Filed Pursuant to Rule 424(b)(5)
Registration No. 333-227624

PROSPECTUS SUPPLEMENT
(to Prospectus dated October 22, 2018)

15,555,556 American Depositary Shares

NuCana plc

Representing 15,555,556 Ordinary Shares

We are offering 15,555,556 American Depositary Shares, or ADSs, in this offering. Each ADS will represent one ordinary share, nominal value £0.04 per share.

Our ADSs are listed on The Nasdaq Global Select Market under the symbol “NCNA”. On September 16, 2020, the last reported sale price of our ADSs was $5.69 per ADS.

Investing in our ADSs involves a high degree of risk. See “Risk Factors” beginning on page S-10.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement. Any representation to the contrary is a criminal offense.

	PER ADS	TOTAL
Public Offering Price	$ 4.50	$70,000,002
Underwriting Discounts and Commissions (1)	$ 0.27	$ 4,200,000
Proceeds, before expenses, to us	$ 4.23	$65,800,002

(1) We refer you to “Underwriting” beginning on page S-75 for additional information regarding underwriting compensation.

The underwriters have the option to purchase up to an additional 2,333,333 ADSs from us at the public offering price less the underwriting discount.

Delivery of the ADSs will be made against payment in New York, New York on or about September 21, 2020.

Jefferies **Cowen** **William Blair** **Truist Securities**

Prospectus Supplement dated September 16, 2020

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Prospectus Supplement

Prospectus

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a "shelf" registration statement on Form F-3 (File No. 333-227624) that we filed with the Securities and Exchange Commission, or SEC, on October 1, 2018, and that was declared effective by the SEC on October 22, 2018. This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering of ADSs representing our ordinary shares and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

You should rely only on the information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein. We have not authorized, and the underwriters have not authorized, anyone to provide you with information that is different. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of the securities offered hereby. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled "Where You can Find More Information" and "Incorporation of Documents by Reference" in this prospectus supplement and in the sections entitled "Where You can Find More Information" and "Incorporation of Documents by Reference" in the accompanying prospectus, respectively.

We are offering to sell, and seeking offers to buy, ADSs representing our ordinary shares only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the ADSs in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the ADSs and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless otherwise indicated or the context otherwise requires, in this prospectus supplement, "NuCana," "NuCana plc," the "Group," the "company," "we," "us" and "our" refer to NuCana plc and its consolidated subsidiaries.

PRESENTATION OF FINANCIAL INFORMATION

We report under International Financial Reporting Standards, or IFRS, as issued by the International Accounting Standards Board, or the IASB. None of the financial statements presented or incorporated by reference in this prospectus supplement 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 as issued by the IASB. 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 supplement have been translated into pounds sterling at the rate on June 30, 2020 of £1.00 to $1.2356. 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 supplement. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them.

PROSPECTUS SUMMARY

The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus supplement. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth in our most recent filings with the SEC including our Annual Reports on Form 20-F and reports on Form 6-K, as well as other information in this prospectus supplement and the documents incorporated by reference herein or therein, before purchasing our securities. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.

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 and hematological 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 multiple clinical trials, including a Phase 3 clinical trial for patients with biliary tract cancer, a Phase 1b clinical trial for patients with biliary tract cancer, a Phase 2 clinical trial for patients with platinum-resistant ovarian cancer, and a Phase 3 clinical trial for patients with metastatic pancreatic cancer for which enrollment has been suspended. NUC-3373 is currently in a Phase 1 clinical trial in patients with advanced solid tumors and a Phase 1b clinical trial in patients with advanced colorectal cancer. Our third ProTide, NUC-7738, is a transformation of a novel nucleoside analog (3'-deoxyadenosine) that has never been successfully developed or approved as a chemotherapy but has shown potent anti-cancer activity in preclinical studies. We are evaluating NUC-7738 in a Phase 1 clinical trial for patients with advanced solid tumors. 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 first-in-class ProTide that has been evaluated in over 300 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 observed, a Phase 1b trial of Acelarin is being conducted in patients with locally advanced or metastatic biliary tract cancers to determine the optimal dose in combination with cisplatin. In October 2018, at the European Society for Medical Oncology (ESMO) 2018 Congress, we announced combined results from cohorts 1 and 2 of this trial, also known as the ABC-08 trial, in which Acelarin in combination with cisplatin was observed to continue to achieve approximately a doubling of the response rate expected with the standard of care, gemcitabine plus cisplatin. In addition, these results showed the combination was well-tolerated and several patients achieved significant reductions in their tumor volume as well as further tumor shrinkage over time. In June 2019, the FDA granted orphan drug designation for Acelarin for the treatment of advanced biliary tract cancer. In October 2019, the FDA cleared the IND for our Phase 3 clinical trial, also known as the NuTide:121 trial, of Acelarin in combination with cisplatin for patients with previously untreated locally advanced

or metastatic biliary tract cancer. We expect to complete recruitment for the first interim analysis in the second half of 2021. We believe Acelarin in combination with cisplatin has the potential to significantly improve the survival outcomes of patients with advanced biliary tract cancer. If approved, our goal is to establish Acelarin in combination with cisplatin as the global standard of care for the first-line treatment of patients with advanced biliary tract 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 the 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, also known as the NuTide:301 trial, of patients with advanced solid tumors. In this trial, NUC-3373 has generated high levels of the active anti-cancer metabolite inside the patients' white blood cells resulting in complete inhibition of the target enzyme associated with cancer cell growth. The pharmacokinetic profile of NUC-3373 appears favorable, which supports our belief that NUC-3373 may enhance efficacy, improve safety and provide a more convenient dosing regimen compared with the standard of care 5-FU. In October 2018, we reported further interim data from this trial at ESMO 2018. These interim data showed that three patients had achieved stable disease after treatment, with progression-free survival, or PFS, lasting more than nine months at September 25, 2018, as well as a continued promising pharmacokinetic and pharmacodynamic, tolerability and dosage administration profile. Importantly, no patients developed hand-foot syndrome, as of data cut-off, which is a debilitating side effect occurring in 34% to 72% of patients treated with fluoropyrimidine therapy. The results of this trial suggest that NUC-3373 has the potential to overcome the key cancer resistance mechanisms associated with 5-FU and may be capable of achieving anti-cancer activity even in patients who have progressed on prior treatment with a fluoropyrimidine. We expect to report further data from the NuTide:301 trial in the first half of 2021.

In October 2018, we commenced a Phase 1b trial, also known as the NuTide:302 trial, in patients with advanced colorectal cancer in which NUC-3373 will be combined with agents typically combined with 5-FU, including leucovorin, irinotecan, oxaliplatin and monoclonal antibodies. In October 2019, we presented interim data from this trial at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. These interim data supported the previously reported favorable pharmacokinetic profile of NUC-3373. The anti-cancer mechanism of action of NUC-3373 has been previously observed in preclinical studies, which we believe further supports the biological advantages of NUC-3373 over 5-FU. We believe NUC-3373 has significant commercial potential as approximately 500,000 patients in North America are estimated to receive intravenous 5-FU each year. The next stage of NUC-3373's development has commenced in the NuTide:302 trial which is investigating NUC-3373 in patients with advanced colorectal cancer in combination with oxaliplatin or irinotecan. We then plan to open an expansion cohort in less heavily pre-treated patients. We expect to report data from the NuTide:302 trial in the second half of 2020 and in 2021. Contingent on regulatory guidance and other factors, we also plan to initiate a Phase 3 clinical trial in patients with advanced colorectal cancer in the second half of 2021.

NUC-7738, our third product candidate, is a ProTide transformation of 3'-deoxyadenosine, or 3'-dA, a novel nucleoside analog that has shown potent anti-cancer activity in preclinical studies. In March 2019, we opened a Phase 1 clinical trial, known as the NuTide:701 trial, with NUC-7738 in patients with advanced solid tumors. In October 2019, we announced preclinical data on NUC-7738, detailing multiple potential anti-cancer modes of action. In preclinical studies of NUC-7738, we have observed additional anti-cancer mechanisms of action to those previously reported for 3'-deoxyadenosine. Significantly higher levels of anti-cancer metabolites are generated inside cancer cells than with 3'-deoxyadenosine, causing increased cell injury. Preclinical data also suggest that NUC-7738 activates AMPK, which may inhibit the mTOR pathway, highlighting another potential anti-cancer mechanism of this candidate. We expect to report interim clinical data from the Phase 1 trial in the second half of 2020 and the first half of 2021. Contingent on regulatory guidance and other factors, we also plan to initiate a Phase 2 clinical trial in the second half of 2021.

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, 5-FU and 3'-deoxyadenosine.

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.

Recent Developments

Interim Data Presentation at ESMO Virtual Congress 2020

In August 2020, we announced that we had three posters accepted for presentation at the upcoming ESMO Virtual Congress 2020 to be held September 19, 2020 to September 21, 2020.

The first poster presents six patient case studies from the ongoing Phase 1 clinical trial of NUC-3373 in heavily pre-treated patients with metastatic colorectal cancer. These interim data from the trial showed that (i) some patients achieved stable disease for a longer period of time on NUC-3373 than the patient had achieved on their prior line of therapy, and (ii) some patients experienced tumor shrinkage, including one fluoropyrimidine-refractory patient. We believe these data support the potential of NUC-3373 to improve progression-free survival in patients who had relapsed or were refractory to prior 5-FU-containing regimens. We also believe these data show that NUC-3373's pharmacokinetic and tolerability profile is favorable and unaffected by leucovorin.

The second poster presents two patient case studies from the ongoing Phase 1 clinical trial of NUC-7738 in patients with advanced solid tumors who have exhausted all standard therapies. These interim data observed significant reductions in tumor volume maintained over time in these patients. Additionally, we observed a positive change in character of a target lesion of one of the patients in the trial. We believe these data support the potential anti-cancer activity of NUC-7738 and indicate a favorable pharmacokinetic and tolerability profile.

The third poster provides an overview of the ongoing global Phase 3 clinical trial of Acelarin as a first-line treatment for patients with advanced biliary tract cancer currently being conducted at approximately 100 clinical sites across North America, Europe and Asia Pacific.

The patient case studies presented in the posters for NUC-3373 and NUC-7738 are preliminary and subject to change as further analyses are conducted. In addition, both of these clinical trials are ongoing and these patient cases studies represent only a subset of the patients expected to enroll in the trials. As a result, the interim data from both trials may change as further patient follow up occurs and more patient data become available.

Potential Appointment of a New Director

Following completion of this offering, we expect to appoint an individual designated by Abingworth LLP, an expected investor in this offering, to serve as a member of our board of directors.

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:

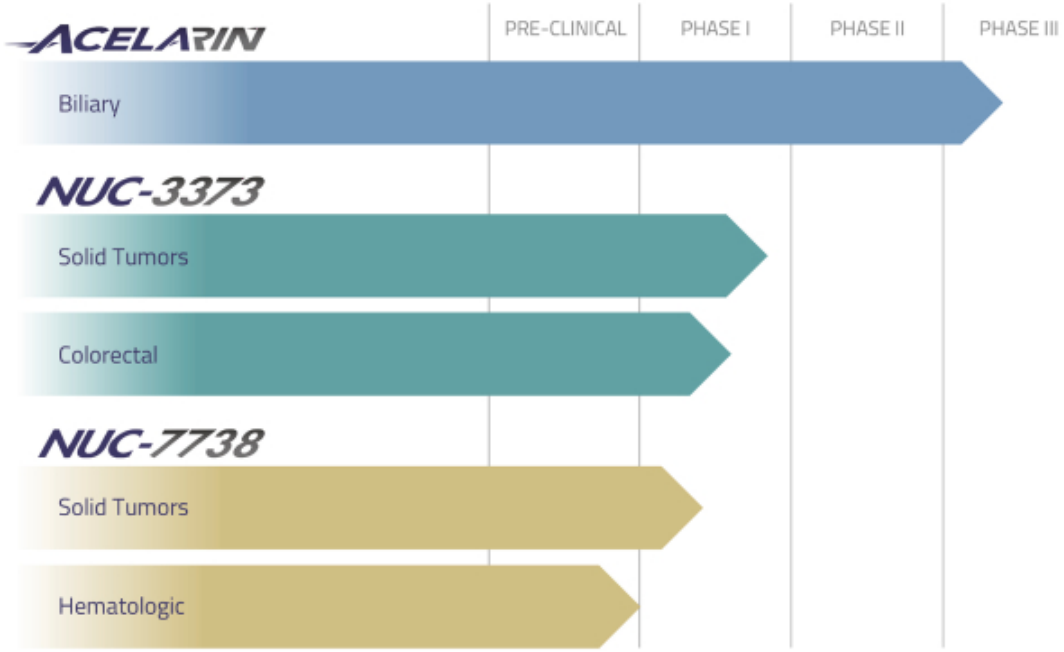
- **Rapidly develop Acelarin as a first-in-class nucleotide analog for the treatment of patients with cancer**. We believe that Acelarin has the potential to replace the core chemotherapy component of treatment regimens for patients with various cancers, focusing initially on:
  - *Biliary tract cancer.* We reported interim data from a Phase 1b trial of Acelarin in combination with cisplatin in January 2018 and in October 2018. Following the FDA's clearance of our IND in October 2019, we opened a global Phase 3 trial of Acelarin in combination with cisplatin as a first-line treatment for patients with biliary tract cancer. We expect to complete recruitment for the first interim analysis in the second half of 2021.
- **Rapidly develop NUC-3373 to replace 5-FU as the standard of care for the treatment of patients with various cancers.**
  - *Colorectal cancer*. In October 2019, we presented interim data from NuTide:302, our Phase lb trial in patients with advanced, metastatic colorectal cancer who have already received 5-FU in combination with oxaliplatin and irinotecan. In this study NUC-3373 is being assessed for safety and a recommended Phase 2 dose when combined with many of the agents typically combined with 5-FU, including leucovorin, irinotecan, oxaliplatin and monoclonal antibodies. These interim data supported the previously reported favorable pharmacokinetic profile of NUC-3373. We plan to report further interim data from the NuTide:302 trial in the second half of 2020 and the first half of 2021. Contingent on regulatory guidance and other factors, we plan to initiate a Phase 3 clinical trial of NUC-3373 in combination with other agents for patients with colorectal cancer in the second half of 2021.
  - *Advanced solid tumors*. We plan to continue our Phase 1 monotherapy trial of NUC-3373 to establish the optimal dose and dosing schedule of single-agent NUC-3373 in patients with advanced solid tumors and report interim data in the first half of 2021.
- **Rapidly develop NUC-7738 as a treatment for patients with solid tumors**. Our Phase 1 clinical trial with NUC-7738, a ProTide based on a novel nucleoside analog, for patients with advanced solid tumors is ongoing, and we expect to report interim data from the trial in the second half of 2020 and the first half of 2021. We expect to initiate a Phase 2 clinical trial in the second half of 2021.
- **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 been 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. We also have been granted or allowed patent protection in key markets for the proposed commercial formulation of Acelarin and for uses of Acelarin in targeting

cancer. Our patent portfolio has grown substantially in the past year and we are actively evaluating new intellectual property opportunities as they arise, with the intention of further expanding 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.



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” included in this prospectus.

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 7, 2020, we owned 610 granted patents (of which 14 are U.S.-issued patents) and 396 pending patent applications (of which 22 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, India, Israel, Japan, South Korea, Malaysia, Mexico, Philippines, Singapore and South Africa.

Acelarin

We own 91 granted patents covering the composition of matter of our Acelarin product candidate. The patent claims are directed to the Acelarin product candidate and to a genus around that candidate. Acelarin was originally formed as a mixture of two diastereoisomers, both of which are biologically active, and each of these composition of matter patents cover Acelarin both as a single diastereoisomer and as a mixture of diastereoisomers. The composition of matter patents for Acelarin have been granted in major territories, including United States, Europe and Japan. These granted patents are expected to expire in 2024, excluding any patent term adjustments and any patent term extensions.

Additionally, we own 85 granted patents, as well as 16 pending patent applications, directed towards Acelarin in single diastereoisomer form. The more soluble single diastereoisomer is being used for clinical development in our ongoing and planned upcoming clinical trials. A patent claiming the more soluble single diastereoisomer of Acelarin has been granted in the United States and Europe, and corresponding patent applications are pending in other major territories, including 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 granted patents and 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 and Acelarin in combination with cisplatin. Patents claiming the clinical formulation of Acelarin have been granted in the United States and Europe. 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 60 granted patents and five 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.

We own patent applications covering formulations of NUC-3373 (including those used in the clinical trials), methods of making NUC-3373, and specific uses of NUC-3373. These patents and patents arising from these pending applications are expected to expire in 2036, 2037 and 2038 excluding any patent term adjustments and any patent term extensions.

NUC-7738

We own 47 granted patents and 25 pending applications covering the composition of matter of NUC-7738, a genus around NUC-7738 and specific uses of NUC-7738. This includes a granted composition of matter patent in the United States, Europe and Japan. There are patent applications pending in major territories,

including the United States, Europe and Japan. These granted patents and patents arising from these pending applications, if issued, are expected to expire in 2035 excluding any patent term adjustments and any patent term extensions.

We own patent applications covering formulations of NUC-7738, methods of making NUC-7738, and specific uses of NUC-7738. Patents arising from these pending applications are expected to expire in 2036, 2038 and 2040 excluding any patent term adjustments and any patent term extensions.

Additional Information

For additional information related to our business and operations, please refer to the reports incorporated herein by reference, including the Annual Report on Form 20-F of NuCana plc for the year ended December 31, 2019 and the Reports on Form 6-K furnished on January 27, 2020, March 4, 2020, March 10, 2020, April 2, 2020, May 5, 2020, May 15, 2020, May 18, 2020, May 19, 2020, June 2, 2020, June 26, 2020 and August 19, 2020 as described under the caption “Incorporation of Documents by Reference” on page S-87 of this prospectus supplement.

Our 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. ADSs representing our ordinary shares were admitted to trading on The Nasdaq Global Select Market on September 28, 2017. Our ADSs are traded under the symbol “NCNA.”

Our principal executive offices are located at 3 Lochside Way, Edinburgh, EH12 9DT, United Kingdom. Our telephone number at this address is +44 (0)131 357 1111.

We maintain a website at *www.nucana.com* to which we regularly post copies of our press releases as well as additional information about us. The information contained on, or that can be accessed through, our website is not a part of this prospectus supplement. We have included our website address in this prospectus supplement solely as an inactive textual reference.

We use our registered trademarks, NuCana® and Acelarin®, and our trademark, ProTides™, in this prospectus supplement. This prospectus supplement also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this prospectus supplement appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

THE OFFERING

Issuer	NuCana plc
ADSs offered by us	15,555,556 ADSs
Option to purchase additional ADSs	We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to 2,333,333 additional ADSs.
Ordinary shares to be outstanding immediately after this offering	48,495,006 ordinary shares (or 50,828,339 ordinary shares if the underwriters exercise in full their option to purchase additional ADSs).
The ADSs	Each ADS represents one ordinary share, nominal value £0.04 per share. The offered ADSs may be evidenced by American Depositary Receipts, or ADRs. 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. Under certain limited circumstances, 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. To better understand the terms of the ADSs, you should carefully read the section in the accompanying prospectus titled “Description of American Depositary Shares”. You should also read the deposit agreement, which is an exhibit to the registration statement that includes this prospectus.
Depositary	Citibank, N.A.
Custodian	Citibank, N.A. (London)
Use of proceeds	We currently intend to use the net proceeds of this offering to fund the ongoing clinical development of Acelarin, NUC-3373 and NUC-7738 and for other research and development activities, working capital and general corporate purposes. See the section titled “Use of Proceeds” on page S-65 of this prospectus supplement.
Risk factors	See “Risk Factors” beginning on page S-10 of this prospectus supplement and the other information included in, or incorporated by reference into, this prospectus supplement for a discussion of certain factors you should carefully consider before deciding to invest in our ADSs.
Nasdaq Global Select Market symbol	“NCNA”

The number of our ordinary shares to be outstanding immediately after this offering is 48,495,006, which is based on 32,939,450 ordinary shares outstanding as of June 30, 2020. The number of shares outstanding excludes:

- 7,335,370 ordinary shares issuable upon exercise of outstanding options under our equity plans as of June 30, 2020 at a weighted average exercise price of £4.08 per share;
- 398,859 ordinary shares issuable upon exercise of outstanding options under our equity plans granted subsequent to June 30, 2020 through the date of this prospectus supplement at a weighted average exercise price of £0.04 per share; and
- 3,601,141 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

To the extent that outstanding options are exercised, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities may result in further dilution to our shareholders.

In addition, subsequent to June 30, 2020 through the date of this prospectus supplement, we have sold and issued 346,206 ADSs, representing 346,206 ordinary shares, pursuant to an “at-the-market” (ATM) sales agreement with Cowen and Company, LLC, resulting in gross proceeds, before deducting sales commissions and other related expenses, of $2.1 million.

RISK FACTORS

An investment in our ADSs involves a high degree of risk. Before deciding whether to invest in our ADSs, you should consider carefully the risks described below and discussed under the sections captioned "Risk Factors" contained in our most recent Annual Report on Form 20-F, which is incorporated by reference herein in their entirety, together with other information in this prospectus supplement, the information and documents incorporated by reference in this prospectus supplement, and in any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our ADSs to decline, resulting in a loss of all or part of your investment.

Our business, financial condition or results of operations could be materially adversely affected by any of these risks. The trading price of our securities could decline due to any of these risks, and you may lose part or all of your investment. This prospectus supplement and the incorporated documents also contain forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks mentioned below. Forward-looking statements included in this prospectus supplement are based on information available to us on the date hereof, and all forward-looking statements in documents incorporated by reference are based on information available to us as of the date of such documents. We disclaim any intent to update any forward-looking statements.

Risks Related to This Offering

Our management will have broad discretion over the use of the net proceeds from this offering, and you may not agree with how we use the proceeds and the proceeds may not be invested successfully.

Our management will have broad discretion as to the use of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of this offering. Accordingly, you are relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds will be used appropriately. It is possible that the proceeds will be invested in a way that does not yield a favorable, or any, return for us.

Purchasers will experience immediate dilution in the book value per share of the ADSs purchased in the offering.

We expect that the offering price of our ADSs will be substantially higher than the net tangible book value per ADS, and per each underlying ordinary share, prior to this offering. After giving effect to the sale of 15,555,556 ADSs at the public offering price of $4.50 per ADS and after deducting estimated underwriting discounts and commissions and estimated offering expenses, our as adjusted net tangible book value as of June 30, 2020 would have been £105.6 million, or £2.18 per ordinary share, equivalent to $2.69 per ordinary share and $2.69 per ADS. This represents an immediate increase in net tangible book value of $0.72 per ordinary share and ADS to our existing shareholders and an immediate dilution in as adjusted net tangible book value of $1.81 per ordinary share and ADS to purchasers of ADSs in this offering.

In addition to this offering, subject to market conditions and other factors, we may pursue additional equity financings in the future, including future public offerings or future private placements of equity securities or securities convertible into or exchangeable for equity securities. Further, the exercise of outstanding options could result in further dilution to investors and any additional ordinary shares or ADSs issued in connection with acquisitions, should we choose to pursue any, will result in dilution to investors. In addition, the market price of our ADS could fall as a result of resales of any of these ADSs due to an increased number of ADSs available for sale in the market.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional of our ADSs or other securities convertible into or exchangeable for our ADSs. We cannot assure you that we will be able to sell ADSs or other securities in any other offering at a price per ADS or per ordinary share that is equal to or greater than the price per ADS paid by investors in this offering, and investors purchasing ADSs or other securities in the future could have rights superior to existing shareholders. The price per ADS at which we sell additional ADSs or other securities convertible into or exchangeable for our ADSs in future transactions may be higher or lower than the price per ADS in this offering.

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 £6.0 million for the year ended December 31, 2016, £23.1 million for the year ended December 31, 2017, £13.8 million for the year ended December 31, 2018, £21.4 million for the year ended December 31, 2019 and £10.0 million for the six months ended June 30, 2020. As of June 30, 2020, we had an accumulated deficit of £90.0 million. Our most advanced product candidate, Acelarin, is currently being evaluated in multiple clinical trials, including a Phase 3 clinical trial for patients with biliary tract cancer, a Phase 1b clinical trial for patients with biliary tract cancer, a Phase 2 clinical trial for patients with platinum-resistant ovarian cancer, and a Phase 3 clinical trial for patients with metastatic pancreatic cancer for which enrollment has been suspended. Our second most advanced product candidate, NUC-3373, is currently in a Phase 1 clinical trial and a Phase 1b clinical trial, and our third clinical-stage product candidate, NUC-7738, is currently in a Phase 1 clinical 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 public and 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, NUC-3373 and NUC-7738;
- complete preclinical studies and potentially initiate clinical trials of our preclinical-stage product candidates;
- 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; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

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 Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, 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 the 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;
- 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 with respect to 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 its commercialization unfeasible;
- 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.

Although we have reached alignment with the FDA on the design of our NuTide:121 trial of Acelarin in combination with cisplatin, the clinical data we generate from NuTide:121 may not be sufficient to support our strategy to submit an NDA for Acelarin using the accelerated approval regulatory pathway. If we are unable to obtain accelerated approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, reduce the likelihood of obtaining and/or delay the timing of obtaining, necessary marketing approvals. Even if we receive accelerated approval of Acelarin from the FDA, if our post-marketing confirmatory trial does not verify clinical benefit, or if other evidence demonstrates that the drug is not safe or effective for its conditions of use, among others, the FDA may seek to withdraw accelerated approval.

Products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval from the FDA and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality. Discussions with the FDA about the feasibility of an accelerated approval typically begin early in the development of a new drug or biological product in order to identify, among other things, an appropriate surrogate or intermediate clinical endpoint. We intend to seek accelerated approval for Acelarin in combination with cisplatin for patients with previously untreated locally advanced or metastatic biliary tract cancer using results from NuTide:121, our Phase 3 clinical trial. NuTide:121 is a global, multi-center, randomized Phase 3 trial that is expected to enroll up to 828 patients in approximately 130 sites across North America, Europe, Asia and Australia. We have designed the Phase 3 study protocol to include three interim analyses in addition to the final analysis. Based on discussions with the FDA and subject to any further regulatory guidance, we believe that a statistically significant improvement in objective response rate, or ORR, at either of the first two interim analyses, supported by positive trends in other clinical endpoints, could potentially allow for an accelerated approval of an NDA for Acelarin for this biliary tract cancer treatment use.

Even if we generate clinical data sufficient to support an NDA submission seeking accelerated approval for Acelarin, there can be no assurance that such marketing application will be accepted by the FDA for substantive review or that approval will be granted on a timely basis, or at all. In addition, if another company receives full approval from the FDA to market a product for treatment of biliary tract cancer, our ability to seek and obtain accelerated approval for Acelarin in the same or similar indication may be materially adversely affected. The FDA or foreign regulatory authorities also could require us to conduct further studies or trials prior to considering our application or granting a marketing approval of any type. We might not be able to fulfill the FDA's requirements in a timely manner, which would cause delays, or approval might not be granted because our submission is deemed incomplete by the FDA. A failure to obtain accelerated approval for Acelarin would result in a longer time period to obtain approval for and commercialize such product candidate, could increase the cost of development of Acelarin and could harm our competitive position in the marketplace.

Even if we receive accelerated approval from the FDA for Acelarin or any of our other product candidates, we will be subject to rigorous post-marketing requirements, including the submission of confirmatory clinical data verifying the clinical benefit of the product. Drug products marketed under an accelerated approval NDA also are subject to a requirement that all promotional materials must be submitted to the FDA at least 30 days prior to their dissemination. The FDA could seek to withdraw accelerated approval for multiple reasons, including if we fail to conduct the required post-marketing study with due diligence, the post-marketing study fails to verify the product's clinical benefit, other evidence shows that the product is not safe or effective under the conditions of use, or we disseminate promotional materials that are found by the FDA to be false and misleading.

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, NUC-3373 and NUC-7738. 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 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, we will continue to incur 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, 2020, we had £47.8 million in cash and cash equivalents. We believe, based upon our current operating plan, that, our cash and cash equivalents on hand will be sufficient to fund our anticipated operations for at least the next twelve months. 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 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, 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. 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.

Inadequate funding for the FDA, the SEC and other, government agencies could hinder such agencies' ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, in our operations as a public company, future government shutdowns could impact our ability to access the public market and obtain necessary capital in order to properly capitalize and continue our operations.

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 December 31, 2019, we had cumulative carry forward tax losses of £32.2 million. Subject to any relevant restrictions, including the Corporate Income Loss Restriction and the Corporate Capital Loss Restriction that, broadly, restrict the amount of carried forward losses that can be utilized to 50% of group profits or gains arising above £5.0 million per tax year, 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. On October 29, 2018 the U.K. Government announced its intention to cap the amount of payable credit that a qualifying loss-making SME business can receive through R&D relief in any one year. Although the implementation of this measure has been delayed, the U.K. Government has stated that it remains committed to the reform and, subject to the outcome of further consultation, intends to introduce the cap on payable credit claims in excess of £20,000 with effect from April 2021 by reference to, broadly, three times the total PAYE and NICs liability of the company. If such cap comes into force, this could restrict the amount of payable credit that we claim. We may not be able to continue to claim payable research and development tax credits in the future 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 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.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, or may apply existing rules in an arbitrary or unforeseen manner, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, Her Majesty's Revenue & Customs (HMRC), the U.S. Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including methodologies for valuing developed technology and amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions.

A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, for example where there has been a technical violation of contradictory laws and regulations that are relatively new and have not been subject to extensive review or interpretation, in which case we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

Changes and uncertainties in the tax system in the countries in which we have operations, could materially adversely affect our financial condition and results of operations, and reduce net returns to our shareholders.

We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices in jurisdictions in which we operate or in the future into which we sell our products, could increase the estimated tax liability that we have expensed to date and paid or accrued on our balance sheets, and otherwise affect our financial position, future results of operations, cash flows in a particular period and overall or effective tax rates in the future in countries where we have operations or may sell our products, reduce post-tax returns to our shareholders and increase the complexity, burden and cost of tax compliance.

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 United Kingdom's withdrawal 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.

The outbreak of the novel strain of coronavirus, SARS-CoV-2, which causes COVID-19, could adversely impact our business, including our non-clinical studies and clinical trials.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. In December 2019, a novel strain of coronavirus, SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), surfaced in Wuhan, China. Since then, COVID-19 has spread worldwide, including to the United Kingdom and the United States. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic. In response to the spread of COVID-19, we have closed our offices, with our employees continuing their work outside of our offices, and restricted on-site staff to only those required to execute their job responsibilities.

As a result of the COVID-19 outbreak, or similar pandemics, we have and may in the future experience disruptions that could severely impact our business, preclinical studies and clinical trials, including:

- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays or disruptions in non-clinical experiments and investigational new drug application-enabling good laboratory practice standard toxicology studies due to unforeseen circumstances at contract research organizations and vendors along their supply chain;
- increased rates of patients withdrawing from our clinical trials following enrollment as a result of contracting COVID-19, being forced to quarantine, or not wanting to attend hospital visits;

- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by national, state or local governments, employers and others or interruption of clinical trial subject visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of subject data and clinical study endpoints;
- interruption or delays in the operations of the U.S. Food and Drug Administration, the European Medicines Agency or other foreign regulatory agencies, which may impact approval timelines;
- interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages and disruptions in our supply chain or distribution vendors' ability to ship product candidates; and
- limitations on employee resources that would otherwise be focused on the conduct of our non-clinical studies and clinical trials, including because of sickness of employees or their families, the desire of employees to avoid contact with large groups of people, an increased reliance on working from home or mass transit disruptions.

These and other factors arising from the COVID-19 pandemic could worsen in countries that are already afflicted with COVID-19, could continue to spread to additional countries, or could return to countries where the pandemic has been partially contained, each of which could further adversely impact our ability to conduct clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results.

In addition, the trading prices for our ADSs and for the securities of other biopharmaceutical companies have been highly volatile as a result of the COVID-19 pandemic. As a result, we may face difficulties raising capital through sales of our ADSs or such sales may be on unfavorable terms. The COVID-19 outbreak continues to rapidly evolve. The extent to which the outbreak may impact our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the outbreak, the continued imposition of travel restrictions and actions to contain the outbreak or treat its impact, such as social distancing and quarantines or lock-downs in the United Kingdom, the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United Kingdom, the United States and other countries to contain and treat the disease.

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 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.

Our business may be negatively impacted by changes in the applicable regulatory regime and BREXIT.

We may face new regulatory costs and challenges that could have an adverse effect on our operations. The regulatory framework applicable to our operations and the development of our product candidates can change at any time as a result of political decisions. Any changes to the regulatory framework could have a material impact on our plans and development strategy, including our supply of investigational medicinal products. Furthermore, BREXIT and any other significant European political changes could result in disruption that could in turn delay the approval of new

medicines at the European Medicines Agency. However, at this stage, we do not anticipate a significant change in the legal framework in the U.K. (or the European Union) as a result of BREXIT.

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 multiple clinical trials across numerous solid tumor indications: one Phase 3 clinical trial for patients with biliary tract cancer, one Phase 1b clinical trial for patients with biliary tract cancer, one Phase 2 clinical trial for patients with platinum-resistant ovarian cancer and one Phase 3 clinical trial for patients with metastatic pancreatic cancer for which enrollment has been suspended. While Acelarin has shown high disease control rates and a favorable tolerability profile in early-stage trials, including in its dose-ranging Phase 1 trials, we may not see such favorable data in future clinical trials involving Acelarin. Similarly, favorable results obtained from our Phase 1 clinical trial of NUC-3373 in patients with advanced solid tumors and our Phase 1b clinical trial of NUC-3373 in patients with advanced colorectal cancer may not be replicated in any future clinical trials. In addition, data generated in these early stage Phase 1 trials in particular 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 that we may announce or publish from time to time may change as patient enrollment continues, patient data are further examined and more patient data become available.

From time to time, we may announce or publish preliminary or interim data from our client studies. Preliminary or interim data from our clinical trials, including those from the Phase 3 trial of Acelarin for patients with advanced biliary tract cancer, a Phase 1b trial of Acelarin for patients with biliary tract cancer, a Phase 2 trial of Acelarin for patients with platinum-resistant ovarian cancer, the Phase 3 trial of Acelarin for patients with metastatic pancreatic cancer for which enrollment has been suspended, the Phase 1 trial of NUC-3373 for the potential treatment of a wide range of advanced solid tumors, the Phase 1b trial of NUC-3373 in patients with advanced colorectal cancer, the Phase 1 trial of NUC-7738 for patients with advanced solid tumors, and any future clinical trials of any of product candidates. In addition, while the Phase 1b trial of Acelarin in combination with cisplatin in patients with biliary cancer (the ABC-08 clinical trial) was conducted by the same investigators that conducted the earlier ABC-02 clinical trial in a similar patient population comparing single agent gemcitabine to the combination of gemcitabine plus cisplatin, the ABC-08 trial has many fewer patients than did the ABC-02 trial, which enrolled 410 patients. Preliminary and interim data from a clinical trial are not always entirely representative of final data. 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 depend on the successful development and eventual commercialization of Acelarin, for which one Phase 1b trial and two Phase 3 trials are ongoing, NUC-3373, for which one Phase 1 trial and one Phase 1b trial are ongoing, and NUC-7738, for which one Phase 1 trial is ongoing. 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;
- 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 two Phase 3 trials, NUC-3373 is currently being studied in one Phase 1 trial and one Phase 1b trial, and NUC-7738 is in a Phase 1 trial. 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;
- 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 3'-deoxyadenosine, 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;
- 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.

We face regulation and potential liability related to the privacy of health information we obtain from clinical trials sponsored by us or our collaborators.

The regulatory environment surrounding information security and privacy is increasingly demanding. We are subject to numerous regulations governing the protection of personal and confidential information of our clinical trial subjects, clinical investigators, and employees, including in relation to medical records, credit card data and financial information. For example, on May 25, 2018, the European General Data Protection Regulation, or GDPR, became applicable in all E.U. member states and member states of the European Economic Area, or E.E.A. Following the U.K.'s withdrawal from the E.U. on January 31, 2020, pursuant to the transitional arrangements agreed between the U.K. and E.U., the GDPR will continue to have effect in U.K. law until the end of the transition period on December 31, 2020 in the same fashion as was the case prior to that withdrawal, as if the U.K. remained an E.U. member state for such purposes. Following December 31, 2020, and the anticipated expiry of those transitional arrangements, it is intended that the data protection obligations of the GDPR will continue to apply to U.K.-related processing of personal data in substantially unvaried form and fashion.

We are subject to the GDPR when conducting clinical trials involving U.K. or E.E.A. based data subjects (whether the trials are conducted directly by us or through a clinical vendor or collaborator) or offering approved products (or any other products or services) to U.K. or E.E.A. based data subjects (regardless of whether involving an U.K. or E.E.A. based subsidiary or operations), when monitoring of their behavior of data subjects in the U.K. or E.E.A. and/or when acting through an U.K. or E.E.A. based subsidiary, operation or other establishment.

The GDPR sets out a number of requirements that must be complied with when handling personal data (i.e. data relating to an identified or identifiable living individual) in these circumstances, including: the obligation to appoint data protection officers in certain circumstances; increased accountability and record-keeping obligations; increased transparency obligations for data controllers; the obligation to carry out so-called data protection impact assessments in certain circumstances; increased rights for data subjects (such as rights for individuals to be "forgotten", rights to data portability, rights to object etc); a heightened and more-codified standard of data subject consent; and the obligation to notify certain significant personal data breaches to the relevant Supervisory Authority(ies) and affected individuals. In addition, the GDPR materially expanded the definition of what is expressly provided to constitute personal data (including, for example, by expressly clarifying that the GDPR applies to 'pseudonymized' (i.e., key-coded) data).

The GDPR also imposes strict rules on the transfer of personal data out of the E.E.A and U.K. to U.S. and other Third Countries. Recent legal developments in the E.U. have created further complexity and uncertainty regarding transfers of personal data from the E.E.A and U.K. to the U.S., e.g. on July 16, 2020, the Court of Justice of the European Union, or CJEU, invalidated the EU-U.S. Privacy Shield Framework, or Privacy Shield, under which personal data could be transferred from the E.E.A and U.K. to U.S. entities who had self-certified under the Privacy Shield. While the CJEU upheld the adequacy of the standard contractual clauses (a standard form of contract approved by the European Commission as an adequate personal data transfer mechanism, and potential alternative to the Privacy Shield), it made clear that reliance on those clauses alone may not necessarily be sufficient in all circumstances. Use of the standard contractual clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals and additional measures and/or contractual provisions may need to be put in place, however, the nature of these additional measures is currently uncertain. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses can/cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints, and/or regulatory scrutiny, investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results and generally increase compliance risk.

The GDPR also provides that E.E.A. member states may make their own further laws and regulations to introduce specific requirements related to the processing of: "special categories of personal data", including personal data related to health, biometric data used for unique identification purposes and genetic information; as well as personal data related to criminal offences or convictions — for example, in the U.K., the Data Protection Act 2018 complements the GDPR in this regard in the U.K. This fact may lead to greater divergence on the law that applies to the processing of such data types across the E.E.A. and U.K., compliance with which as and where applicable may increase our costs and could increase our overall risk.

Notwithstanding the notes in the introduction to this risk factor relating to the continued application of the GDPR in substantially unvaried form and effect, it appears that, following December 31, 2020, there will be increasing scope for divergence in application, interpretation and enforcement of the data protection law between the U.K. and E.U. Furthermore, the relationship between the U.K. and the E.U. in relation to certain aspects of data protection law remains unclear. For example, it is not yet clear whether the U.K. will be the subject of a so-called "adequacy decision" of the European Commission, and it is therefore unclear how data transfers between E.E.A member states and the U.K. will be treated. Any changes relating to the U.K. and E.U. position regarding aspects of data protection law may lead to additional compliance costs and could increase our overall risk.

These laws and regulations are increasing in complexity and number, and new regulatory guidance and case law means the regulatory landscape changes frequently. Complying with these numerous, complex and often changing regulations is expensive and difficult. Failure by us, any partners, our service providers, or our employees or contractors to comply with the GDPR could result in regulatory investigations, enforcement notices and/or fines of up to the higher of €20 million or up to 4% of our total worldwide annual turnover. Further, following the withdrawal of the U.K. from the E.U. and the end of the transition period, we will have to comply with the GDPR and separately

the GDPR as implemented in the U.K., each regime separately having the ability to fine up to the higher of €20 million / £17.5 million or 4% of global turnover. In addition to administrative fines, a wide variety of other potential enforcement powers are available to competent authorities in respect of potential and suspected violations of the GDPR, including extensive audit and inspection rights, and powers to order temporary or permanent bans on all or some processing of personal data carried out by non-compliant actors.

In addition to the foregoing, a breach of privacy laws or data security laws, particularly those resulting in a significant security incident or breach involving the misappropriation, loss or other unauthorized use or disclosure of sensitive or confidential patient or consumer information, could have a material adverse effect on our business, reputation and financial condition. In addition, widely publicized security breaches are increasingly being followed in the E.U. by large 'class action' style claims, which could result in significant liability for compensation and legal fees. As a data controller, we are accountable for any third-party service providers we engage to process personal data on our behalf, including our CROs. We attempt to mitigate the associated risks by performing security assessments and due diligence of our vendors and requiring all such third-party providers with data access to sign agreements, and obligating them to only process data according to our instructions and to take sufficient security measures to protect such data. There is no assurance that these contractual measures and our own privacy and security-related safeguards will protect us from the risks associated with the third-party processing, storage and transmission of such information. Any violation of data or security laws by our third-party processors could have a material adverse effect on our business and result in the fines, penalties and/or other enforcement actions outlined above.

We strive to comply with all applicable laws, but they may conflict with each other, and by complying with the laws or regulations of one jurisdiction, we may find that we are violating the laws or regulations of another jurisdiction. Despite our efforts, we may not have fully complied in the past and may not in the future. If we become liable under laws or regulations applicable to us, we could be required to pay significant fines and penalties (including those described above), our reputation may be harmed and we may be forced to change the way we operate. That could require us to incur significant expenses or to discontinue certain services, which could negatively affect our business.

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 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 an 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;
- 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.

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.

Acelarin has been granted orphan drug designation by the FDA for the treatment of biliary tract cancer. We may be unable to maintain the benefits associated with orphan drug designation for Acelarin in this indication, 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 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.

In June 2019, the FDA granted orphan drug designation for Acelarin for the treatment of advanced biliary tract cancer. We may seek orphan drug designation for other product candidates in the future. Orphan drug exclusivity may not effectively protect the product from competition in the United States because different drugs can be approved for the same condition. Even after an orphan drug is approved and granted exclusivity, the FDA and EMA can subsequently approve the same or a similar drug for the same condition during the exclusivity period if the FDA or the EMA concludes that the later drug is clinically superior in that it is shown to be 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.

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.

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 significant penalties, including criminal sanctions, administrative and 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, including 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 current and future arrangements with healthcare providers, 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 research as well as 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;
- 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, among other things, 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, requires certain 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, as defined by such law, 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;
- The Federal Food, Drug and Cosmetic Act, or FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- 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; state laws that require the reporting of information related to drug pricing; state and local laws requiring the registration of pharmaceutical sales representatives; 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 are found to be not in compliance with applicable laws, they may be subject to significant 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.

We expect that there will continue to be a number of federal and state proposals to implement governmental pricing controls and limit the growth of healthcare costs, including the cost of prescription drugs. For example, the ACA, enacted in March 2010, was expected to have a significant impact on the health care industry and result in expanded coverage for the uninsured. With regard to pharmaceutical products, among other things, ACA was expected to expand and increase industry rebates for drugs covered under Medicaid programs and make changes to the coverage requirements under the Medicare Part D program. We cannot predict the impact of ACA on pharmaceutical companies as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions which has not yet occurred. There remain judicial and Congressional challenges to certain aspects of the ACA, as well as efforts by the Trump administration to repeal or replace certain aspects of the ACA. Since January 2017, President Trump has signed several Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the ACA were signed into law, and one of these laws was subject to federal judicial review. The subject tax was ruled unconstitutional, and on March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review that ruling. It is unclear how such litigation and other efforts to repeal and replace the ACA will impact the ACA and our business.

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 2030

unless additional Congressional action is taken. The Coronavirus Aid, Relief and Economic Security Act, or CARES Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. 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.

At the federal level, President Trump and his administration and Congress have been considering ways to decrease drug prices and increase access to drugs. Although a number of the considered measures may require additional authorization to become effective, Congress and the Trump administration have indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. In addition, individual states in the U.S. have also passed legislation and implemented regulations designed to control pharmaceutical product pricing, and 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.

In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or E.U. member state level may result in significant additional requirements or obstacles that may increase our operating costs.

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. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic. For example, on August 6, 2020, the U.S. Presidential administration issued another executive order that instructs the federal government to develop a list of “essential” medicines and then buy them and other medical supplies from U.S. manufacturers instead of from companies around the world, including China. The order is meant to reduce regulatory barriers to domestic pharmaceutical manufacturing and catalyze manufacturing technologies needed to keep drug prices low and the production of drug products in the United States.

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. 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 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.

We are subject to the U.K. Bribery Act, the U.S. Foreign Corrupt Practices Act and other anti-corruption laws, as well as export control laws, import and customs laws, trade and economic sanctions laws and other laws governing our operations.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or the Bribery Act, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, soliciting, requesting, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to or from persons in the public or private sector to obtain or retain business or gain some other business advantage.

Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and those acting on our behalf operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anticorruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

Compliance with the Bribery Act, the FCPA and these other laws is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, anti-corruption laws present particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials under anti-corruption laws. Certain payments to health care providers in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to enforcement actions.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United States and the United Kingdom, and authorities in the European Union, including applicable export control regulations, economic sanctions and embargoes on certain countries and persons, anti-money laundering laws, import and customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws. Such Trade Control laws include restrictions or prohibitions on the sale or supply of certain products and services to embargoed countries or sanctioned countries, governments, persons and entities.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United States, United Kingdom or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition. Further, the failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting.

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, and the operations of our contracted third parties, may involve the use of hazardous and flammable materials, including chemicals and biological materials. The risk of contamination or injury from these materials cannot be eliminated. In the event of contamination or injury resulting from the use of hazardous materials, we could be held liable for any resulting damages, and the amount of the liability could exceed our resources or those of our contracted third parties. 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, this insurance may not provide adequate coverage. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us. 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.

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 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 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 non-renewal 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 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 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. In February 2020, we amended our agreement to expire at the end of 2020, which amendment afforded us (at our sole discretion) an option to extend the agreement for one additional year until the end of 2021, and for further periods thereafter upon written agreement by both parties. See "Collaboration and License Agreements–Cardiff University License" in in our Annual Report on Form 20-F for the year ended December 31, 2019, incorporated by reference into this prospectus supplement, for more information on the terms of our agreement. 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
- 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 supplement 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 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 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 successfully commercialize any product candidates, if approved, 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 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.

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;
- 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.

Although we maintain product liability insurance coverage, 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.

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 Third Party Observations 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.

Third parties seeking to acquire intellectual property rights in our technology and products may be successful in securing such rights through the grant of patent applications in the United States and in other jurisdictions; if we are forced to defend our granted intellectual property rights for any of our product candidates, we may become involved in costly litigation or other administrative proceedings before the USPTO or comparable non-U.S. regulatory authorities, which could delay or prevent the development and commercialization of our current or future product candidates.

Biopharmaceutical drug development is inherently uncertain in a rapidly evolving technological environment such as ours in which there may be numerous patent applications pending in multiple jurisdictions at any given time, many of which are confidential when filed, with regard to the same or similar technologies. Any patents issued to third parties may contain claims that conflict with our patents and that may place restrictions on the commercial viability of our products and technologies. For example, we are aware of several issued, allowed or pending patent applications in several countries, including the U.S., filed by BrightGene Bio-Medical Technology Co., Ltd., a

pharmaceutical company based in Suzhou, China, directed to a process for the manufacture of Acelarin that is currently used by us to manufacture clinical trial supplies of Acelarin for human studies. We are currently exempt from any patent infringement allegations during the clinical trials. While we believe that BrightGene's process patent filings are invalid over third party patent filings prior to BrightGene's filing dates and are currently challenging or intend to challenge these filings, such filings could compel us to engage in costly patent litigation or certain other administrative proceedings before the USPTO, in U.S. federal courts, or in the courts or patent offices of other countries. If unsuccessful, the maintenance of any of the process patents in relevant jurisdictions could require us to either obtain a license, which may not be available at all or on reasonable terms, or to change our process of manufacture. These activities could result in substantial cost to us and could result in diversion of the efforts of our management and technical personnel.

In addition, BrightGene has also pursued patent claims to the composition of matter of Acelarin in the United States and several other foreign countries. While the USPTO and the Australian PTO have not granted BrightGene's composition of matter patents and we believe that their claims are invalid as a result of our earlier patent filings, were such patents to be granted by those patent offices or patent offices in other jurisdictions, patent litigation or other administrative proceedings may be necessary to enforce our rights under granted patents or to determine the scope and validity of third-party rights, which may be costly and time-consuming. If we do not choose to challenge any such granted patent, then there is the possibility of a patent infringement lawsuit by BrightGene, which may also be costly and time-consuming for us to challenge in order to establish our ownership of the rights. These activities could also result in substantial cost to us and could result in significant diversion of the efforts of our management and technical personnel.

An adverse outcome of any such litigation or proceeding could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using our technology, which could delay or prevent the development and commercialization of our current or future product candidates. If we engage in patent litigation or other administrative proceedings to defend our patents, there is no guarantee that we will be successful in defending our patents, which would result in a loss of the challenged patent right to us and thus adversely affect our business.

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 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.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest, and our business may be adversely affected.

NuCana® and Acelarin® are our registered trademarks and ProTides™ is our trademark. Any additional trademark applications in the United States, Europe and in other foreign jurisdictions where we may file may not be allowed or may subsequently be opposed. Once filed and registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. As a means to enforce our trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition proceedings. This can be expensive and time-consuming, particularly for a company of our size. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our business, financial condition, results of operations, or prospects.

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, NUC-7738 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 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 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 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 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, our clinical research organizations and other third parties on which we rely, 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 June 30, 2020, had 29 employees. 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 service 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 the 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.

On January 31, 2020, the United Kingdom left the European Union on the terms of a withdrawal agreement (the "Withdrawal Agreement"). The Withdrawal Agreement sets out the arrangements for the United Kingdom's withdrawal from the European Union, and includes the transitional arrangements that govern the U.K.-E.U. relationship during a transition period from January 31, 2020 to December 31, 2020 (the "Transition Period"). The Transition Period could have been extended by agreement between the United Kingdom and the European Union, provided that agreement was reached by June 30, 2020. No such agreement was reached and, accordingly, the Transition Period will end on December 31, 2020. During the Transition Period, the United Kingdom is treated, for most purposes, as if it were still an E.U. member state, and provides a short standstill period of continuity whilst the United Kingdom and the European Union negotiate the terms of agreements governing the U.K.-E.U. relationship after December 31, 2020. The fact that no such agreements have yet been reached has created significant uncertainty about the future relationship between the United Kingdom and the European Union, particularly given that the future relationship cannot replicate the United Kingdom's status as an E.U. member state.

Lack of clarity about future United Kingdom laws and regulations as the United Kingdom determines which European Union-derived laws and regulations to replace or replicate as part of the negotiation of the future U.K.-E.U. relationship, 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.

The European Commission has made public statements that the negotiations between the United Kingdom and the European Union with respect to the future U.K.-E.U. relationship must be concluded by the time of the European Council meetings scheduled for October 15 to 16, 2020, and that the legal text of the agreements governing that relationship must be agreed by October 31, 2020, so that the agreements can be ratified by the relevant E.U. institutions and, if necessary, each E.U. member state, by the end of the Transition Period. The United Kingdom's Prime Minister has also made public announcements confirming that there needs to be an agreement by October 15, 2020. If the United Kingdom and the European Union are unable to negotiate acceptable terms by then, or at the very latest, the expiry of the Transition Period, 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 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

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

The trading price of the ADSs has fluctuated, and is likely to continue to fluctuate substantially. The trading price of those securities depends on a number of factors, including those described in this "Risk Factors" section, many of which are beyond our control and may not be related to our operating performance. In addition, although the ADSs are listed on the Nasdaq Global Select Market, we cannot assure you that a trading market for those securities will be maintained.

Since the ADSs were sold in our initial public offering in October 2017 at a price of $15.00 per ADS, the closing price per ADS has ranged as low as $3.81 and as high as $32.00 through September 15, 2020. The market price of our ADSs may fluctuate significantly due to a variety of factors, many of which are beyond our control, 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;
- 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;
- price and volume fluctuations attributable to inconsistent trading volume levels of the ADSs; and
- 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 continue to incur increased costs as a result of operating as a public company in the United States, and our management is required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company whose ADSs commenced trading in the United States in September 2017, we incur, and particularly after we no longer qualify as an "emerging growth company", or EGC, we will continue to 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 need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, these rules and regulations have made it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn makes 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 are required to furnish a report by our senior management on our internal control over financial reporting. However, while we remain an EGC we are not 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 are engaged in a process to document and evaluate our internal control 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.

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

As of June 30, 2020, our senior management, board of directors and greater than 5% shareholders and their respective affiliates, in the aggregate, owned 72.7% of our ordinary shares (including ordinary shares in the form of ADSs). 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 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 and the approval of certain significant corporate transactions. 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. If any of our large shareholders or members of our management team 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 securities in the future could be adversely affected. We have also entered into a registration rights agreement 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.

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 the sole source of potential gains with respect to such securities.

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 the sole source of potential gains with respect to such securities for the foreseeable future.

Holders 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 supplement and in our Annual Report on Form 20-F for the year ended December 31, 2019, incorporated by reference into this prospectus supplement, 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 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. Holders of ADSs 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 ADSs may be voted contrary to the holder's instructions and the holder may be deemed to have instructed the depositary to give a discretionary proxy to a person we designate to vote shares represented by the 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, holders of ADSs may not be able to exercise voting rights and may lack 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.

Holders 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 depositary for our ADSs has agreed to pay to holders 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. Holders 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 holders 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.

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

ADSs are transferable on the books of the depositary. However, the depositary 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 depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary 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 "Issued Share Capital—Differences in Corporate Law" in our Annual Report on Form 20-F for the year ended December 31, 2019, incorporated by reference into this prospectus supplement, 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 (the "Panel") 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 Panel has prepared a brief summary of some of the most important rules of the Takeover Code, which we quote here:

- "When a person or group acquires interests in shares carrying 30% or more of the voting rights of a company, they must make a cash offer to all other shareholders at the highest price paid in the 12 months

before the offer was announced (30% of the voting rights of a company is treated by the Code as the level at which effective control is obtained).

- 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 that price at least.
- 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.
- 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's 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.

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 are not subject to U.S. proxy rules and are 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.

We 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, our shareholders 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 are 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 do include non-independent directors as members of our nominations and remuneration committees; and our independent directors are not required to 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.

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, 2021 (the end of our next second fiscal quarter), 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, 2022. 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 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 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(b), 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 until the last day of 2022, 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 is 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(b). 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 depends 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. In addition, for purposes of the PFIC asset test, the value of our assets will depend in part on the market price of our ordinary shares, which may fluctuate significantly. 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, 2020. However, the determination of PFIC status is based on an annual determination that cannot be made until the close of the taxable year and involves extensive factual and legal investigation. Accordingly, there can be no assurance that we will not be considered a PFIC for our current taxable year ending December 31, 2020 or for any future taxable year.

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 supplement and the documents incorporated by reference in this prospectus supplement include forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act that relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Words such as, but not limited to, "believe," "expect," "anticipate," "estimate," "intend," "may," "plan," "potential," "predict," "project," "targets," "likely," "will," "would," "could," "should," "continue," and similar expressions or phrases, or the negative of those expressions or phrases, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus supplement and incorporated by reference in this prospectus supplement, we caution you that these statements are based on our projections of the future that are subject to known and unknown risks and uncertainties and other factors that may cause our actual results, level of activity, performance or achievements expressed or implied by these forward-looking statements, to differ. The sections in our periodic reports, including our Annual Report on Form 20-F for the fiscal year ended December 31, 2019, titled "Business," "Risk Factors," and "Operating and Financial Review and Prospects," as well as other sections in this prospectus supplement and the documents or reports incorporated by reference in this prospectus supplement, discuss some of the factors that could contribute to these differences. These forward-looking statements include, among other things, 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 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.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important cautionary statements in this prospectus supplement or in the documents incorporated by reference in this prospectus supplement, particularly in the "Risk Factors" section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section titled "Risk Factors" in this prospectus supplement, as updated and supplemented by the discussion of risks and uncertainties under "Risk Factors" contained in any supplements to this prospectus supplement and in our most recent Annual Report on Form 20-F, as revised or supplemented by our subsequent periodic reports filed under the Exchange Act, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this prospectus supplement or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus supplement or the date of the document incorporated by reference in this prospectus supplement. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

CAPITALIZATION

The following table presents our cash and cash equivalents and total capitalization as of June 30, 2020 derived from our unaudited condensed consolidated financial statements incorporated by reference into this prospectus supplement on:

- an actual basis; and
- an as adjusted basis to give effect to the sale by us of 15,555,556 ADSs in this offering at the public offering price of $4.50 per ADS, after deduction of the estimated underwriting discounts and commissions and estimated offering expenses payable by us in connection with this offering and assuming no exercise of the option to purchase additional ADSs by the underwriters.

You should read the financial data in the following table in conjunction with our unaudited condensed consolidated financial statements, audited consolidated financial statements and related notes incorporated by reference into this prospectus supplement.

	AS OF JUNE 30, 2020	
	ACTUAL (unaudited)	AS ADJUSTED (unaudited)
	(in thousands)	
Cash and cash equivalents	£ 47,800	£ 100,770
Total equity attributable to equity holders of the Company:		
Share capital and share premium	82,783	135,753
Other reserves	64,360	64,360
Accumulated deficit	(90,014)	(90,014)
Total equity attributable to equity holders of the Company	57,129	110,099
Total capitalization	£ 57,129	£ 110,099

The number of our ordinary shares to be outstanding immediately after this offering is based on 32,939,450 ordinary shares outstanding as of June 30, 2020 and excludes:

- 7,335,370 ordinary shares issuable upon exercise of outstanding options under our equity plans as of June 30, 2020 at a weighted average exercise price of £4.08 per share;
- 398,859 ordinary shares issuable upon exercise of outstanding options under our equity plans granted subsequent to June 30, 2020 through the date of this prospectus supplement at a weighted average exercise price of £0.04 per share; and
- 3,601,141 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

In addition, subsequent to June 30, 2020 through the date of this prospectus supplement, we have sold and issued 346,206 ADSs, representing 346,206 ordinary shares, pursuant to an “at-the-market” (ATM) sales agreement with Cowen and Company, LLC, resulting in gross proceeds, before deducting sales commissions and other related expenses, of $2.1 million.

USE OF PROCEEDS

We estimate that we will receive total estimated net proceeds from this offering of approximately $65.5 million, based on the public offering price of $4.50 per ADS, or approximately $75.3 million if the underwriters exercise their option to purchase additional ADSs in full, in each case after deducting estimated underwriting discounts and commissions and estimated expenses of the offering payable by us. We intend to use any net proceeds from the sale of securities under this prospectus supplement to fund (i) the development of Acelarin for biliary tract cancer, (ii) the development of NUC-3373 for colorectal cancer and other solid tumors, (iii) the development of NUC-7738 for solid tumors and hematological malignancies, and (iv) for other research and development activities, working capital and general corporate purposes. The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our clinical trials and other development efforts and other factors described under “Risk Factors” in this prospectus supplement and the documents incorporated by reference herein, as well as the amount of cash used in our operations. As a result, our management will have broad discretion to allocate the net proceeds, if any, we receive in connection with securities offered pursuant to this prospectus supplement for any purpose.

DILUTION

If you invest in our ADSs, your interest will be diluted to the extent of the difference between the public offering price per ADS and the net tangible book value per ADS immediately after this offering. As of June 30, 2020, our net tangible book value was £52.6 million, or £1.60 per ordinary share, equivalent to $1.97 per ordinary share and $1.97 per ADS. Net tangible book value per ordinary share is equal to our total assets minus intangible assets and total liabilities, divided by 32,939,450, the total number of ordinary shares outstanding as of June 30, 2020.

After giving effect to the sale of 15,555,556 ADSs at the public offering price of $4.50 per ADS, and after deducting estimated commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2020 would have been £105.6 million, or £2.18 per ordinary share, equivalent to $2.69 per ordinary share and $2.69 per ADS. This represents an immediate increase in net tangible book value of $0.72 per ordinary share and ADS to our existing shareholders and an immediate dilution in net tangible book value of $1.81 per ordinary share and ADS to new investors in this offering. The following table presents this dilution to new investors purchasing ADSs in the offering:

Public offering price per ADS		$4.50
Net tangible book value per ADS as of June 30, 2020	$1.97	
Increase in net tangible book value per ADS attributable to the offering	$0.72	
As adjusted net tangible book value per ADS after giving effect to the offering		$2.69
Dilution per ADS to new investors participating in the offering		$1.81

If the underwriters exercise their option to purchase 2,333,333 additional ADSs in full, the as adjusted net tangible book value per ADS after the offering would be $2.76, the increase in net tangible book value per ordinary share and ADS to existing shareholders would be $0.79 and the immediate dilution in net tangible book value per ordinary share and ADS to new investors in this offering would be $1.74.

The share information excludes:

- 7,335,370 ordinary shares issuable upon exercise of outstanding options under our equity plans as of June 30, 2020 at a weighted average exercise price of £4.08 per share;
- 398,859 ordinary shares issuable upon exercise of outstanding options under our equity plans granted subsequent to June 30, 2020 through the date of this prospectus supplement at a weighted average exercise price of £0.04 per share; and
- 3,601,141 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

To the extent that outstanding options are exercised, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities may result in further dilution to our shareholders.

In addition, subsequent to June 30, 2020 through the date of this prospectus supplement, we have sold and issued 346,206 ADSs, representing 346,206 ordinary shares, pursuant to an “at-the-market” (ATM) sales agreement with Cowen and Company, LLC, resulting in gross proceeds, before deducting sales commissions and other related expenses, of $2.1 million.

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 supplement and on U.S. Treasury regulations in effect or, in some cases, proposed, as of the date of this prospectus supplement, 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 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 or value. 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. The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. U.S. Treasury has expressed concerns that parties to whom ADSs are released before shares are delivered to the depositary or intermediaries in the chain of ownership between the U.S. Holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the claiming of foreign tax credits by U.S. Holders of ADSs. These actions would also be inconsistent with the claiming of the reduced rate of tax, described below, applicable to dividends received by certain noncorporate U.S. Holders. As a result, the creditability of non-U.S. withholding taxes (if any), and the availability of the reduced tax rate for dividends received by certain non-corporate U.S. Holders, each described below, could be affected by actions taken by such parties or intermediaries. Accordingly, U.S. persons considering an investment in ADSs should consult their own tax advisors as to the particular tax consequences applicable to them relating to the purchase, ownership and disposition of ADSs, including the applicability of U.S. federal, state and local tax laws and non U.S. tax laws.

You are urged to consult your tax advisors about the application of the U.S. federal income tax rules to your particular circumstances as well as the state, local, non-U.S. and other tax consequences 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 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. In addition, for purposes of the PFIC asset test, the value of our assets will depend in part on the market price of our ordinary shares, which may fluctuate significantly. 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 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, 2020. However, the determination of PFIC status is based on an annual determination that cannot be made until the close of the taxable year and involves extensive factual and legal investigation. Accordingly, there can be no assurance that we will not be considered a PFIC for our current taxable year ending December 31, 2020 or for any future taxable 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 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.

Controlled Foreign Corporation

The Tax Cuts and Jobs Act (the "Tax Act") eliminated the prohibition on "downward attribution" from non-U.S. persons to U.S. persons under Section 958(b)(4) of the Code for purposes of determining constructive stock ownership under the controlled foreign corporation ("CFC") rules. As a result, our U.S. subsidiary will be deemed to own all of the stock of our non-U.S. subsidiaries held by the Company for CFC purposes. To the extent a non-U.S. subsidiary is treated as a CFC for any taxable year, each U.S. person treated as a "10% U.S. Shareholder" with respect to such CFC that held our common shares directly or indirectly through non-U.S. entities (including the Company) as of the last day in such taxable year that the subsidiary was a CFC would generally be required to include in gross income as ordinary income its pro rata share of certain investment income of the CFC, regardless of whether that income was actually distributed to such U.S. person (with certain adjustments). For tax years beginning on or after January 1, 2018, a "10% U.S. Shareholder" of a non-U.S. corporation includes any U.S. person that owns (or is treated as owning) stock of the non-U.S. corporation possessing 10% or more of the total voting power or total value of such non-U.S. corporation's stock. The legislative history under the Tax Act indicates that this change was not intended to cause our non-U.S. subsidiaries to be treated as CFCs with respect to a 10% U.S. Shareholder that is not related to our U.S. subsidiary. However, it is not clear whether the IRS or a court would interpret the change made by the Tax Act in a manner consistent with such indicated intent.

You are strongly urged to consult your own tax advisors to determine whether your ownership of the ADSs will cause you to become a 10% U.S. Shareholder and the impact of such a classification.

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. 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." Dividend payments may be made without withholding or deduction for or on account of U.K. tax.

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

An additional 3.8% Medicare tax may be imposed 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 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 purchasers are urged to consult their tax advisors concerning the tax consequences related to 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 supplement, 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 or deemed 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 or deemed 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.

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
- 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, on the basis of HMRC guidance, that a holder of ADSs will be regarded by HMRC as the beneficial owner of the underlying ordinary shares and of any dividends paid in respect of the related ordinary shares (where the dividends are regarded for U.K. tax purposes as that person's own income (and not the income of some other person)) 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. For the tax year 2020/2021, an individual U.K. Holder will generally pay income tax at a rate of 0% on the first £2,000 of dividends received by such U.K. Holder. Dividend income taxed at 0% will be taken into account in determining the rate at which income in excess of this tax-free allowance will (subject to the availability of any income tax personal allowance) be taxed.

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 marginal 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.

Individuals who are Scottish taxpayers will pay tax on dividends at the same dividend tax rates as other U.K. taxpayers and as if they paid income tax by reference to the U.K. income tax thresholds rather than by reference to the thresholds otherwise applicable to Scottish taxpayers.

An individual who is not a U.K. Holder (other than one carrying on a trade, profession or vocation in the United Kingdom through a branch or agency to which the ADSs are attributable) 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 U.K. 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 2020/2021 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 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 U.K. 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 2020/2021 tax year is £12,300. 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 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 or deemed 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. Indexation allowance (which historically would have applied to reduce the amount of chargeable gain that is subject to corporation tax) will not operate to reduce any gains on disposals of ADSs acquired on or after January 1, 2018 that arise to corporate U.K. Holders.

Non-United Kingdom Holders. The paragraphs below relating to the liability of non U.K. Holders to U.K. tax on chargeable gains assume that the company does not (and will not) derive 75% or more of its gross asset value from U.K. land:

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 permanent establishment 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.

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.

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 The Depositary Trust Company, or DTC, as a clearance service for United Kingdom stamp duty and SDRT purposes.

Transfer to a depositary or clearance service. Transfers of, and unconditional agreements to transfer, 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 SDRT (and, where the transfer is effected by a written instrument, stamp duty) 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, in the case of a clearance service, it has made an election under section 97A(1) Finance Act 1986, or such transfer can be regarded as an integral part of an issue of share capital. In a recent Court of Justice of the European Union judgment (Air Berlin plc v HMRC [2017]) the Court considered the application of this test but, as yet, the UK domestic law and HMRC's published practice remain unchanged. Accordingly, we anticipate that the charge will continue to be collected and 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 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.

Issue or Transfer of ADSs

Based on current HMRC published practice, no U.K. stamp duty or SDRT should be payable on the issue or transfer of (including an unconditional agreement to transfer) an ADS, on the basis that an ADS is not regarded as "stock" or a "marketable security" for UK stamp duty purposes and is not considered a "chargeable security" for the purposes of SDRT.

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement among us and Jefferies LLC, Cowen and Company LLC, William Blair & Company, L.L.C. and Truist Securities, Inc. as the representatives of the underwriters named below and the joint book-running managers of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the respective number of shares of ADSs shown opposite its name below:

Underwriter	NUMBER OF ADSs
Jefferies LLC	6,222,222
Cowen and Company, LLC	5,055,556
William Blair & Company, L.L.C.	2,722,222
Truist Securities, Inc.	1,555,556
Total	15,555,556

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers' certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the ADSs if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated. We have agreed to indemnify the underwriters and certain of their controlling persons against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the underwriters may be required to make in respect of those liabilities.

The underwriters have advised us that, following the completion of this offering, they currently intend to make a market in the ADSs as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the ADSs, that you will be able to sell any of the ADSs held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters are offering the ADSs subject to their acceptance of the ADSs from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commission and Expenses

The underwriters have advised us that they propose to offer the ADSs to the public at the public offering price set forth on the cover page of this prospectus and to certain dealers, which may include the underwriters, at that price less a concession not in excess of $0.162 per ADS. After the offering, the public offering price, concession and reallowance to dealers may be reduced by the representatives. No such reduction will change the amount of proceeds to be received by us as set forth on the cover page of this prospectus.

The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional ADSs.

	PER ADS		TOTAL	
	WITHOUT OPTION TO PURCHASE ADDITIONAL ADSs	WITH OPTION TO PURCHASE ADDITIONAL ADSs	WITHOUT OPTION TO PURCHASE ADDITIONAL ADSs	WITH OPTION TO PURCHASE ADDITIONAL ADSs
Public offering price	$ 4.50	$ 4.50	$70,000,002	$80,500,001
Underwriting discounts and commissions paid by us	$ 0.27	$ 0.27	$ 4,200,000	$ 4,830,000
Proceeds to us, before expenses	$ 4.23	$ 4.23	$65,800,002	$75,670,001

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately $350,000.

Stamp Taxes

If you purchase ADSs offered in this prospectus, you may be required to pay stamp taxes and other charges under the laws and practices of the country of purchase, in addition to the offering price listed on the cover page of this prospectus.

Listing

Our common stock is listed on The Nasdaq Global Select Market under the trading symbol "NCNA".

Option to Purchase Additional ADSs

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase, from time to time, in whole or in part, up to an aggregate of 2,333,333 ADSs from us at the public offering price set forth on the cover page of this prospectus, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional ADSs proportionate to that underwriter's initial purchase commitment as indicated in the table above. This option may be exercised only if the underwriters sell more ADSs than the total number set forth on the cover page of this prospectus.

No Sales of Similar Securities

We and our officers, directors have agreed that, for a period of 90 days from the date of this prospectus supplement, and a holder of our ADSs have agreed that, for a period of 60 days from the date of this prospectus supplement, subject to specified exceptions, not to directly or indirectly:

- sell, offer, contract or grant any option to sell (including any short sale), pledge, transfer, establish an open "put equivalent position" within the meaning of Rule 16a-l(h) under the Securities Exchange Act of 1934, as amended, or
- otherwise dispose of any ordinary shares or ADSs, options or warrants to acquire ordinary shares or ADSs, or securities exchangeable or exercisable for or convertible into ordinary shares or ADSs currently or hereafter owned either of record or beneficially, or
- publicly announce an intention to do any of the foregoing without the prior written consent of Jefferies LLC, Cowen and Company LLC and William Blair & Company, L.L.C.

Jefferies LLC, Cowen and Company and William Blair & Company, L.L.C. may, in their discretion and at any time or from time to time before the termination of the 90-day period and 60-day period for our officers and directors and certain holders of our ordinary shares or ADSs, respectively, release all or any portion of the securities subject to lock-up agreements. There are no existing agreements between the underwriters and any of our shareholders who will execute a lock-up agreement, providing consent to the sale of ADSs or ordinary shares prior to the expiration of the lock-up period.

Stabilization

The underwriters have advised us that they, pursuant to Regulation M under the Securities Exchange Act of 1934, as amended, certain persons participating in the offering may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the ADSs at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either “covered” short sales or “naked” short sales.

“Covered” short sales are sales made in an amount not greater than the underwriters’ option to purchase additional shares of our ADSs in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional ADSs or purchasing our ADSs in the open market. In determining the source of ADSs to close out 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 option to purchase additional ADSs.

“Naked” short sales are sales in excess of the option to purchase additional ADSs. The underwriters must close out any naked short position by purchasing 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 our ADSs in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of ADSs on behalf of the underwriters for the purpose of fixing or maintaining the price of the ADSs. A syndicate covering transaction is the bid for or the purchase of ADSs on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriter’s purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our ADSs or preventing or retarding a decline in the market price of our ADSs. As a result, the price of our ADSs may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the ADSs originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of ADSs. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our ADSs on The Nasdaq Global Select Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of our ADSs in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker’s bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of ADSs for sale to 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' web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriter and certain of its affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. The underwriter and certain of its affiliates have, from time to time, performed, and may in the future perform, various commercial and investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses. Cowen and Company LLC is the agent under our Sale Agreement, dated October 1, 2018, relating to our "at the market" program.

In the ordinary course of their various business activities, the underwriter and certain of its affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers, and such investment and securities activities may involve securities and/or instruments issued by us and our affiliates. If the underwriters or their respective affiliates have a lending relationship with us, they routinely hedge their credit exposure to us consistent with their customary risk management policies. The underwriters and their respective affiliates may hedge such exposure by entering into transactions which consist of either the purchase of credit default swaps or the creation of short positions in our securities or the securities of our affiliates, including potentially the ADSs offered hereby. Any such short positions could adversely affect future trading prices of the ADSs offered hereby. The underwriters and certain of their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Disclaimers About Non-U.S. Jurisdictions

European Economic Area and the United Kingdom

In relation to each Member State of the EEA and the UK, each a Relevant State, no ADSs have been offered or will be offered pursuant to the offering to the public in that Relevant State, except that offers of ADSs may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

(A) to any legal entity which is a qualified investor as defined under the Prospectus Regulation;

(B) to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the underwriters; or

(C) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of ADSs shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation and each person who initially acquires any ADSs or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with us and each of the underwriters and that it is a "qualified investor" within the meaning of Article 2(e) of the Prospectus Regulation.

In the case of any ADSs being offered to a financial intermediary as that term is used in Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the ADSs acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any ADSs to the public other than their offer or resale in a Relevant State to qualified investors as so defined or in circumstances in which the prior consent of the underwriters have been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression an "offer to the public" in relation to ADSs in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any

ADSs to be offered so as to enable an investor to decide to purchase or subscribe for any ADSs, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129.

United Kingdom

In addition, in the UK, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are “qualified investors” (as defined in the Prospectus Regulation) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, the Order, and/or (ii) who are high net worth companies , unincorporated associations, etc. falling within Article 49(2)(a) to (d) of the Order and/or (iii) to whom it may otherwise be lawfully communicated, all such persons together being referred to as relevant persons, and in circumstances which have not resulted and will not result in an offer to the public of the ADSs in the UK within the meaning of the Financial Services and Markets Act 2000.

Any person in the UK that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the UK, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons.

Canada

(A) Resale Restrictions

The distribution of ADSs in Canada is being made only in the provinces of Ontario, Quebec, Alberta and British Columbia on a private placement basis exempt from the requirement that we prepare and file a prospectus with the securities regulatory authorities in each province where trades of these securities are made. Any resale of the ADSs in Canada must be made under applicable securities laws which may vary depending on the relevant jurisdiction, and which may require resales to be made under available statutory exemptions or under a discretionary exemption granted by the applicable Canadian securities regulatory authority. Purchasers are advised to seek legal advice prior to any resale of the securities.

(B) Representations of Canadian Purchasers

By purchasing ADSs in Canada and accepting delivery of a purchase confirmation, a purchaser is representing to us and the dealer from whom the purchase confirmation is received that:

- the purchaser is entitled under applicable provincial securities laws to purchase the ADSs without the benefit of a prospectus qualified under those securities laws as it is an “accredited investor” as defined under National Instrument 45-106—*Prospectus Exemptions*,
- the purchaser is a “permitted client” as defined in National Instrument 31-103—*Registration Requirements, Exemptions and Ongoing Registrant Obligations*,
- where required by law, the purchaser is purchasing as principal and not as agent, and
- the purchaser has reviewed the text above under Resale Restrictions.

(C) Conflicts of Interest

Canadian purchasers are hereby notified that the representatives are relying on the exemption set out in section 3A.3 or 3A.4, if applicable, of National Instrument 33-105—*Underwriting Conflicts* from having to provide certain conflict of interest disclosure in this document.

(D) Statutory Rights of Action

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if the offering memorandum (including any amendment thereto) such as this document 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 of these securities in Canada 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.

(E) Enforcement of Legal Rights

All of our directors and officers as well as the experts named herein may be located outside of Canada and, as a result, it may not be possible for Canadian purchasers to effect service of process within Canada upon us or those persons. All or a substantial portion of our assets and the assets of those persons may be located outside of Canada and, as a result, it may not be possible to satisfy a judgment against us or those persons in Canada or to enforce a judgment obtained in Canadian courts against us or those persons outside of Canada.

(F) Taxation and Eligibility for Investment

Canadian purchasers of ADSs should consult their own legal and tax advisors with respect to the tax consequences of an investment in the ADSs in their particular circumstances and about the eligibility of the ADSs for investment by the purchaser under relevant Canadian legislation.

Hong Kong

No securities have been offered or sold, and no securities may be offered or sold, in Hong Kong, by means of any document, other than to persons whose ordinary business is to buy or sell shares or debentures, whether as principal or agent; or to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong ("SFO") and any rules made under that Ordinance; or in other circumstances which do not result in the document being a "prospectus" as defined in the Companies Ordinance (Cap. 32) of Hong Kong ("CO") or which do not constitute an offer or invitation to the public for the purpose of the CO or the SFO. No document, invitation or advertisement relating to the securities has been issued or 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 of Hong Kong (except if permitted under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the SFO and any rules made under that Ordinance.

This prospectus has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this prospectus may not be issued, circulated or distributed in Hong Kong, and the securities may not be offered for subscription to members of the public in Hong Kong. Each person acquiring the securities will be required, and is deemed by the acquisition of the securities, to confirm that he is aware of the restriction on offers of the securities described in this prospectus and the relevant offering documents and that he is not acquiring, and has not been offered any securities in circumstances that contravene any such restrictions.

Singapore

This prospectus has not been and will not be lodged or 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.

Where the ADSs are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

(a) 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

(b) 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 (as defined in Section 239(1) of the SFA) 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 ADSs pursuant to an offer made under Section 275 of the SFA except:

(i) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;

(ii) where no consideration is or will be given for the transfer;

(iii) where the transfer is by operation of law;
(iv) as specified in Section 276(7) of the SFA; or
(v) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Japan

The offering has not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948 of Japan, as amended), or FIEL, and the Initial Purchaser will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the FIEL and any other applicable laws, regulations and ministerial guidelines of Japan.

Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange ("SIX") or on any other stock exchange or regulated trading facility in Switzerland. This prospectus has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this prospectus nor any other offering or marketing material relating to the securities or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this prospectus nor any other offering or marketing material relating to the offering, the Company or the securities have been or will be filed with or approved by any Swiss regulatory authority. In particular, this prospectus will not be filed with, and the offer of securities will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, and the offer of securities has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes ("CISA"). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of securities.

Israel

This document does not constitute a prospectus under the Israeli Securities Law, 5728-1968, or the Securities Law, and has not been filed with or approved by the Israel Securities Authority. In Israel, this prospectus is being distributed only to, and is directed only at, and any offer of the common stock is directed only at, (i) a limited number of persons in accordance with the Israeli Securities Law and (ii) investors listed in the first addendum, or the Addendum, to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters, venture capital funds, entities with equity in excess of NIS 50 million and "qualified individuals," each as defined in the Addendum (as it may be amended from time to time), collectively referred to as qualified investors (in each case, purchasing for their own account or, where permitted under the Addendum, for the accounts of their clients who are investors listed in the Addendum). Qualified investors are required to submit written confirmation that they fall within the scope of the Addendum, are aware of the meaning of same and agree to it.

Australia

This prospectus is not a disclosure document for the purposes of Australia's Corporations Act 2001 (Cth) of Australia, or Corporations Act, has not been lodged with the Australian Securities & Investments Commission and is only directed to the categories of exempt persons set out below. Accordingly, if you receive this prospectus in Australia:

You confirm and warrant that you are either:

- a "sophisticated investor" under section 708(8)(a) or (b) of the Corporations Act;
- a "sophisticated investor" under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to the Company 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;

- a person associated with the Company under Section 708(12) of the Corporations Act; or
- a “professional investor” within the meaning of section 708(11)(a) or (b) of the Corporations Act.

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 prospectus is void and incapable of acceptance.

(B) You warrant and agree that you will not offer any of the securities issued to you pursuant to this prospectus for resale in Australia within 12 months of those securities being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

LEGAL MATTERS

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, London, United Kingdom. Certain matters of U.S. federal law will be passed upon for us by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts. The underwriters are being represented in connection with this offering by Cooley LLP, New York, New York, and Cooley (UK) LLP, London, United Kingdom.

EXPERTS

The consolidated financial statements of NuCana plc appearing in NuCana plc's Annual Report on Form 20-F for the year ended December 31, 2019, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference 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 144 Morrison Street, Edinburgh, EH3 8EX, United Kingdom.

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 supplement reside outside of the United States, and a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible for an investor to effect service of process on us or our directors and executive officers in the United States 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 federal 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 instead 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 in civil and commercial matters (although the United States and the United Kingdom are both parties to the New York Convention on the Recognition and Enforcement of Foreign Arbitral Awards).

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the periodic reporting and other informational requirements of the Exchange Act. Under the Exchange Act, we file Annual Reports on Form 20-F and other information with the SEC. As a foreign private issuer, we are exempt from, among other things, the rules under the Exchange Act prescribing the furnishing and content of proxy statements and our officers, directors and principal shareholders are exempt from the reporting and short-swing profit recovery provisions contained in Section 16 of the Exchange Act.

The SEC maintains a web site that contains reports and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is *www.sec.gov*.

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement of which this prospectus supplement forms a part. Statements in this prospectus supplement or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

We also maintain a website at *www.nucana.com* through which you can access our SEC filings. The information set forth on our website is not part of this prospectus supplement.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with them. Incorporation by reference allows us to disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus supplement, and information that we file later with the SEC will automatically update and supersede this information. We filed a registration statement on Form F-3 under the Securities Act of 1933, as amended, with the SEC with respect to the securities we may offer pursuant to this prospectus. This prospectus supplement omits certain information contained in the registration statement, as permitted by the SEC. You should refer to the registration statement, including the exhibits, for further information about us and the securities we may offer pursuant to this prospectus supplement. Statements in this prospectus supplement regarding the provisions of certain documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. Copies of all or any part of the registration statement, including the documents incorporated by reference or the exhibits, may be obtained upon payment of the prescribed rates at the offices of the SEC listed above in "Where You Can Find More Information." The documents we are incorporating by reference are:

- our Annual Report on Form 20-F for the year ended December 31, 2019, filed with the SEC on March 10, 2020;
- our Reports on Form 6-K furnished to the SEC on January 27, 2020, March 4, 2020, March 10, 2020, April 2, 2020, May 5, 2020, May 15, 2020, May 18, 2020, May 19, 2020, June 2, 2020, June 26, 2020, August 19, 2020 and September 16, 2020 that we incorporate by reference into this prospectus supplement; and
- the description of ADSs representing our ordinary shares contained in our Registration Statement on Form 8-A filed with the SEC on September 22, 2017, including any amendments or reports filed for the purpose of updating such description.

We are also incorporating by reference all subsequent Annual Reports on Form 20-F that we file with the SEC and certain reports on Form 6-K that we furnish to the SEC after the date of this prospectus supplement (if they state that they are incorporated by reference into this prospectus supplement) prior to the termination of this offering. In all cases, you should rely on the later information over different information included in this prospectus supplement or any accompanying prospectus.

Unless expressly incorporated by reference, nothing in this prospectus supplement shall be deemed to incorporate by reference information furnished to, but not filed with, the SEC. Copies of all documents incorporated by reference in this prospectus supplement, other than exhibits to those documents unless such exhibits are specifically incorporated by reference in this prospectus supplement, will be provided at no cost to each person, including any beneficial owner, who receives a copy of this prospectus supplement on the written or oral request of that person made to:

NuCana plc
3 Lochside Way
Edinburgh, EH12 9DT
United Kingdom
Telephone: +44 (0)131 357 1111

You may also access these documents on our website, *www.nucana.com*. The information contained on, or that can be accessed through, our website is not a part of this prospectus supplement. We have included our website address in this prospectus supplement solely as an inactive textual reference.

You should rely only on information contained in, or incorporated by reference into, this prospectus supplement. We have not authorized anyone to provide you with information different from that contained in this prospectus supplement or incorporated by reference in this prospectus supplement. We are not making offers to sell the securities in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

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PROSPECTUS

$400,000,000

American Depositary Shares representing Ordinary Shares
Debt Securities
Warrants
Rights
Units

This prospectus will allow us to issue, from time to time at prices and on terms to be determined at or prior to the time of the offering, up to $400,000,000 of any combination of the securities described in this prospectus, either individually or in units. We may also offer: American Depositary Shares, or ADSs, representing ordinary shares upon conversion of or exchange for the debt securities or upon the exercise of the warrants or rights.

This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide you with the specific terms of any offering in one or more supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any prospectus supplement, as well as any documents incorporated by reference into this prospectus or any prospectus supplement, carefully before you invest.

Our securities may be sold directly by us to you, through agents designated from time to time or to or through underwriters or dealers. For additional information on the methods of sale, you should refer to the section titled “Plan of Distribution” in this prospectus and in the applicable prospectus supplement. If any underwriters or agents are involved in the sale of our securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Our ADSs are listed on The Nasdaq Global Select Market under the symbol “NCNA.” On September 28, 2018, the last reported sale price of our ADSs on The Nasdaq Global Select Market was $24.94 per ADS. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The Nasdaq Global Select Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. Prospective purchasers of our securities are urged to obtain current information as to the market prices of our securities, where applicable.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks that we have described on page 4 of this prospectus under the caption “Risk Factors.” We may also include specific risk factors in supplements to this prospectus under the caption “Risk Factors.” This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission 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.

The date of this prospectus is October 22, 2018.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a "shelf" registration process. Under this shelf registration process, we may offer ADSs representing our ordinary shares, various series of debt securities or warrants, and rights to purchase any of such securities, either individually or in units, in one or more offerings, with a total value of up to $400,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained or incorporated by reference in this prospectus. However, no prospectus supplement will offer a security that is not registered and described in this prospectus at the time of its effectiveness. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to the offering of securities under this prospectus. You should carefully read this prospectus, the applicable prospectus supplement, the information and documents incorporated herein by reference and the additional information under the headings "Where You Can Find More Information" and "Incorporation of Documents by Reference" before making an investment decision.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in this prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

This prospectus may not be used to consummate sales of our securities unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference, the document with the most recent date will control.

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."

PROSPECTUS SUMMARY

The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC or included in any applicable prospectus supplement. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth in any prospectus supplements and in our most recent filings with the SEC including our Annual Reports on Form 20-F and reports on Form 6-K, as well as other information in this prospectus and any prospectus supplements and the documents incorporated by reference herein or therein, before purchasing our securities. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.

About NuCana plc

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, including a Phase 1b trial for patients with biliary tract cancer, a Phase 2 trial for patients with ovarian cancer and a Phase 3 trial for patients with pancreatic cancer. NUC-3373 is currently in a Phase 1 trial for the potential treatment of a wide range of advanced solid tumors. 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.

Additional Information

For additional information related to our business and operations, please refer to the reports incorporated herein by reference, including the Annual Report on Form 20-F of NuCana plc for the year ended December 31, 2017 and the Report on Form 6-K furnished on October 1, 2018, as described under the caption “Incorporation of Documents by Reference” on page 59 of this prospectus.

Our 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. ADSs representing our ordinary shares were admitted to trading on The Nasdaq Global Select Market on September 28, 2017. Our ADSs are traded under the symbol “NCNA.”

Our principal executive offices are located at 3 Lochside Way, Edinburgh, EH12 9DT, United Kingdom. Our telephone number at this address is +44 (0)131 357 1111.

We maintain a website at *www.nucana.com* to which we regularly post copies of our press releases as well as additional information about us. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

We use our registered trademarks, NuCana® and Acelarin®, and our trademark, ProTides™, in this prospectus. This prospectus also includes trademarks, trade names and service marks that are the property of other organizations. Solely for convenience, trademarks and trade names referred to in this prospectus appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and trade names.

Offerings Under This Prospectus

Under this prospectus, we may offer ADSs representing our ordinary shares, various series of debt securities or warrants or rights to purchase any of such securities, either individually or in units, with a total value of up to $400,000,000, from time to time at prices and on terms to be determined by market conditions at the time of the offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity, if applicable;
- rates and times of payment of interest or dividends, if any;
- redemption, conversion or sinking fund terms, if any;
- voting or other rights, if any; and
- conversion or exercise prices, if any.

The prospectus supplement also may add, update or change information contained in this prospectus or in documents we have incorporated by reference into this prospectus. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we offer securities through agents or underwriters, we will include in the applicable prospectus supplement:

- the names of those agents or underwriters;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the net proceeds to us.

This prospectus may not be used to consummate a sale of any securities unless it is accompanied by a prospectus supplement.

RISK FACTORS

Investing in our securities involves significant risk. The prospectus supplement applicable to each offering of our securities will contain a discussion of the risks applicable to an investment in the company. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading “Risk Factors” in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under the heading “Risk Factors” included in our most recent Annual Report on Form 20-F and any subsequent Annual Reports on Form 20-F we file after the date of this prospectus, and all other information contained in or incorporated by reference into this prospectus or the registration statement of which this prospectus forms a part, as updated by our subsequent filings under the Securities Exchange Act of 1934, as amended, or the Exchange Act, and the risk factors and other information contained in any applicable prospectus supplement before acquiring any of our securities. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

RATIO OF EARNINGS TO FIXED CHARGES

Any time debt securities are offered pursuant to this prospectus, we will provide a table setting forth our ratio of earnings to fixed charges on a historical basis in the applicable prospectus supplement, if required.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference in this prospectus include forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act that relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Words such as, but not limited to, “believe,” “expect,” “anticipate,” “estimate,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “targets,” “likely,” “will,” “would,” “could,” “should,” “continue,” and similar expressions or phrases, or the negative of those expressions or phrases, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus and incorporated by reference in this prospectus, we caution you that these statements are based on our projections of the future that are subject to known and unknown risks and uncertainties and other factors that may cause our actual results, level of activity, performance or achievements expressed or implied by these forward-looking statements, to differ. The sections in our periodic reports, including our Annual Report on Form 20-F for the fiscal year ended December 31, 2017, titled “Business,” “Risk Factors,” and “Operating and Financial Review and Prospects,” as well as other sections in this prospectus and the documents or reports incorporated by reference in this prospectus, discuss some of the factors that could contribute to these differences. These forward-looking statements include, among other things, 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 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.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important cautionary statements in this prospectus or in the documents incorporated by reference in this prospectus, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section titled “Risk Factors” in this prospectus, as updated and supplemented by the discussion of risks and uncertainties under “Risk Factors” contained in any supplements to this prospectus and in our most recent Annual Report on Form 20-F, as revised or supplemented by our subsequent periodic reports filed under the Exchange Act, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this prospectus or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus or the date of the document incorporated by reference in this prospectus. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

CAPITALIZATION

The following table presents our total capitalization and cash and cash equivalents as of June 30, 2018 derived from our unaudited condensed consolidated financial statements incorporated by reference into this prospectus.

You should read the financial data in the following table in conjunction with our unaudited condensed consolidated financial statements, audited consolidated financial statements and related notes incorporated by reference into this prospectus.

	As of June 30, 2018 (unaudited) (in thousands)
Cash and cash equivalents	£ 81,469
Total equity attributable to equity holders:	
Ordinary shares, nominal value £0.04 per share, 31,811,146 shares issued and outstanding	£ 1,272
Share premium	79,236
Other reserves	59,072
Accumulated deficit	(52,871)
Total equity attributable to equity holders	86,709
Total capitalization	£ 86,709

The outstanding share information excludes:

- 4,802,814 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans as of June 30, 2018 at a weighted average exercise price of £1.66 per share; and
- 112,500 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans that were granted after June 30, 2018 at a weighted average exercise price of £18.05 per share; and
- 374,062 ordinary shares issued upon exercise of options under our equity incentive plans subsequent to June 30, 2018 at a weighted average exercise price of £0.49 per share; and
- 3,349,097 ordinary shares authorized for issuance pursuant to future awards under our equity incentive plans.

EXCHANGE RATE INFORMATION

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 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.

	Noon Buying Rate			
	Period End	Average (1)	High	Low
	($ per £ 1.00)			
Period:				
2013	1.6574	1.5668	1.6574	1.4837
2014	1.5578	1.6461	1.7165	1.5517
2015	1.4746	1.5250	1.5882	1.4648
2016	1.2337	1.3444	1.4800	1.2155
2017	1.3259	1.2957	1.3578	1.2118
2018 (through September 21, 2018)	1.3067	1.3489	1.4332	1.2685
April 2018	1.3751	1.4079	1.4332	1.3751
May 2018	1.3289	1.3470	1.3611	1.3258
June 2018	1.3197	1.3294	1.3429	1.3095
July 2018	1.3125	1.3162	1.3266	1.2987
August 2018	1.2964	1.2878	1.3120	1.2685
September 2018 (through September 21, 2018)	1.3067	1.3045	1.3237	1.2833

(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 21, 2018, the noon buying rate of the Federal Reserve Bank of New York for the U.S. dollar was £1.00 to $1.3067.

PRICE HISTORY OF OUR ADSs

Our ADSs shares have been listed on The Nasdaq Global Select Market under the symbol “NCNA” since September 28, 2017. Prior to that date, there was no public trading market for our ADSs or our ordinary shares. Our initial public offering was priced at $15.00 per ADS on September 28, 2017. The following table sets forth for the periods indicated the high and low sales prices per ADS as reported on The Nasdaq Global Select Market:

	Price Per ADS	
	High	Low
Annual (Year Ended December 31):		
2017 (September 28, 2017 through December 31, 2017)	$18.72	$10.00
2018 (through September 30, 2018)	$28.25	$10.04
Quarterly:		
Third Quarter 2017 (September 28, 2017 through September 30, 2017)	$18.37	$16.15
Fourth Quarter 2017	$18.72	$10.00
First Quarter 2018	$28.25	$10.04
Second Quarter 2018	$32.00	$20.49
Third Quarter 2018	$30.10	$19.32
Most Recent Six Months:		
April 2018	$30.41	$20.49
May 2018	$29.01	$23.00
June 2018	$32.00	$21.20
July 2018	$25.35	$21.00
August 2018	$30.10	$20.59
September 2018	$26.25	$22.08

On September 28, 2018, the last reported sale price of our ADSs on The Nasdaq Global Select Market was $24.94 per ADS.

USE OF PROCEEDS

Unless otherwise indicated in the applicable prospectus supplement, we intend to use any net proceeds from the sale of securities under this prospectus to fund activities relating to the advancement of our drug discovery and development programs, and for other general corporate purposes, including, but not limited to, working capital, capital expenditures, investments, acquisitions, should we choose to pursue any, and collaborations. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds, if any, we receive in connection with securities offered pursuant to this prospectus for any purpose. Pending application of the net proceeds as described above, we may initially invest the net proceeds in short-term, investment-grade and interest-bearing securities.

PLAN OF DISTRIBUTION

We may offer securities under this prospectus from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities (1) through underwriters or dealers, (2) through agents or (3) directly to one or more purchasers, or through a combination of such methods. We may distribute the securities from time to time in one or more transactions at:

- a fixed price or prices, which may be changed from time to time;
- market prices prevailing at the time of sale;
- prices related to the prevailing market prices; or
- negotiated prices.

We may directly solicit offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time, and may enter into arrangements for “at-the-market,” equity line or similar transactions. We will name in a prospectus supplement any underwriter or agent involved in the offer or sale of the securities.

If we utilize a dealer in the sale of the securities being offered by this prospectus, we will sell the securities to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale, and we will provide the name of any underwriter in the prospectus supplement which the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we, or the purchasers of the securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and the underwriter may compensate those dealers in the form of discounts, concessions or commissions.

With respect to underwritten public offerings, negotiated transactions and block trades, we will provide in the applicable prospectus supplement information regarding any compensation we pay to underwriters, dealers or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof.

If so indicated in the applicable prospectus supplement, we will authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in each applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in each applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other

institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

One or more firms, referred to as "remarketing firms," may also offer or sell the securities, if a prospectus supplement so indicates, in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own accounts or as our agents. These remarketing firms will offer or sell the securities in accordance with the terms of the securities. Each prospectus supplement will identify and describe any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm's compensation. Remarketing firms may be deemed to be underwriters in connection with the securities they remarket. Remarketing firms may be entitled under agreements that may be entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

Certain underwriters may use this prospectus and any accompanying prospectus supplement for offers and sales related to market-making transactions in the securities. These underwriters may act as principal or agent in these transactions, and the sales will be made at prices related to prevailing market prices at the time of sale. Any underwriters involved in the sale of the securities may qualify as "underwriters" within the meaning of Section 2(a)(11) of the Securities Act. In addition, the underwriters' commissions, discounts or concessions may qualify as underwriters' compensation under the Securities Act and the rules of the Financial Industry Regulatory Authority, Inc., or FINRA.

ADSs representing our ordinary shares sold pursuant to the registration statement of which this prospectus is a part will be authorized for listing and trading on The Nasdaq Global Select Market. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The Nasdaq Global Select Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. Underwriters may make a market in our ADSs, but will not be obligated to do so and may discontinue any market making at any time without notice. We can make no assurance as to the liquidity of or the existence, development or maintenance of trading markets for any of the securities.

In order to facilitate the offering of the securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing the applicable security in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if the securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

The underwriters, dealers and agents may engage in other transactions with us, or perform other services for us, in the ordinary course of their business.

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.

Issued Share Capital

Our issued share capital as of August 31, 2018 was £1,287,408, comprised of 32,185,208 ordinary 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.

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.

On October 2, 2017, immediately prior to closing our initial public offering, we converted 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. For the purpose of facilitating the conversion of each series B convertible participating share (nominal value £0.004 per share), into an ordinary share (nominal value £0.04 per share), immediately prior to this conversion, on October 2, 2017, we allotted to holders of series B convertible participating shares an additional nine series B convertible participating shares for each series B convertible participating share held.

On October 2, 2017, we issued 7,596,505 ordinary shares pursuant to our initial public offering.

Ordinary Shares

As of August 31, 2018, we had issued and outstanding 32,185,208 ordinary shares of £0.04 each, held by 18 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.

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.

Options

We have established equity incentive plans pursuant to which we have issued options to purchase ordinary shares to employees and directors. As of August 31, 2018, there were 3,689,708 ordinary shares issuable upon exercise of outstanding options under our equity incentive plans. The options lapse after ten years from the date of the grant.

Registration Rights

We have entered into a registration rights agreement 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.

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 our initial public offering and (ii) the date on which there are no registrable securities remaining pursuant to the registration rights agreement.

Articles of Association

The following is a summary of certain provisions of our 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, which is included as an exhibit to our most recent Annual Report on Form 20-F.

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 disapplied, 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.

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 U.K. Companies Act 2006, the provisions of all other relevant legislation, and our articles of association, 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 check 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 check or warrants have been returned undelivered or remain uncashed or the transfer has failed, or in respect of one dividend the check 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.

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 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 is divided into three classes, "Class I," whose initial term expires at the annual general meeting of the shareholders to be held in 2020, "Class II," whose initial term expires at the annual general meeting of the shareholders to be held in 2019, and "Class III", whose term expires at the annual general meeting of the shareholders to be held in 2021, with the classes as nearly equal in number as possible. The Class I directors are Hugh Griffith and Christopher Wood, the Class II directors are Rafaèle Tordjman, James Healy and Cyrille Leperlier, and the Class III directors are Isaac Cheng, Martin Mellish and Adam George.

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.

(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.

(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 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 the takeover 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 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 are 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.

Preemptive Rights. English law generally provides shareholders with preemptive rights when new shares are issued for cash; however, it is possible for a company's articles of association, or shareholders in general meeting, to exclude preemptive rights. Such an exclusion of preemptive rights may be for a maximum period of up to five years from the date of adoption of the articles of association, if the exclusion is contained in the articles of association, or from the date of the shareholder resolution, if the exclusion is by shareholder resolution. In either case, this exclusion would need to be renewed by our shareholders upon its expiration (i.e., at least every five years). On June 27, 2018, our shareholders approved the exclusion of preemptive rights in connection with the allotment of shares with an aggregate nominal value of up to £640,000, for a period ending at the conclusion of our next annual general meeting. On September 14, 2017, our shareholders also approved the exclusion of preemptive rights for the allotment of ordinary shares in connection with our share schemes, up to an aggregate nominal value of £200,331 for a period of five years from the date of approval, which exclusion will need to be renewed upon expiration (i.e., at least every five years) to remain effective, but may be sought more frequently for additional five-year terms (or any shorter period).

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.

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.

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.

	England and Wales	Delaware
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 a single resolution of the shareholders such resolution must not be put to shareholders unless a resolution that it should be so made has first been agreed to by the shareholders without any vote being against it.	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 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.

	England and Wales	Delaware
Annual General Meeting	Under the Companies Act 2006, a public limited company must hold an annual general meeting in each six-month period beginning with the day 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	Under the Companies Act 2006, a general meeting of the shareholders of a public limited company may be called by the directors. 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, or any of them representing more than one half of the total voting rights of all of them, call a general meeting.	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 of a public limited company which fulfil certain conditions. 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.

	England and Wales	Delaware
Quorum	Subject to the provisions of a company's Articles, the Companies Act provides that two shareholders present at a meeting (in person, by proxy or authorized under the Companies Act) shall constitute a quorum for companies with more than one shareholder.	The certificate of incorporation or bylaws may specify the number of shares, the holders of which shall be present or represented by proxy at any meeting in order to constitute a quorum, but in no event shall a quorum consist of less than one third of the shares entitled to vote at the meeting. In the absence of such specification in the certificate of incorporation or bylaws, a majority of the shares entitled to vote, present in person or represented by proxy, shall constitute a quorum at a meeting of stockholders.
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 the period during which any such offer may be accepted as expired or the company has received notice of acceptance of refusal, or 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.

	England and Wales	Delaware
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 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; 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 Delaware law, a corporation's certificate of incorporation may include a 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.

	England and Wales	Delaware
Voting Rights	Under the model articles of public companies, 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 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.	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.

	England and Wales	Delaware
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 a class thereof, the class of shareholders or creditors, 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;	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

	England and Wales	Delaware
	• 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.	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, the board of directors may, in certain circumstances, have a duty to obtain the highest value reasonably available to the shareholders.
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.	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 plaintiffs 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.

England and Wales	Delaware
	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.

Listing

Our ADSs are listed on The Nasdaq Global Select Market under the symbol “NCNA.”

Transfer Agent and Registrar

Our share register is maintained by our registrar, Computershare Investor Services plc. The transfer agent and registrar for our ADSs is Citibank N.A.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future debt securities we may offer pursuant to this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. If we so indicate in a prospectus supplement, the terms of any debt securities offered under such prospectus supplement may differ from the terms we describe below, and to the extent the terms set forth in a prospectus supplement differ from the terms described below, the terms set forth in the prospectus supplement shall control.

We may sell from time to time, in one or more offerings under this prospectus, debt securities, which may be senior or subordinated. We will issue any such senior debt securities under a senior indenture that we will enter into with a trustee to be named in the senior indenture. We will issue any such subordinated debt securities under a subordinated indenture, which we will enter into with a trustee to be named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, of which this prospectus is a part. We use the term “indentures” to refer to either the senior indenture or the subordinated indenture, as applicable. The indentures will be qualified under the Trust Indenture Act of 1939, as in effect on the date of the indenture. We use the term “debenture trustee” to refer to either the trustee under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all the provisions of the indenture applicable to a particular series of debt securities.

General

Each indenture provides that debt securities may be issued from time to time in one or more series and may be denominated and payable in foreign currencies or units based on or relating to foreign currencies. Neither indenture limits the amount of debt securities that may be issued thereunder, and each indenture provides that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution and/or a supplemental indenture, if any, relating to such series.

We will describe in each prospectus supplement the following terms relating to a series of debt securities:

- title or designation;
- the aggregate principal amount and any limit on the amount that may be issued;
- the currency or units based on or relating to currencies in which debt securities of such series are denominated and the currency or units in which principal or interest or both will or may be payable;
- whether we will issue the series of debt securities in global form, the terms of any global securities and who the depositary will be;
- the maturity date and the date or dates on which principal will be payable;
- the interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining such dates;

- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- the terms of the subordination of any series of subordinated debt;
- the place or places where payments will be payable;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- the date, if any, after which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional redemption provisions;
- the date, if any, on which, and the price at which we are obligated, pursuant to any mandatory sinking fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities;
- whether the indenture will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;
- whether we will be restricted from incurring any additional indebtedness;
- a discussion of any material or special U.S. federal income tax considerations applicable to a series of debt securities;
- the denominations in which we will issue the series of debt securities, if other than denominations of $1,000 and any integral multiple thereof; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities. We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our ordinary shares or our other securities. We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of ordinary shares or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction

The indentures do not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indentures or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders of the debt securities protection in the event we have a change of control or in the event of a highly leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect holders of debt securities.

Events of Default Under the Indenture

The following are events of default under the indentures with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;

- if we fail to pay the principal, or premium, if any, when due and the time for payment has not been extended or delayed;
- if we fail to observe or perform any other covenant set forth in the debt securities of such series or the applicable indentures, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the debenture trustee or holders of not less than a majority in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur as to us.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under any bank credit agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the debenture trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of and premium and accrued and unpaid interest, if any, on all debt securities of that series. Before a judgment or decree for payment of the money due has been obtained with respect to debt securities of any series, the holders of a majority in principal amount of the outstanding debt securities of that series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such acceleration). We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the debenture trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the debenture trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the debenture trustee, or exercising any trust or power conferred on the debenture trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the debenture trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will only have the right to institute a proceeding under the indentures or to appoint a receiver or trustee, or to seek other remedies if:

- These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.
- the holder previously has given written notice to the debenture trustee of a continuing event of default with respect to that series;
- the holders of at least a majority in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the debenture trustee to institute the proceeding as trustee; and
- the debenture trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series (or at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

We will periodically file statements with the applicable debenture trustee regarding our compliance with specified covenants in the applicable indenture.

Modification of Indenture; Waiver

The debenture trustee and we may change the applicable indenture without the consent of any holders with respect to specific matters, including:

- to fix any ambiguity, defect or inconsistency in the indenture; and
- to change anything that does not materially adversely affect the interests of any holder of debt securities of any series issued pursuant to such indenture.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the debenture trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) that is affected. However, the debenture trustee and we may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of the series of debt securities;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or any premium payable upon the redemption of any debt securities;
- reducing the principal amount of discount securities payable upon acceleration of maturity;
- making the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such

series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt security of the series affected; *provided*, *however*, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for obligations to:

- the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged with respect to a series, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, the premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange, and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of $1,000 and any integral multiple thereof. The indentures provide that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company or another depositary named by us and identified in a prospectus supplement with respect to that series.

At the option of the holder, subject to the terms of the indentures and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indentures and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange or in the applicable indenture, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Debenture Trustee

The debenture trustee, other than during the occurrence and continuance of an event of default under the applicable indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the debenture trustee under such indenture must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the debenture trustee is under no obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay the principal of and any premium and interest due on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, will we make interest payments by check which we will mail to the holder. Unless we otherwise indicate in a prospectus supplement, we will designate the corporate trust office of the debenture trustee in the City of New York as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the debenture trustee for the payment of the principal of or any premium or interest on any debt securities which remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the security thereafter may look only to us for payment thereof.

Governing Law

The indentures and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Subordination of Subordinated Debt Securities

Our obligations pursuant to any subordinated debt securities will be unsecured and will be subordinate and junior in priority of payment to certain of our other indebtedness to the extent described in a prospectus supplement. The subordinated indenture does not limit the amount of senior indebtedness we may incur. It also does not limit us from issuing any other secured or unsecured debt.

DESCRIPTION OF WARRANTS

General

We may issue warrants to purchase our ordinary shares represented by ADSs and/or debt securities in one or more series together with other securities or separately, as described in the applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that we may offer. Particular terms of the warrants will be described in the warrant agreements and the prospectus supplement relating to the warrants.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the designation, amount and terms of the securities purchasable upon exercise of the warrants;
- if applicable, the exercise price for our ADSs and the number of ADSs to be received upon exercise;
- if applicable, the exercise price for our debt securities, the amount of debt securities to be received upon exercise, and a description of that series of debt securities;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences and any applicable material U.K. tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the ADSs and/or debt securities will be separately transferable;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of the warrants, if any;
- any redemption or call provisions;
- whether the warrants may be sold separately or with other securities as parts of units; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

Transfer Agent and Registrar

The transfer agent and registrar for any warrants will be set forth in the applicable prospectus supplement.

DESCRIPTION OF RIGHTS

General

We may issue rights to our shareholders to purchase our ordinary shares represented by ADSs or the other securities described in this prospectus. We may offer rights separately or together with one or more additional rights, debt securities, ordinary shares represented by ADSs, or warrants, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. Each series of rights will be issued under a separate rights agreement to be entered into between us and a bank or trust company, as rights agent. The rights agent will act solely as our agent in connection with the certificates relating to the rights of the series of certificates and will not assume any obligation or relationship of agency or trust for or with any holders of rights certificates or beneficial owners of rights. The following description sets forth certain general terms and provisions of the rights to which any prospectus supplement may relate. The particular terms of the rights to which any prospectus supplement may relate and the extent, if any, to which the general provisions may apply to the rights so offered will be described in the applicable prospectus supplement. To the extent that any particular terms of the rights, rights agreement or rights certificates described in a prospectus supplement differ from any of the terms described below, then the terms described below will be deemed to have been superseded by that prospectus supplement. We encourage you to read the applicable rights agreement and rights certificate for additional information before you decide whether to purchase any of our rights. We will provide in a prospectus supplement the following terms of the rights being issued:

- the date of determining the shareholders entitled to the rights distribution;
- the aggregate number of ordinary shares represented by ADSs or other securities purchasable upon exercise of the rights;
- the exercise price;
- the aggregate number of rights issued;
- whether the rights are transferrable and the date, if any, on and after which the rights may be separately transferred;
- the date on which the right to exercise the rights will commence, and the date on which the right to exercise the rights will expire;
- the method by which holders of rights will be entitled to exercise;
- the conditions to the completion of the offering, if any;
- the withdrawal, termination and cancellation rights, if any;
- whether there are any backstop or standby purchaser or purchasers and the terms of their commitment, if any;
- whether shareholders are entitled to oversubscription rights, if any;
- any applicable material U.S. federal income tax considerations and any applicable material U.K. tax considerations; and
- any other terms of the rights, including terms, procedures and limitations relating to the distribution, exchange and exercise of the rights, as applicable.

Each right will entitle the holder of rights to purchase for cash the principal amount of ordinary shares represented by ADSs or other securities at the exercise price provided in the applicable prospectus supplement. Rights may be exercised at any time up to the close of business on the expiration date for the rights provided in the applicable prospectus supplement.

Holders may exercise rights as described in the applicable prospectus supplement. Upon receipt of payment and the rights certificate properly completed and duly executed at the corporate trust office of

the rights agent or any other office indicated in the prospectus supplement, we will, as soon as practicable, forward the ordinary shares represented by ADS or other securities, as applicable, purchasable upon exercise of the rights. If less than all of the rights issued in any rights offering are exercised, we may offer any unsubscribed securities directly to persons other than shareholders, to or through agents, underwriters or dealers or through a combination of such methods, including pursuant to standby arrangements, as described in the applicable prospectus supplement.

Rights Agent

The rights agent for any rights we offer will be set forth in the applicable prospectus supplement.

DESCRIPTION OF UNITS

The following description, together with the additional information that we include in any applicable prospectus supplements summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms we have summarized below will apply generally to any units that we may offer under this prospectus, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement. The terms of any units offered under a prospectus supplement may differ from the terms described below.

We will incorporate by reference from reports that we file with the SEC, the form of unit agreement that describes the terms of the series of units we are offering, and any supplemental agreements, before the issuance of the related series of units. The following summaries of material terms and provisions of the units are subject to, and qualified in their entirety by reference to, all the provisions of the unit agreement and any supplemental agreements applicable to a particular series of units. We urge you to read the applicable prospectus supplements related to the particular series of units that we may offer under this prospectus, as well as any related free writing prospectuses and the complete unit agreement and any supplemental agreements that contain the terms of the units.

General

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each security included in the unit. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We will describe in the applicable prospectus supplement the terms of the series of units being offered, including:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The provisions described in this section, as well as those set forth in any prospectus supplement or as described under “Description of Share Capital,” “Description of American Depositary Shares,” “Description of Debt Securities,” “Description of Warrants,” and “Description of Rights” will apply to each unit, as applicable, and to any ordinary shares represented by ADSs, debt security, warrant or right included in each unit, as applicable.

Unit Agent

The name and address of the unit agent, if any, for any units we offer will be set forth in the applicable prospectus supplement.

Issuance in Series

We may issue units in such amounts and in such numerous distinct series as we determine.

Enforceability of Rights by Holders of Units

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

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 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 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 depositary 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 depositary 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 depositary 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 depositary 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 depositary 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 depositary and we will assist the depositary in determining whether it is lawful and reasonably practicable to distribute rights to purchase additional ADSs to holders.

The depositary 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 depositary 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 depositary 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 depositary; or
- it is not reasonably practicable to distribute the rights.

The depositary 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 depositary 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.

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

Any 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 pursuant to our instruction.

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, disapplied 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;
- 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.

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:

Service	Fee
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;
- 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.

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).

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.
- The depositary 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 depositary shall not be liable for acts or omissions of any successor depositary in connection with any matter arising wholly after the resignation or removal of the depositary.
- We and the depositary will not be obligated to perform any act that is inconsistent with the terms of the deposit agreement.
- We and the depositary disclaim any liability if we or the depositary 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 depositary's control.

- We and the depositary 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 depositary 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 depositary 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 depositary 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 depositary also disclaim liability for any consequential or punitive damages for any breach of the terms of the deposit agreement.
- We and the depositary 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 depositary 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 depositary 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 depositary'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 depositary may retain the compensation received from the pre-release transactions.

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 depositary 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 depositary 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 depositary 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 depositary and to the custodian proof of taxpayer status and residence and such other information as the depositary and the custodian may require to fulfill legal obligations. You are required to indemnify us, the depositary and the custodian for any claims with respect to taxes based on any tax benefit obtained for you.

Foreign Currency Conversion

The depositary 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 depositary 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.

EXPENSES

The following is an estimate of the expenses (all of which are to be paid by us) that we may incur in connection with the securities being registered hereby, other than the SEC registration fee and the FINRA filing fee.

SEC registration fee	$48,480
FINRA filing fee	60,500
Legal fees and expenses	(1)
Accounting fees and expenses	(1)
Printing expenses	(1)
Miscellaneous expenses	(1)
Total	$ (1)

(1) These fees are calculated based on the securities offered and the number of issuances and accordingly cannot be estimated at this time.

LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the debt securities, warrants and units governed by U.S. law and certain other matters of U.S. law will be passed upon for us by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. Unless the applicable prospectus supplement indicates otherwise, 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. Additional legal matters may be passed upon for any underwriters, dealers or agents by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of NuCana plc appearing in NuCana's Annual Report on Form 20-F for the year ended December 31, 2017, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference 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 144 Morrison Street, Edinburgh, EH3 8EX, United Kingdom.

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.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the periodic reporting and other informational requirements of the Exchange Act. Under the Exchange Act, we file Annual Reports and other information with the SEC. As a foreign private issuer, we are exempt from, among other things, the rules under the Exchange Act prescribing the furnishing and content of proxy statements and our officers, directors and principal shareholders are exempt from the reporting and short-swing profit recovery provisions contained in Section 16 of the Exchange Act.

Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Room of the SEC at prescribed rates. Further

information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site that contains reports and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is *www.sec.gov*.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement of which this prospectus forms a part. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement at the SEC's Public Reference Room in Washington, D.C. or through the SEC's website, as provided above.

We also maintain a website at *www.nucana.com* through which you can access our SEC filings. The information set forth on our website is not part of this prospectus.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with them. Incorporation by reference allows us to disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We filed a registration statement on Form F-3 under the Securities Act of 1933, as amended, with the SEC with respect to the securities we may offer pursuant to this prospectus. This prospectus omits certain information contained in the registration statement, as permitted by the SEC. You should refer to the registration statement, including the exhibits, for further information about us and the securities we may offer pursuant to this prospectus. Statements in this prospectus regarding the provisions of certain documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. Copies of all or any part of the registration statement, including the documents incorporated by reference or the exhibits, may be obtained upon payment of the prescribed rates at the offices of the SEC listed above in "Where You Can Find More Information." The documents we are incorporating by reference are:

- our Annual Report on Form 20-F for the year ended December 31, 2017, filed with the SEC on March 22, 2018;
- our Report on Form 6-K furnished to the SEC on October 1, 2018 that we incorporate by reference into this prospectus; and
- the description of ADSs representing our ordinary shares contained in our Registration Statement on Form 8-A filed with the SEC on September 22, 2017, including any amendments or reports filed for the purpose of updating such description.

We are also incorporating by reference all subsequent Annual Reports on Form 20-F that we file with the SEC and certain reports on Form 6-K that we furnish to the SEC after the date of this prospectus (if they state that they are incorporated by reference into this prospectus) prior to the termination of this offering. In all cases, you should rely on the later information over different information included in this prospectus or any accompanying prospectus supplement.

Unless expressly incorporated by reference, nothing in this prospectus shall be deemed to incorporate by reference information furnished to, but not filed with, the SEC. Copies of all documents incorporated by reference in this prospectus, other than exhibits to those documents unless such exhibits are specifically incorporated by reference in this prospectus, will be provided at no cost to each person, including any beneficial owner, who receives a copy of this prospectus on the written or oral request of that person made to:

NuCana plc
3 Lochside Way
Edinburgh, EH12 9DT
United Kingdom
Telephone: +44 (0)131 357 1111

You may also access these documents on our website, *www.nucana.com*. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

You should rely only on information contained in, or incorporated by reference into, this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus or incorporated by reference in this prospectus. We are not making offers to sell the securities in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

15,555,556 American Depositary Shares

NuCana plc

Representing 15,555,556 Ordinary Shares

PROSPECTUS SUPPLEMENT

Jefferies
Cowen
William Blair
Truist Securities

September 16, 2020