UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO RULE 13a-16 OR 15d-16
OF THE SECURITIES EXCHANGE ACT OF 1934

For the month of September 2020

(Commission File No. 001-38215)

NUCANA PLC
(Translation of registrant's name into English)

3 Lochside Way
Edinburgh EH12 9DT
United Kingdom
(Address of registrant's principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover Form 20-F or Form 40-F.

Form 20-F ☒ Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101 (b) (1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101 (b) (7): ☐

Other Events.

On September 16, 2020, NuCana plc (the "Company") issued a press release announcing it has commenced an underwritten public offering of its American Depositary Shares ("ADSs"), and its intention to grant the underwriters a 30-day option to purchase up to an additional 15% of the ADSs offered in the public offering. All of the ADSs in the offering will be sold by the Company. A copy of the press release is attached hereto as Exhibit 99.1, and is incorporated herein by reference. The offering is subject to market and other conditions, and there can be no assurance as to whether or when the offering may be completed, or as to the actual size or terms of the offering.

Jefferies LLC, Cowen and Company, LLC, William Blair & Company L.L.C. and Truist Securities, Inc. are acting as joint book-running managers for the offering. On September 16, 2020, the Company filed with the Securities and Exchange Commission a preliminary prospectus supplement to its effective shelf registration statement on Form F-3 (File No. 333-227624) (the "Preliminary Prospectus Supplement") pursuant to Rule 424 under the Securities Act of 1933, as amended, relating to the aforementioned proposed public offering of the Company's ADSs. The Preliminary Prospectus Supplement contains (i) an updated summary description of the Company's business in the section entitled "Prospectus Supplement Summary," which is attached hereto as Exhibit 99.2 and incorporated herein by reference, and (ii) updated risk factor disclosure in the section entitled "Risk Factors," which is attached hereto as Exhibit 99.3 and incorporated herein by reference.

This Report on Form 6-K, including the exhibits hereto, shall not constitute an offer to sell or the solicitation of an offer to buy the securities of the Company, which is being made only by means of a written prospectus meeting the requirements of Section 10 of the Securities Act, nor shall there be any offer, solicitation, or sale of the securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.

Exhibits

99.1	Press Release of NuCana plc, dated September 16, 2020.
99.2	Prospectus Supplement Summary included in NuCana plc's Preliminary Prospectus Supplement dated September 16, 2020 to the Registration Statement on Form F-3 (File No. 333-227624).
99.3	Risk Factors included in NuCana plc's Preliminary Prospectus Supplement dated September 16, 2020 to the Registration Statement on Form F-3 (File No. 333-227624).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

NuCana plc

By: /s/ Donald Munoz
Name: Donald Munoz
Title: Chief Financial Officer

Date: September 16, 2020

Exhibit 99.1

NuCana Announces Proposed Public Offering of American Depositary Shares

Edinburgh, United Kingdom, September 16, 2020 (GLOBE NEWSWIRE) – NuCana plc, a clinical-stage biopharmaceutical company focused on significantly improving treatment outcomes for patients with cancer, announced today that it has commenced an underwritten public offering of its American Depositary Shares ("ADSs"). Each ADS represents one ordinary share of NuCana. In addition, NuCana expects to grant the underwriters a 30-day option to purchase up to an additional 15% of its ADSs at the public offering price, less underwriting discounts and commissions. All of the ADSs are being offered by NuCana. The offering is subject to market and other conditions, and there can be no assurance as to whether or when the offering may be completed or as to the actual size or terms of the offering.

Jefferies, Cowen, William Blair, and Truist Securities are acting as joint book-running managers for the offering.

The securities are being offered pursuant to a registration statement on Form F-3 which has been filed with the U.S. Securities and Exchange Commission (the "SEC") and was declared effective on October 22, 2018. This offering is being made only by means of a prospectus supplement and accompanying prospectus that form a part of the registration statement. Copies of the preliminary prospectus supplement related to this offering and the accompanying prospectus will be filed with the SEC and will be available on the SEC's website at www.sec.gov and may be obtained, when available, by contacting Jefferies LLC, Attention: Equity Syndicate Prospectus Department, 520 Madison Avenue, 2nd Floor, New York, NY 10022, or by telephone at (877) 547-6340 or by e-mail at Prospectus_Department@Jefferies.com, or Cowen and Company, LLC, c/o Broadridge Financial Solutions, 1155 Long Island Avenue, Edgewood, NY 11717, Attention: Prospectus Department, email: PostSaleManualRequests@broadridge.com, telephone: 1-833-297-2926, or William Blair & Company, L.L.C., Attention: Prospectus Department, 150 North Riverside Plaza, Chicago, IL 60606, by telephone at (800) 621-0687, or by email at prospectus@williamblair.com, or Truist Securities, Inc., 3333 Peachtree Road NE, 9th Floor, Atlanta, GA 30326, Attention: Prospectus Department; email: TruistSecurities.prospectus@Truist.com. For the avoidance of doubt, such prospectus will not constitute a "prospectus" for the purposes of the Prospectus Regulation (as defined below) and will not have been reviewed by any competent authority in any EEA member state or the United Kingdom.

This press release shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to the registration or qualification under the securities laws of such state or jurisdiction.

For readers in the European Economic Area (EEA) and the United Kingdom

In any EEA Member State and the United Kingdom (a "Relevant State"), this communication is only addressed to and directed at "qualified investors" in that Relevant State within the meaning of the Prospectus Regulation (Regulation (EU) 2017/1129).

Further notice for readers in the United Kingdom

There will be no offer of ADSs to the public in the United Kingdom. This communication, in so far as it constitutes an invitation or inducement to enter into investment activity (within the meaning of section 21 of the Financial Services and Markets Act 2000 as amended ("FSMA")) in connection with the securities which are the subject of the offering described in this press release or otherwise, is being directed only at (i) persons who are outside the United Kingdom or (ii) persons who have professional experience in matters relating to investments who fall within Article 19(5) ("Investment professionals") of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order") or (iii) certain high value persons and entities who fall within Article 49(2)(a) to (d) ("High net worth companies, unincorporated associations etc.") of the Order; or (iv) any other person to whom it may lawfully be communicated (all such persons in (i) to (iv) together being referred to as "relevant persons"). The ADSs are only available to, and any invitation, offer or agreement to subscribe, purchase or otherwise acquire such ADSs will be engaged in only with relevant persons. Any person who is not a relevant person should not act or rely on this document or any of its contents. This communication does not contain an offer or constitute any part of an offer to the public within the meaning of ss. 85 and 102B of FSMA or otherwise.

About NuCana plc

NuCana is 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. NuCana's robust pipeline includes three ProTides in clinical development. 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 four clinical studies, including a Phase III study for patients with biliary tract cancer, a Phase Ib study for patients with biliary tract cancer, a Phase II study for patients with platinum-resistant ovarian cancer and a Phase III study for patients with metastatic pancreatic cancer for which enrollment has been suspended. NUC-3373 is currently in a Phase I study for the potential treatment of a wide range of advanced solid tumors and a Phase Ib study for patients with metastatic colorectal cancer. Our third ProTide, NUC-7738, is a transformation of a novel nucleoside analog (3'-deoxyadenosine) and is in a Phase I study for patients with advanced solid tumors.

Forward-Looking Statements

This press release may contain "forward-looking" statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are based on the beliefs and assumptions and on information currently available to management of NuCana plc (the "Company"). All statements other than statements of historical fact contained in this press release are forward-looking statements, including statements

regarding the anticipated final terms including the amount of ADSs the Company intends to sell, timing and completion of the proposed offering. In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "expects," "plans," "anticipates," "believes," "estimates," "predicts," "potential" or "continue" or the negative of these terms or other comparable terminology. Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause the Company's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These risks and uncertainties include, but are not limited to, the risks and uncertainties set forth in the "Risk Factors" section of the Company's Annual Report on Form 20-F for the year ended December 31, 2019 filed with the Securities and Exchange Commission ("SEC") on March 10, 2020, subsequent reports that the Company files with the SEC and the preliminary prospectus supplement related to this offering. Forward-looking statements represent the Company's beliefs and assumptions only as of the date of this press release. Although the Company believes that the expectations reflected in the forward-looking statements are reasonable, it cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, the Company assumes no obligation to publicly update any forward-looking statements for any reason after the date of this press release to conform any of the forward-looking statements to actual results or to changes in its expectations.

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PROSPECTUS SUPPLEMENT SUMMARY

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:

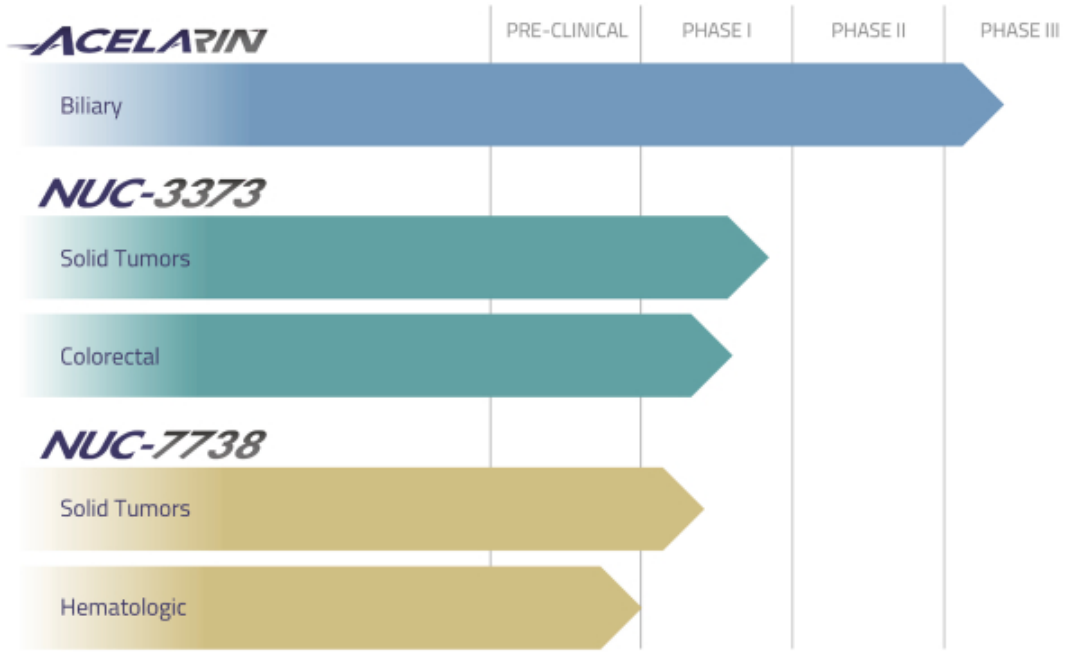
- **Rapidly develop Acelarin as a first-in-class nucleotide analog for the treatment of patients with cancer**. We believe that Acelarin has the potential to replace the core chemotherapy component of treatment regimens for patients with various cancers, focusing initially on:
  - *Biliary tract cancer.* 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.

Risk Factors

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."