partner at Sofinnova Partners SAS, the management company of Sofinnova Capital VI FCPR, at the time of the Series B Placement.

(3) James Healy, a member of our board of directors, is a managing member of Sofinnova Management VIII, L.L.C., the general partner of Sofinnova Venture Partners VIII, L.P.

(4) Isaac Cheng is a member of our board of directors who has been designated by Morningside Venture Investments Limited.

(5) Christopher McGuigan was our Chief Scientific Officer at the time of the Series B Placement.

Shareholders’ Agreement and Registration Rights

In connection with the Series B Placement, we entered into a shareholders’ agreement with all of our then-existing shareholders, including certain of our directors and executive officers, on March 31, 2014, or the 2014 Shareholders’ Agreement. Among other things, the 2014 Shareholders’ Agreement provided piggyback registration rights to certain of our then-existing shareholders. The 2014 Shareholders’ Agreement will terminate upon the completion of this offering. We have entered into a registration rights agreement to be effective upon the completion of this offering and pursuant to which we have agreed under specified circumstances to file a registration statement to register the resale of the ordinary shares (which may be converted into ADSs) held by some of our existing shareholders, as well as to cooperate in specified public offerings of such shares. See “Description of Share Capital – Registration Rights”.

Management Rights Letter

In connection with the Series B Placement, we entered into a management rights letter with Sofinnova Venture Partners VIII, L.P., or Sofinnova Ventures, on March 31, 2014, which holds more than 5% of our Series B Shares, pursuant to which Sofinnova Ventures is entitled to consult and advise our management on significant business. The management rights letter will terminate upon the completion of this offering.

[Table of Contents](#)

Agreements with Our Executive Officers and Directors

We have entered into service agreements with our three executive officers.

Related Person Transaction Policy

Prior to the completion of this offering, we intend to adopt a related person transaction policy requiring that all related person transactions required to be disclosed by a foreign private issuer pursuant to the Exchange Act be approved by the audit committee or another independent body of our board of directors.

Indemnification Agreements

In connection with this offering, we expect to enter into deeds of indemnity with each of our directors and executive officers. See “Management — Compensation — Insurance and Indemnification.”

PRINCIPAL SHAREHOLDERS

The following table and related footnotes set forth information with respect to the beneficial ownership of our ordinary shares as of September 15, 2017 and as of the consummation of this offering, in each case, giving effect to the automatic conversion, immediately prior to the completion of this offering, of all of our outstanding series A convertible participating shares, series B convertible participating shares, founder ordinary 1 shares and founder ordinary 2 shares into ordinary shares, by:

- each of our executive officers and directors;
- each person beneficially owning more than 5% of our share capital as of September 15, 2017; and
- all executive officers and directors as a group.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC. In computing the number of ordinary shares owned by a person and the percentage ownership of that person, we have included shares that the person has the right to acquire within 60 days from September 15, 2017, including through the exercise of any option, warrant or other right or the conversion of any other security. These ordinary shares, however, are not included in the computation of the percentage ownership of any other person except with respect to the percentage ownership of all board members and executive officers, as a group. Ownership of our ordinary shares by the “principal shareholders” identified below has been determined by reference to our share register, which provides us with information regarding the registered holders of our ordinary shares but generally provides limited, or no, information regarding the ultimate beneficial owners of such ordinary shares. As a result, we may not be aware of each person or group of affiliated persons who beneficially owns more than 5% of our ordinary shares. Based on our share register and other information made available to us by certain of our shareholders, as of September 15, 2017, 4,790,480 ordinary shares, representing 19.8% of our issued and outstanding ordinary shares, were held by four U.S. record holders.

This table assumes no exercise of the underwriters’ over-allotment option to purchase additional ADSs.

Unless otherwise indicated, the address for each of the shareholders in the table below is c/o NuCana plc, 3 Lochside Way, Edinburgh, EH12 9DT, United Kingdom.

Certain of our existing shareholders have agreed to purchase an aggregate of 933,332 ADSs in this offering at the initial public offering price. The following table does not reflect any potential purchases by these investors or their affiliated entities.

Table of Contents

<u>Name of Beneficial Owner</u>	<u>Ordinary Shares Beneficially Owned(1)</u>	<u>Percentage of Ordinary Shares Beneficially Owned</u>	
		<u>Before the Offering</u>	<u>After the Offering</u>
Greater than 5% Shareholders			
Sofinnova Capital VI FCPR(2)	7,833,334	32.35%	25.37%
Sofinnova Venture Partners VIII, L.P.(3)	4,000,000	16.52	12.95
Morningside Venture Investments Limited(4)	2,911,111	12.02	9.43
Scottish Enterprise(5)	2,246,915	9.28	7.27
Named Executive Officers and Directors			
Hugh Griffith(6)	3,403,531	12.79	10.23
Christopher Wood(7)	1,949,374	7.75	6.13
Donald Munoz(8)	135,345	*	*
Rafaèle Tordjman	—	—	—
James Healy(9)	4,045,750	16.71	13.10
Isaac Cheng(10)	—	—	—
Martin Mellish(11)	28,312	*	*
All of our current executive officers and directors, as a group (7 persons)	9,562,312	34.53%	27.83%

* Indicates beneficial ownership of less than one percent of our ordinary shares.

- (1) Number of shares owned as shown both in this table and the accompanying footnotes and percentage ownership before the offering is based on 24,214,641 ordinary shares outstanding on September 15, 2017, which gives effect to the automatic conversion of all of the 1,000,000 founder ordinary 1 shares, 1,000,000 founder ordinary 2 shares, 7,483,334 series A convertible participating shares preferred shares and 8,462,500 series B convertible participating shares outstanding into ordinary shares on a one-for-one basis.
- (2) All shares are held by Sofinnova Capital VI FCPR (“Sofinnova Capital”). Sofinnova Partners SAS, a French corporation, is the management company of Sofinnova Capital, and may be deemed to have sole voting and investment power with respect to the shares held by Sofinnova Capital. Denis Lucquin, Antoine Papiernik, Monique Saulnier and Graziano Seghezzi are the managing partners of Sofinnova Partners SAS, and, as such, may be deemed to have joint voting and investment power with respect to the shares held by Sofinnova Capital. The address of Sofinnova Capital is Sofinnova Partners, Immeuble le Centorial, 16-18 Rue du Quatre-Septembre, 75002 Paris, France.
- (3) All shares are held by Sofinnova Venture Partners VIII, L.P. (“Sofinnova Ventures”). Dr. James Healy, a member of our board of directors, together with Dr. Michael F. Powell and Dr. Anand Mehra, are the managing members of Sofinnova Management VIII, L.L.C., the general partner of Sofinnova Ventures, and as such, may be deemed to have joint voting and dispositive power with respect to the shares held by Sofinnova Ventures. Each of Dr. Powell, Dr. Mehra and Dr. Healy disclaims beneficial ownership of the shares held by Sofinnova Ventures, except to the extent of his pecuniary interest therein, if any. The mailing address of Sofinnova Ventures is c/o Sofinnova Ventures, Inc., 3000 Sand Hill Road, Bldg. 4, Suite 250, Menlo Park, CA 94025.
- (4) All shares are held by Morningside Venture Investments Limited (“MVIL”). Raymond Tang, Louise Garbarino, Peter Stuart Allenby Edwards and Jill Franklin are directors of MVIL, and may be deemed to have joint voting and dispositive power with respect to the shares held by MVIL. Each of Mr. Tang, Ms. Garbarino, Mr. Edwards and Ms. Franklin disclaim beneficial ownership of the shares held by MVIL, except to the extent of his or her pecuniary interest therein, if any. The mailing address of MVIL is 2nd Floor, Le Prince de Galles, 3-5 Avenue des Citronniers, MC 98000, Monaco.
- (5) Consists of 2,246,915 ordinary shares owned of record by Scottish Enterprise. Scottish Enterprise is a non-departmental body of the Scottish government and has sole voting and investment power with respect to the shares. The address of Scottish Enterprise is Atrium Court, 50 Waterloo Street, Glasgow G2 6HQ, Scotland.
- (6) Consists of (a) 1,000,000 ordinary shares and (b) options to purchase 2,403,531 ordinary shares that are or will be immediately exercisable within 60 days of September 15, 2017.

Table of Contents

- (7) Consists of (a) 1,011,875 ordinary shares and (b) options to purchase 937,499 ordinary shares that are or will be immediately exercisable within 60 days of September 15, 2017.
- (8) Consists of (a) 30,000 ordinary shares and (b) options to purchase 105,345 ordinary shares that are or will be immediately exercisable within 60 days of September 15, 2017.
- (9) Consists of (a) 45,750 ordinary shares held in the Healy Family Trust, for which Dr. James Healy's spouse is the trustee, and (b) 4,000,000 ordinary shares owned of record by Sofinnova Ventures. Dr. James Healy, a member of our board of directors, together with Dr. Michael F. Powell and Dr. Anand Mehra, are the managing members of Sofinnova Management VIII, L.L.C., the general partner of Sofinnova Ventures, and as such, may be deemed to share voting and investment power with respect to such shares. Dr. Healy disclaims beneficial ownership with regard to the 4,000,000 shares owned by Sofinnova Ventures, except to the extent of his proportionate pecuniary interest therein.
- (10) Isaac Cheng is a member of our board of directors who has been designated by MVIL. Dr. Cheng has no voting or investment power with respect to the shares held by MVIL.
- (11) Consists of options to purchase 28,312 ordinary shares that are or will be immediately exercisable within 60 days of September 15, 2017.

DESCRIPTION OF SHARE CAPITAL

The following describes our issued share capital, summarizes the material provisions of our articles of association and highlights certain differences in corporate law in the United Kingdom and the United States. Please note that this summary is not intended to be exhaustive. For further information please refer to the full version of our articles of association, which is included as an exhibit to the registration statement of which this prospectus is part.

General

We were incorporated in England and Wales with the Registrar of Companies of England and Wales, United Kingdom on January 28, 1997 under the name Biomed (UK) Limited as a private company limited by shares with company number 03308778.

On April 28, 2008, our name was changed to NuCana BioMed Limited. On August 29, 2017, we re-registered as a public limited company and changed our name to NuCana plc. Such re-registration required the passing of special resolutions by our shareholders to approve the re-registration as a public limited company, the name change to NuCana plc and to effect certain amendments to our articles of association.

Our registered office is located at 77/78 Cannon Street, London, EC4N 6AF, United Kingdom. The principal legislation under which we operate and our shares are issued is the Companies Act 2006.

Prior to completion of this offering, certain resolutions will be passed by our shareholders. These include resolutions for:

- The adoption of new articles of association that will become effective upon the completion of this offering. See “—Articles of Association” below.
- The general authorization of our directors for purposes of section 551 Companies Act 2006 to issue shares in the company and grant rights to subscribe for or convert any securities into shares in the company up to a maximum aggregate nominal amount of £791,497.28 for a period expiring at the conclusion of our next annual general meeting.
- The empowering of our directors pursuant to section 570 Companies Act 2006 to issue equity securities for cash pursuant to the section 551 authority referred to above as if the statutory pre-emption rights under section 561(1) Companies Act 2006 did not apply to such allotments.

Issued Share Capital

Our issued share capital as of August 31, 2017 is £663,935, divided into: 7,483,334 series A convertible participating shares of £0.04 each; 8,462,500 series B convertible participating shares of £0.004 each; 6,268,807 ordinary shares of £0.04 each; 1,000,000 founder ordinary 1 shares of £0.04 each; and 1,000,000 founder ordinary 2 shares of £0.04 each. A summary of increases in, and changes to, our issued share capital since our incorporation is set out below.

We issued one quarter of one ordinary share of £4.00 each to each of London Law Services Limited and London Law Secretarial Limited, respectively, upon incorporation.

On March 20, 2008, we subdivided the outstanding issued fractions of ordinary shares of £4.00 each into 50 ordinary shares of £0.04 each and we subdivided the remaining authorized yet unissued fractions of the ordinary shares of £4.00 each into 2,450 ordinary shares of £0.04 each. Further, our authorized share capital was increased from £100 to £500,000 by the creation of 12,497,500 new ordinary shares of £0.04 each. On March 20, 2008, we issued 4,499,950 ordinary shares of £0.04 each.

[Table of Contents](#)

On July 27, 2008, we issued a further 200,000 ordinary shares of £0.04 each. On August 20, 2009, we issued 350,000 ordinary shares of £0.04 each. On December 18, 2009, we issued 1,816,976 ordinary shares of £0.04 each (500,000 of which were available for such issue, having previously been issued to, but subsequently surrendered by, a shareholder). On December 14, 2010, we issued 1,566,359 ordinary shares of £0.04 each.

On November 24, 2011, we issued 7,483,334 series A convertible participating shares of £0.04 each.

On March 28, 2012, we issued 222,222 ordinary shares of £0.04 each.

On March 31, 2014, we issued 8,462,500 series B convertible participating shares of £0.004 each.

On November 30, 2016, we issued 37,500 ordinary shares of £0.04 each, pursuant to the exercise of share options granted under the 2012 Share Option Scheme.

On December 31, 2016, we issued 45,750 ordinary shares of £0.04 each, pursuant to the exercise of share options granted under the 2016 Share Option Scheme.

On August 17, 2017, we issued 30,000 ordinary shares of £0.04 each, pursuant to the exercise of share options granted under the 2016 Share Option Scheme.

On September 14, 2017, we completed a one-for-four reverse share split and an associated, prior, bonus allotment of three ordinary shares and five series A convertible participating shares to eliminate fractional entitlements. References to the one-for-four reverse share split in this prospectus include the associated bonus allotment. The share numbers and nominal values set out above have, for presentational purposes, been adjusted to reflect the aforementioned reverse share split (which has necessitated reference to notional fractions of shares and resulted in certain numbers of shares having been rounded up). These share numbers and nominal values are therefore not representative of, for example, the entries made at the relevant time in our statutory registers nor filings we have made at the UK Registrar of Companies.

Ordinary Shares

As of August 31, 2017, we had issued and outstanding 6,268,807 ordinary shares of £0.04 each, held by 20 shareholders of record. Each issued ordinary share is fully paid.

Holders of ordinary shares are entitled to one vote for each share held of record on all matters submitted to a vote of shareholders and do not have cumulative voting rights.

Prior to this offering, in the event of any distribution of capital, whether as a result of winding-up, dissolution or liquidation of the company or otherwise, or payment of any dividend, the holders of ordinary shares will rank *pari passu* with the holders of founder ordinary 1 shares, founder ordinary 2 shares, series A convertible participating shares and series B convertible participating shares in proportion to the number of fully paid shares held.

Following this offering, any distribution made as result of winding-up, dissolution or liquidation of our company and any dividend declared will be distributed in proportion to the number of fully paid ordinary shares held.

Founder Ordinary 1 Shares

As of August 31, 2017, we had issued and outstanding 1,000,000 founder ordinary 1 shares of £0.04 each, held by one shareholder of record, Hugh S. Griffith. Each issued founder ordinary 1 share is fully paid.

[Table of Contents](#)

Holders of founder ordinary 1 shares are entitled to vote on all matters submitted to a vote of shareholders either on a show of hands or on a poll. As an exception to the general rule that, on a poll, each of our shareholders has one vote for each share held: the holders of the founder ordinary 1 shares are, collectively entitled, on a poll, to exercise such number of votes that equals at least 5% of all votes exercisable by our shareholders.

Accordingly, (i) where the holders of the founder ordinary 1 shares, as a class, hold a number of shares that would (on a one vote per share basis) entitle them to exercise a number of votes less than 5% of the total number of votes exercisable by all shareholders on a poll vote, the holders of the founder ordinary 1 shares shall, as a class, be entitled to exercise such number of votes as equals 5% of the total number of votes exercisable by all shareholders on such poll; and (ii) where the holders of the founder ordinary 1 shares, as a class, hold a number of shares that would (on a one vote per share basis) entitle them to exercise 5% or more of the total number of votes exercisable by all shareholders on a poll vote, the holders of the founder ordinary 1 shares shall, as a class, be entitled to exercise the number of votes equal to the number of founder ordinary 1 shares so held.

The founder ordinary 1 shares will automatically convert into ordinary shares on a one-for-one basis immediately prior to the completion of this offering. Upon completion of this offering, there will be no founder ordinary 1 shares outstanding, and we have no present intention to issue any founder ordinary 1 shares at any time after completion of this offering.

Founder Ordinary 2 Shares

As of August 31, 2017, we had issued and outstanding 1,000,000 founder ordinary 2 shares of £0.04 each, held by one shareholder of record, Christopher Wood. Each issued founder ordinary 2 share is fully paid.

Holders of founder ordinary 2 shares are entitled to vote on all matters submitted to a vote of shareholders either on a show of hands or on a poll. As an exception to the general rule that, on a poll, each of our shareholders has one vote for each share held: the holders of the founder ordinary 2 shares are, collectively entitled, on a poll, to exercise such number of votes that equals at least 5% of all votes exercisable by our shareholders.

Accordingly, (i) where the holders of the founder ordinary 2 shares, as a class, hold a number of shares that would (on a one vote per share basis) entitle them to exercise a number of votes less than 5% of the total number of votes exercisable by all shareholders on a poll vote, the holders of the founder ordinary 2 shares shall, as a class, be entitled to exercise such number of votes as equals 5% of the total number of votes exercisable by all shareholders on such poll; and (ii) where the holders of the founder ordinary 2 shares, as a class, hold a number of shares that would (on a one vote per share basis) entitle them to exercise 5% or more of the total number of votes exercisable by all shareholders on a poll vote, the holders of the founder ordinary 2 shares shall, as a class, be entitled to exercise the number of votes equal to the number of founder ordinary 2 shares so held.

The founder ordinary 2 shares will automatically convert into ordinary shares on a one-for-one basis immediately prior to the completion of this offering. Upon completion of this offering, there will be no founder ordinary 2 shares outstanding, and we have no present intention to issue any founder ordinary 2 shares at any time after completion of this offering.

Series A Convertible Participating Shares

As of August 31, 2017, we had issued and outstanding 7,483,334 series A convertible participating shares of £0.04 each. Each issued series A convertible participating share is fully paid.

The holders of series A convertible participating shares are entitled to one vote for each share held of record on all matters submitted to a vote of shareholders and do not have cumulative voting rights. The series A

[Table of Contents](#)

convertible participating shares will automatically convert into ordinary shares on a one-for-one basis immediately prior to the completion of this offering. Upon completion of this offering, there will be no series A convertible participating shares outstanding, and we have no present intention to issue any series A convertible participating shares at any time after completion of this offering.

Series B Convertible Participating Shares

As of August 31, 2017, we had issued and outstanding 8,462,500 series B convertible participating shares of £0.004 each, or Series B Shares. Each issued Series B Share is fully paid.

The holders of Series B Shares are entitled to one vote for each share held of record on all matters submitted to a vote of shareholders and do not have cumulative voting rights. Following the allotment and consolidation described below, the Series B Shares will automatically convert into ordinary shares on a one-for-one basis immediately prior to the completion of this offering. Upon completion of this offering, there will be no Series B Shares outstanding, and we have no present intention to issue any Series B Shares at any time after completion of this offering.

Conversion of Series B Shares into Ordinary Shares

For the purpose of facilitating a conversion of each Series B Share (nominal value £0.004 per share), into an ordinary share (nominal value £0.04 per share), immediately prior to the completion of this offering, we will allot to holders of Series B Shares an additional nine Series B Shares for each Series B Share held.

Subject to and conditional upon this allotment, every 10 Series B Shares of £0.004 will be consolidated into a single Series B Share of £0.04. Immediately prior to the completion of this offering, each Series B Share of £0.04 will then be automatically converted into one ordinary share of £0.04.

We will fund the allotment of these additional shares with reserves that are standing to the credit of our share premium account and obtain all shareholder resolutions and permissions as are necessary for the purpose of authorizing our directors to (i) capitalize the specified sum; (ii) allot the additional Series B Shares; and (iii) consolidate the Series B Shares.

Registration Rights

In connection with the Series B Placement, we entered into a shareholders' agreement with all of our then-existing shareholders, including certain of our directors and executive officers, on March 31, 2014, or the 2014 Shareholders' Agreement. Among other things, the 2014 Shareholders Agreement provided certain piggyback registration rights to certain of our then-existing shareholders. The 2014 Shareholders' Agreement will terminate effective upon completion of this offering.

We have entered into a registration rights agreement to be effective upon the completion of this offering and pursuant to which we have agreed under specified circumstances to file a registration statement to register the resale of the ordinary shares held by some of our existing shareholders, as well as to cooperate in specified public offerings of such shares. These rights are described below.

Demand Registration Rights. If at any time when we are eligible to use a Form F-3 registration statement, the holders of at least 25% of the registrable securities then outstanding have the right to demand that we file a Form F-3 registration statement with respect to such registrable securities. These registration rights are subject to specified conditions and limitations, including the right of the underwriters, if any, to limit the number of shares included in any such registration under specified circumstances. Upon such a request, we are required to use commercially reasonable efforts to effect such registration.

[Table of Contents](#)

Company Registration. If we propose to register any of our equity securities under the Securities Act, other than in connection with certain specified registrations, including a registration relating solely to our employee equity incentive plans or a registration relating solely to certain business combinations or mergers involving us, the holders of these registrable securities are entitled to notice of such registration and are entitled to include their ordinary shares in the registration. Under certain circumstances, the underwriters, if any, may limit the number of ordinary shares included in any such registration.

Termination of Registration Rights. The registration rights granted under the registration rights agreement shall terminate upon the earlier to occur of (i) the fifth anniversary of the closing of this offering and (ii) the date on which there are no registrable securities remaining pursuant to the registration rights agreement.

Articles of Association

As described above, prior to this offering, our shareholders will pass a special resolution to adopt new articles of association which will become effective upon the completion of this offering. The following is a summary of certain provisions of the new articles of association.

Please note that this is only a summary and is not intended to be exhaustive. For further information please refer to the full version of our articles of association that will become effective upon the completion of this offering, which is included as an exhibit to the registration statement of which this prospectus is a part.

Shares and Rights Attaching to Them

General. All ordinary shares have the same rights and rank pari passu in all respects. Subject to the provisions of the Companies Act 2006 and any other relevant legislation, our board of directors may, from time to time, allot and issue shares following an ordinary resolution of the shareholders granting authority to the directors to allot shares (and if applicable, and not already disappplied, a special resolution to disapply pre-emption rights).

Our shares may be issued with or have attached to them any preferred, deferred, qualified or other special rights or restrictions, whether in relation to dividends, returns of capital, voting or otherwise, as set out in our articles of association or as the shareholders may determine by ordinary resolution (or, if the shareholders have not so determined, as our board of directors may determine).

Voting rights. Subject to any other provisions of our articles of association and without prejudice to any special rights, privileges or restrictions as to voting attached to any shares forming part of our share capital, the voting rights of shareholders are as follows. Unless a poll vote is demanded, shareholders shall vote on all resolutions on a show of hands. Our articles of association provide that a poll vote may be demanded before, or on the declaration of, the result of a vote on a show of hands: (a) by the chairman of a general meeting, (b) by at least five shareholders present at a meeting and entitled to vote, or (c) by any shareholder or shareholders present representing not less than ten per cent of the total voting rights or more than ten per cent of the total sum paid up on all voting shares. For these purposes, a shareholder will be present at a meeting if attending in person, by proxy, or, in the case of a shareholder that is a corporation (as broadly defined under the Companies Act 2006), by duly authorized representative.

On a show of hands, each shareholder present in person, and each duly authorized representative present in person of a shareholder that is a corporation, has one vote. On a show of hands, each proxy present in person who has been duly appointed by one or more shareholders has one vote, but a proxy has one vote for and one vote against a resolution if the proxy is instructed to vote on a resolution by more than one shareholder and is instructed to vote in different ways on such resolution.

[Table of Contents](#)

On a poll, each shareholder present in person or by proxy or, with respect to a corporation, by a duly authorized representative has one vote for each share held by the shareholder. We are prohibited from exercising any rights to attend or vote at meetings in respect of any shares held by us as treasury shares.

Restrictions on voting where sums overdue on shares. None of our shareholders is entitled to vote at any general meeting or at any separate class meeting in respect of any share held by him or her unless all calls or other sums payable by him or her in respect of that share have been paid.

Calls on shares. The directors may from time to time make calls on shareholders in respect of any amounts unpaid on their shares, whether in respect of nominal value of the shares or by way of premium. Shareholders are required to pay the called amount on shares subject to receiving at least 14 clear days' notice specifying the time and place for payment. Under our articles of association, a period of "clear days" excludes the day on which a notice is given or deemed to have been given and the day for which it is given or on which it is to take effect. If a shareholder fails to pay any part of a call, the board of directors may serve further notice naming another day not being less than 14 clear days from the date of the further notice requiring payment and stating that in the event of non-payment the shares in respect of which the call was made will be liable to be forfeited. Subsequent forfeiture requires a resolution by the board of directors.

Dividends. Subject to the Companies Act 2006 and the provisions of all other relevant legislation, we may by ordinary resolution declare dividends out of profits available for distribution in accordance with the respective rights of shareholders, but no such dividend shall exceed the amount recommended by the board of directors. If, in the opinion of the board of directors, our profits available for distribution justify such payments, the board of directors may pay fixed dividends payable on any of our shares with preferential rights, half-yearly or otherwise, on fixed dates and from time to time pay interim dividends to the holders of any class of shares. Subject to any special rights attaching to, or terms of issue of, any shares, all dividends shall be declared and paid according to the amounts paid up on the shares on which the dividend is paid. No dividend shall be payable to us in respect of any shares held by us as treasury shares.

We may, upon the recommendation of the board of directors, by ordinary resolution, direct payment of a dividend wholly or partly by the distribution of specific assets.

All dividends unclaimed for one year after having been declared may be invested or otherwise used at the directors' discretion for our benefit until claimed (subject as provided in the articles of association), and all dividends unclaimed after a period of 12 years from the date when such dividend became due for payment shall be forfeited and shall revert to us.

The board of directors may, if so authorized by ordinary resolution passed at any general meeting, offer any holders of the ordinary shares the right to elect to receive in lieu of that dividend an allotment of ordinary shares credited as fully paid.

We may cease to send any cheque or warrant by mail or may stop the transfer of any sum by any bank or other funds transfer system for any dividend payable on any of our shares, which is normally paid in that manner on those shares if in respect of at least two consecutive dividends the cheque or warrants have been returned undelivered or remain uncashed or the transfer has failed, or in respect of one dividend the cheque or warrant has been returned undelivered or remains uncashed or the transfer has failed and reasonable inquiries made by us have failed to establish any new address of the holder.

We or the directors may specify a "record date" on which persons registered as the holders of shares shall be entitled to receipt of any dividend.

[Table of Contents](#)

Distribution of assets on winding-up. Subject to any special rights attaching to, or the terms of issue of any shares, on any winding-up of the company our surplus assets remaining after satisfaction of our liabilities will be distributed among our shareholders in proportion to their respective holdings of shares and the amounts paid up on those shares.

On any winding-up of the company (whether the liquidation is voluntary, under supervision or by the Court), the liquidator may with the authority of a special resolution of the company and any other sanction required by any relevant legislation, divide among our shareholders (excluding the company itself to the extent that it is a shareholder by virtue of its holding any shares or treasury shares) in specie or in kind the whole or any part of our assets (subject to any special rights attached to any shares issued by us in the future) and may for that purpose set such value as he deems fair upon any one or more class or classes of property and may determine how that division shall be carried out as between the shareholders or different classes of shareholders. The liquidator may, with that sanction, vest the whole or any part of the assets in trustees upon such trusts for the benefit of the shareholders as he with the relevant authority determines, and the liquidation of the company may be closed and the company dissolved, but so that no shareholders shall be compelled to accept any shares or other property in respect of which there is a liability.

Variation of rights. The rights or privileges attached to any class of shares may (unless otherwise provided by the terms of the issue of the shares of that class) be varied or abrogated with the consent in writing of the holders of three-fourths in requisite nominal value of the issued shares of that class (excluding any shares of that class held as treasury shares) or with the approval of a special resolution passed at a separate general meeting of the shareholders of that class, but not otherwise.

Transfer of shares. All of our shares are in registered form and may be transferred by a transfer in any usual or common form or any form acceptable to the board of directors and permitted by the Companies Act 2006 and any other relevant legislation.

The board of directors may decline to register a transfer of a share that is:

- not fully paid or on which we have a lien;
- (except where uncertificated shares are transferred without a written instrument) not lodged duly stamped (if it is required to be stamped) at our registered office or at such other place as the board of directors may appoint;
- (except where a certificate has not been issued) not accompanied by the certificate of the share to which it relates or such other evidence reasonably required by the directors to show the right of the transferor to make the transfer;
- in respect of more than one class of share; or
- in the case of a transfer to joint holders of a share, the number of joint holders to whom the share is to be transferred exceeds four.

Capital variations. We may, by ordinary resolution, consolidate and divide all or any of our share capital into shares of a larger nominal amount than our existing shares or sub-divide our shares, or any of them, into shares of a smaller nominal amount than our existing shares. Subject to the provisions of the Companies Act 2006 and any other applicable legislation, we may by special resolution reduce our share capital, any capital redemption reserve fund or any share premium account and may redeem or purchase any of our own shares.

Pre-emption rights. There are no rights of pre-emption under our articles of association in respect of transfers of issued ordinary shares. In certain circumstances, our shareholders may have statutory pre-emption

[Table of Contents](#)

rights under the Companies Act 2006 in respect of the allotment of new shares in the company. These statutory pre-emption rights, when applicable, would require us to offer new shares for allotment to existing shareholders on a pro rata basis before allotting them to other persons. In such circumstances, the procedure for the exercise of such statutory pre-emption rights would be set out in the documentation by which such ordinary shares would be offered to our shareholders. These statutory pre-emption rights may be disapplied by a special resolution passed by shareholders in a general meeting in accordance with the provisions of the Companies Act 2006.

Directors

Number. Unless and until we in a general meeting of our shareholders otherwise determine, the number of directors comprising our board of directors shall not be subject to any maximum but shall not be less than two.

Classified board of directors. Our board of directors will be divided into three classes, “Class I,” whose initial term shall expire at the annual general meeting of the shareholders to be held in 2020, “Class II,” whose initial term shall expire at the annual general meeting of the shareholders to be held in 2019, and “Class III,” whose initial term shall expire at the annual general meeting of the shareholders to be held in 2018, with the classes as nearly equal in number as possible. At the closing of the offering made hereby, the Class I directors will be Hugh Griffith and Christopher Wood, the Class II directors will be Rafaèle Tordjman and James Healy, and the Class III directors will be Isaac Cheng and Martin Mellish.

Borrowing powers. Our board of directors may exercise all the powers of the company to borrow money, mortgage or charge all or any part or parts of its undertaking, property and uncalled capital, and issue debentures and other securities whether outright or as collateral security for any debt, liability or obligation of the company or of any third party.

Directors’ interests and restrictions

(a) The board of directors may, in accordance with our articles of association and the requirements of the Companies Act 2006, authorize a matter proposed to us which would, if not authorized, involve a breach by a director of his or her duty under section 175 of the Companies Act 2006 to avoid a situation in which he or she has, or can have, a direct or indirect interest that conflicts, or possibly may conflict, with our interests. A director is not required, by reason of being a director, to account to the company for any remuneration or other benefit that he or she derives from a relationship involving a conflict of interest or possible conflict of interest that has been authorized by the board of directors.

(b) Subject to the provisions of any relevant legislation and provided that he or she has disclosed to the directors the nature and extent of any material interest of his or hers, a director may be a party to, or otherwise interested in, any transaction, contract or arrangement and that director shall not, by reason of his or her office, be accountable to the company for any benefit that he or she derives from any such transaction or arrangement; and no such transaction or arrangement shall be liable to be voided on the ground of any such interest or benefit.

(c) Except as provided in our articles of association, a director shall not vote at a meeting of the directors in respect of any transaction or arrangement or any other proposal whatsoever in which he or she has an interest that is to his or her knowledge material (together with any person connected with him or her within the meaning of section 252 of the Companies Act 2006), other than (i) an interest in shares or debentures or other securities of the company, (ii) where permitted by the terms of any authorization of a conflict of interest or by an ordinary resolution, or (iii) in the circumstances set out in paragraph (d) below, and shall not be counted in the quorum at a meeting in relation to any resolution on which he or she is not entitled to vote.

Table of Contents

(d) A director shall (in the absence of some material interest other than those indicated below) be entitled to vote (and be counted in the quorum) in respect of any resolution concerning any of the following matters:

(i) the giving of any guarantee, security or indemnity to him or her in respect of money lent to or an obligation incurred by him or her at the request of or for the benefit of us or any of our subsidiaries;

(ii) the giving to a third party of any guarantee, security or indemnity in respect of a debt or obligation of ours or any of our subsidiaries for which he himself or she herself has assumed responsibility in whole or in part under a guarantee or indemnity or by the giving of security;

(iii) any proposal or contract concerning an offer of shares or debentures or other securities of or by the company or any of its subsidiaries, if he or she takes part because he or she is or may be entitled to participate as a holder of shares, debentures or other securities, or if he or she takes part in the underwriting, sub-underwriting or guarantee of the offer;

(iv) any proposal concerning any other company in which he or she is interested, directly or indirectly and whether as an officer or shareholder or otherwise, provided that he or she (together with persons connected with him or her) does not to his or her knowledge hold an interest in shares representing one percent or more of the issued shares of any class of such company or of the voting rights available to shareholders of the relevant company;

(v) any proposal concerning arrangements pursuant to which benefits are made available to our employees and which does not award him or her any privilege or benefit not generally awarded to the employees to whom such arrangement relates;

(vi) any proposal under which he or she may benefit concerning the giving of indemnities to our directors or other officers that the directors are empowered to give under our articles of association;

(vii) any proposal under which he or she may benefit concerning the purchase or maintenance of insurance for any of our directors or other officers; and

(viii) any proposal under which he or she may benefit concerning the provision to directors of funds to meet expenditures in defending proceedings.

(e) Where proposals are under consideration to appoint two or more directors to offices or employments with us or with any company in which we are interested or to fix or vary the terms of such appointments, such proposals may be divided and considered in relation to each director separately and in such case each of the directors concerned (if not debarred from voting under paragraph (d)(iv) above) shall be entitled to vote (and be counted in the quorum) in respect of each resolution, except that concerning his or her own appointment.

(f) If any question shall arise at any meeting as to the materiality of a director's interest or as to the entitlement of any director to vote and such question is not resolved by his or her agreeing voluntarily to abstain from voting, such question shall be referred to the chairman of the meeting (or where the interest concerns the chairman himself to the deputy chairman of the meeting) and his or her ruling in relation to any director shall be final and conclusive, except in a case where the nature or extent of the interests of the director concerned have not been fairly disclosed.

Remuneration

(a) Each of the directors (other than alternate directors) may (in addition to any amounts payable under paragraph (b) and (c) below or under any other provision of our articles of association) be paid out of the funds of the company such sum by way of directors' fees as the board of directors may from time to time determine.

Table of Contents

(b) Any director who is appointed to hold any employment or executive office with us or who, by our request, goes or resides abroad for any purposes of the company or who otherwise performs services that in the opinion of the board of directors are outside the scope of his or her ordinary duties may be paid such additional remuneration (whether by way of salary, commission, participation in profits or otherwise) as the board of directors (or any duly authorized committee of the board of directors) may determine and either in addition to or in lieu of any remuneration provided for by or pursuant to any other article.

(c) Each director may be paid his or her reasonable traveling expenses (including hotel and incidental expenses) of attending and returning from meetings of the directors or committees of the board of directors or general meetings or any separate meeting of the holders of any class of our shares or any other meeting that as a director he or she is entitled to attend and shall be paid all expenses properly and reasonably incurred by him or her in the conduct of the company's business or in the discharge of his or her duties as a director.

Pensions and other benefits. The board of directors may exercise all the powers of the company to provide benefits, either by the payment of gratuities or pensions or by insurance or in any other manner whether similar to the foregoing or not, for any director or former director, or any person who is or was at any time employed by, or held an executive or other office or place of profit in, the company or any body corporate that is or has been a subsidiary of the company or a predecessor of the business of the company or of any such subsidiary and for the families and persons who are or was a dependent of any such persons and for the purpose of providing any such benefits contribute to any scheme trust or fund or pay any premiums.

Appointment and retirement of directors

(a) The board of directors shall have power to appoint any person who is willing to act to be a director, either to fill a casual vacancy or as an additional director but so that the total number of directors shall not exceed the maximum number fixed (if any) by or in accordance with our articles of association. Any director so appointed shall retire from office at our annual general meeting following such appointment, and then shall be eligible for re-election for the remaining portion of the term of office of the Class to which he or she is eligible for election.

(b) Subject as provided in our articles of association, the shareholders may by ordinary resolution elect any person who is willing to act as a director either to fill a casual vacancy or as an addition to the existing directors or to replace a director removed from office under our articles of association but so that the total number of directors shall not at any one time exceed any maximum number fixed by or in accordance with our articles of association.

(c) Subject to paragraph (a) above and the initial terms described in "Description of Share Capital—Articles of Association—Directors—Classified board of directors", each director within each class shall retire at the third annual general meeting following the annual general meeting at which he or she was elected or last re-elected. Except where there is an increase in the number of directors (in which case the newly created directorships shall be apportioned by our board amongst our existing classes) or in accordance with paragraph (a) above, directors elected or re-elected at an annual general meeting shall be appointed to the class whose term expires at such meeting.

(d) A director retiring at an annual general meeting shall be eligible for re-election. If a retiring director is not re-elected, he or she shall hold office until the meeting elects someone in his or her place or, if it does not do so, until the end of the meeting.

Company name. The board of directors may resolve to change our company name.

Indemnity of officers. Subject to the provisions of any relevant legislation, each of our directors and other officers may be indemnified by us against all costs, charges, losses, expenses and liabilities incurred by him in the execution and discharge of his duties or in relation to those duties. The Companies Act 2006 renders void an

[Table of Contents](#)

indemnity for a director against any liability attaching to him or her in connection with any negligence, default, breach of duty or breach of trust in relation to the company of which he or she is a director as described in “—Differences in Corporate Law—Liability of Directors and Officers.”

Shareholders’ Meetings

Annual general meetings. We shall in each year hold an annual general meeting of our shareholders in addition to any other meetings in that year, and shall specify the meeting as such in the notice convening it. The annual general meeting shall be held at such time and place as the board of directors may appoint.

Calling of general meetings. The board of directors may call a general meeting of shareholders. The board of directors must call a general meeting if the shareholders and the Companies Act 2006 require them to do so. The arrangements for the calling of general meetings are described in “—Differences in Corporate Law—Notice of General Meetings” below.

Quorum of meetings. No business shall be transacted at any general meeting unless a quorum is present when the meeting proceeds to business but the absence of a quorum shall not preclude the appointment of a chairman, which shall not be treated as part of the business of a meeting. One or more qualifying persons present at a meeting and between them holding (or being the proxy or corporate representative of the holders of) at least one-third in number of the issued shares (excluding any shares held as treasury shares) entitled to vote on the business to be transacted are a quorum. A qualifying person for these purposes is an individual who is a shareholder, a person authorized to act as the representative of a shareholder (being a corporation) in relation to the meeting or a person appointed as proxy of a shareholder in relation to the meeting.

Other United Kingdom law considerations

Mandatory purchases and acquisitions. Pursuant to Sections 979 to 991 of the Companies Act 2006, where a takeover offer has been made for us and the offeror has acquired or unconditionally contracted to acquire not less than 90% in value of the shares to which the offer relates and not less than 90% of the voting rights carried by those shares, the offeror may give notice to the holder of any shares to which the offer relates which the offeror has not acquired or unconditionally contracted to acquire that he wishes to acquire, and is entitled to so acquire, those shares on the same terms as the general offer. The “squeeze-out” of the minority shareholders can be completed at the end of six weeks from the date the notice has been given, subject to the minority shareholders failing to successfully lodge an application to the court to prevent such squeeze-out any time prior to the end of those six weeks, following which the offeror can execute a transfer of the outstanding shares in its favor and pay the consideration to us, to be held on trust for the outstanding minority shareholders. The consideration offered to the outstanding minority shareholders whose shares are compulsorily acquired under the Companies Act 2006 must, in general, be the same as the consideration that was available under the takeover offer.

Sell-out. The Companies Act 2006 also gives our minority shareholders a right to be bought out in certain circumstances by an offeror who has made a takeover offer for all of our shares. The holder of shares to which the offer relates, and who has not otherwise accepted the offer, may require the offeror to acquire his shares if, prior to the expiry of the acceptance period for such offer, (i) the offeror has acquired or agreed to acquire not less than 90% in value of our voting shares, and (ii) not less than 90% of the voting rights carried by those shares. The offeror may impose a time limit on the rights of minority shareholders to be bought out that is not less than three months after the end of the acceptance period. If a shareholder exercises his rights to be bought out, the offeror is required to acquire those shares on the terms of this offer or on such other terms as may be agreed.

Disclosure of interest in shares. Pursuant to Part 22 of the Companies Act 2006 and our articles of association, we are empowered to require, by notice in writing, any person whom we know to be, or have

[Table of Contents](#)

reasonable cause to believe to be, interested in our shares, or at any time during the three years immediately preceding the date on which the notice is issued has been so interested, within a reasonable time to disclose to us particulars of that person's own interest and (so far as is within that person's knowledge) particulars of any other interest, agreement or arrangement relating to the exercise of any rights conferred by the holding of the shares that subsists or subsisted in those shares.

Under our articles of association, if a person defaults in supplying us with the required particulars in relation to the shares in question (referred to herein as "default shares"), the board of directors may by notice direct that:

- in respect of the default shares, the relevant shareholder shall not be entitled to vote or exercise any other right conferred by his holding shares in relation to general meetings; or
- where the default shares represent at least 0.25% of their class, (a) any dividend or other money payable in respect of the default shares shall be retained by us without liability to pay interest and, if applicable, any election to receive ordinary shares instead of money in respect of the default shares shall be ineffective; (b) no transfers of shares by the relevant shareholder other than certain approved transfers may be registered (unless the shareholder himself is not in default and the transfer does not relate to default shares) or (c) any shares held by the relevant shareholder in uncertificated form shall be converted into certificated form.

Purchase of own shares. Under English law, a limited company may only purchase its own shares out of its distributable profits or the proceeds of a fresh issue of shares made for the purpose of financing the purchase, provided it is not restricted from doing so by its articles. A limited company may not purchase its own shares if, as a result of the purchase, there would no longer be any issued shares of the company other than redeemable shares or shares held as treasury shares. Shares must be fully paid in order to be repurchased.

We may purchase our own fully paid shares otherwise than on a recognized investment exchange pursuant to a purchase contract authorized by resolution of shareholders before the purchase takes place. Any authority will not be effective if any shareholder from whom we propose to purchase shares votes on the resolution and the resolution would not have been passed if he had not done so. The resolution authorizing the purchase must specify a date, not being later than five years after the passing of the resolution, on which the authority to purchase is to expire.

City code on takeovers and mergers, or the Takeover Code. As a public company incorporated in England and Wales with its place of central management and control in the United Kingdom, we are subject to the United Kingdom City Code on Takeovers and Mergers (referred to herein as the Takeover Code). The Takeover Code contains rules concerning the conduct of takeover offers for the company. For example, under Rule 9 of the Takeover Code, if a person:

(a) acquires an interest in our shares that, when taken together with shares in which he or persons acting in concert with him are interested, carries 30% or more of the voting rights of our shares; or

(b) who, together with persons acting in concert with him, is interested in shares that in the aggregate carry not less than 30% and not more than 50% of the voting rights in the company, acquires additional interests in shares that increase the percentage of shares carrying voting rights in which that person is interested;

the acquirer and, depending on the circumstances, its concert parties, would be required (except with the consent of the Takeover Panel) to make a cash offer for our outstanding shares at a price not less than the highest price paid for any interests in the shares by the acquirer or its concert parties during the previous 12 months. Some provisions in the Takeover Code might have anti-takeover effects that could discourage an acquisition of us by others even if an acquisition would be beneficial to our shareholders.

[Table of Contents](#)

Distributions and dividends. Under the Companies Act 2006, before a company can lawfully make a distribution or dividend, it must ensure that it has sufficient distributable reserves (on a non-consolidated basis). The basic rule is that a company's profits available for the purpose of making a distribution are its accumulated, realized profits, so far as not previously utilized by distribution or capitalization, less its accumulated, realized losses, so far as not previously written off in a reduction or reorganization of capital duly made. The requirement to have sufficient distributable reserves before a distribution or dividend can be paid applies to us and to each of our subsidiaries that has been incorporated under English law.

It is not sufficient that we, as a public company, have made a distributable profit for the purpose of making a distribution. An additional capital maintenance requirement is imposed on us to ensure that the net worth of the company is at least equal to the amount of its capital. A public company can only make a distribution:

(a) if, at the time that the distribution is made, the amount of its net assets (that is, the total excess of assets over liabilities) is not less than the total of its called up share capital and undistributable reserves; and

(b) if, and to the extent that, the distribution itself, at the time that it is made, does not reduce the amount of the net assets to less than that total.

Exchange controls. There are no governmental laws, decrees, regulations or other legislation in the United Kingdom that may affect the import or export of capital, including the availability of cash, cash equivalents and short-term deposits for use by us, or that may affect the remittance of dividends, interest, or other payments by us to non-resident holders of our ordinary shares or ADSs, other than withholding tax requirements. There is no limitation imposed by English law or in the articles of association on the right of non-residents to hold or vote shares.

[Table of Contents](#)

Differences in Corporate Law

The applicable provisions of the Companies Act 2006 differ from laws applicable to U.S. corporations and their shareholders. Set forth below is a summary of certain differences between the provisions of the Companies Act 2006 applicable to us and the Delaware General Corporation Law relating to shareholders' rights and protections. This summary is not intended to be a complete discussion of the respective rights and it is qualified in its entirety by reference to Delaware law and English law.

	<u>England and Wales</u>	<u>Delaware</u>
Number of Directors	Under the Companies Act 2006, a public limited company must have at least two directors and the number of directors may be fixed by or in the manner provided in a company's articles of association.	Under Delaware law, a corporation must have at least one director and the number of directors shall be fixed by or in the manner provided in the bylaws.
Removal of Directors	Under the Companies Act 2006, shareholders may remove a director without cause by an ordinary resolution (which is passed by a simple majority of those voting in person or by proxy at a general meeting) irrespective of any provisions of any service contract the director has with the company, provided 28 clear days' notice of the resolution has been given to the company and its shareholders. On receipt of notice of an intended resolution to remove a director, the company must forthwith send a copy of the notice to the director concerned. Certain other procedural requirements under the Companies Act 2006 must also be followed such as allowing the director to make representations against his or her removal either at the meeting or in writing.	Under Delaware law, any director or the entire board of directors may be removed, with or without cause, by the holders of a majority of the shares then entitled to vote at an election of directors, except (a) unless the certificate of incorporation provides otherwise, in the case of a corporation whose board of directors is classified, shareholders may effect such removal only for cause, or (b) in the case of a corporation having cumulative voting, if less than the entire board of directors is to be removed, no director may be removed without cause if the votes cast against his removal would be sufficient to elect him if then cumulatively voted at an election of the entire board of directors, or, if there are classes of directors, at an election of the class of directors of which he is a part.
Vacancies on the Board of Directors	Under English law, the procedure by which directors (other than a company's initial directors) are appointed is generally set out in a company's articles of association, provided that where two or more persons are appointed as directors of a public limited company by resolution of the shareholders at a general meeting, resolutions appointing each director must be voted on individually unless the shareholders present vote to	Under Delaware law, vacancies and newly created directorships may be filled by a majority of the directors then in office (even though less than a quorum) or by a sole remaining director unless (a) otherwise provided in the certificate of incorporation or by-laws of the corporation or (b) the certificate of incorporation directs that a particular class of stock is to elect such director, in

Table of Contents

	disapply this requirement without any vote in opposition.	which case a majority of the other directors elected by such class, or a sole remaining director elected by such class, will fill such vacancy.
Annual General Meeting	Under the Companies Act 2006, a public limited company must hold an annual general meeting in each six-month period following the company's annual accounting reference date.	Under Delaware law, the annual meeting of stockholders shall be held at such place, on such date and at such time as may be designated from time to time by the board of directors or as provided in the certificate of incorporation or by the bylaws.
General Meeting	<p>Under the Companies Act 2006, a general meeting of the shareholders of a public limited company may be called by the directors.</p> <p>Shareholders holding at least 5% of the paid-up capital of the company carrying voting rights at general meetings can require the directors to call a general meeting and, if the directors fail to do so within a prescribed period, may themselves call a general meeting.</p>	Under Delaware law, special meetings of the stockholders may be called by the board of directors or by such person or persons as may be authorized by the certificate of incorporation or by the bylaws.
Notice of General Meetings	Under the Companies Act 2006, 21 clear days' notice must be given for an annual general meeting and any resolutions to be proposed at the meeting. Subject to a company's articles of association providing for a longer period, at least 14 clear days' notice is required for any other general meeting. In addition, certain matters, such as resolutions to remove directors or auditors, require special notice, which is 28 clear days' notice. The shareholders of a company may in all cases consent to a shorter notice period, the proportion of shareholders' consent required being 100% of those entitled to attend and vote in the case of an annual general meeting and, in the case of any other general meeting, a majority in number of the shareholders having a right to attend and vote at the meeting, being a majority who together hold not less than 95% in nominal value of the shares giving a right to attend and vote at the meeting.	Under Delaware law, unless otherwise provided in the certificate of incorporation or bylaws, written notice of any meeting of the stockholders must be given to each stockholder entitled to vote at the meeting not less than 10 nor more than 60 days before the date of the meeting and shall specify the place, date, hour, and purpose or purposes of the meeting.

Table of Contents

Proxy	Under the Companies Act 2006, at any meeting of shareholders, a shareholder may designate another person to attend, speak and vote at the meeting on their behalf by proxy.	Under Delaware law, at any meeting of stockholders, a stockholder may designate another person to act for such stockholder by proxy, but no such proxy shall be voted or acted upon after three years from its date, unless the proxy provides for a longer period. A director of a Delaware corporation may not issue a proxy representing the director's voting rights as a director.
Pre-emptive Rights	Under the Companies Act 2006, "equity securities", being (i) shares in the company other than shares that, with respect to dividends and capital, carry a right to participate only up to a specified amount in a distribution ("ordinary shares") or (ii) rights to subscribe for, or to convert securities into, ordinary shares, proposed to be allotted for cash must be offered first to the existing equity shareholders in the company in proportion to the respective nominal value of their holdings, unless an exception applies or a special resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise (in each case in accordance with the provisions of the Companies Act 2006).	Under Delaware law, shareholders have no preemptive rights to subscribe to additional issues of stock or to any security convertible into such stock unless, and except to the extent that, such rights are expressly provided for in the certificate of incorporation.
Authority to Allot	Under the Companies Act 2006, the directors of a company must not allot shares or grant rights to subscribe for or to convert any security into shares unless an exception applies or an ordinary resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise (in each case in accordance with the provisions of the Companies Act 2006).	Under Delaware law, if the corporation's charter or certificate of incorporation so provides, the board of directors has the power to authorize the issuance of stock. It may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the corporation or any combination thereof. It may determine the amount of such consideration by approving a formula. In the absence of actual fraud in the transaction, the judgment of the directors as to the value of such consideration is conclusive.
Liability of Directors and Officers	Under the Companies Act 2006, any provision (whether contained in a company's articles of association or	Under Delaware law, a corporation's certificate of incorporation may include a

any contract or otherwise) that purports to exempt a director of a company, to any extent, from any liability that would otherwise attach to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company is void.

Any provision by which a company directly or indirectly provides an indemnity, to any extent, for a director of the company or of an associated company against any liability attaching to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company of which he is a director is also void except as permitted by the Companies Act 2006, which provides exceptions for the company to (a) purchase and maintain insurance against such liability; (b) provide a “qualifying third party indemnity” (being an indemnity against liability incurred by the director to a person other than the company or an associated company as long as he is successful in defending the claim or criminal proceedings or in obtaining relief from the court); and (c) provide a “qualifying pension scheme indemnity” (being an indemnity against liability incurred in connection with the company’s activities as trustee of an occupational pension plan).

Under English law, unless a poll is demanded by the shareholders of a company or is required by the chairman of the meeting or by the company’s articles of association, shareholders shall vote on all resolutions on a show of hands. Under the Companies Act 2006, a poll may be demanded by (a) not fewer than five shareholders having the right to vote on the resolution; (b) any shareholder(s) representing not less than 10% of the total voting rights of all the shareholders having the right to vote on the resolution; or (c) any shareholder(s) holding shares in the company conferring a right to vote on the

provision eliminating or limiting the personal liability of a director to the corporation and its stockholders for damages arising from a breach of fiduciary duty as a director. However, no provision can limit the liability of a director for:

- any breach of the director’s duty of loyalty to the corporation or its stockholders;
- acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- intentional or negligent payment of unlawful dividends or stock purchases or redemptions; or
- any transaction from which the director derives an improper personal benefit.

Delaware law provides that, unless otherwise provided in the certificate of incorporation, each stockholder is entitled to one vote for each share of capital stock held by such stockholder.

Voting Rights

resolution being shares on which an aggregate sum has been paid up equal to not less than 10% of the total sum paid up on all the shares conferring that right. A company's articles of association may provide more extensive rights for shareholders to call a poll.

Under English law, an ordinary resolution is passed on a show of hands if it is approved by a simple majority (more than 50%) of the votes cast by shareholders present (in person or by proxy) and entitled to vote. If a poll is demanded, an ordinary resolution is passed if it is approved by holders representing a simple majority of the total voting rights of shareholders present, in person or by proxy, who, being entitled to vote, vote on the resolution. Special resolutions require the affirmative vote of not less than 75% of the votes cast by shareholders present, in person or by proxy, at the meeting.

Shareholder Vote on Certain Transactions

The Companies Act 2006 provides for schemes of arrangement, which are arrangements or compromises between a company and any class of shareholders or creditors that are used in certain types of reconstructions, amalgamations, capital reorganizations or takeovers. These arrangements require:

- the approval at a shareholders' or creditors' meeting convened by order of the court, of a majority in number of shareholders or creditors representing 75% in value of the capital held by, or debt owed to, the class of shareholders, or class thereof present and voting, either in person or by proxy; and
- the approval of the court.

Generally, under Delaware law, unless the certificate of incorporation provides for the vote of a larger portion of the stock, completion of a merger, consolidation, sale, lease or exchange of all or substantially all of a corporation's assets or dissolution requires:

- the approval of the board of directors; and
- approval by the vote of the holders of a majority of the outstanding stock or, if the certificate of incorporation provides for more or less than one vote per share, a majority of the votes of the outstanding stock of a corporation entitled to vote on the matter.

Standard of Conduct for Directors

Under English law, a director owes various statutory and fiduciary duties to the company, including:

- to act in the way he considers, in good faith, would be most likely to promote the success of the company for the benefit of its shareholders as a whole, subject in certain specified circumstances to consider or act in the interests of the creditors of the company;
- to avoid a situation in which he has, or can have, a direct or indirect interest that conflicts, or possibly conflicts, with the interests of the company;
- to act in accordance with the company's constitution and only exercise his powers for the purposes for which they are conferred;
- to exercise independent judgement;
- to exercise reasonable care, skill and diligence;
- not to accept benefits from a third party conferred by reason of his being a director or doing, or not doing, anything as a director; and
- a duty to declare any interest that he has, whether directly or indirectly, in a proposed or existing transaction or arrangement with the company.

Delaware law does not contain specific provisions setting forth the standard of conduct of a director. The scope of the fiduciary duties of directors is generally determined by the courts of the State of Delaware. In general, directors have a duty to act without self-interest, on a well-informed basis and in a manner they reasonably believe to be in the best interest of the stockholders.

Directors of a Delaware corporation owe fiduciary duties of care and loyalty to the corporation and to its shareholders. The duty of care generally requires that a director act in good faith, with the care that an ordinarily prudent person would exercise under similar circumstances. Under this duty, a director must inform himself of all material information reasonably available regarding a significant transaction. The duty of loyalty requires that a director act in a manner he reasonably believes to be in the best interests of the corporation. He must not use his corporate position for personal gain or advantage. In general, but subject to certain exceptions, actions of a director are presumed to have been made on an informed basis, in good faith and in the honest belief that the action taken was in the best interests of the corporation. However, this presumption may be rebutted by evidence of a breach of one of the fiduciary duties. Delaware courts have also imposed a heightened standard of conduct upon directors of a Delaware corporation who take any action designed to defeat a threatened change in control of the corporation.

In addition, under Delaware law, when the board of directors of a Delaware corporation approves the sale or break-up of a corporation,

Shareholder Litigation

Under English law, generally, the company, rather than its shareholders, is the proper claimant in an action in respect of a wrong done to the company or where there is an irregularity in the company's internal management. Notwithstanding this general position, the Companies Act 2006 provides that (i) a court may allow a shareholder to bring a derivative claim (that is, an action in respect of and on behalf of the company) in respect of a cause of action arising from an act or omission involving a director's negligence, default, breach of duty or breach of trust and (ii) a shareholder may bring a claim for a court order where the company's affairs have been or are being conducted in a manner that is unfairly prejudicial to some or all of its shareholders.

the board of directors may, in certain circumstances, have a duty to obtain the highest value reasonably available to the shareholders.

Under Delaware law, a stockholder may initiate a derivative action to enforce a right of a corporation if the corporation fails to enforce the right itself. The complaint must:

- state that the plaintiff was a stockholder at the time of the transaction of which the plaintiff complains or that the plaintiff's shares thereafter devolved on the plaintiff by operation of law; and
- allege with particularity the efforts made by the plaintiff to obtain the action the plaintiff desires from the directors and the reasons for the plaintiff's failure to obtain the action; or
- State the reasons for not making the effort.

Additionally, the plaintiff must remain a stockholder through the duration of the derivative suit. The action will not be dismissed or compromised without the approval of the Delaware Court of Chancery.

DESCRIPTION OF AMERICAN DEPOSITARY SHARES

American Depositary Shares

Citibank, N.A., or Citibank, has agreed to act as the depositary for the ADSs. Citibank's depositary offices are located at 388 Greenwich Street, New York, New York 10013. ADSs represent ownership interests in securities that are on deposit with the depositary. ADSs may be represented by certificates that are commonly known as American Depositary Receipts, or ADRs. The depositary typically appoints a custodian to safekeep the securities on deposit. In this case, the custodian is Citibank, N.A., London Branch.

We have appointed Citibank as depositary pursuant to a deposit agreement. A copy of the deposit agreement is on file with the SEC under cover of a registration statement on Form F-6. You may obtain a copy of the deposit agreement from the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549 and from the SEC's website (www.sec.gov). Please refer to registration number 333-220392 when retrieving such copy.

We are providing you with a summary description of the material terms of the ADSs and of your material rights as an owner of ADSs. Please remember that summaries by their nature lack the precision of the information summarized and that the rights and obligations of an owner of ADSs will be determined by reference to the terms of the deposit agreement and not by this summary. We urge you to review the deposit agreement in its entirety.

Each ADS represents the right to receive, and to exercise the beneficial ownership interests in, one ordinary share that is on deposit with the depositary or custodian. An ADS also represents the right to receive, and to exercise the beneficial interests in, any other property received by the depositary or the custodian on behalf of the owner of the ADS but that has not been distributed to the owners of ADSs because of legal restrictions or practical considerations. We and the depositary may agree to change the ADS-to-share ratio by amending the deposit agreement. This amendment may give rise to, or change, the depositary fees payable by ADS owners. The custodian, the depositary and their respective nominees will hold all deposited property for the benefit of the holders and beneficial owners of ADSs. The deposited property does not constitute the proprietary assets of the depositary, the custodian or their nominees. Beneficial ownership in the deposited property will under the terms of the deposit agreement be vested in the beneficial owners of the ADSs. The depositary, the custodian and their respective nominees will be the record holders of the deposited property represented by the ADSs for the benefit of the holders and beneficial owners of the corresponding ADSs. A beneficial owner of ADSs may or may not be the holder of ADSs. Beneficial owners of ADSs will be able to receive, and to exercise beneficial ownership interests in, the deposited property only through the registered holders of the ADSs, the registered holders of the ADSs (on behalf of the applicable ADS owners) only through the depositary, and the depositary (on behalf of the owners of the corresponding ADSs) directly, or indirectly, through the custodian or their respective nominees, in each case upon the terms of the deposit agreement.

If you become an owner of ADSs, you will become a party to the deposit agreement and therefore will be bound to its terms and to the terms of any ADR that represents your ADSs. The deposit agreement and the ADR specify our rights and obligations as well as your rights and obligations as owner of ADSs and those of the depositary. As an ADS holder you appoint the depositary to act on your behalf in certain circumstances. The deposit agreement and the ADRs are governed by New York law. However, our obligations to the holders of ordinary shares will continue to be governed by the laws of England and Wales, which may be different from the laws in the United States.

In addition, applicable laws and regulations may require you to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. You are solely responsible for complying with such reporting requirements and obtaining such approvals. Neither the depositary, the custodian, us or any of their or our respective agents or affiliates shall be required to take any actions whatsoever on your behalf to satisfy such

[Table of Contents](#)

reporting requirements or obtain such regulatory approvals under applicable laws and regulations. You agree to comply with information requests from us pursuant to applicable laws, stock exchange rules and our Articles of Association. We may restrict transfers of ADSs and take other actions necessary to comply with any applicable ownership restrictions.

As an owner of ADSs, we will not treat you as one of our shareholders and you will not have direct shareholder rights. The depositary will hold on your behalf the shareholder rights attached to the ordinary shares underlying your ADSs. As an owner of ADSs you will be able to exercise the shareholders rights for the ordinary shares represented by your ADSs through the depositary only to the extent contemplated in the deposit agreement. To exercise any shareholder rights not contemplated in the deposit agreement you will, as an ADS owner, need to arrange for the cancellation of your ADSs and become a direct shareholder.

As an owner of ADSs, you may hold your ADSs either by means of an ADR registered in your name, through a brokerage or safekeeping account, or through an account established by the depositary in your name reflecting the registration of uncertificated ADSs directly on the books of the depositary (commonly referred to as the direct registration system or DRS). The direct registration system reflects the uncertificated (book-entry) registration of ownership of ADSs by the depositary. Under the direct registration system, ownership of ADSs is evidenced by periodic statements issued by the depositary to the holders of the ADSs. The direct registration system includes automated transfers between the depositary and The Depository Trust Company, or DTC, the central book-entry clearing and settlement system for equity securities in the United States. If you decide to hold your ADSs through your brokerage or safekeeping account, you must rely on the procedures of your broker or bank to assert your rights as ADS owner. Banks and brokers typically hold securities such as the ADSs through clearing and settlement systems such as DTC. The procedures of such clearing and settlement systems may limit your ability to exercise your rights as an owner of ADSs. Please consult with your broker or bank if you have any questions concerning these limitations and procedures. All ADSs held through DTC will be registered in the name of a nominee of DTC, which nominee will be the only “holder” of such ADSs for purposes of the deposit agreement and any applicable ADR. This summary description assumes you have opted to own the ADSs directly by means of an ADS registered in your name and, as such, we will refer to you as the “holder.” When we refer to “you,” we assume the reader owns ADSs and will own ADSs at the relevant time.

The registration of the ordinary shares in the name of the depositary or the custodian shall, to the maximum extent permitted by applicable law, vest in the depositary or the custodian the record ownership in the applicable ordinary shares with the beneficial ownership rights and interests in such ordinary shares being at all times vested with the beneficial owners of the ADSs representing the ordinary shares. The depositary or the custodian shall at all times be entitled to exercise the beneficial ownership rights in all deposited property, in each case only on behalf of the holders and beneficial owners of the ADSs representing the deposited property.

Dividends and Other Distributions

As a holder of ADSs, you generally have the right to receive the distributions we make on the securities deposited with the custodian. Your receipt of these distributions may be limited, however, by practical considerations and legal limitations. Holders of ADSs will receive such distributions under the terms of the deposit agreement in proportion to the number of ADSs held as of the specified record date, after deduction the applicable fees, taxes and expenses.

Distributions of Cash

Whenever we make a cash distribution for the securities on deposit with the custodian, we will deposit the funds with the custodian. Upon receipt of confirmation of the deposit of the requisite funds, the depositary will arrange for the funds to be converted into U.S. dollars and for the distribution of the U.S. dollars to the holders, subject to the laws and regulations of England and Wales. The conversion into U.S. dollars will take place only if practicable and if the U.S. dollars are transferable to the United States. The depositary will apply the same

[Table of Contents](#)

method for distributing the proceeds of the sale of any property (such as undistributed rights) held by the custodian in respect of securities on deposit.

The distribution of cash will be made net of the fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. The depository will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable holders and beneficial owners of ADSs until the distribution can be effected or the funds that the depository holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States.

Distributions of Shares

Whenever we make a free distribution of ordinary shares for the securities on deposit with the custodian, we will deposit the applicable number of ordinary shares with the custodian. Upon receipt of confirmation of such deposit, the depository will either distribute to holders new ADSs representing the ordinary shares deposited or modify the ADS-to-ordinary shares ratio, in which case each ADS you hold will represent rights and interests in the additional ordinary shares so deposited. Only whole new ADSs will be distributed. Fractional entitlements will be sold and the proceeds of such sale will be distributed as in the case of a cash distribution.

The distribution of new ADSs or the modification of the ADS-to-ordinary shares ratio upon a distribution of ordinary shares will be made net of the fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes or governmental charges, the depository may sell all or a portion of the new ordinary shares so distributed.

No such distribution of new ADSs will be made if it would violate a law (e.g., the U.S. securities laws) or if it is not operationally practicable. If the depository does not distribute new ADSs as described above, it may sell the ordinary shares received upon the terms described in the deposit agreement and will distribute the proceeds of the sale as in the case of a distribution of cash.

Distributions of Rights

Whenever we intend to distribute rights to purchase additional ordinary shares, we will give prior notice to the depository and we will assist the depository in determining whether it is lawful and reasonably practicable to distribute rights to purchase additional ADSs to holders.

The depository will establish procedures to distribute rights to purchase additional ADSs to holders and to enable such holders to exercise such rights if it is lawful and reasonably practicable to make the rights available to holders of ADSs, and if we provide all of the documentation contemplated in the deposit agreement (such as opinions to address the lawfulness of the transaction). You may have to pay fees, expenses, taxes and other governmental charges to subscribe for the new ADSs upon the exercise of your rights. The depository is not obligated to establish procedures to facilitate the distribution and exercise by holders of rights to purchase new ordinary shares other than in the form of ADSs.

The depository will *not* distribute the rights to you if:

- we do not timely request that the rights be distributed to you or we request that the rights not be distributed to you; or
- we fail to deliver satisfactory documents to the depository; or
- it is not reasonably practicable to distribute the rights.

The depository will sell the rights that are not exercised or not distributed if such sale is lawful and reasonably practicable. The proceeds of such sale will be distributed to holders as in the case of a cash distribution. If the depository is unable to sell the rights, it will allow the rights to lapse.

Elective Distributions

Whenever we intend to distribute a dividend payable at the election of shareholders either in cash or in additional shares, we will give prior notice thereof to the depositary and will indicate whether we wish the elective distribution to be made available to you. In such case, we will assist the depositary in determining whether such distribution is lawful and reasonably practicable.

The depositary will make the election available to you only if it is reasonably practicable and if we have provided all of the documentation contemplated in the deposit agreement. In such case, the depositary will establish procedures to enable you to elect to receive either cash or additional ADSs, in each case as described in the deposit agreement.

If the election is not made available to you, you will receive either cash or additional ADSs, depending on what a shareholder in England and Wales would receive upon failing to make an election, as more fully described in the deposit agreement.

Other Distributions

Whenever we intend to distribute property other than cash, ordinary shares or rights to purchase additional ordinary shares, we will notify the depositary in advance and will indicate whether we wish such distribution to be made to you. If so, we will assist the depositary in determining whether such distribution to holders is lawful and reasonably practicable.

If it is reasonably practicable to distribute such property to you and if we provide all of the documentation contemplated in the deposit agreement, the depositary will distribute the property to the holders in a manner it deems practicable.

The distribution will be made net of fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes and governmental charges, the depositary may sell all or a portion of the property received.

The depositary will *not* distribute the property to you and will sell the property if:

- we do not request that the property be distributed to you or if we ask that the property not be distributed to you; or
- we do not deliver satisfactory documents to the depositary; or
- the depositary determines that all or a portion of the distribution to you is not reasonably practicable.

The proceeds of such a sale will be distributed to holders as in the case of a cash distribution.

Redemption

Whenever we decide to redeem any of the securities on deposit with the custodian, we will notify the depositary in advance. If it is practicable and if we provide all of the documentation contemplated in the deposit agreement, the depositary will provide notice of the redemption to the holders.

The custodian will be instructed to surrender the shares being redeemed against payment of the applicable redemption price. The depositary will convert the redemption funds received into U.S. dollars upon the terms of the deposit agreement and will establish procedures to enable holders to receive the net proceeds from the redemption upon surrender of their ADSs to the depositary. You may have to pay fees, expenses, taxes and other governmental charges upon the redemption of your ADSs. If less than all ADSs are being redeemed, the ADSs to be retired will be selected by lot or on a *pro rata* basis, as the depositary may determine.

[Table of Contents](#)

Changes Affecting Ordinary Shares

The ordinary shares held on deposit for your ADSs may change from time to time. For example, there may be a change in nominal or par value, split-up, cancellation, consolidation or any other reclassification of such ordinary shares or a recapitalization, reorganization, merger, consolidation or sale of assets of our company.

If any such change were to occur, your ADSs would, to the extent permitted by law, represent the right to receive the property received or exchanged in respect of the ordinary shares held on deposit. The depositary may in such circumstances deliver new ADSs to you, amend the deposit agreement, the ADRs and the applicable registration statement(s) on Form F-6, call for the exchange of your existing ADSs for new ADSs and take any other actions that are appropriate to reflect as to the ADSs the change affecting the ordinary shares. If the depositary may not lawfully distribute such property to you, the depositary may sell such property and distribute the net proceeds to you as in the case of a cash distribution.

Issuance of ADSs upon Deposit of Ordinary Shares

Upon closing of this offering, the ordinary shares being offered pursuant to this prospectus will be deposited by us with the custodian. Upon receipt of confirmation of such deposit, the depositary will issue ADSs to the underwriters named in this prospectus.

After the closing of this offering, the depositary may create ADSs on your behalf if you or your broker deposit ordinary shares with the custodian. The depositary will deliver these ADSs to the person you indicate only after you pay any applicable issuance fees and any charges and taxes payable for the transfer of the ordinary shares to the custodian and provide such documentation as may be required pursuant to the deposit agreement. Your ability to deposit ordinary shares and receive ADSs may be limited by U.S. and England and Wales legal considerations applicable at the time of deposit.

The issuance of ADSs may be delayed until the depositary or the custodian receives confirmation that all required approvals have been given and that the ordinary shares have been duly transferred to the custodian. The depositary will only issue ADSs in whole numbers.

When you make a deposit of ordinary shares, you will be responsible for transferring good and valid title to the depositary. As such, you will be deemed to represent and warrant that:

- the ordinary shares are duly authorized, validly allotted and issued, fully paid, not subject to any call for the payment of further capital and legally obtained;
- all preemptive (and similar) rights, if any, with respect to such ordinary shares have been validly waived, disappplied or exercised;
- you are duly authorized to deposit the ordinary shares;
- the ordinary shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage or adverse claim, and are not, and the ADSs issuable upon such deposit will not be, “restricted securities” (as defined in the deposit agreement); and
- the ordinary shares presented for deposit have not been stripped of any rights or entitlements.

If any of the representations or warranties are incorrect in any way, we and the depositary may, at your cost and expense, take any and all actions necessary to correct the consequences of the misrepresentations.

Transfer, Combination and Split Up of ADRs

As an ADR holder, you will be entitled to transfer, combine or split up your ADRs and the ADSs evidenced thereby. For transfers of ADRs, you will have to surrender the ADRs to be transferred to the depositary and also must:

- ensure that the surrendered ADR is properly endorsed or otherwise in proper form for transfer;

[Table of Contents](#)

- provide such proof of identity and genuineness of signatures, and of such other matters contemplated in the deposit agreement, as the depositary deems appropriate;
- comply with applicable laws and regulations, including regulations imposed by us and the depositary consistent with the deposit agreement, the ADR and applicable law;
- provide any transfer stamps required by the State of New York or the United States; and
- pay all applicable fees, charges, expenses, taxes and other government charges payable by ADR holders pursuant to the terms of the deposit agreement, upon the transfer of ADRs.

To have your ADRs either combined or split up, you must surrender the ADRs in question to the depositary with your request to have them combined or split up, and you must pay all applicable fees, charges and expenses payable by ADR holders, pursuant to the terms of the deposit agreement, upon a combination or split up of ADRs.

Withdrawal of Ordinary Shares Upon Cancellation of ADSs

As a holder, you will be entitled to present your ADSs to the depositary for cancellation and then receive the corresponding number of underlying ordinary shares at the custodian's offices. Your ability to withdraw the ordinary shares held in respect of the ADSs may be limited by U.S. and England and Wales considerations applicable at the time of withdrawal. In order to withdraw the ordinary shares represented by your ADSs, you will be required to pay to the depositary the fees for cancellation of ADSs and any charges and taxes payable upon the transfer of the ordinary shares. You assume the risk for delivery of all funds and securities upon withdrawal. Once canceled, the ADSs will not have any rights under the deposit agreement.

If you hold ADSs registered in your name, the depositary may ask you to provide proof of identity and genuineness of any signature and such other documents as the depositary may deem appropriate before it will cancel your ADSs. The withdrawal of the ordinary shares represented by your ADSs may be delayed until the depositary receives satisfactory evidence of compliance with all applicable laws and regulations. Please keep in mind that the depositary will only accept ADSs for cancellation that represent a whole number of securities on deposit.

You will have the right to withdraw the securities represented by your ADSs at any time except as a result of:

- temporary delays that may arise because (i) the transfer books for the ordinary shares or ADSs are closed, or (ii) ordinary shares are immobilized on account of a shareholders' meeting or a payment of dividends;
- obligations to pay fees, taxes and similar charges; or
- restrictions imposed because of laws or regulations applicable to ADSs or the withdrawal of securities on deposit.

The deposit agreement may not be modified to impair your right to withdraw the securities represented by your ADSs except to comply with mandatory provisions of law.

Voting Rights

As a holder, you generally have the right under the deposit agreement to instruct the depositary to exercise the voting rights for the ordinary shares represented by your ADSs. The voting rights of holders of ordinary shares are described in "Description of Share Capital—Articles of Association" in this prospectus.

At our request, the depositary will distribute to you any notice of shareholders' meeting received from us together with information explaining how to instruct the depositary to exercise the voting rights of the securities represented by ADSs.

[Table of Contents](#)

If the depositary timely receives voting instructions from a holder of ADSs, it will endeavor to vote the securities (in person or by proxy) represented by the holder's ADSs as follows:

- *In the event of voting by show of hands*, the depositary will vote (or cause the custodian to vote) all ordinary held on deposit at that time in accordance with the voting instructions received from a majority of holders of ADSs who provide timely voting instructions.
- *In the event of voting by poll*, the depositary will vote (or cause the custodian to vote) the ordinary shares held on deposit in accordance with the voting instructions received from the holders of ADSs.

The depositary will not join in demanding a vote by poll.

Securities for which no voting instructions have been received will not be voted (except as otherwise contemplated herein). If voting is by poll and the depositary does not receive timely voting instructions from a holder of ADSs, such holder shall be deemed to have instructed the depositary to give a discretionary proxy to a person designated by us to vote the deposited securities represented by such ADSs in any manner such person wishes, which may not be in your best interests; provided, however, that no such discretionary proxy shall be given with respect to any matter to be voted upon as to which we inform the depositary that (a) we do not wish such proxy to be given, (b) substantial opposition exists, or (c) the rights of holders of deposited securities may be adversely affected. Please note that the ability of the depositary to carry out voting instructions may be limited by practical and legal limitations and the terms of the securities on deposit. We cannot assure you that you will receive voting materials in time to enable you to return voting instructions to the depositary in a timely manner.

Fees and Charges

As an ADS holder, you will be required to pay the following fees under the terms of the deposit agreement:

<u>Service</u>	<u>Fee</u>
Issuance of ADSs (e.g., an issuance of ADS upon a deposit of ordinary shares or upon a change in the ADS(s)-to-ordinary shares ratio), excluding ADS issuances as a result of distributions of ordinary shares	Up to \$0.05 per ADS issued
Cancellation of ADSs (e.g., a cancellation of ADSs for delivery of deposited property or upon a change in the ADS(s)-to-ordinary shares ratio)	Up to \$0.05 per ADS cancelled
Distribution of cash dividends or other cash distributions (e.g., upon a sale of rights and other entitlements)	Up to \$0.05 per ADS held
Distribution of ADSs pursuant to (i) share dividends or other distributions, or (ii) exercise of rights to purchase additional ADSs	Up to \$0.05 per ADS held
Distribution of securities other than ADSs or rights to purchase additional ADSs (e.g., upon a spin-off)	Up to \$0.05 per ADS held
ADS services	Up to \$0.05 per ADS held on the applicable record date(s) established by the depositary

As an ADS holder you will also be responsible to pay certain charges such as:

- taxes (including applicable interest and penalties) and other governmental charges;
- the registration fees as may from time to time be in effect for the registration of ordinary shares on the share register and applicable to transfers of ordinary shares to or from the name of the custodian, the depositary or any nominees upon the making of deposits and withdrawals, respectively;

Table of Contents

- certain cable, telex and facsimile transmission and delivery expenses;
- the expenses and charges incurred by the depositary in the conversion of foreign currency;
- the fees and expenses incurred by the depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to ordinary shares, ADSs and ADRs; and
- the fees and expenses incurred by the depositary, the custodian, or any nominee in connection with the servicing or delivery of deposited property.

ADS fees and charges payable upon (i) the issuance of ADSs, and (ii) the cancellation of ADSs are charged to the person to whom the ADSs are issued (in the case of ADS issuances) and to the person whose ADSs are cancelled (in the case of ADS cancellations). In the case of ADSs issued by the depositary into DTC, the ADS issuance and cancellation fees and charges may be deducted from distributions made through DTC, and may be charged to the DTC participant(s) receiving the ADSs being issued or the DTC participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the beneficial owner(s) and will be charged by the DTC participant(s) to the account of the applicable beneficial owner(s) in accordance with the procedures and practices of the DTC participants as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are charged to the holders as of the applicable ADS record date. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, holders as of the ADS record date will be invoiced for the amount of the ADS fees and charges and such ADS fees and charges may be deducted from distributions made to holders of ADSs. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC participants in accordance with the procedures and practices prescribed by DTC and the DTC participants in turn charge the amount of such ADS fees and charges to the beneficial owners for whom they hold ADSs.

In the event of refusal to pay the depositary fees or charges, the depositary may, under the terms of the deposit agreement, refuse the requested service until payment is received or may set off the amount of the depositary fees and charges from any distribution to be made to the ADS holder.

Certain of the depositary fees and charges (such as the ADS services fee) may become payable shortly after the closing of the ADS offering. Note that the fees and charges you may be required to pay may vary over time and may be changed by us and by the depositary. You will receive prior notice of such changes. The depositary may reimburse us for certain expenses incurred by us in respect of the ADR program, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as we and the depositary agree from time to time.

Amendments and Termination

We may agree with the depositary to modify the deposit agreement at any time without your consent. We undertake to give ADS holders 30 days' prior notice of any modifications that would materially prejudice any of their substantial rights under the deposit agreement. We will not consider to be materially prejudicial to your substantial rights any modifications or supplements that are reasonably necessary for the ADSs to be registered under the Securities Act or to be eligible for book-entry settlement, in each case without imposing or increasing the fees and charges you are required to pay. In addition, we may not be able to provide you with prior notice of any modifications or supplements that are required to accommodate compliance with applicable provisions of law.

You will be bound by the modifications to the deposit agreement if you continue to hold your ADSs after the modifications to the deposit agreement become effective. The deposit agreement cannot be amended to prevent you from withdrawing the ordinary shares represented by your ADSs (except as permitted by law).

[Table of Contents](#)

We have the right to direct the depositary to terminate the deposit agreement. Similarly, the depositary may in certain circumstances on its own initiative terminate the deposit agreement. In either case, the depositary must give notice to the holders at least 30 days before termination. Until termination, your rights under the deposit agreement will be unaffected.

Termination

After termination, the depositary will continue to collect distributions received (but will not distribute any such property until you request the cancellation of your ADSs) and may sell the securities held on deposit. After the sale, the depositary will hold the proceeds from such sale and any other funds then held for the holders of ADSs in a non-interest bearing account. At that point, the depositary will have no further obligations to ADS holders other than to account for the funds then held for the holders of ADSs still outstanding (after deduction of applicable fees, taxes and expenses).

In connection with the termination of the deposit agreement, the depositary may, but shall not be obligated to, independently and without the need for any action by us, make available to holders a means to withdraw the ordinary shares and other deposited securities represented by their ADSs and to direct the deposit of such ordinary shares and other deposited securities into an unsponsored American depositary shares program established by the depositary, upon such terms and conditions as the depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored American depositary shares program under the Securities Act, and to receipt by the depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the depositary.

Books of Depositary

The depositary will maintain ADS holder records at its depositary office. You may inspect such records at such office during regular business hours but solely for the purpose of communicating with other holders in the interest of business matters relating to the ADSs and the deposit agreement.

The depositary will maintain in New York facilities to record and process the issuance, cancellation, combination, split-up and transfer of ADSs. These facilities may be closed from time to time, to the extent not prohibited by law.

Transmission of Notices, Reports and Proxy Soliciting Material

The depositary will make available for your inspection at its office all communications that it receives from us as a holder of deposited securities that we make generally available to holders of deposited securities. Subject to the terms of the deposit agreement, the depositary will send you copies of those communications or otherwise make those communications available to you if we ask it to.

Limitations on Obligations and Liabilities

The deposit agreement limits our obligations and the depositary's obligations to you. Please note the following:

- We and the depositary are obligated only to take the actions specifically stated in the deposit agreement without negligence or bad faith.
- The depositary disclaims any liability for any failure to carry out voting instructions, for any manner in which a vote is cast or for the effect of any vote, provided it acts in good faith and in accordance with the terms of the deposit agreement.

Table of Contents

- The depository disclaims any liability for any failure to accurately determine the lawfulness or practicality of any action, for the content of any document forwarded to you on our behalf or for the accuracy of any translation of such a document, for the investment risks associated with investing in ordinary shares, for the validity or worth of the ordinary shares, for any tax consequences that result from the ownership of ADSs or other deposited property, for the credit-worthiness of any third party, for allowing any rights to lapse under the terms of the deposit agreement, for the timeliness of any of our notices or for our failure to give notice or for any act or omission of or information provided by DTC or any DTC participant.
- The depository shall not be liable for acts or omissions of any successor depository in connection with any matter arising wholly after the resignation or removal of the depository.
- We and the depository will not be obligated to perform any act that is inconsistent with the terms of the deposit agreement.
- We and the depository disclaim any liability if we or the depository are prevented or forbidden from or subject to any civil or criminal penalty or restraint on account of, or delayed in, doing or performing any act or thing required by the terms of the deposit agreement, by reason of any provision, present or future of any law or regulation, including regulations of any stock exchange or by reason of present or future provisions of our Articles of Association, or any provision of or governing the securities on deposit, or by reason of any act of God or war or other circumstances beyond our or the depository's control.
- We and the depository disclaim any liability by reason of any exercise of, or failure to exercise, any discretion provided for in the deposit agreement or in our Articles of Association or in any provisions of or governing the securities on deposit.
- We and the depository further disclaim any liability for any action or inaction in reliance on the advice or information received from legal counsel, accountants, any person presenting ordinary shares for deposit, any holder of ADSs or authorized representatives thereof, or any other person believed by either of us in good faith to be competent to give such advice or information.
- We and the depository also disclaim liability for the inability by any ADS holder or beneficiary owner to benefit from any distribution, offering, right or other benefit that is made available to holders of ordinary shares but is not, under the terms of the deposit agreement, made available to you.
- We and the depository may rely without any liability upon any written notice, request or other document believed to be genuine and to have been signed or presented by the proper parties.
- We and the depository also disclaim liability for any consequential or punitive damages for any breach of the terms of the deposit agreement.
- We and the depository disclaim liability arising out of losses, liabilities, taxes, charges or expenses resulting from the manner in which a holder or beneficial owner of ADSs holds ADSs, including resulting from holding ADSs through a brokerage account.
- No disclaimer of any Securities Act liability is intended by any provision of the deposit agreement.

Pre-Release Transactions

Subject to the terms and conditions of the deposit agreement, the depository may issue to broker/dealers ADSs before receiving a deposit of ordinary shares or release ordinary shares to broker/dealers before receiving ADSs for cancellation. These transactions are commonly referred to as "pre-release transactions," and are entered into between the depository and the applicable broker/dealer. The deposit agreement limits the aggregate size of pre-release transactions (not to exceed 30% of the ordinary shares on deposit in the aggregate, such limit being subject to change or disregard in the depository's discretion) and imposes a number of conditions on such transactions (e.g., the need to receive collateral, the type of collateral required, the representations required from brokers, etc.). The depository may retain the compensation received from the pre-release transactions.

[Table of Contents](#)

Taxes

You will be responsible for the taxes and other governmental charges payable on the ADSs and the securities represented by the ADSs. We, the depository and the custodian may deduct from any distribution the taxes and governmental charges payable by ADS holders and may sell any and all property on deposit to pay the taxes and governmental charges payable by ADS holders. You will be liable for any deficiency if the sale proceeds do not cover the taxes that are due.

The depository may refuse to issue ADSs, to deliver, transfer, split and combine ADRs or to release securities on deposit until all taxes and charges are paid by the applicable ADS holder. The depository and the custodian may take reasonable administrative actions to obtain tax refunds and reduced tax withholding for any distributions on your behalf. However, you may be required to provide to the depository and to the custodian proof of taxpayer status and residence and such other information as the depository and the custodian may require to fulfill legal obligations. You are required to indemnify us, the depository and the custodian for any claims with respect to taxes based on any tax benefit obtained for you.

Foreign Currency Conversion

The depository will arrange for the conversion of all foreign currency received into U.S. dollars if such conversion is practical, and it will distribute the U.S. dollars in accordance with the terms of the deposit agreement. You may have to pay fees and expenses incurred in converting foreign currency, such as fees and expenses incurred in complying with currency exchange controls and other governmental requirements.

If the conversion of foreign currency is not practical or lawful, or if any required approvals are denied or not obtainable at a reasonable cost or within a reasonable period, the depository may take any of the following actions in its discretion:

- Convert the foreign currency to the extent practical and lawful and distribute the U.S. dollars to the ADS holders for whom the conversion and distribution is lawful and practical.
- Distribute the foreign currency to ADS holders for whom the distribution is lawful and practical.
- Hold the foreign currency (without liability for interest) for the applicable ADS holders.

Governing Law/Waiver of Jury Trial

The deposit agreement and the ADRs will be interpreted in accordance with the laws of the State of New York. The rights of holders of ordinary shares (including ordinary shares represented by ADSs) are governed by the laws of England and Wales.

AS A PARTY TO THE DEPOSIT AGREEMENT, YOU WAIVE YOUR RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF THE DEPOSIT AGREEMENT OR THE ADRs AGAINST US OR THE DEPOSITARY.

SHARES AND ADSs ELIGIBLE FOR FUTURE SALE

Before this offering, there has been no public market for our ordinary shares or ADSs. Upon completion of this offering, we will have outstanding 30,881,641 ordinary shares (including 6,667,000 ordinary shares in the form of ADSs), after giving effect to the sale of 6,667,000 ADSs in this offering, assuming no exercise by the underwriters of their over-allotment option to purchase additional ADSs from us. All of the ADSs to be sold in this offering will be freely tradable without restriction under the Securities Act unless purchased by our “affiliates,” as that term is defined in Rule 144. ADSs or ordinary shares purchased by our affiliates may not be resold except pursuant to an effective registration statement or an exemption from registration, including the safe harbor under Rule 144 described below. In addition, following this offering, ordinary shares issuable pursuant to awards granted under our equity plans that are covered by a registration statement on Form S-8 will be freely tradable in the public market, subject to contractual and legal restrictions described below. The remaining ordinary shares outstanding after this offering will be “restricted securities,” as that term is defined in Rule 144, and we expect that substantially all of these restricted securities will be subject to the lock-up agreements described below. These restricted securities may be sold in the public market only if the sale is registered or pursuant to an exemption from registration, such as Rule 144.

Lock-Up Agreements

All of our directors and officers and the other existing holders of substantially all of our equity securities have agreed, subject to limited exceptions, not to offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, including the filing (or participation in the filing) of a registration statement with the Securities and Exchange Commission in respect of, or establish or increase a put equivalent position or liquidate or decrease a call equivalent position, with respect to, any ADSs, ordinary shares or securities convertible into, or exercisable or exchangeable for ADSs or ordinary shares of the Company, or publicly announce an intention to effect any such transaction, for a period of 180 days after the date of this prospectus, without the prior written consent of the representatives of the underwriters; provided that the restrictions in such lock-up agreements do not apply to ADSs purchased in this offering, among other exceptions. See the section titled “Underwriting.”

Rule 144

In general, a person who has beneficially owned our ordinary shares or ADSs that are restricted securities for at least six months would be entitled to sell such securities, provided that (i) such person is not deemed to have been one of our affiliates at the time of, or at any time during the 90 days preceding, a sale and (ii) we are subject to the Exchange Act periodic reporting requirements for at least 90 days before the sale. Persons who have beneficially owned our ordinary shares or ADSs that are restricted securities for at least six months but who are our affiliates at the time of, or any time during the 90 days preceding, a sale, would be subject to additional restrictions, by which such person would be entitled to sell within any three-month period only a number of securities that does not exceed the greater of either of the following:

- 1% of the number of our ordinary shares then outstanding, which will equal approximately 308,816 ordinary shares or ADSs immediately after this offering, assuming no exercise of the underwriters’ over-allotment option; or
- the average weekly trading volume of our ordinary shares in the form of ADSs on Nasdaq during the four calendar weeks preceding the filing of a notice on Form 144 with respect to the sale; provided, in each case, that we are subject to the Exchange Act periodic reporting requirements for at least 90 days before the sale. Such sales both by affiliates and by non-affiliates must also comply with the manner of sale, current public information and notice provisions of Rule 144 to the extent applicable.

Regulation S

Regulation S under the Securities Act provides that securities owned by any person may be sold without registration in the United States, provided that the sale is effected in an offshore transaction and no directed

[Table of Contents](#)

selling efforts are made in the United States (as these terms are defined in Regulation S), subject to certain other conditions. In general, this means that our ordinary shares may be sold in some manner outside the United States without requiring registration in the United States.

Rule 701

In general, under Rule 701 of the Securities Act as currently in effect, each of our employees, consultants or advisors who purchases our ordinary shares from us in connection with a compensatory share plan or other written agreement executed prior to the completion of this offering is eligible to resell such ordinary shares in reliance on Rule 144, but without compliance with some of the restrictions, including the holding period, contained in Rule 144.

Equity Incentive Plans

We intend to file with the SEC a registration statement on Form S-8 under the Securities Act covering the ordinary shares or ADSs reserved for issuance under our equity incentive plans. The registration statement is expected to be filed and become effective as soon as practicable after the closing of this offering. Accordingly, ordinary shares or ADSs registered under the registration statement will be available for sale in the open market following its effective date, subject to Rule 144 volume limitations and the lock-up agreements described above, if applicable.

TAXATION

Material U.S. Federal Income Tax Considerations

The following discussion describes the material U.S. federal income tax consequences to U.S. Holders (as defined below) under present law of the purchase, ownership and disposition of the ADSs. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended or the Code for purposes of this discussion, in effect as of the date of this prospectus and on U.S. Treasury regulations in effect or, in some cases, proposed, as of the date of this prospectus, as well as judicial and administrative interpretations thereof available on or before such date. All of the foregoing authorities are subject to change, which change could apply retroactively and could affect the tax consequences described below.

This discussion applies only to U.S. Holders that acquire the ADSs in the initial offering and hold the ADSs as capital assets for U.S. federal income tax purposes. It does not purport to be a comprehensive description of all tax considerations that may be relevant to a decision to purchase the ADSs by any particular investor. In particular, this discussion does not address tax considerations applicable to a U.S. Holder that may be subject to special tax rules, including, without limitation, a dealer in securities or currencies, a trader in securities that elects to use a mark-to-market method of accounting for securities holdings, banks, thrifts, or other financial institutions, an insurance company, a tax-exempt organization, a person that holds the ADSs as part of a hedge, straddle or conversion transaction for tax purposes, a person whose functional currency for tax purposes is not the U.S. dollar, certain former citizens or residents of the United States or a person that owns directly, indirectly or constructively 10% or more of the company's voting shares. Moreover, this description does not address the U.S. federal estate, gift, or alternative minimum tax consequences, or any state, local or non-U.S. tax consequences, of the acquisition, ownership and disposition of the ADSs. In addition, the discussion does not address tax consequences to an entity or arrangement treated as a partnership for U.S. federal income tax purposes that holds the ADSs, or a partner in such partnership. The U.S. federal income tax treatment of each partner of such partnership generally will depend upon the status of the partner and the activities of the partnership. Prospective purchasers that are partners in a partnership holding the ADSs are urged to consult their own tax advisers.

The discussion below of the U.S. federal income tax consequences to "U.S. Holders" will apply to an investor that is a beneficial owner of ADSs and that is, for U.S. federal income tax purposes,

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes) organized under the laws of the United States, any state therein or the District of Columbia;
- an estate whose income is subject to U.S. federal income taxation regardless of its source; or
- a trust that (i) is subject to the primary supervision of a court within the United States and subject to the control of one or more U.S. persons for all substantial decisions or (ii) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

For U.S. federal income tax purposes, a beneficial owner of ADSs generally will be treated as the owner of the underlying ordinary shares represented by such ADSs. Accordingly, deposits or withdrawals of the underlying ordinary shares for ADSs generally will not be subject to U.S. federal income tax.

Prospective purchases are urged to consult their tax advisors about the application of the U.S. federal income tax rules to their particular circumstances as well as the state, local, non-U.S. and other tax consequences to them of the purchase, ownership and disposition of the ADSs.

Passive Foreign Investment Company Considerations

In general, a corporation organized outside the United States will be classified as a passive foreign investment company, or PFIC, in a particular taxable year if either (i) 75% or more of the corporation's gross

[Table of Contents](#)

income for the taxable year is passive income or (ii) on average at least 50% of the value of the corporation's assets produce passive income or are held for the production of passive income. Passive income for this purpose generally includes, among other things, certain dividends, interest, royalties, rents and gains from commodities and securities transactions and from the sale or exchange of property that gives rise to passive income.

In making this determination, we will be treated as earning our proportionate share of any income and owning our proportionate share of any assets of any corporation in which we hold a 25% or greater interest (by value). Because PFIC status must be determined annually based on tests which are factual in nature, our PFIC status will depend on our income, assets and activities each year, including whether certain research and development tax credits received from the government of the United Kingdom will constitute gross income, and, if they do, whether they will constitute passive income for purposes of the PFIC income test. If we are classified as a PFIC for any taxable year, a U.S. Holder may be able to mitigate some of the resulting adverse U.S. federal income tax consequences described below with respect to owning the ADSs, provided that such U.S. Holder is eligible to make, and validly makes a "mark-to-market" election, described below. In certain circumstances a U.S. Holder can make a "qualified electing fund" election to mitigate some of the adverse tax consequences described with respect to an ownership interest in a PFIC by including in income its share of the PFIC's income on a current basis. However, we do not currently intend to prepare or provide the information that would enable a U.S. Holder to make a qualified electing fund election.

In the event that we are classified as a PFIC in any year in which a U.S. Holder holds the ADSs, and the "mark-to-market" election described below is not made by a taxable U.S. Holder, a special tax regime will apply with respect to such U.S. Holder to both (a) any gain realized on the sale or other disposition of the ADSs and (b) any "excess distribution" by us to such U.S. Holder (generally, such U.S. Holder's ratable portion of distributions received by such U.S. Holder in any year which are greater than 125% of the average annual distribution received by such U.S. Holder in the shorter of the three preceding years or such U.S. Holder's holding period for the ADSs). Any gain recognized by such U.S. Holder on a sale or other disposition (including a pledge) of the ADSs and any excess distribution would be allocated ratably over such U.S. Holder's holding period for the ADSs. The amounts allocated to the taxable year of the sale or other disposition and to any year before we became a PFIC would be taxed as ordinary income. The amount allocated to each other taxable year would be subject to tax at the highest rate in effect for individuals or corporations, as appropriate, for that taxable year, and the interest charge generally applicable to underpayments of tax would be imposed on taxes deemed to have been payable in for the relevant taxable PFIC years. Classification as a PFIC may also have other adverse tax consequences, including, in the case of U.S. Holders that are individuals, the denial of a step-up in the basis of such U.S. Holder's ADSs at death.

Based on current estimates of our gross income and gross assets, the nature of our business and our current business plan (all of which are subject to change), we believe that we will not be classified as a PFIC for the year ending December 31, 2017. The PFIC tests must be applied each year, and it is possible that we may become a PFIC in a future year.

Mark-to-Market Election

If we are a PFIC for any taxable year during which a U.S. Holder holds the ADSs, then in lieu of being subject to the special tax regime and interest charge rules discussed above, a U.S. Holder may make an election to include gain on the ADSs as ordinary income under a mark-to-market method, provided that the ADSs are treated as "regularly traded" on a "qualified exchange." In general, the ADSs will be treated as "regularly traded" for a given calendar year if more than a *de minimis* quantity of the ADSs are traded on a qualified exchange on at least 15 days during each calendar quarter of such calendar year. Although the U.S. Internal Revenue Service, or the IRS, has not published any authority identifying specific exchanges that may constitute "qualified exchanges," Treasury Regulations provide that a qualified exchange is (a) a U.S. securities exchange that is registered with the Securities and Exchange Commission, or the SEC, (b) the U.S. market system established pursuant to section 11A of the Securities and Exchange Act of 1934, or (c) a non-U.S. securities exchange that is

[Table of Contents](#)

regulated or supervised by a governmental authority of the country in which the market is located, provided that (i) such non-U.S. exchange has trading volume, listing, financial disclosure, surveillance and other requirements designed to prevent fraudulent and manipulative acts and practices, to remove impediments to and perfect the mechanism of a free and open, fair and orderly, market, and to protect investors; and the laws of the country in which such non-U.S. exchange is located and the rules of such non-U.S. exchange ensure that such requirements are actually enforced and (ii) the rules of such non-U.S. exchange effectively promote active trading of listed shares. We have received approval to list our ADSs on the Nasdaq Global Select Market, which is a U.S. securities exchange that is registered with the SEC. However, no assurance can be given that the ADSs will meet the requirements to be treated as “regularly traded” for purposes of the mark-to-market election. In addition, because a mark-to-market election cannot be made for any lower-tier PFICs that we may own, a U.S. Holder may continue to be subject to the special tax regime with respect to such holder’s indirect interest in any investments held by us that are treated as an equity interest in a PFIC for U.S. federal income tax purposes, including shares in any future subsidiary of ours that is treated as a PFIC.

If a U.S. Holder makes this mark-to-market election, such U.S. Holder will be required in any year in which we are a PFIC to include as ordinary income the excess of the fair market value of such U.S. Holder’s ADSs at year-end over its basis in those ADSs. In addition, the excess, if any, of such U.S. Holder’s basis in the ADSs over the fair market value of such U.S. Holder’s ADSs at year-end is deductible as an ordinary loss in an amount equal to the lesser of (i) the amount of the excess or (ii) the amount of the net mark-to-market gains that have been included in income in prior years by such U.S. Holder. Any gain recognized by such U.S. Holder upon the sale of such U.S. Holder’s ADSs will be taxed as ordinary income in the year of sale. Amounts treated as ordinary income will not be eligible for the preferential tax rate applicable to qualified dividend income or long-term capital gains. A U.S. Holder’s adjusted tax basis in the ADSs will be increased by the amount of any income inclusion and decreased by the amount of any deductions under the mark-to-market rules. If a U.S. Holder makes a mark-to-market election, it will be effective for the taxable year for which the election is made and all subsequent taxable years unless the ADSs are no longer regularly traded on a qualified exchange or the IRS consents to the revocation of the election.

Information Reporting Requirements

If we are a PFIC for any taxable year during which a U.S. Holder holds the ADSs, each such U.S. Holder generally will be required to file an annual information return on IRS Form 8621 containing such information as the U.S. Treasury Department may require. The failure to file IRS Form 8621 could result in the imposition of penalties and the extension of the statute of limitations with respect to U.S. federal income tax.

The U.S. federal income tax rules relating to PFICs are complex. U.S. Holders are urged to consult their tax advisors with respect to the purchase, ownership and disposition of the ADSs, the availability of the mark-to-market election and whether making the election would be advisable in their particular circumstances, and the IRS information reporting obligations with respect to the purchase, ownership and disposition of the ADSs.

Taxation of Dividends and Other Distributions on the ADSs

Subject to the discussion above under the heading “—Passive Foreign Investment Company Considerations,” generally, the gross amount of distributions made by us, if any, to a U.S. Holder with respect to the ADSs, before reduction for any non-U.S. taxes withheld therefrom, will be includable in gross income as a dividend to the extent that such distribution is paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). To the extent, if any, that the amount of any cash distribution exceeds our current and accumulated earnings and profits, it will be treated first as a tax-free return of such U.S. Holder’s tax basis in its ADSs, and to the extent the amount of the distribution exceeds such U.S. Holder’s tax basis, the excess will be taxed as capital gain. We do not intend to calculate our earnings and profits under U.S. federal income tax principles. Therefore, a U.S. Holder should expect that a distribution will generally

be treated as a dividend even if that distribution would otherwise be treated as a non-taxable return of capital or as capital gain under the rules described above. A dividend in respect of the ADSs will not be eligible for the dividends-received deduction allowed to corporations in respect of dividends received from other U.S. corporations. Non-corporate U.S. Holders may qualify for the lower rates of taxation with respect to dividends on ADSs applicable to long term capital gains (i.e., gains from the sale of capital assets held for more than one year), provided that certain conditions are met, including certain holding period requirements and the absence of certain risk reduction transactions. However, such reduced rate shall not apply if we are a PFIC for the taxable year in which we pay a dividend, or were a PFIC in the preceding taxable year. As indicated in the section titled “Dividends and Dividend Policy” herein, we intend to retain any earnings for use in our business and do not currently intend to pay dividends on our ordinary shares.

Subject to the paragraph below, dividends generally will constitute income from sources outside the United States, which may be relevant in calculating a U.S. Holder’s foreign tax credit limitation. Subject to certain conditions and limitations, non-U.S. tax withheld on dividends may be deducted from such U.S. Holder’s taxable income or credited against such U.S. Holder’s U.S. federal income tax liability. The limitation on foreign taxes eligible for credit is calculated separately with respect to specific classes of income. For this purpose, dividends that we distribute generally should constitute “passive category income,” or, in the case of certain U.S. Holders, “general category income.” A foreign tax credit for foreign taxes imposed on distributions may be denied if a U.S. Holder does not satisfy certain minimum holding period requirements.

Notwithstanding the paragraph above, if 50% or more of the ADSs are treated as held by U.S. persons, we will be treated as a “U.S.-owned foreign corporation.” In that case, dividends may be treated for U.S. foreign tax credit purposes as income from sources outside the United States to the extent paid out of our non-U.S. source earnings and profits, and as income from sources within the United States to the extent paid out of our U.S. source earnings and profits. There can be no assurance that we will not be treated as a U.S.-owned foreign corporation. If the dividends are taxed at the lower tax rates generally applicable to long-term capital gains (as discussed above), the amount of the dividend taken into account for purposes of calculating the U.S. foreign tax credit limitation will generally be limited to the gross amount of the dividend, multiplied by the preferential rate divided by the highest rate of tax normally applicable to dividends. The rules relating to the determination of the foreign tax credit are complex, and U.S. Holders are urged to consult their tax advisors to determine whether and to what extent such U.S. Holder will be entitled to a foreign tax credit.

Taxation of Dispositions of ADSs

Subject to the discussion above under “—Passive Foreign Investment Company Considerations,” a U.S. Holder will recognize taxable gain or loss on any sale, exchange or other taxable disposition of an ADS equal to the difference between the amount realized (the amount of cash (in U.S. dollars) plus the fair market value of any property received) for the ADS and such U.S. Holder’s tax basis (in U.S. dollars) in the ADS. The gain or loss will generally be capital gain or loss. Such capital gain or loss generally will be long-term capital gain taxable at a reduced rate for non-corporate U.S. Holders or long-term capital loss if, on the date of sale, exchange or other disposition, the ADSs were held by the U.S. Holder for more than one year. The deductibility of capital losses is subject to limitations. Any such gain or loss generally will be treated as U.S. source income or loss for U.S. foreign tax credit purposes.

Disposition of Foreign Currency

U.S. Holders are urged to consult their tax advisors regarding the tax consequences of receiving, converting or disposing of any non-U.S. currency received as dividends on our ADSs or on the sale or retirement of an ADS.

Tax on Net Investment Income

Additional 3.8% Medicare tax on some or all of such U.S. Holder’s “net investment income.” Net investment income generally includes income from the ADSs unless such income is derived in the ordinary

[Table of Contents](#)

course of the conduct of a trade or business (other than a trade or business that consists of certain passive or trading activities). You should consult your tax advisors regarding the effect this Medicare tax may have, if any, on your acquisition, ownership or disposition of the ADSs.

Information Reporting and Backup Withholding

Distributions with respect to ADSs and proceeds from the sale, exchange or disposition of ADSs may be subject to information reporting to the IRS, and possible U.S. backup withholding. Backup withholding will not apply, however, to a U.S. Holder who furnishes a correct taxpayer identification number and makes any other required certification or who is otherwise exempt from backup withholding. U.S. Holders who are required to establish their exempt status generally must provide such certification on U.S. Internal Revenue Service Form W-9. U.S. Holders are urged to consult their tax advisors regarding the application of the U.S. information reporting and backup withholding rules.

Backup withholding is not an additional tax. Amounts withheld as backup withholding may be credited against a U.S. Holder's U.S. federal income tax liability, and a U.S. Holder may obtain a refund of any excess amounts withheld under the backup withholding rules by filing the appropriate claim for refund with the IRS and furnishing any required information.

Foreign Financial Asset Information Reporting

U.S. Holders who are either individuals or certain domestic entities may be required to submit certain information to the IRS with respect to such holder's beneficial ownership of the ADSs, if such ADSs are not held on such holder's behalf by a financial institution, as our ordinary shares are considered "specified foreign financial assets." This law also imposes penalties and potential other adverse tax consequences if a U.S. Holder is required to submit such information to the IRS and fails to do so. U.S. Holders are urged to consult their tax advisors regarding the potential information reporting obligations that may be imposed with respect to the ownership and disposition of the ADSs.

The above description is not intended to constitute a complete analysis of all tax consequences relating to acquisition, ownership and disposition of the ADSs. Prospective purchases are urged to consult their tax advisors concerning the tax consequences related their particular circumstances.

United Kingdom Tax Considerations

The following is a general summary of certain United Kingdom tax considerations relating to the ownership and disposal of the ADSs and does not address all possible tax consequences relating to an investment in the ADSs. It is based on current U.K. tax law and published HM Revenue & Customs, or HMRC, practice as of the date of this prospectus, both of which are subject to change, possibly with retrospective effect.

This United Kingdom taxation section is written on the basis that the company is and remains resident for tax purposes in the United Kingdom only and will therefore be subject to the U.K. tax regime and not the U.S. tax regime (save as discussed in the section titled "Material U.S. Federal Income Tax Considerations" above). On this basis, dividends paid by the company will be regarded as U.K. dividends, not U.S. dividends.

Except as provided otherwise, this summary applies only to persons who are resident (and, in the case of individuals, domiciled) in the United Kingdom for tax purposes and who are not resident for tax purposes in any other jurisdiction, and do not have a permanent establishment or fixed base in any other jurisdiction with which the holding of the ADSs is connected. Such persons are referred to herein as U.K. Holders. Persons (a) who are not resident (or, if resident, are not domiciled) in the United Kingdom for tax purposes, including those individuals and companies who trade in the United Kingdom through a branch, agency or permanent establishment in the United Kingdom to which the ADSs are attributable, or (b) who are resident or otherwise subject to tax in a jurisdiction outside the United Kingdom, are recommended to seek the advice of professional advisers in relation to their taxation obligations.

[Table of Contents](#)

This summary is for general information only and is not intended to be, nor should it be considered to be, legal or tax advice to any particular investor. It does not address all of the tax considerations that may be relevant to specific investors in light of their particular circumstances or to investors subject to special treatment under U.K. tax law. In particular:

- this summary only applies to the absolute beneficial owners of the ADSs (and where the ADSs are not held through an Individual Savings Account or a Self-Invested Personal Pension) and any dividends paid in respect of the related ordinary shares or ADSs where the dividends are regarded for U.K. tax purposes as that person's own income (and not the income of some other person); and
- this summary: (a) only addresses the principal U.K. tax consequences for investors who hold the ADSs as capital assets, (b) does not address the tax consequences that may be relevant to certain special classes of investor such as dealers, brokers or traders in shares or securities and other persons who hold the ADSs otherwise than as an investment, (c) does not address the tax consequences for holders that are financial institutions, insurance companies, collective investment schemes, pension schemes, charities or tax-exempt organizations, (d) assumes that the holder is not an officer or employee of the company (or of any related company) and has not (and is not deemed to have) acquired the ADSs or related ordinary shares by virtue of an office or employment, and (e) assumes that the holder does not control or hold (and is not deemed to control or hold), either alone or together with one or more associated or connected persons, directly or indirectly (including through the holding of the related ordinary shares or ADSs), an interest of 10% or more in the issued share capital (or in any class thereof or ADSs), voting power, rights to profits or capital of the company, and is not otherwise connected with the company.

This summary further assumes that a holder of ADSs is the beneficial owner of the underlying ordinary shares for U.K. tax purposes.

Potential investors in ADSs should satisfy themselves prior to investing as to the overall tax consequences, including, specifically, the consequences under U.K. tax law and HMRC practice of the acquisition, ownership and disposal of ADSs in their own particular circumstances by consulting their own tax advisers. In particular, non-U.K. resident or domiciled persons are advised to consider the potential impact of any relevant double taxation agreements.

Taxation of dividends

Withholding Tax. Dividend payments in respect of ADSs or ordinary shares may be made without withholding or deduction for or on account of U.K. tax.

United Kingdom Income Tax. An individual U.K. Holder (being an individual who is resident for tax purposes in the United Kingdom) who receives a dividend from the company will generally be subject to income tax on the dividend. An individual U.K. Holder will generally pay tax at a rate of zero per cent on the first £5,000 of dividends received by such U.K. Holder. Finance Bill 2017, or the Bill, as published on September 8, 2017, contained a provision reducing the current £5,000 limit in respect of the tax-free allowance to £2,000 from April 2018. The Bill is expected to become law later this year although it is possible that this provision will either be amended or will not be retained in the resulting Finance Act.

An individual U.K. Holder who is subject to income tax at the basic rate will be liable to tax on the dividend at the rate of 7.5%. An individual U.K. Holder who is subject to income tax at the higher rate (but not the additional rate) will be liable to income tax on the dividend at the rate of 32.5% to the extent that such sum, when treated as the top slice of that holder's income, exceeds the threshold for higher rate income tax.

An individual U.K. Holder liable to income tax at the additional rate will be subject to income tax on the dividend at the rate of 38.1% to the extent that the holder's income (including the dividend) exceeds the threshold for the additional rate.

[Table of Contents](#)

An individual who is not a U.K. Holder (other than one carrying on a trade, profession or vocation in the United Kingdom) who is resident for tax purposes outside the United Kingdom will not have any U.K. tax to pay on dividends received from the company.

United Kingdom Corporation Tax. A U.K. Holder within the charge to U.K. corporation tax may be entitled to exemption from U.K. corporation tax in respect of dividend payments. If the conditions for the exemption are not satisfied, or such United Kingdom Holder elects for an otherwise exempt dividend to be taxable, United Kingdom corporation tax will be chargeable on the amount of any dividends. The main rate of United Kingdom corporation tax for the 2017/2018 tax year is 19%. If potential investors are in any doubt as to their position, they should consult their own professional advisers.

A corporate holder of ADSs that is not a U.K. Holder will not be subject to U.K. corporation tax on dividends received from the company, unless it carries on a trade in the United Kingdom through a permanent establishment to which the ordinary shares or the ADSs are attributable. In these circumstances, such holder may, depending on its individual circumstances and if the exemption from U.K. corporation tax discussed above does not apply, be chargeable to U.K. corporation tax on dividends received from the company.

Taxation of Disposals

U.K. Holders. A disposal or deemed disposal of ADSs by an individual U.K. Holder may, depending on his or her individual circumstances, give rise to a chargeable gain or to an allowable loss for the purpose of U.K. capital gains tax. The principal factors that will determine the capital gains tax position on a disposal of ADSs are the extent to which the holder realizes any other capital gains in the tax year in which the disposal is made, the extent to which the holder has incurred capital losses in that or any earlier tax year and the level of the annual allowance of tax-free gains in that tax year (the “annual exemption”). The annual exemption for the 2017/2018 tax year is £11,300. If, after all allowable deductions, an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate becomes liable to U.K. capital gains tax on the disposal of ordinary shares or ADSs, the current applicable rate would be 20%. For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and, after all allowable deductions, liable to U.K. capital gains tax on such disposal, the current applicable rate would be 10%, save to the extent that any capital gains exceed the unused basic rate tax band. In that case, the current rate applicable to the excess would be 20%.

An individual U.K. Holder who ceases to be resident in the United Kingdom (or who fails to be regarded as resident in a territory outside the United Kingdom for the purposes of double taxation relief) for a period of less than five years and who disposes of his or her ADSs during that period of temporary non-residence may be liable to U.K. capital gains tax on a chargeable gain accruing on such disposal on his or her return to the United Kingdom (or upon ceasing to be regarded as resident outside the United Kingdom for the purposes of double taxation relief) (subject to available exemptions or reliefs).

A disposal of ADSs by a corporate U.K. Holder may give rise to a chargeable gain or an allowable loss for the purpose of U.K. corporation tax. Such a holder should be entitled to an indexation allowance, which applies to reduce capital gains to the extent that such gains arise due to inflation. The allowance may reduce a chargeable gain but will not create or increase an allowable loss.

Non-United Kingdom Holders. An individual holder who is not a U.K. Holder will not be liable to U.K. capital gains tax on capital gains realized on the disposal of his or her ADSs unless such holder carries on (whether solely or in partnership) a trade, profession or vocation in the United Kingdom through a branch or agency in the United Kingdom to which the ADSs are attributable. In these circumstances, such holder may, depending on his or her individual circumstances, be chargeable to U.K. capital gains tax on chargeable gains arising from a disposal of his or her ADSs.

[Table of Contents](#)

A corporate holder of ADSs that is not a U.K. Holder will not be liable for U.K. corporation tax on chargeable gains realized on the disposal of its ADSs unless it carries on a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable. In these circumstances, a disposal of ADSs by such holder may give rise to a chargeable gain or an allowable loss for the purposes of U.K. corporation tax.

Inheritance Tax

If, for the purposes of the Taxes on Estates of Deceased Persons and on Gifts Treaty 1978 between the United States and the United Kingdom (enacted in the United Kingdom as Statutory Instrument No 1454 of 1979), an individual holder is domiciled in the United States and is not a national of the United Kingdom, any ADSs beneficially owned by that holder will not generally be subject to U.K. inheritance tax on that holder's death or on a gift made by that holder during his or her lifetime, provided that any applicable U.S. federal gift or estate tax liability is paid, except where (i) the ADSs are part of the business property of a U.K. permanent establishment or pertain to a U.K. fixed base used for the performance of independent personal services; or (ii) the ADSs are comprised in a settlement unless, at the time the settlement was made, the settlor was domiciled in the United States and not a national of the United Kingdom.

Stamp Duty and Stamp Duty Reserve Tax

The statements below in relation to U.K. stamp duty and stamp duty reserve tax, or SDRT, apply irrespective of whether the relevant holder of ADSs is resident or domiciled in the United Kingdom.

Issue and Transfer of Ordinary Shares

Issue (including to a depositary or clearance service). No U.K. stamp duty is payable on the issue of the ordinary shares.

Based on current published HMRC practice and recent case law, there should be no SDRT payable on the issue of ordinary shares to a depositary receipt system or a clearance service. We understand that HMRC recognizes DTC as a clearance service for United Kingdom stamp duty and SDRT purposes.

Transfer to a depositary or clearance service. Transfers of ordinary shares to, or to a nominee or agent for, a person whose business is or includes issuing depositary receipts or the provision of clearance services, will generally be regarded by HMRC as subject to stamp duty or SDRT at a rate of 1.5% of the amount or value of the consideration or, in certain circumstances, the value of the ordinary shares transferred unless such transfer can be regarded as an integral part of an issue of share capital. We anticipate that this liability for stamp duty or SDRT would be borne by the person depositing the relevant shares in the depositary receipt system or clearance service. Transfers of ordinary shares between depositary receipt systems and clearance services will generally be exempt from stamp duty and SDRT unless, in the case of a clearance service, it has made an election under section 97A(1) Finance Act 1986. Our understanding is that DTC has not made such an election.

Transfer on sale. The transfer on sale of ordinary shares by a written instrument of transfer will generally be liable to U.K. stamp duty at the rate of 0.5% of the amount or value of the consideration for the transfer. The purchaser normally pays the stamp duty.

The transfer of ordinary shares within a depositary receipt system or clearance service should not be subject to stamp duty or SDRT, except where a clearance service has made an election under section 97A(1) Finance Act 1986. Our understanding is that DTC has not made such an election.

An agreement to transfer ordinary shares outside a depositary receipt system or a clearance service will generally give rise to a liability on the purchaser to SDRT at the rate of 0.5% of the amount or value of the

[Table of Contents](#)

consideration. Such SDRT is payable on the seventh day of the month following the month in which the charge arises, but where an instrument of transfer is executed and duly stamped before the expiry of a period of six years beginning with the date of that agreement, (i) any SDRT that has not been paid ceases to be payable, and (ii) any SDRT that has been paid may be recovered from HMRC, generally with interest.

Transfer of ADSs

No U.K. stamp duty will be payable on a written instrument transferring an ADS or on a written agreement to transfer an ADS provided that the instrument of transfer or the agreement to transfer is executed and remains at all times outside the United Kingdom. Where these conditions are not met, the written instrument for the transfer of, or written agreement to transfer, an ADS could, depending on the circumstances, attract a charge to U.K. stamp duty at the rate of 0.5% of the value of the consideration given in connection with the transfer.

No SDRT will be payable in respect of an agreement to transfer an ADS.

UNDERWRITING

Citigroup Global Markets Inc., Jefferies LLC and Cowen and Company, LLC are acting as joint book-running managers for the offering and as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement, dated the date of this prospectus, each underwriter named below has severally agreed to purchase, and we have agreed to sell to that underwriter, the number of ADSs set forth opposite the underwriter's name.

<u>Underwriter</u>	<u>Number of ADSs</u>
Citigroup Global Markets Inc.	2,333,450
Jefferies LLC	2,000,100
Cowen and Company, LLC	1,500,075
William Blair & Company, L.L.C.	833,375
Total	<u>6,667,000</u>

The underwriting agreement provides that the obligations of the underwriters to purchase the ADSs included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the ADSs (other than those covered by the over-allotment option described below) if they purchase any of the ADSs.

ADSs sold by the underwriters to the public will initially be offered at the initial public offering price set forth on the cover of this prospectus. Any ADSs sold by the underwriters to securities dealers may be sold at a discount from the initial public offering price not to exceed \$0.63 per ADS. If all the ADSs are not sold at the initial offering price, the underwriters may change the offering price and the other selling terms. The representatives have advised us that the underwriters do not intend to make sales to discretionary accounts. Delivery of the ADSs will be made against payment in New York, New York on or about October 2, 2017.

If the underwriters sell more ADSs than the total number set forth in the table above, we have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to 1,000,050 additional ADSs at the initial public offering price less the underwriting discount. The underwriters may exercise the option solely for the purpose of covering over-allotments, if any, in connection with the offering. To the extent the option is exercised, each underwriter must purchase a number of additional ADSs approximately proportionate to that underwriter's initial purchase commitment set forth in the table above. Any ADSs issued or sold under the option will be issued and sold on the same terms and conditions as the other ADSs that are the subject of this offering.

We, our officers and directors and substantially all of our other securityholders have agreed that, subject to specified limited exceptions, for a period of 180 days from the date of this prospectus, we and they will not, without the prior written consent of Citigroup Global Markets Inc., Jefferies LLC and Cowen and Company, LLC, offer, sell, contract, sell, pledge or otherwise dispose of, including the filing of a registration statement in respect of, or hedge any of our ordinary shares, ADSs, or any securities convertible into, or exercisable or exchangeable for our ordinary shares; provided, that these restrictions do not apply to ADSs purchased in this offering, among other exceptions. Citigroup Global Markets Inc., Jefferies LLC and Cowen and Company, LLC in their sole discretion may release any of the securities subject to these lock-up agreements at any time, which, in the case of officers and directors, shall be with notice.

Prior to this offering, there has been no public market for our ADSs. Consequently, the initial public offering price for our ADSs was determined by negotiations between us and the representatives. Among the factors considered in determining the initial public offering price were our results of operations, our current financial condition, our future prospects, our markets, the economic conditions in and future prospects for the

[Table of Contents](#)

industry in which we compete, our management, and currently prevailing general conditions in the equity securities markets, including current market valuations of publicly traded companies considered comparable to our company. We cannot assure you, however, that the price at which our ADSs will sell in the public market after this offering will not be lower than the initial public offering price or that an active trading market in our ADSs will develop and continue after this offering.

We have received approval to list our ADSs on the Nasdaq Global Select Market under the symbol “NCNA.”

The following table shows the offering price, underwriting discounts and commissions that we are to pay to the underwriters and proceeds to us, before expenses, in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters’ over-allotment option.

	Per ADS	Total	
		No exercise	Full exercise
Public offering price	\$ 15.00	\$ 100,005,000	\$ 115,005,750
Underwriting discounts and commissions paid by us	\$ 1.05	\$ 7,000,350	\$ 8,050,403
Proceeds to us, before expenses	\$ 13.95	\$ 93,004,650	\$ 106,955,347

We estimate that expenses payable by us in connection with this offering, exclusive of underwriting discounts and commissions, will be approximately \$2.3 million. We have also agreed to reimburse the underwriters for expenses in an amount up to \$30,000 relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc.

In connection with this offering, the underwriters may purchase and sell ADSs in the open market. Purchases and sales of ADSs in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to the underwriters’ over-allotment option, and other transactions that would stabilize, maintain or otherwise affect the price of our ADSs.

- Short sales involve secondary market sales by the underwriters of a greater number of ADSs than they are required to purchase in the offering.
 - “Covered” short sales are sales of ADSs in an amount up to the number of ADSs represented by the underwriters’ over-allotment option.
 - “Naked” short sales are sales of ADSs in an amount in excess of the number of ADSs represented by the underwriters’ over-allotment option.
- Covering transactions involve purchases of ADSs either pursuant to the underwriters’ over-allotment option or in the open market in order to cover short positions.
 - To close a naked short position, the underwriters must purchase ADSs in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the ADSs in the open market after pricing that could adversely affect investors who purchase in this offering.
 - To close a covered short position, the underwriters must purchase ADSs in the open market or exercise their over-allotment option. In determining the source of ADSs to close the covered short position, the underwriters will consider, among other things, the price of ADSs available for purchase in the open market as compared to the price at which they may purchase ADSs through the over-allotment option.
- As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of our common stock on the Nasdaq Global Select Market, as long as such bids do not exceed a specified maximum, to stabilize the price of the shares of our common stock.

[Table of Contents](#)

Certain of our existing shareholders have agreed to purchase an aggregate of 933,332 ADSs in this offering at the initial public offering price. The underwriters will receive the same underwriting discount on any securities purchased by these investors as they will on any other securities sold to the public in this offering.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of our ADSs. They may also cause the price of the ADSs to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on the NASDAQ Global Select Market, in the over-the-counter market or otherwise. The underwriters are not required to engage in any of these transactions and, may discontinue them at any time.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

A prospectus in electronic format may be made available on websites maintained by one or more of the underwriters or their respective affiliates. The representatives may agree with us to allocate a number of ADSs to underwriters for sale to their online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters' or their respective affiliates' websites and any information contained in any other website maintained by any of the underwriters or their respective affiliates is not part of this prospectus, has not been approved or endorsed by us or the underwriters and should not be relied upon by investors in this offering.

Conflicts of Interest

The underwriters are full-service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, principal investment, hedging, financing and brokerage activities. The underwriters and their respective affiliates may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (which may include bank loans and/or credit default swaps) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investments and securities activities may involve securities or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Notice to Prospective Investors in the European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of ADSs described in this prospectus may not be made to the public in that relevant member state other than:

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- to fewer than 100 or, if the relevant member state has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the relevant Dealer or Dealers nominated by us for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive;

[Table of Contents](#)

provided that no such offer of securities shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an “offer of securities to the public” in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and the expression “Prospectus Directive” means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the relevant member state) and includes any relevant implementing measure in the relevant member state. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

The sellers of the ADSs have not authorized and do not authorize the making of any offer of ADSs through any financial intermediary on their behalf, other than offers made by the underwriters with a view to the final placement of the ADSs as contemplated in this prospectus. Accordingly, no purchaser of the ADSs, other than the underwriters, is authorized to make any further offer of the ADSs on behalf of the sellers or the underwriters.

Notice to Prospective Investors in the United Kingdom

This prospectus is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order) or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a “relevant person”). This prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to Prospective Investors in Australia

No prospectus or other disclosure document, as defined in the Corporations Act 2001 (Cth) of Australia, or Corporations Act, in relation to our ADSs has been or will be lodged with the Australian Securities & Investments Commission, or ASIC. This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

- (a) you confirm and warrant that you are either:
 - (i) a “sophisticated investor” under section 708(8)(a) or (b) of the Corporations Act;
 - (ii) a “sophisticated investor” under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant’s certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;
 - (iii) a person associated with the company under section 708(12) of the Corporations Act; or
 - (iv) a “professional investor” within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act, any offer made to you under this document is void and incapable of acceptance; and
- (b) you warrant and agree that you will not offer any of our ADSs for resale in Australia within 12 months of that ADSs being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Notice to Prospective Investors in Canada

The ADSs may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the ADSs must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* ("NI 33-105"), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in Chile

The ADSs are not registered in the Securities Registry (Registro de Valores) or subject to the control of the Chilean Securities and Exchange Commission (Superintendencia de Valores y Seguros de Chile). This prospectus and other offering materials relating to the offer of the ADSs do not constitute a public offer of, or an invitation to subscribe for or purchase, the ADSs in the Republic of Chile, other than to individually identified purchasers pursuant to a private offering within the meaning of Article 4 of the Chilean Securities Market Act (Ley de Mercado de Valores) (an offer that is not "addressed to the public at large or to a certain sector or specific group of the public").

Notice to Prospective Investors in France

Neither this prospectus nor any other offering material relating to the ADSs described in this prospectus has been submitted to the clearance procedures of the *Autorité des Marchés Financiers* or of the competent authority of another member state of the European Economic Area and notified to the *Autorité des Marchés Financiers*. The ADSs have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus nor any other offering material relating to the ADSs has been or will be:

- released, issued, distributed or caused to be released, issued or distributed to the public in France; or
- used in connection with any offer for subscription or sale of the ADSs to the public in France.

Such offers, sales and distributions will be made in France only:

- to qualified investors (*investisseurs qualifiés*) and/or to a restricted circle of investors (*cercle restreint d'investisseurs*), in each case investing for their own account, all as defined in, and in accordance with articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French *Code monétaire et financier*;
- to investment services providers authorized to engage in portfolio management on behalf of third parties; or

[Table of Contents](#)

- in a transaction that, in accordance with article L.411-2-II-1° -or-2° -or 3° of the French *Code monétaire et financier* and article 211-2 of the General Regulations (*Règlement Général*) of the *Autorité des Marchés Financiers*, does not constitute a public offer (*appel public à l'épargne*).
- The ADSs may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French *Code monétaire et financier*.

Notice to Prospective Investors in Hong Kong

The ADSs may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a “prospectus” within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the ADSs may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to the ADSs which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to Prospective Investors in Japan

The ADSs offered in this prospectus have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The ADSs have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (i) pursuant to an exemption from the registration requirements of the Financial Instruments and Exchange Law and (ii) in compliance with any other applicable requirements of Japanese law.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the ADSs may not be circulated or distributed, nor may the ADSs be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the “SFA”), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

Where the ADSs are subscribed or purchased under Section 275 of the SFA by a relevant party which is:

- a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,
- securities of that corporation or the beneficiaries’ rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the securities pursuant to an offer made under Section 275 of the SFA except:

Table of Contents

- to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such securities of that corporation or such rights and interest in that trust are acquired at a consideration of not less than \$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions specified in Section 275 of the SFA;
- where no consideration is or will be given for the transfer; or
- where the transfer is by operation of law.

EXPENSES OF THE OFFERING

We estimate that the expenses payable by us in connection with this offering, other than the underwriting discounts and commissions, will be as follows:

	<u>Amount</u>
SEC registration fee	\$ 14,218
FINRA filing fee	18,901
Transfer agent and registrar fees and expenses	50,000
Nasdaq listing fee	125,000
Printing and engraving expenses	130,000
Legal fees and expenses	1,300,000
Accounting fees and expenses	450,000
Road show expenses	100,000
Miscellaneous costs	102,844
Total	<u>\$ 2,290,963</u>

All amounts in the table are estimates except the SEC registration fee, the Nasdaq listing fee and the FINRA filing fee.

LEGAL MATTERS

We are being represented by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. with respect to certain legal matters of U.S. federal securities and New York State law. The validity of our ordinary shares underlying the ADSs and certain matters governed by English law will be passed on for us by Bristows LLP. Legal counsel for the underwriters is Cooley LLP.

EXPERTS

The consolidated financial statements as of December 31, 2015 and December 31, 2016, and for each of the two years in the period ended December 31, 2016, appearing in this prospectus and the registration statement, have been audited by Ernst & Young LLP, an independent registered public accounting firm, as set forth in their report thereon appearing elsewhere, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

The registered business address of Ernst & Young LLP is 10 George Street, Edinburgh, EH2 2DZ, United Kingdom.

SERVICE OF PROCESS AND ENFORCEMENT OF JUDGMENTS

We are a public limited company incorporated under the laws of England and Wales. Certain of our directors and executive officers and experts named in this prospectus reside outside of the United States, and all or a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may be difficult for an investor to serve process on us or our directors and executive officers or to compel any of them to appear in Court in the United States or to enforce judgments obtained in U.S. courts against them or us, including judgments based on civil liability provisions of the securities laws of the United States. In addition, awards of punitive damages in actions brought in the United States or elsewhere may be unenforceable in the United Kingdom. An award for monetary damages under the U.S. securities laws would be considered punitive in the United Kingdom if it does not seek to compensate the claimant for loss or damage suffered and is intended to punish the defendant. The enforceability of any judgment in the United Kingdom will depend on the particular facts of the case as well as the laws and treaties in effect at the time. The United States and the United Kingdom do not currently have a treaty providing for the mutual recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters.

We have appointed Corporation Service Company as our authorized agent upon whom process may be served in any action instituted in any U.S. federal or state court having subject matter jurisdiction in the Borough of Manhattan in New York, New York, arising out of or based upon the ADSs, the deposit agreement or the underwriting agreement related to the ADSs.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form F-1, including amendments and relevant exhibits and schedules, under the Securities Act. This prospectus, which constitutes a part of the registration statement, summarizes material provisions of contracts and other documents that we refer to in the prospectus. Since this prospectus does not contain all of the information contained in the registration statement, you should read the registration statement and its exhibits and schedules for further information with respect to us and the ADSs. You may review and copy the registration statement, reports and other information we file at the SEC's public reference room at 100 F Street, N.E., Washington, D.C. 20549. You may also request copies of these documents upon payment of a duplicating fee by writing to the SEC. For further information on the public reference facility, please call the SEC at 1-800-SEC-0330. Our SEC filings, including the registration statement, are also available to you on the SEC's website at <http://www.sec.gov>.

[Table of Contents](#)

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Unaudited Consolidated Interim Statements of Operations for the six months ended June 30, 2017 and 2016	F-2
Unaudited Consolidated Interim Statements of Comprehensive Loss for the six months ended June 30, 2017 and 2016	F-3
Consolidated Statements of Financial Position	F-4
Unaudited Consolidated Interim Statements of Changes in Equity for the six months ended June 30, 2017 and 2016	F-5
Unaudited Consolidated Interim Statements of Cash Flows for the six months ended June 30, 2017 and 2016	F-6
Notes to the Unaudited Consolidated Interim Financial Statements	F-7
Report of Independent Registered Public Accounting Firm	F-14
Consolidated Statements of Operations for the years ended December 31, 2016 and 2015	F-15
Consolidated Statements of Comprehensive Loss for the years ended December 31, 2016 and 2015	F-16
Consolidated Statements of Financial Position as of December 31, 2016 and 2015	F-17
Consolidated Statements of Changes in Equity for the years ended December 31, 2016 and 2015	F-18
Consolidated Statements of Cash Flows for the years ended December 31, 2016 and 2015	F-19
Notes to the Consolidated Financial Statements	F-20

NUCANA BIOMED LIMITED
UNAUDITED CONSOLIDATED INTERIM STATEMENTS OF OPERATIONS
FOR THE SIX MONTHS ENDED JUNE 30,

	<u>Notes</u>	<u>2017</u>	<u>2016</u>
		(in thousands except per share data)	
		£	£
Research and development expenses		(3,689)	(3,784)
Administrative expenses		(637)	(908)
Initial public offering related expenses	3	(1,066)	—
Net foreign exchange (losses) gains		(161)	318
Operating loss		(5,553)	(4,374)
Finance income		91	167
Loss before tax		(5,462)	(4,207)
Income tax credit	4	1,077	1,090
Loss for the period		(4,385)	(3,117)
Basic and diluted loss per share	5	(0.18)	(0.13)

The accompanying notes form an integral part of these unaudited consolidated financial statements.

NUCANA BIOMED LIMITED
UNAUDITED CONSOLIDATED INTERIM STATEMENTS OF COMPREHENSIVE LOSS
FOR THE SIX MONTHS ENDED JUNE 30,

	<u>2017</u>	<u>2016</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Loss for the period	(4,385)	(3,117)
Other comprehensive expense:		
Items that may be reclassified subsequently to profit or loss:		
Exchange differences on translation of foreign operations	<u>(1)</u>	<u>4</u>
Other comprehensive (expense) income for the period	<u>(1)</u>	<u>4</u>
Total comprehensive loss for the period	<u>(4,386)</u>	<u>(3,113)</u>
Attributable to:		
Equity holders of the Company	<u>(4,386)</u>	<u>(3,113)</u>

The accompanying notes form an integral part of these unaudited consolidated financial statements.

NUCANA BIOMED LIMITED
CONSOLIDATED STATEMENTS OF FINANCIAL POSITION
AS AT

	<u>Notes</u>	<u>June 30,</u> <u>2017</u> <u>(unaudited)</u>	<u>December 31,</u> <u>2016</u>
		£	£
(in thousands)			
Assets			
Non-current assets			
Intangible assets	6	1,791	1,377
Property, plant and equipment		17	18
		<u>1,808</u>	<u>1,395</u>
Current assets			
Prepayments, accrued income and other receivables		2,882	3,634
Current income tax receivable		3,035	2,195
Cash and cash equivalents	7	15,918	19,990
		<u>21,835</u>	<u>25,819</u>
Total assets		<u><u>23,643</u></u>	<u><u>27,214</u></u>
Equity and liabilities			
Capital and reserves			
Share capital and share premium	10	967	43,433
Other reserves	11	47,061	4,064
Accumulated deficit		(26,641)	(22,256)
Total equity attributable to equity holders		<u>21,387</u>	<u>25,241</u>
Current liabilities			
Trade payables		570	728
Payroll taxes and social security		66	61
Accrued expenditure		1,620	1,184
		<u>2,256</u>	<u>1,973</u>
Total liabilities		<u>2,256</u>	<u>1,973</u>
Total equity and liabilities		<u><u>23,643</u></u>	<u><u>27,214</u></u>

The accompanying notes form an integral part of these unaudited consolidated financial statements.

NUCANA BIOMED LIMITED
UNAUDITED CONSOLIDATED INTERIM STATEMENTS OF CHANGES IN EQUITY
FOR THE SIX MONTHS ENDED JUNE 30,

	Share capital	Share premium	Own Share reserve	Share option reserve	Foreign currency translation reserve	Capital reserve	Accumulated deficit	Total equity attributable to equity holders
	£	£	£	£	(in thousands) £	£	£	£
Balance at December 31, 2015	659	42,574	(339)	3,291	(1)	—	(16,224)	29,960
Loss for the period	—	—	—	—	—	—	(3,117)	(3,117)
Other comprehensive income for the period	—	—	—	—	4	—	—	4
Total comprehensive income (loss) for the period	—	—	—	—	4	—	(3,117)	(3,113)
Share-based payments	—	—	—	139	—	—	—	139
Balance at June 30, 2016	659	42,574	(339)	3,430	3	—	(19,341)	26,986
Balance at December 31, 2016	663	42,770	(339)	4,406	(3)	—	(22,256)	25,241
Loss for the period	—	—	—	—	—	—	(4,385)	(4,385)
Other comprehensive loss for the period	—	—	—	—	(1)	—	—	(1)
Total comprehensive loss for the period	—	—	—	—	(1)	—	(4,385)	(4,386)
Share-based payments	—	—	—	532	—	—	—	532
Reduction in share premium	—	(42,466)	—	—	—	42,466	—	—
Balance at June 30, 2017	663	304	(339)	4,938	(4)	42,466	(26,641)	21,387

The accompanying notes form an integral part of these unaudited consolidated financial statements.

NUCANA BIOMED LIMITED
UNAUDITED CONSOLIDATED INTERIM STATEMENTS OF CASH FLOWS
FOR THE SIX MONTHS ENDED JUNE 30,

	<u>2017</u>	<u>2016</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Cash flows from operating activities		
Loss for the period	(4,385)	(3,117)
Adjustments for:		
Income tax credit	(1,077)	(1,090)
Amortization and depreciation	84	28
Finance income	(91)	(167)
Share-based payments	532	139
	<u>(4,937)</u>	<u>(4,207)</u>
Movements in working capital:		
Decrease (increase) in other receivables	746	(179)
(Decrease) increase in trade payables	(155)	170
Increase (decrease) in payroll taxes, social security and accrued expenditure	441	(164)
Movements in working capital	<u>1,032</u>	<u>(173)</u>
Cash used in operations	<u>(3,905)</u>	<u>(4,380)</u>
Corporation tax	235	—
Net cash used in operating activities	<u>(3,670)</u>	<u>(4,380)</u>
Cash flows from investing activities		
Interest received	98	235
Payments for office and computer equipment	(5)	(15)
Payments for intangible assets	(492)	(85)
Proceeds from short-term deposits	—	5,075
Net cash (used in) provided by investing activities	<u>(399)</u>	<u>5,210</u>
Net (decrease) increase in cash	(4,069)	830
Cash and cash equivalents at beginning of period	<u>19,990</u>	<u>14,112</u>
Foreign currency translation differences	(3)	9
Cash and cash equivalents at end of period	<u>15,918</u>	<u>14,951</u>

The accompanying notes form an integral part of these unaudited consolidated financial statements.

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

1. General information

NuCana BioMed Limited (“NuCana” or the “Company”) is a clinical-stage biopharmaceutical company developing a portfolio of new medicines to treat cancer. We are harnessing the power of phosphoramidate chemistry to generate new medicines called ProTides. These compounds have the potential to improve cancer treatment by enhancing the efficacy and safety of several current standards of care.

The Company is registered in England and Wales and domiciled in the United Kingdom.

The Company has two wholly owned subsidiaries, NuCana, Inc. and NuCana BioMed Trustee Company Limited.

2. Significant accounting policies

Basis of preparation

The interim condensed consolidated financial statements for the six months ended June 30, 2017 have been prepared in accordance with International Accounting Standard 34 “Interim Financial Reporting” (“IAS 34”). The accounting policies and methods of computation applied in the preparation of the interim financial statements are consistent with those applied in the Company’s annual financial statements for the year ended December 31, 2016.

The Company’s financial statements comprise the financial statements of the Company and its subsidiaries at June 30, 2017. The financial statements are presented in pounds sterling, which is also the Company’s functional currency. All values are rounded to the nearest thousand, except where otherwise indicated.

The interim consolidated financial statements do not include all the information and disclosures required in the annual financial statements, and should be read in conjunction with the Company’s annual financial statements as at December 31, 2016.

Going concern

In common with many companies in the biopharmaceutical sector, the Company incurs significant expenditure in its early years as it researches and develops its potential products for market.

The board of directors, having reviewed the operating budgets and development plans, consider that the Company has adequate resources to continue in operation for the foreseeable future. The board of directors is therefore satisfied that it is appropriate to adopt the going concern basis of accounting in preparing the financial statements. The Company believes that its cash and cash equivalents of £15.9 million at June 30, 2017, will be sufficient to fund its current operating plan for at least the next 12 months. As the Company continues to incur losses, the transition to profitability is dependent upon the successful development, approval and commercialization of its product candidates and achieving a level of revenues adequate to support its cost structure. The Company may never achieve profitability, and unless and until it does, it will continue to need to raise additional capital.

The Company intends to fund future operations through additional equity offerings and may seek additional capital through arrangements from other sources. There can be no assurances, however, that additional funding will be available on acceptable terms.

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

2. Significant accounting policies (continued)*Initial public offering (“IPO”) related expenses*

Incremental costs incurred and directly attributable to the expected offering of securities are deferred and deducted from the related proceeds of the offering. The net amount will be recorded as contributed shareholders’ equity in the period when such shares are issued. Other costs incurred in the offering will be expensed as incurred and included in IPO related costs.

Segment reporting

The Company operates in one operating segment. The Company’s chief operating decision maker (the “CODM”), its Chief Executive Officer, manages the Company’s operations on an integrated basis for the purposes of allocating resources. The Company’s principal operations and decision-making functions are located in the United Kingdom. The CODM makes decisions on a global basis from there. Accordingly, the Company has determined that it operates in a single reporting segment.

3. IPO related expenses

	For Six Months ended June 30,	
	2017	2016
	(in thousands)	
	£	£
IPO related expenses	1,066	—

IPO related expenses primarily relates to legal, accounting and other advisors’ fees in relation to the Company’s anticipated listing on the Nasdaq Global Market.

4. Income tax credit

The Company’s consolidated effective tax rate for the full financial year 2017 is estimated at 19.7% (December 31, 2016: 25.9%). Therefore, the consolidated effective tax rate used for the six months ended June 30, 2017 was 19.7% (June 30, 2016: 25.9%). The income tax credit for the six months ended June 30, 2017 is £1.1 million (June 30, 2016: £1.1 million).

There is no deferred tax charge for the six months ended June 30, 2017 (June 30, 2016: £nil).

5. Basic and diluted loss per share

	For Six Months ended June 30,	
	2017	2016
	(in thousands)	
	£	£
Loss for the period	(4,385)	(3,117)
Basic and diluted weighted average number of shares	24,185	24,101
Basic and diluted loss per share	(0.18)	(0.13)

Basic loss per share is calculated by dividing the loss for the period attributable to the equity holders of the Company by the weighted average number of shares outstanding during the period.

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

5. Basic and diluted loss per share (continued)

The dilutive effect of potential shares through equity settled transactions were considered to be anti-dilutive as they would have decreased the loss per share and were therefore excluded from the calculation of diluted loss per share.

6. Intangible assets

Intangible assets comprise patents with a carrying value of £1.7 million as of June 30, 2017 (as of December 31, 2016: £1.4 million) and computer software with a carrying value of £0.1 million as of June 30, 2017 (as of December 31, 2016: £7,000).

During the six months ended June 30, 2017, the Company acquired intangible assets with a cost of £0.5 million. The additions comprised £0.4 million in relation to patents and £0.1 million in relation to computer software (year ended December 31, 2016: £0.5 million on patents, £10,602 on computer software).

There were no disposals of assets in the six months ended June 30, 2017 (year ended December 31, 2016: £nil).

7. Cash and cash equivalents

	<u>June 30, 2017</u> (unaudited)	<u>December 31, 2016</u>
	(in thousands)	
	£	£
Cash and cash equivalents	<u>15,918</u>	<u>19,990</u>

Cash and cash equivalents comprise cash at bank with maturity of three months or less, which are subject to insignificant risk of changes in value. Cash at bank earns interest at fixed or variable rates based on the terms agreed for each account.

Cash and cash equivalents are measured at fair value and classified as Level 1 under the fair value level hierarchy.

8. Share-based payments

The Company has three share-based payment plans for employees, directors and consultants. The share options granted will be settled in equity.

On May 16, 2017, 23,250 share options were granted to a director under the U.K. share-based payment agreement, which will vest equally over a period of four years if the option holder remains a director of the Company. Upon vesting, each option allows the holder to purchase one ordinary share at a specified option price determined at grant date.

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

8. Share-based payments (continued)

The following principal assumptions were used in the valuation for share options:

	Options granted on May 16, 2017
Vesting dates	Oct 28, 2017 Oct 28, 2018 Oct 28, 2019 Oct 28, 2020
Volatility	66.56%
Dividend yield	0%
Risk-free investment rate	0.12%
Fair value of option at grant date	£ 7.70
Fair value of share at grant date	£ 11.08
Exercise price at date of grant	£ 4.00
Lapse date	May 16, 2027
Expected option life (years)	2.63
Number of options granted	23,250

The fair values of options granted were determined using the Black-Scholes model that takes into account factors specific to the share incentive plan such as the assumption that the options will be exercised at a single point in time, in December 2019. This has been incorporated into the measurement by means of actuarial modelling. As NuCana BioMed Limited was unlisted on the grant date of the options, it was not possible to derive historical volatility from the Company's own share price. The underlying expected volatility was therefore determined by using the historical volatility of similar listed entities as a proxy. The volatility percentage applied to each tranche is the average of the historical volatility of comparable companies to NuCana BioMed Limited.

The weighted average remaining contractual life of the share options outstanding as at June 30, 2017 is 5.71 years (June 30, 2016: 6.49).

For the six months ended June 30, 2017, the Company has recognized £0.5 million of share-based payment expense in the statement of operations (June 30, 2016: £0.1 million).

9. Related party disclosures*Compensation of key management personnel of the Company*

	For Six Months ended June 30,	
	2017	2016
	(in thousands)	
	£	£
Short-term employee benefits	446	612
Severance payments	—	150
Pension and other benefits	29	26
Share-based payments	355	123
	<u>830</u>	<u>911</u>

The amounts disclosed in the table above are the amounts recognized as an expense during the reporting period related to key management personnel.

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

10. Share capital and share premium

	June 30, 2017 (unaudited)	December 31, 2016
	(in thousands)	
	£	£
Share capital	663	663
Share premium	304	42,770
	<u>967</u>	<u>43,433</u>

<u>Issued share capital comprises:</u>	June 30, 2017 (unaudited)	December 31, 2016
	Number (in thousands)	
Ordinary shares of £0.01 each	6,239	6,239
Founder Ordinary 1 shares of £0.01 each	1,000	1,000
Founder Ordinary 2 shares of £0.01 each	1,000	1,000
Series A shares of £0.01 each	7,483	7,483
Series B shares of £0.001 each	8,463	8,463
	<u>24,185</u>	<u>24,185</u>

The table above does not total due to rounding.

In order to facilitate the Company being re-registered as a public company, the directors of the Company signed a solvency statement on June 29, 2017 with the agreement of the shareholders and undertook a capital reduction reducing its share premium by £42.5 million, from £42.8 million to £0.3 million with the amount by which the share premium was reduced credited to the Company's capital reserve.

Fully paid shares	No. of shares	Share capital (in thousands) £	Share premium £
Balance at December 31, 2016	24,185	663	42,770
Reduction in share premium account	—	—	(42,466)
Balance at June 30, 2017	<u>24,185</u>	<u>663</u>	<u>304</u>

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

11. Other reserves

	June 30, 2017	December 31, 2016
	(unaudited) (in thousands)	
Own share reserve	(339)	(339)
Foreign currency translation reserve	(4)	(3)
Share option reserve		
Balance at beginning of year	4,406	3,291
Share-based payments	532	1,132
Exercise of share options	—	(17)
Balance at end of year	<u>4,938</u>	<u>4,406</u>
Capital reserve		
Balance at beginning of year	—	—
Reduction in share premium account	42,466	—
Balance at end of year	<u>42,466</u>	<u>—</u>
Total other reserves	<u><u>47,061</u></u>	<u><u>4,064</u></u>

Foreign currency translation reserve

The foreign currency translation reserve is used to record exchange differences arising from the translation of the financial statements of foreign operations.

Own share reserve

The own share reserve represents the cost of 500,000 shares of NuCana BioMed Limited purchased by NuCana Employee Benefit Trust and that may, at the discretion of the trustee, be used to satisfy future exercise of options under the Company's share options plan.

Share option reserve

The share option reserve is used to recognize the value of equity-settled share-based payments provided to employees, directors and consultants as part of their remuneration.

Capital reserve

In order to facilitate the Company being re-registered as a public limited company, the directors of the Company signed a solvency statement on June 29, 2017, with the agreement of the shareholders and undertook a capital reduction reducing its share premium by £42.5 million, from £42.8 million to £0.3 million with the amount by which the share premium was reduced credited to the Company's capital reserve.

12. Events after the reporting period

On August 11, 2017 and August 31, 2017, the Company entered into new lease obligations for office space. The lease obligations are for a period of five years with a break clause after three years.

On August 29, 2017, the Company re-registered as a public limited company and changed its name to NuCana plc.

NUCANA BIOMED LIMITED
NOTES TO THE UNAUDITED CONSOLIDATED INTERIM FINANCIAL STATEMENTS

12. Events after the reporting period (continued)

On September 14, 2017, the Company completed a one-for-four reverse share split and an associated bonus allotment of shares to take into account fractional entitlements. This had the effect of consolidating every four ordinary shares of £0.01 to one ordinary share of £0.04, every four founder ordinary 1 shares of £0.01 to one founder ordinary 1 share of £0.04, every four founder ordinary 2 shares of £0.01 to one founder ordinary 2 share of £0.04, every four series A shares of £0.01 to one series A share of £0.04 and every four series B shares of £0.001 to one series B share of £0.004. After the reverse share split, the Company has 24,214,641 shares outstanding. This includes an issue of 30,000 shares in August 2017, upon the exercise of options.

As a result of the reverse share split, the exercise prices and the numbers of shares issuable upon the exercise of any outstanding options to purchase ordinary shares were proportionally adjusted pursuant to the respective anti-dilution terms of the share based payment plans. All references in these financial statements and accompanying notes to units of ordinary shares or per share amounts are reflective of the reverse share split for all periods presented.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors of NuCana plc:

We have audited the accompanying consolidated statements of financial position of NuCana plc (formerly known as NuCana Biomed Limited) (the “Company”) and subsidiaries as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, changes in equity and cash flows for each of the two years in the period ended December 31, 2016. These financial statements are the responsibility of the Company’s management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company’s internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company’s internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of NuCana plc and subsidiaries at December 31, 2016 and 2015, and the consolidated results of their operations and their cash flows for each of the two years in the period ended December 31, 2016, in conformity with International Financial Reporting Standards as issued by the International Accounting Standards Board.

/s/ Ernst & Young LLP
Edinburgh, United Kingdom

June 26, 2017, except for the restatement to give effect to the reverse share split described in Note 16 to the financial statements, as to which the date is September 18, 2017

NUCANA BIOMED LIMITED
CONSOLIDATED STATEMENTS OF OPERATIONS
YEAR ENDED DECEMBER 31,

	<u>Notes</u>	<u>2016</u>	<u>2015</u>
		(in thousands, except per-share data)	
		£	£
Research and development expenses		(7,904)	(5,655)
Administrative expenses		(1,143)	(1,251)
Net foreign exchange gains (losses)		599	(8)
Operating loss		(8,448)	(6,914)
Finance income		283	406
Loss before tax		(8,165)	(6,508)
Income tax credit	6	2,116	1,176
Loss for the year		(6,049)	(5,332)
Basic and diluted loss per share	4	(0.25)	(0.22)

The accompanying notes form an integral part of these consolidated financial statements.

NUCANA BIOMED LIMITED
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
YEAR ENDED DECEMBER 31,

	<u>Notes</u>	<u>2016</u> <u>(in thousands)</u> <u>£</u>	<u>2015</u> <u>£</u>
Loss for the year		(6,049)	(5,332)
Other comprehensive expense:			
Items that may be reclassified subsequently to profit or loss:			
Exchange differences on translation of foreign operations		(2)	(1)
Other comprehensive expense for the year		(2)	(1)
Total comprehensive loss for the year		<u>(6,051)</u>	<u>(5,333)</u>
Attributable to:			
Equity holders of the Company		<u>(6,051)</u>	<u>(5,333)</u>

The accompanying notes form an integral part of these consolidated financial statements.

NUCANA BIOMED LIMITED
CONSOLIDATED STATEMENTS OF FINANCIAL POSITION
AT DECEMBER 31,

	<u>Notes</u>	<u>December 31,</u> <u>2016</u>	<u>December 31,</u> <u>2015</u>
		(in thousands)	
		£	£
ASSETS			
Non-current assets			
Intangible assets	7	1,377	927
Property, plant and equipment	8	18	14
		<u>1,395</u>	<u>941</u>
Current assets			
Prepayments, accrued income and other receivables	9	3,634	375
Current income tax receivable	6	2,195	1,182
Short-term deposits	14	—	15,075
Cash and cash equivalents	14	19,990	14,112
		<u>25,819</u>	<u>30,744</u>
Total assets		<u>27,214</u>	<u>31,685</u>
EQUITY AND LIABILITIES			
Capital and reserves			
Share capital and share premium	10	43,433	43,233
Other reserves	11	4,064	2,951
Accumulated deficit		(22,256)	(16,224)
Total equity attributable to equity holders		<u>25,241</u>	<u>29,960</u>
Current liabilities			
Trade payables		728	507
Payroll taxes and social security		61	52
Accrued expenditure		1,184	1,160
Current income tax payable	6	—	6
		<u>1,973</u>	<u>1,725</u>
Total liabilities		<u>1,973</u>	<u>1,725</u>
Total equity and liabilities		<u>27,214</u>	<u>31,685</u>

The accompanying notes form an integral part of these consolidated financial statements.

NUCANA BIOMED LIMITED
CONSOLIDATED STATEMENTS OF CHANGES IN EQUITY
FOR THE YEAR ENDED DECEMBER 31,

	Share capital	Share premium	Own share reserve	Share option reserve	Foreign currency translation reserve	Accumulated deficit	Total equity attributable to equity holders
	£	£	£	£	£	£	£
	(in thousands)						
Balance at January 1, 2015	659	42,574	(339)	2,506	—	(10,892)	34,508
Loss for the year	—	—	—	—	—	(5,332)	(5,332)
Other comprehensive expense for the year	—	—	—	—	(1)	—	(1)
Total comprehensive loss for the year	—	—	—	—	(1)	(5,332)	(5,333)
Share-based payments	—	—	—	785	—	—	785
Balance at December 31, 2015	659	42,574	(339)	3,291	(1)	(16,224)	29,960
Loss for the year	—	—	—	—	—	(6,049)	(6,049)
Other comprehensive expense for the year	—	—	—	—	(2)	—	(2)
Total comprehensive loss for the year	—	—	—	—	(2)	(6,049)	(6,051)
Share-based payments	—	—	—	1,132	—	—	1,132
Exercise of share options	—	—	—	(17)	—	17	—
Issue of share capital	4	196	—	—	—	—	200
Balance at December 31, 2016	663	42,770	(339)	4,406	(3)	(22,256)	25,241

The accompanying notes form an integral part of these consolidated financial statements.

NUCANA BIOMED LIMITED
CONSOLIDATED STATEMENTS OF CASH FLOWS
FOR THE YEAR ENDED DECEMBER 31,

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Cash flows from operating activities		
Loss for the year	(6,049)	(5,332)
Adjustments for:		
Income tax credit	(2,116)	(1,176)
Amortization and depreciation	101	44
Finance income	(283)	(406)
Share-based payments	1,132	785
	<u>(7,215)</u>	<u>(6,085)</u>
Movements in working capital:		
(Increase) decrease in other receivables	(3,404)	36
Increase in trade payables	220	133
Increase in payroll taxes, social security and accrued expenditure	33	418
Movements in working capital	<u>(3,151)</u>	<u>587</u>
Cash used in operations	(10,366)	(5,498)
Corporation tax	1,102	1,031
Net cash used in operating activities	(9,264)	(4,467)
Cash flows from investing activities		
Interest received	410	290
Payments for office and computer equipment	(15)	(6)
Payments for intangible assets	(539)	(390)
Proceeds from (investment in) short-term deposits	15,075	(75)
Net cash provided by (used in) investing activities	14,931	(181)
Cash flows from financing activities		
Proceeds from issue of share capital	200	—
Net cash from financing activities	200	—
Net increase (decrease) in cash and cash equivalents	5,867	(4,648)
Cash and cash equivalents at beginning of year	14,112	18,761
Foreign currency translation differences	11	(1)
Cash and cash equivalents at end of year	19,990	14,112

The accompanying notes form an integral part of these consolidated financial statements.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

1. General information

NuCana BioMed Limited (“NuCana” or the “Company”) is a clinical-stage biopharmaceutical company developing a portfolio of new medicines to treat cancer. We are harnessing the power of phosphoramidate chemistry to generate new medicines called ProTides. These compounds have the potential to improve cancer treatment by enhancing the efficacy and safety of several current standards of care.

The Company is incorporated in England and Wales and domiciled in the United Kingdom.

The Company has two wholly owned subsidiaries, NuCana, Inc. and NuCana BioMed Trustee Company Limited. The financial statements for the Company were authorized for issue by the board of directors on June 26, 2017.

Re-registration

Prior to completion of the initial public offering (“IPO”), the Company intends to re-register as a public limited company and change its name to NuCana plc.

2. Significant accounting policies

Basis of preparation

The financial statements have been prepared in accordance with International Financial Reporting Standards (“IFRS”) as issued by the International Accounting Standards Board (“IASB”).

The Company’s financial statements comprise the financial statements of the Company and its subsidiaries at December 31, 2016. The financial statements are presented in pounds sterling, which is also the Company’s functional currency. All values are rounded to the nearest thousand, except where otherwise indicated.

Going concern

In common with many companies in the biopharmaceutical sector, the Company incurs significant expenditure in its early years as it researches and develops its potential products for market.

The board of directors, having reviewed the operating budgets and development plans, consider that the Company has adequate resources to continue in operation for the foreseeable future. The board of directors is therefore satisfied that it is appropriate to adopt the going concern basis of accounting in preparing the financial statements. The Company believes that its cash and cash equivalents of £20.0 million at December 31, 2016, will be sufficient to fund its current operating plan for at least the next 12 months. As the Company continues to incur losses, the transition to profitability is dependent upon the successful development, approval and commercialization of its product candidates and achieving a level of revenues adequate to support its cost structure. The Company may never achieve profitability, and unless and until it does, it will continue to need to raise additional capital.

The Company intends to fund future operations through additional equity offerings and may seek additional capital through arrangements from other sources. There can be no assurances, however, that additional funding will be available on acceptable terms.

Judgements and estimates

The preparation of the financial statements requires management to make estimates and assumptions that affect the amounts reported for assets and liabilities at the balance sheet dates and the amounts reported for

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

revenue and expenses during the year. The nature of estimations means that actual outcomes could differ from those estimates.

The following judgements have had the most significant effect on the amounts recognized in the financial statements:

Research and development expenses

The Company recognizes research and development expenses in the statement of operations in the period in which it is incurred. When development activities reach the advanced stage, as set out in the specific criteria of International Accounting Standard (“IAS”) 38, *Intangible Assets*, there will be a requirement to capitalize such costs as intangible assets. Management will continue to exercise judgement in the appropriate treatment of development costs.

Taxation

Management judgement is required to determine the amount of deferred tax assets that should be recognized, based upon the likely timing and level of future taxable profits. Further details are contained in Note 6.

The following estimate has had the most significant effect on the amounts recognized in the financial statements:

Share-based payments

Estimating fair value for share-based payment transactions requires determination of the most appropriate valuation model, which depends on the terms and conditions of the grant. This estimate also requires determination of the most appropriate inputs to the valuation model, including the expected life of the share option or appreciation right, volatility, dividend yield and making assumptions about them and, in the case of the Company, the value of an ordinary share. For the measurement of the fair value of equity-settled transactions with employees at the grant date, the Company uses the Black-Scholes model. The assumptions and models used for estimating fair value for share-based payment transactions are disclosed in Note 12.

Basis of consolidation

The consolidated financial statements comprise the financial statements of the Company as of December 31, 2016 and 2015.

Subsidiaries are consolidated from the date of acquisition, being the date on which the Company obtains control, and continue to be consolidated until the date when such control ceases. The financial statements of the subsidiaries are prepared for the same reporting period as the parent company, using consistent accounting policies. All intra-group balances, transactions, unrealized gains and losses resulting from intra-group transactions and dividends are eliminated in full.

Assets, liabilities, income and expenses of a subsidiary acquired or disposed of during the year are included in the consolidated financial statements from the date the Company gains control until the date the Company ceases to control the subsidiary.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

Segment reporting

The Company operates in one operating segment. The Company's chief operating decision maker (the "CODM"), its Chief Executive Officer, manages the Company's operations on an integrated basis for the purposes of allocating resources. The Company's principal operations and decision-making functions are located in the United Kingdom. The CODM makes decisions on a global basis from there. Accordingly, the Company has determined that it operates in a single reporting segment.

Property, plant and equipment

Office and computer equipment is stated at cost, net of accumulated depreciation and accumulated impairment losses, if any. There are no restrictions on title or equipment pledged as security for liabilities.

Depreciation is provided on office and computer equipment over their expected useful economic life as follows:

Asset class	Depreciation method and rate
Office and computer equipment	Straight-line over 3 years

Intangible assets

Intangible assets are stated at cost, net of accumulated amortization and accumulated impairment losses, if any. Cost in relation to patents includes registration, documentation and other legal fees associated with obtaining the patent. Software costs represent the initial purchase price of the asset.

The amortization method and period for the principal categories of intangible assets is calculated as follows:

Asset class	Amortization method and rate
Patents	Reverse sum of digits over 20 years
Computer software	Straight-line between 3 and 5 years

The amortization period and the amortization method for an intangible asset with a finite useful life are reviewed at least at each financial year-end. We also consider the profile of patents on a case-by-case basis and in appropriate circumstances we will use the straight-line method. Changes in the expected useful economic life or the expected pattern of consumption of future economic benefits embodied in the asset are accounted for by changing the amortization period or method, as appropriate. These changes are made on a prospective basis and treated as changes in accounting estimates.

Intangible assets are tested for impairment when a trigger event occurs.

Cash, cash equivalents and short-term deposits

Cash and cash equivalents in the statement of financial position include cash at banks with a maturity of less than three months, which are subject to an insignificant risk of changes in value.

Short-term deposits represent certificates of deposits with banks with maturities of greater than three months but less than one year.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

Research and development

Research and development expenses are currently recognized in the statement of operations in the year in which it is incurred. Development expenditures on an individual project will be recognized as an intangible asset when the Company can demonstrate:

- the technical feasibility of completing the intangible asset so that the asset will be available for use or sale;
- its intention to complete and its ability and intention to use or sell the asset;
- how the asset will generate future economic benefits;
- the availability of resources to complete the asset; and
- the ability to measure reliably the expenditure during development.

Income Taxes

Current income tax

Current income tax assets and liabilities are measured at the amount expected to be recovered from or paid to the taxation authorities. The tax rates and tax laws used to compute the amount are those that are enacted or substantively enacted at the reporting date in the countries where the Company operates and generates taxable income.

Deferred income tax

Deferred income tax is provided in full, using the liability method, on temporary differences arising between the tax bases of assets and liabilities and their carrying amounts in the Company's financial statements. However, the deferred income tax is not accounted for, if it arises from initial recognition of an asset or liability in a transaction other than a business combination that at the time of the transaction affects neither accounting nor taxable profit or loss. Deferred income tax is determined using tax rates and laws that have been enacted or substantially enacted by the balance sheet date and are expected to apply when the related deferred income tax asset is realized or the deferred tax liability is settled. Deferred tax assets are recognized to the extent that it is probable that future taxable profit will be available against which the temporary differences can be utilized.

Income tax credit

The Company benefits from the U.K. research and development tax credit regime whereby a portion of the Company's losses can be surrendered for a cash rebate of up to 33.35% of eligible expenditures. Such credits are accounted for within the tax provision, in the year in which the expenditures were incurred.

Operating leases

Leases where the lessor retains substantially all the risks and benefits of ownership of the asset are classified as operating leases and rentals payable are charged in the consolidated statement of operations on a straight-line basis over the lease term.

Impairment of non-financial assets

The Company assesses, at each reporting date, whether there is an indication that an asset may be impaired. If any indication exists, the Company estimates the asset's recoverable amount.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

An impairment loss is recognized whenever the carrying amount of an asset or its cash-generating unit exceeds its recoverable amount. Impairment losses are recognized in the consolidated statements of operations.

A cash-generating unit is the smallest identifiable group of assets that generates cash inflows that are largely independent of the cash inflows from other assets or groups of assets.

Calculation of recoverable amount

The recoverable amount of assets and cash-generating units is the higher of their fair value less costs to sell and value in use. In assessing value in use, the estimated future cash flows are discounted to their present value using a pre-tax discount rate that reflects current market assessments of the time value of money and the risks specific to the asset. For an asset that does not generate largely independent cash inflows, the recoverable amount is determined for the cash-generating unit to which the asset belongs.

Reversal of impairment

An assessment is made at each reporting date as to whether there is an indication that a previously recognized impairment loss may no longer exist or may have decreased. If such an indication exists, the recoverable amount is estimated.

A previously recognized impairment loss is reversed only if there has been a change in the estimates used to determine the recoverable amount since the last impairment loss was recognized. If that is the case, the carrying value is increased to its recoverable amount. An impairment loss is reversed only to the extent that the asset's carrying amount does not exceed the carrying amount that would have been determined, net of depreciation or amortization, if no impairment loss had been recognized.

Share-based payments

Employees, directors and consultants of the Company receive remuneration in the form of share-based payments, whereby individuals render services as consideration for equity instruments (share options).

Under IFRS 2 *Share-based Payment*, equity share-based payments are measured at the fair value of the equity instruments at the grant date. Details regarding the determination of fair value of equity settled share-based transactions are set out in Note 12.

The fair value determined at the grant date of equity settled share-based payments is expensed on a straight line basis over the vesting period, with a corresponding increase in equity to the share option reserve.

Fair value measurement

Fair value is based on the price that would be received from the sale of an asset or that would be paid to transfer a liability in an orderly transaction between market participants at the measurement date. In order to increase consistency and comparability in fair value measurements, IFRS 7 establishes a fair value hierarchy that prioritizes observable and unobservable inputs used to measure fair value into three broad levels, which are described as follows:

Level 1: Quoted (unadjusted) prices in active markets for identical assets or liabilities.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

Level 2: Other techniques for which all inputs that have a significant effect on the recorded fair value are observable, either directly or indirectly.

Level 3: Techniques that use inputs that have a significant effect on the recorded fair value that are not based on observable market data.

Accounting Standards

In preparing these financial statements, the Company has applied all relevant IAS, IFRS and International Financial Reporting Interpretations Committee (“IFRIC”) Interpretations as of the date of approval of these financial statements and which are mandatory for the financial year ended December 31, 2016.

The following accounting standards and interpretations have been adopted as of January 1, 2016 in these financial statements and have not had a material impact on the Company’s accounts in the period of initial application:

Amendments to IAS 1 Disclosure Initiative

The amendments to IAS 1 clarify, rather than significantly change, existing IAS 1 requirements. The amendments clarify:

- The materiality requirements in IAS 1
- That specific line items in the statement(s) of operations and other comprehensive income (“OCI”) and the statement of financial position may be disaggregated
- That entities have flexibility as to the order in which they present the notes to financial statements
- That the share of OCI of associates and joint ventures accounted for using the equity method must be presented in aggregate as a single line item, and classified between those items that will or will not be subsequently reclassified to profit or loss. Furthermore, the amendments clarify the requirements that apply when additional subtotals are presented in the statement of financial position and the statement(s) of operations and OCI.

Amendments to IAS 27: Equity Method in Separate Financial Statements

The amendments allow entities to use the equity method to account for investments in subsidiaries, joint ventures and associates in their separate financial statements. Entities already applying IFRS and electing to change to the equity method in their separate financial statements have to apply that change retrospectively.

Annual Improvements 2012-2014 Cycle

These improvements include:

IFRS 5 Non-current Assets Held for Sale

Assets (or disposal groups) are generally disposed of either through sale or distribution to the owners. The amendment clarifies that changing from one of these disposal methods to the other would not be considered a new plan of disposal, rather it is a continuation of the original plan. There is, therefore, no interruption of the application of the requirements in IFRS 5. This amendment is applied prospectively.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

IFRS 7 Financial Instruments: Disclosures

(i) *Servicing contracts*

The amendment clarifies that a servicing contract that includes a fee can constitute continuing involvement in a financial asset. An entity must assess the nature of the fee and the arrangement against the guidance for continuing involvement in IFRS 7 in order to assess whether the disclosures are required. The assessment of which servicing contracts constitute continuing involvement must be done retrospectively. However, the required disclosures need not be provided for any period beginning before the annual period in which the entity first applies the amendments.

(ii) *Applicability of the amendments to IFRS 7 to condensed interim financial statements*

The amendment clarifies that the offsetting disclosure requirements do not apply to condensed interim financial statements, unless such disclosures provide a significant update to the information reported in the most recent annual report. This amendment is applied retrospectively.

IAS 19 Employee Benefits

The amendment clarifies that market depth of high quality corporate bonds is assessed based on the currency in which the obligation is denominated, rather than the country where the obligation is located. When there is no deep market for high quality corporate bonds in that currency, government bond rates must be used. This amendment is applied prospectively.

IAS 34 Interim Financial Reporting

The amendment clarifies that the required interim disclosures must either be in the interim financial statements or incorporated by cross-reference between the interim financial statements and wherever they are included within the interim financial report (e.g., in the management commentary or risk report). The other information within the interim financial report must be available to users on the same terms as the interim financial statements and at the same time. This amendment is applied retrospectively.

Amendments to IAS 16 and IAS 38: Clarification of Acceptable Methods of Depreciation and Amortization

The amendments clarify the principle in IAS 16 *Property, Plant and Equipment* and IAS 38 *Intangible Assets* that revenue reflects a pattern of economic benefits that are generated from operating a business (of which the asset is a part) rather than the economic benefits that are consumed through use of the asset. As a result, a revenue-based method cannot be used to depreciate property, plant and equipment and may only be used in very limited circumstances to amortise intangible assets. The amendments are applied prospectively and do not have any impact on the Company, given that it has not used a revenue-based method to depreciate its non-current assets.

The IASB and IFRIC have issued the following standards and interpretations, which are considered relevant to the Company, with an effective date after the date of these financial statements.

Amendments to IAS 12: Recognition of Deferred Tax Assets for Unrealized Losses

The amendments clarify that an entity needs to consider whether tax law restricts the sources of taxable profits against which it may make deductions on the reversal of that deductible temporary difference. Furthermore, the amendments provide guidance on how an entity should determine future taxable profits and

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

explain the circumstances in which taxable profit may include the recovery of some assets for more than their carrying amount. Entities are required to apply the amendments retrospectively. However, on initial application of the amendments, the change in the opening equity of the earliest comparative period may be recognized in opening retained earnings (or in another component of equity, as appropriate), without allocating the change between opening retained earnings and other components of equity. Entities applying this relief must disclose that fact. These amendments are effective for annual periods beginning on or after January 1, 2017, with early application permitted. These amendments are not expected to have a material impact on the Company.

Amendments to IAS 7: Disclosure Initiative

The amendments to IAS 7 *Statement of Cash Flows* aim to help users of financial statements better understand changes in an entity's debt. The amendments require entities to provide disclosures about changes in their liabilities arising from financing activities, including both changes arising from cash flows and non-cash changes (such as foreign exchange gains or losses). This amendment is effective for annual periods on or after January 1, 2017. This amendment is not expected to have a material impact on the Company's disclosure.

IFRS 9: Financial Instruments

In July 2014, the IASB issued the final version of IFRS 9 *Financial Instruments* that replaces IAS 39 *Financial Instruments: Recognition and Measurement* and all previous versions of IFRS 9. IFRS 9 brings together all three aspects of the accounting for financial instruments project: classification and measurement, impairment and hedge accounting. IFRS 9 is effective for annual periods beginning on or after January 1, 2018, with early application permitted. Except for hedge accounting, retrospective application is required but providing comparative information is not compulsory. For hedge accounting, the requirements are generally applied prospectively, with some limited exceptions. The Company expects no material impact on its balance sheet and equity.

IFRS 16: Leases

IFRS 16 was issued in January 2016 and it replaces IAS 17 *Leases*, IFRIC 4 *Determining Whether an Arrangement Contains a Lease*, SIC-15 *Operating Leases-Incentives* and SIC-27 *Evaluating the Substance of Transactions Involving the Legal Form of a Lease*. IFRS 16 sets out the principles for the recognition, measurement, presentation and disclosure of leases and requires lessees to account for all leases under a single on-balance sheet model similar to the accounting for finance leases under IAS 17. The standard includes two recognition exemptions for lessees—leases of 'low-value' assets (e.g., personal computers) and short-term leases (i.e., leases with a lease term of 12 months or less). At the commencement date of a lease, a lessee will recognize a liability to make lease payments (i.e., the lease liability) and an asset representing the right to use the underlying asset during the lease term (i.e., the right-of-use asset). Lessees will be required to separately recognize the interest expense on the lease liability and the depreciation expense on the right-of-use asset. Lessees will also be required to remeasure the lease liability upon the occurrence of certain events (e.g., a change in the lease term, a change in future lease payments resulting from a change in an index or rate used to determine those payments). The lessee will generally recognize the amount of the remeasurement of the lease liability as an adjustment to the right-of-use asset.

Lessor accounting under IFRS 16 is substantially unchanged from today's accounting under IAS 17. Lessors will continue to classify all leases using the same classification principle as in IAS 17 and distinguish between two types of leases: operating and finance leases. IFRS 16 also requires lessees and lessors to make more

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

2. Significant accounting policies (continued)

extensive disclosures than under IAS 17. IFRS 16 is effective for annual periods beginning on or after January 1, 2019. Early application is permitted, but not before an entity applies IFRS 15 *Revenue from Contracts with Customers*. A lessee can choose to apply the standard using either a full retrospective or a modified retrospective approach. The standard's transition provisions permit certain reliefs. The Company is currently assessing the potential impact of IFRS 16 on its consolidated financial statements.

Amendments to IFRS 2: Classification and Measurement of Share-based Payment Transactions

The IASB issued amendments to IFRS 2 *Share-based Payment* that address three main areas: the effects of vesting conditions on the measurement of a cash-settled share-based payment transaction; the classification of a share-based payment transaction with net settlement features for withholding tax obligations; and accounting where a modification to the terms and conditions of a share-based payment transaction changes its classification from cash settled to equity settled. On adoption, entities are required to apply the amendments without restating prior periods, but retrospective application is permitted if elected for all three amendments and other criteria are met. The amendments are effective for annual periods beginning on or after January 1, 2018, with early application permitted. This amendment is not expected to have a material impact on the Company.

Annual Improvements to IFRSs 2014-2016 Cycle

IFRS 1 First-time Adoption of IFRS

This amendment deleted the short-term exemptions in paragraphs E3–E7 of IFRS 1, because they have now served their intended purpose.

IFRS 12 Disclosure of Interests in Other Entities

This amendment clarified the scope of the standard by specifying that the disclosure requirements in the standard, except for those in paragraphs B10–B16, apply to an entity's interests listed in paragraph 5 that are classified as held for sale, as held for distribution or as discontinued operations in accordance with IFRS 5 *Non-current Assets Held for Sale and Discontinued Operations*.

These amendments are not expected to have a material impact on the Company.

IFRIC Interpretation 22 Foreign Currency Transactions and Advance Consideration

The interpretation clarifies that in determining the spot exchange rate to use on initial recognition of a related asset, expense or income (or part of it) on the derecognition of a non-monetary asset or non-monetary liability relating to advance consideration, the date of the transaction is the date on which an entity initially recognises the non-monetary asset or non-monetary liability arising from the advance consideration. If there are multiple payments or receipts in advance, then the entity must determine a date of the transactions for each payment or receipt of advance consideration. This interpretation is not expected to have a material impact on the Company.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

3. Staff costs

Included in research and development expenses:

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Wages and salaries	2,241	1,366
Social security costs	205	151
Pension costs and other benefits	102	92
Share-based payments	1,027	709
	<u>3,575</u>	<u>2,318</u>

Included in administrative expenses:

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Wages and salaries	84	108
Social security costs	13	52
Pension costs and other benefits	7	15
Share-based payments	105	76
	<u>209</u>	<u>251</u>
Total employee benefit expense	<u>3,784</u>	<u>2,569</u>

The average number of staff employed under contracts of service were:

	<u>Number</u>	<u>Number</u>
Research and development activities	15	11
Administrative activities	1	1
	<u>16</u>	<u>12</u>

Directors' remuneration & other benefits

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Directors' remuneration	549	526
Pension and other benefits	34	77
	<u>583</u>	<u>603</u>

The number of directors who exercised share options in 2016 is 1 (2015: nil).

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

3. Staff costs (continued)

The above amounts for remuneration include the following in respect of the highest paid director:

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Directors' remuneration	378	318
Pension and other benefits	29	61
	<u>407</u>	<u>379</u>

4. Basic and diluted loss per share

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Loss for the year	(6,049)	(5,332)
Basic and diluted weighted average number of shares	24,107	24,101
	<u>£</u>	<u>£</u>
Basic and diluted loss per share	(0.25)	(0.22)

Basic loss per share is calculated by dividing the loss for the year attributable to the equity holders of the Company by the weighted average number of shares outstanding during the year.

The dilutive effect of potential shares through equity settled transactions were considered to be anti-dilutive as they would have decreased the loss per share and were therefore excluded from the calculation of diluted loss per share.

5. Operating lease arrangements

Operating leases relate to rental of office space. The leases are renewed for 12 or 24 months. All operating lease contracts contain clauses for market rental reviews on renewal. The Company does not have an option to purchase the leased office at the expiry of the lease periods. Operating lease expense for the years ended December 31, 2016 and 2015 was £0.2 million and £0.1 million, respectively.

Future minimum rentals payable under non-cancellable operating leases are as follows:

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Not later than 1 year	192	166
Later than 1 year and not later than 5 years	62	—
Later than 5 years	—	—
	<u>254</u>	<u>166</u>

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

6. Income tax credit

The major components of income tax for the years ended December 31, 2016 and 2015 are as follows:

	2016 (in thousands) £	2015 £
Current tax:		
In respect of current year U.K.	1,906	1,182
In respect of current year U.S.	(28)	(6)
In respect of prior years U.K.	235	—
In respect of prior years U.S.	3	—
Total current tax	2,116	1,176
Deferred tax	—	—
Current income tax receivable:		
U.K. tax	2,141	1,182
U.S. tax	54	—
Current income tax receivable	2,195	1,182
Current income tax payable:		
U.S. tax	—	6

The credit for the year can be reconciled to the loss per the statement of operations as follows:

	2016 (in thousands) £	2015 £
Loss before tax	(8,165)	(6,508)
Tax on loss at standard U.K. tax rate of 20.00% (2015: 20.25%)	(1,633)	(1,318)
Effects of:		
Adjustments in respect of prior years	—	—
Expenses not deductible	1,301	888
Deduction for R&D	(2,629)	(1,650)
Losses surrendered for R&D tax credit	2,629	1,650
Overseas tax payable	24	6
R&D tax credit—current year	(1,906)	(1,182)
R&D tax credit—prior years	(235)	—
Deferred tax asset not recognized	333	430
Income tax credit	(2,116)	(1,176)

The Company has not recognized a deferred tax asset in respect of tax losses carried forward as at December 31, 2016 on the basis that the timing during which tax losses could be regarded as recoverable against future taxable profits cannot be determined with reasonable certainty.

Temporary differences and cumulative carry forward tax losses for which deferred tax has not been recognized amount to £32.5 million (2015: £10.1 million).

U.K. tax legislation, which was substantively enacted on October 26, 2015, includes legislation that will reduce the main rate of U.K. corporation tax from 20% to 18%. This decrease is to be phased in with a reduction

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

6. Income tax credit (continued)

to 19%, effective from April 1, 2017, and a reduction to 18%, effective from April 1, 2020. Further, as announced on March 16, 2016, that the full rate of U.K. corporation tax will reduce by a further 1% to 17% from April 1, 2020. This further reduction was included within the U.K. tax legislation, which was substantively enacted on September 6, 2016.

7. Intangible assets

	Patents	Computer Software	Total
	£	(in thousands) £	£
Cost:			
At December 31, 2014	614	—	614
Additions	390	—	390
At December 31, 2015	1,004	—	1,004
Accumulated amortization:			
At December 31, 2014	41	—	41
Charge for the year	36	—	36
At December 31, 2015	77	—	77
Cost:			
At December 31, 2015	1,004	—	1,004
Additions	529	10	539
At December 31, 2016	1,533	10	1,543
Accumulated amortization:			
At December 31, 2015	77	—	77
Charge for the year	86	3	89
At December 31, 2016	163	3	166
Net book value:			
At December 31, 2016	1,370	7	1,377
At December 31, 2015	927	—	927

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

8. Property, plant and equipment

	<u>Office and computer equipment</u> (in thousands) £
Cost:	
At December 31, 2014	31
Additions	6
Effect of foreign currency exchange differences	—
At December 31, 2015	<u>37</u>
Depreciation:	
At December 31, 2014	15
Charge for the year	8
Effect of foreign currency exchange differences	—
At December 31, 2015	<u>23</u>
Cost:	
At December 31, 2015	37
Additions	15
Disposals	(1)
Effect of foreign currency exchange differences	1
At December 31, 2016	<u>52</u>
Depreciation:	
At December 31, 2015	23
Charge for the year	12
Disposals	(1)
Effect of foreign currency exchange differences	—
At December 31, 2016	<u>34</u>
Net book value:	
At December 31, 2016	<u>18</u>
At December 31, 2015	14

9. Prepayments, accrued income and other receivables

	<u>2016</u> (in thousands) £	<u>2015</u> £
Prepayments—manufacturing and clinical	3,050	—
Prepayments—other	173	54
Accrued income	21	149
VAT	198	154
Other receivables	192	18
	<u>3,634</u>	<u>375</u>

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

10. Share capital and share premium

	2016 (in thousands) £	2015 (in thousands) £
Share capital	663	659
Share premium	42,770	42,574
	43,433	43,233
	Number	Number
	(in thousands)	(in thousands)
Issued share capital comprises:		
Ordinary shares of £0.01 each	6,239	6,156
Founder ordinary 1 shares of £0.01 each	1,000	1,000
Founder ordinary 2 shares of £0.01 each	1,000	1,000
Series A shares of £0.01 each	7,483	7,483
Series B shares of £0.001 each	8,463	8,463
	24,185	24,102

The table above does not total due to rounding.

	Number of shares	Share capital (in thousands) £	Share premium £
Fully paid shares:			
Balance at January 1, 2015 and December 31, 2015	24,102	659	42,574
Issue of shares on exercise of options	83	4	196
Balance at December 31, 2016	24,185	663	42,770

Ordinary shares

The ordinary shares rank equally with all other shares in issue in that on a poll every member shall have one vote for each ordinary share held (save for the enhanced voting rights referred to in the founder ordinary shares). The ordinary shares rank equally with all other shares in issue in respect of any rights to any dividend distribution. The ordinary shares rank equally with all other shares in issue in respect of any rights to any capital distribution. The ordinary shares are not redeemable.

Founder ordinary shares

Upon shareholder vote, the founder ordinary 1 shares and the founder ordinary 2 shares shall as separate classes of shares each confer upon the holders of such classes of shares such number of votes, which equals at least 5% of all votes exercisable by all holders of shares.

Series A shares

The series A shares rank equally with all other shares in issue in that on a vote every member shall have one vote for each series A share held (save for the enhanced voting rights conferred upon the founder ordinary shares). The series A shares rank equally with all others shares in respect of any rights to any dividend

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

10. Share capital and share premium (continued)

distribution. The series A shares rank equally with all other shares in issue in respect of any rights to any capital distribution. The series A shares are not redeemable.

Series B shares

The series B shares rank equally with all other shares in issue (save for the enhanced voting rights conferred upon the founder ordinary shares). The series B shares rank equally with all other shares in issue in respect of any rights to any dividend distribution. The series B shares rank equally with all other shares in respect of any rights to any capital distribution. The series B shares are not redeemable.

Capital management

For the purpose of the Company's capital management, capital includes issued capital, share premium and all other equity reserves attributable to the equity holders of the Company. The purpose of the Company's capital management is to maximize shareholder value and ensure adequate capital is available to meet the medium-term operating plan. Review of operations and commitments is key to identifying future capital management and a full review is undertaken on a quarterly basis.

No changes were made in the objectives, policies or processes for managing capital during the year ended December 31, 2015 or the year ended December 31, 2016.

11. Other reserves

	<u>2016</u>	<u>2015</u>
	<u>(in thousands)</u>	<u>(in thousands)</u>
	<u>£</u>	<u>£</u>
Own share reserve	(339)	(339)
Foreign currency translation reserve	(3)	(1)
Share option reserve		
Balance at beginning of year	3,291	2,506
Share-based payments	1,132	785
Exercise of share options	(17)	—
Balance at end of year	<u>4,406</u>	<u>3,291</u>
Total other reserves	<u>4,064</u>	<u>2,951</u>

Foreign currency translation reserve

The foreign currency translation reserve is used to record exchange differences arising from the translation of the financial statements of foreign operations.

Own share reserve

The own share reserve represents the cost of 500,000 shares of NuCana BioMed Limited purchased by NuCana Employee Benefit Trust and that may, at the discretion of the trustee, be used to satisfy future exercise of options under the Company's share options plan.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

11. Other reserves (continued)

Share option reserve

The share option reserve is used to recognize the value of equity-settled share-based payments provided to employees, directors and consultants as part of their remuneration. Refer to Note 12 for further details of these plans.

12. Share-based payments

The Company has three share-based payment plans for employees, directors and consultants. The share options granted will be settled in equity. In 2016, share options were granted under the following share-based payment plans:

U.K. share-based payment plans

Options granted under these plans will vest if the option holder remains under their respective employment/consultancy contract for the agreed vesting period. The majority of the share options granted under these plans will vest equally over a period of four years, with the exception of the following:

- 1) options granted to a director, under which a third of the options granted vested immediately with the remaining two-thirds vesting each subsequent year; and
- 2) options granted to three employees, under which two thirds of the options vested immediately with the remaining third vesting in 2017.

Upon vesting, each option allows the holder to purchase one ordinary share at a specified option price determined at grant date.

Stock option plan (U.S. Sub-Plan)

On June 30, 2016, share options were granted under this sub-plan, which will vest equally over a period of four years if the option holder remains under the respective employment contract. Upon vesting, each option allows the holder to purchase one ordinary share at a specified option price determined at grant date.

On December 12, 2016, 45,750 share options were granted to a director with an exercise price of £4.00 each, which could be exercised within six months after the grant date. The options were exercised on December 29, 2016. Under the employment requirements within the stock option agreement, the director does not have unconditional ownership of these shares until he has provided four years of service from the grant date. Consequently, these options vest over a period of four years, with the share-based payment expense recognized on a straight line basis.

Cancelled share option arrangement

During the year ended December 31, 2016, the share-based payment arrangements for three employees were cancelled. The cancellation of the original plan resulted in an acceleration of the remaining vesting period, with the remaining charge recognized in 2016 deemed immaterial.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

12. Share-based payments (continued)

Share options and weighted average exercise prices are as follows for the reporting periods presented:

	<u>Number of shares</u>	<u>Weighted average exercise price per share £</u>
Outstanding at January 1, 2015	2,873,747	0.26
Granted	—	—
Forfeited	—	—
Exercised	—	—
Outstanding at December 31, 2015	2,873,747	0.26
Granted	507,690	3.81
Forfeited	—	—
Cancelled	(50,000)	2.95
Exercised	(83,250)	2.40
Outstanding at December 31, 2016	3,248,187	0.72
Vested and exercisable at December 31, 2016	2,841,419	0.36
Vested and exercisable at December 31, 2015	2,262,500	0.23

The weighted average remaining contractual life of the share options outstanding as at December 31, 2016 is 6.66 years (2015: 6.18).

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

12. Share-based payments (continued)

The following principal assumptions were used in the valuation for share options.

	Options granted on				
	Jun 30, 2016	Aug 22, 2016	Aug 22, 2016	Aug 22, 2016	Aug 22, 2016
Vesting dates	Oct 12, 2016	Aug 22, 2016	Aug 22, 2016	Dec 07, 2016	Mar 01, 2017
	Oct 12, 2017	Aug 22, 2017	Aug 22, 2017	Dec 07, 2017	Mar 01, 2018
	Oct 12, 2018			Dec 07, 2018	Mar 01, 2019
	Oct 12, 2019			Dec 07, 2019	Mar 01, 2020
Volatility	69.05%	67.92%	67.92%	67.92%	67.92%
Dividend yield	0%	0%	0%	0%	0%
Risk-free investment rate	0.11%	0.07%	0.07%	0.07%	0.07%
Fair value of option at grant date	£ 4.02	£ 6.15	£ 6.01	£ 5.74	£ 5.62
Fair value of share at grant date	£ 6.97	£ 8.61	£ 8.61	£ 8.61	£ 8.61
Exercise price at date of grant	£ 4.00	£ 2.80	£ 3.00	£ 3.40	£ 3.60
Lapse date	June 30, 2026	Aug 22, 2026	Aug 22, 2026	Aug 22, 2026	Aug 22, 2026
Expected option life (years)	2.50	2.36	2.36	2.36	2.36
Number of options granted	270,690	12,500	37,500	25,000	11,250
	Options granted on				
	Aug 22, 2016	Aug 22, 2016	Oct 28, 2016	Oct 28, 2016	Dec 12, 2016
Vesting dates	May 01, 2017	May 16, 2017	Oct 28, 2017	Oct 28, 2016	Dec 12, 2017
	May 01, 2018	May 16, 2018	Oct 28, 2018	Oct 28, 2017	Dec 12, 2018
	May 01, 2019	May 16, 2019	Oct 28, 2019	Oct 28, 2018	Dec 12, 2019
	May 01, 2020	May 16, 2020	Oct 28, 2020		Dec 12, 2020
Volatility	67.92%	67.92%	68.38%	68.38%	60.92%
Dividend yield	0%	0%	0%	0%	0%
Risk-free investment rate	0.07%	0.07%	0.28%	0.28%	0.06%
Fair value of option at grant date	£ 5.62	£ 5.62	£ 5.85	£ 5.46	£ 5.22
Fair value of share at grant date	£ 8.61	£ 8.61	£ 8.76	£ 8.76	£ 9.19
Exercise price at date of grant	£ 3.60	£ 3.60	£ 3.40	£ 4.00	£ 4.00
Lapse date	Aug 22, 2026	Aug 22, 2026	Oct 28, 2026	Oct 28, 2026	Dec 12, 2026
Expected option life (years)	2.36	2.36	2.17	2.17	0.50
Number of options granted	5,000	37,500	12,500	50,000	45,750

The fair values of options granted were determined using the Black-Scholes model that takes into account factors specific to the share incentive plan such as the assumption that the options will be exercised at a single point in time, in December 2018. This has been incorporated into the measurement by means of actuarial modelling. As NuCana BioMed Limited was unlisted at the grant date of the options, it is not possible to derive historical volatility from the Company's own share price. The underlying expected volatility was therefore determined by using the historical volatility of similar listed entities as a proxy. The volatility percentage applied to each tranche is the average of the historical volatility of comparable companies to NuCana BioMed Limited. In prior years, management made contemporaneous valuation of the share price, based on recent capital transactions, as an input to the Black-Scholes model. For the 2016 awards, the Company's ordinary share valuations were prepared using the guideline public company, or GPC, method under the market approach. In the application of the GPC method, we considered the pricing of IPOs completed by clinical-stage oncology companies between April 2015 and May 2016. We converted prospective IPO value to present value by applying a discount rate of 25%. The discount rate was derived from studies of rates of return required by venture investors in IPO-stage companies. In addition to the IPO GPCs, we considered the enterprise values indicated by a group of eight trading GPCs. The trading prices of these clinical-stage GPCs provided contemporaneous

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

12. Share-based payments (continued)

indications of value as of each appraisal date. We applied a discount for lack of marketability to the ordinary shares to account for the lack of access to an active public market. We estimated the discount for lack of marketability using an Asian put model. In the year ended December 31, 2016, an employee remuneration expense, all of which related to equity-settled share-based payments, of £1.1 million (2015: £0.8 million) has been included in the statement of operations and credited to equity.

13. Related party disclosures*Compensation of key management personnel of the Company*

	2016	2015
	(in thousands)	
	£	£
Short-term employee benefits	1,053	647
Severance payments	150	—
Pension and other benefits	47	77
Share-based payments	731	726
	<u>1,981</u>	<u>1,450</u>

The amounts disclosed in the table above are the amounts recognized as an expense during the reporting year related to key management personnel.

14. Cash, cash equivalents and short-term deposits

	2016	2015
	(in thousands)	
	£	£
Cash and cash equivalents	19,990	14,112

Cash and cash equivalents are comprised of cash at bank with maturity of three months or less, which are subject to insignificant risk of changes in value. Cash at bank earns interest at fixed or variable rates based on the terms agreed for each account.

	2016	2015
	(in thousands)	
	£	£
Short-term deposits	—	15,075

Short-term deposits represent certificates of deposits with maturities greater than three months but less than one year.

Liquidity risk is minimal and is managed using deposits with immediate and varied fixed term dates.

Cash, cash equivalents and short term deposits are measured at fair value and classified as Level 1 under the fair value level hierarchy.

15. Financial instruments

The fair value of the financial assets and liabilities are included at the amount at which the instrument could be exchanged in a current transaction between willing parties, other than in a forced liquidation or sale.

NUCANA BIOMED LIMITED
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

15. Financial instruments (continued)

The following methods and assumptions were used to estimate the fair values:

Cash, cash equivalents, short-term deposits, other receivables, trade payables and other payables approximate their carrying amounts largely due to the short-term maturities of these instruments.

16. Events after the reporting period

On September 14, 2017, the Company completed a one-for-four reverse share split and an associated bonus allotment of shares to take into account fractional entitlements. This had the effect of consolidating every four ordinary shares of £0.01 to one ordinary share of £0.04, every four founder ordinary 1 shares of £0.01 to one founder ordinary 1 share of £0.04, every four founder ordinary 2 shares of £0.01 to one founder ordinary 2 share of £0.04, every four series A shares of £0.01 to one series A share of £0.04 and every four series B shares of £0.001 to one series B share of £0.004. After the reverse share split, the Company has 24,214,641 shares outstanding. This includes an issue of 30,000 shares in August 2017, upon the exercise of options.

As a result of the reverse share split, the exercise prices and the numbers of shares issuable upon the exercise of any outstanding options to purchase ordinary shares were proportionally adjusted pursuant to the respective anti-dilution terms of the share based payment plans. All references in these financial statements and accompanying notes to units of ordinary shares or per share amounts are reflective of the reverse share split for all periods presented.

6,667,000 American Depositary Shares



Representing 6,667,000 Ordinary Shares

PROSPECTUS

September 27, 2017

**Citigroup
Jefferies
Cowen
William Blair**

Through and including October 22, 2017 (25 days after the date of this prospectus), all dealers that buy, sell, or trade the ADSs, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to the dealers' obligation to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscriptions.
