Exchange Rate Information

The following table sets forth, for each period indicated, the low and high exchange rates for euros expressed in U.S. dollars, the exchange rate at the end of such period and the average of such exchange rates on the last day of each month during such period, based on the ECB's reference U.S. Dollar exchange rate for Euro, as published by Banque de France. The exchange rates set forth below are provided for reference only and to demonstrate trends in exchange rates. They should not be relied upon, and the actual exchange rates used throughout this Annual Report may vary.

	Year Ended December 31,				
	2012	2013	2014	2015	2016
High	1.3454	1.3814	1.3953	1.2043	1.1569
Low	1.2089	1.2768	1.2141	1.0552	1.0364
Rate at end of period	1.3194	1.3791	1.2141	1.0887	1.0541
Average rate per period	1.2932	1.3308	1.3211	1.1046	1.1066

The following table sets forth, for each of the periods indicated, the low and high exchange rates for euros expressed in U.S. dollars and the exchange rate at the end of the periods indicated based on the ECB's reference U.S. Dollar exchange rate for Euro, as published by Banque de France.

	September 2016	October 2016	November 2016	December 2016	January 2017	February 2017
High	1.1296	1.1236	1.1095	1.0762	1.0755	1.0808
Low	1.1146	1.0872	1.0548	1.0364	1.0385	1.0513
Rate at end of period	1.1161	1.0946	1.0635	1.0541	1.0755	1.0597

On March 22, 2017, the ECB's reference U.S. Dollar exchange rate for the Euro, as published by the Banque de France, was €1.00 = $1.0807.

Information presented on a constant currency basis in this Annual Report is calculated by translating current year results at prior year average exchange rates. Management reviews and analyzes business results excluding the effect of foreign currency translation because they believe this better represents our underlying business trends.

In various places throughout this Annual Report we show financial amounts in both U.S. dollars and euros. Unless otherwise stated, these translations, which are provided solely for convenience, are made at the exchange rate of €1.00 = $1.0541, the ECB's daily reference exchange rate on December 31, 2016, as published by Banque de France.

B. Capitalization and Indebtedness

Not applicable.

C. Reasons for the Offer and Use of Proceeds

Not applicable.

D. Risk Factors

Our business and our industry are subject to significant risks. You should carefully consider all of the information set forth in this Annual Report, including the following risk factors. Our business, financial condition or results of operations could be materially adversely affected by any of these risks.

Risks Related to Our Business and Industry

We have a limited operating history, which makes it difficult to evaluate our current business and future prospects and may increase the risk of your investment.

We are an early-stage biopharmaceutical gene-editing company with a limited operating history. Investment in biopharmaceutical and agricultural biotechnology product development is a highly speculative endeavor. It entails substantial upfront capital expenditures and there is significant risk that any potential product candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, to gain regulatory approval or to become commercially viable. In our therapeutics

business, we are focused on developing products using our gene-editing platform to develop genetically modified T-cells that express a CAR and are designed to target and kill cancer cells. While there have been significant advances in cell-based immunotherapy, our gene-editing platform and T-cell and CAR technologies are new and unproven. Most of the product candidates that we are developing or co-developing are in pre-clinical stages, while one product candidate, UCART123, has received FDA approval to proceed, subject to the approval of our proposed studies by institutional review boards, or IRBs, with clinical development, and one product candidate, UCART19, which is exclusively licensed to Les Laboratories Servier S.A.S., or Servier, commenced clinical development in 2016 through two clinical studies being sponsored by Servier. We have not yet generated any revenue from product sales to date. In our agricultural biotechnology business, we are exploring the use of our gene-editing technologies to develop healthier food products for a growing population. Our plant products are in various stages of development, and we have not yet generated any revenues from sales of these plant products.

Our limited operating history may make it difficult to evaluate our current business and our future prospects. We have encountered, and will continue to encounter, risks and difficulties frequently experienced by growing companies in rapidly developing and changing industries, such as the biopharmaceutical and agricultural biotechnology industries, including challenges in forecasting accuracy, determining appropriate investments of our limited resources, gaining market acceptance of our gene-editing platform, managing a complex regulatory landscape and developing new product candidates. Our current operating model may require changes in order for us to scale our operations efficiently. You should consider our business and prospects in light of the risks and difficulties we face as an early-stage company focused on developing products in the fields of immunotherapy and agricultural biotechnology.

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We devote most of our financial resources to research and development relating to our CAR T-cell immunotherapy product candidates. We finance our current immuno-oncology operations through strategic alliances with pharmaceutical companies, including Servier and Pfizer Inc., or Pfizer, as well as through the sale of equity securities and, to a lesser extent, obtaining public funding in support of innovation, reimbursements of research tax credit claims, and royalties on our licensed technology. During 2013 and 2014, we have received €61.0 million through sales of equity, and €73.7 million in payments made to us under our collaboration agreements with Pfizer and Servier. In addition, in March 2015, we completed our U.S. Initial Public Offering of 5,500,000 American Depositary Shares on the Nasdaq Global Market for gross proceeds of $228.3 million. In 2015 and 2016, we received respectively €46.9 million and €24.7 million in payments pursuant to the Pfizer and Servier collaborations. Our research and development expenses for the years ended December 31, 2015 and 2016 were €52.4 and €70.9 million, respectively. Our net loss for the years ended December 31, 2015 and 2016 was €20.4 million and €60.8 million, respectively.

Among all the UCART products candidates in development by us or by our collaborators, the UCART19 Clinical Studies (as defined in Item 4.B. Business Overview below) commenced in June 2016 and we obtained FDA approval of an IND for two Phase I UCART123 Clinical Studies (as defined in Item 4.B. Business Overview below) in February 2017. Notwithstanding the commencement of the UCART19 Clinical Studies and the FDA approval to commence the UCART123 Clinical Studies, it will be several years, if ever, before we obtain regulatory approval for, and are ready for commercialization of, a product candidate. Moreover, our submissions for IRB approval for our UCART123 Clinical Studies are pending at New York-Presbyterian/Weill Cornell Medical Center (or “Weill Cornell”) and the University of Texas MD Anderson Cancer Center (“MD Anderson Cancer Center”), and we may not receive approvals from these IRBs, in which case the UCART123 Clinical Studies would not be permitted to commence. Even if we or our collaborators successfully commence and complete clinical studies and obtain regulatory approval to market a product candidate, any future revenues will depend upon the size of any markets in which the product candidates are approved for sale as well as the market share captured by such product candidates, market acceptance of such product candidates and levels of reimbursement from third-party payors.

We expect to continue to incur significant expenses and operating losses for the foreseeable future. We expect our losses and our cash utilization to increase in the near term as we commence the UCART123 Clinical Studies, file additional IND and/or foreign equivalent filings for additional product candidates and conduct research and development for other product candidates. In addition, we anticipate that such expenses will increase further and such increases may be substantial if and as we:

- continue to advance the research and development of our current and future immuno-oncology product candidates;
- continue, through Calyxt, to advance the research and development of our current and future agricultural product candidates;
- initiate additional clinical studies for, or additional pre-clinical development of, our immuno-oncology product candidates;
- conduct and multiply, though Calyxt, additional field trials of our agricultural product candidates;
- further develop and refine the manufacturing process for our immuno-oncology product candidates;

- change or add additional manufacturers or suppliers of biological materials;
- seek regulatory and marketing approvals for our product candidates, if any, that successfully complete development;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- seek to identify and validate additional product candidates;
- acquire or in-license other product candidates, technologies, germplasm or other biological material;
- make milestone or other payments under any in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- secure manufacturing arrangements for commercial production;
- seek to attract and retain new and existing skilled personnel;
- create additional infrastructure to support our operations as a public company; and
- experience any delays or encounter issues with any of the above.

The net losses we incur may fluctuate significantly from year to year and quarter to quarter, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

We may need to raise additional funding. Additional funding may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently preparing to commence the UCART123 Clinical Studies and we are advancing our other product candidates to and through pre-clinical testing. The process of developing CAR T-cell product candidates and conducting clinical studies is expensive, lengthy and risky, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we commence the UCART123 Clinical Studies, file additional protocols under our current IND, file additional IND and/or foreign equivalent filings for additional product candidates, and conduct research and development for our other product candidates. In addition, subject to obtaining regulatory approval of any product candidates, we expect to incur significant commercialization expenses.

As of December 31, 2016, we had cash and cash equivalents and current financial assets of approximately €276 million. We believe our cash and cash equivalents and our cash flow from operations (including payments we expect to receive pursuant to our collaboration agreements) and government funding of research programs will be sufficient to fund our operations through 2019. However, in order to complete the development process, obtain regulatory approval and commercialize, if approved, any of our product candidates and to obtain regulatory approval for, if necessary, and commercialize our lead plant sciences products, we may require additional funding. Also, our operating plan, including our product development plans, may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches.

In addition, our ability to raise additional capital in equity offerings will be significantly limited, as described under “—We are limited in our ability to raise additional share capital, which may make it difficult for us to raise capital to fund our operations.” Debt financing, if available, would result in increased fixed payment obligations and a portion of our operating cash flows, if any, being dedicated to the payment of principal and interest on such indebtedness. In addition, debt financing may involve agreements that include restrictive covenants that impose operating restrictions, such as restrictions on the incurrence of additional debt, the making of certain capital expenditures or the declaration of dividends. To the extent we raise additional funds through arrangements with collaborators or otherwise, we may be required to relinquish some of our technologies, product candidates or revenue streams, license our technologies or product candidates on unfavorable terms, or otherwise agree to terms unfavorable to us.

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. In addition, 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 product candidate development programs or the commercialization of any product candidate or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, operating results and prospects.

We are limited in our ability to raise additional share capital, which may make it difficult for us to raise capital to fund our operations.

Under French law, our share capital generally may be increased with the approval of a two-thirds majority vote of the shareholders present, represented by proxy, or voting by mail obtained at an extraordinary general shareholders' meeting following the recommendation of our board of directors. The shareholders may delegate to our board of directors either the authority (*délégation de compétence*) or the power (*délégation de pouvoir*) to carry out any increase in the share capital. Accordingly, our board of directors may be precluded from issuing additional share capital if the prior approval of the shareholders is not duly obtained.

Risks Related to the Discovery, Development and Commercialization of Our Therapeutic Product Candidates

Our therapeutic product candidate development programs are still in the discovery or pre-clinical proof-of-concept phase and may be unsuccessful.

Except for UCART19 which has been exclusively licensed to Servier, the use of our gene-editing technologies in the product candidates we develop have not been approved for, nor undergone clinical testing in humans and have only undergone limited testing in animals. In February 2017, we received FDA approval under an IND to commence our UCART123 Clinical Studies. However, IRB approvals are still pending at Weill Cornell and MD Anderson Cancer Center, and we may not commence the UCART123 Clinical Studies until such approvals are received. Clinical trial agreements with Weill Cornell are being negotiated and such agreements must be in place before our UCART123 Clinical Studies may be commenced. Results from animal studies are not necessarily predictive of results in clinical studies. Even if certain of our product candidates progress through clinical studies, these product candidates may fail to show the desired safety and efficacy in clinical development despite demonstrating positive results in animal studies. For example, while our animal studies of product candidates may result in evidence of tumor cell elimination, there can be no assurance that the success we achieve in such animal studies for these product candidates will result in success in any clinical studies.

Because our current product candidates are still in the early stages of development, with the majority of our product candidates in the discovery or pre-clinical proof-of-concept phase, there can be no assurance that our research and development activities will result in product candidates we can advance through clinical development. Although Servier commenced the UCART19 Clinical Studies in June 2016 and we are pursuing IRB approvals to commence our UCART123 Clinical Studies, the commencement and results of such clinical studies are subject to a variety of factors and considerations and we cannot assure you that we or our collaborators will achieve the applicable targets in these studies. Our other product candidates are in various stages of pre-clinical development and we have limited pre-clinical data evaluating many of these product candidates. Because of the early stage of development of our product candidates, we have not yet demonstrated the safety, specificity and clinical benefits of our product candidates in humans, and we cannot assure you that the results of any human trials will demonstrate the value and efficacy of our platform. Moreover, there are a number of regulatory requirements that we must satisfy in connection with our UCART123 Clinical Studies, including approval of our proposed studies by IRBs, and that we must satisfy before we can commence additional clinical trials in the United States and the European Union, or EU, with respect to our other product candidates. Satisfaction of these requirements will entail substantial time, effort and financial resources. We may never satisfy these requirements. Any time, effort and financial resources we expend on our other early-stage product candidate development programs may adversely affect our ability to continue development and commercialization of our more advanced product candidates and we may never commence additional clinical studies despite expending significant resources in pursuit of their development. Further, our UCART123 Clinical Studies or other clinical studies, if any, that we commence may not be successful and such product candidates may never be approved by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or any other regulatory agency.

Early data from compassionate use treatment and from clinical trials are not predictive of success in later clinical trials.

In December 2016, during a meeting with the National Institutes of Health's Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC, Pfizer and Servier presented preliminary clinical data for UCART19, including data from UCART19 Clinical Studies and from three clinical uses of UCART19 on a compassionate basis. These three compassionate use patients have been treated under U.K. special licenses from the Medicines & Healthcare products Regulatory Agency (MHRA) to administer UCART19 product candidate to a patient on a compassionate use basis. Compassionate use refers to the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options.

We cannot assure you that the administration of UCART19 to other patients will have results that are similar to those reported by Pfizer and Servier. Such results are necessarily preliminary in nature, do not bear statistical significance and should not be viewed as predictive of ultimate success. It is possible that such results will not continue or may not be repeated in other potential compassionate uses or in ongoing or future clinical trials on UCART19 or other UCART product candidates.

We have limited experience in conducting or managing clinical trials for potential therapeutic products.

In February 2017, we received FDA approval of our IND for the UCART123 Clinical Studies, and we are seeking approval from IRBs, which are pending at Weill Cornell and MD Anderson Cancer Center. We have limited experience in conducting or managing the clinical trials necessary to obtain regulatory approvals for any product candidate. We intend to rely on our collaborators or third parties, such as clinical research organizations, or CROs, medical institutions and clinical investigators to perform these functions. Our reliance on third parties for clinical development activities reduces our control over these activities. Third-party contractors may not complete activities on schedule, or may not conduct clinical trials in accordance with regulatory requirements or our trial design. If these third parties do not successfully carry out their contractual duties or meet required performance standards or expected deadlines, we might be required to replace them or the data that they provide could be rejected by the FDA or comparable foreign regulatory bodies, all of which may result in a delay of the affected trial and additional program costs.

We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Pre-clinical testing of most of our product candidates is still ongoing. Pre-clinical testing and clinical trials, such as our proposed UCART123 Clinical Studies, are long, expensive and unpredictable processes that can be subject to extensive delays. Moreover, our submissions for IRB approval for our UCART123 Clinical Studies are pending at Weill Cornell and MD Anderson Cancer Center, and we may not receive approvals from these IRBs, in which case the UCART123 Clinical Studies would not be permitted to commence. We cannot guarantee that any pre-clinical studies or clinical trials will be conducted as planned or completed on schedule, if at all. It may take several years to complete the pre-clinical testing and clinical development necessary to commercialize a product candidate, and delays or failure can occur at any stage. Interim results of clinical trials do not necessarily predict final results, and success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful. A number of companies in the pharmaceutical, biopharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials even after promising results in earlier trials, including a number of patient deaths in recent CAR-T trials conducted in the United States, and we cannot be certain that our product candidates, including UCART123, will not face similar setbacks. In addition, the design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. An unfavorable outcome in one or more clinical trials would be a major setback for our product candidates and for us and may require us or our collaborators to delay, reduce the scope of, or eliminate one or more product candidate development programs, any of which could have a material adverse effect on our business, financial condition and prospects.

In connection with clinical testing and trials on product candidates we develop for ourselves or on behalf of our collaborators, we may face a number of risks, including:

- pre-clinical results may not be indicative of clinical results in humans;
- a product candidate may be ineffective, inferior to existing approved drugs or therapies or unacceptably toxic, or may have unacceptable side effects;
- patients may die or suffer other adverse effects for reasons that may or may not be related to the product candidate being tested;
- the results may not confirm the favorable results of earlier testing or trials; and
- the results may not meet the level of statistical significance required by the FDA and/or other applicable regulatory agencies to establish the safety and efficacy of our product candidates.

In addition, a number of events, including any of the following, could delay the completion of our future clinical trials (including the UCART123 Clinical Studies) or those of our collaborators (including the UCART19 Clinical Studies) and negatively impact the ability to obtain regulatory approval for, and to market and sell, a particular product candidate:

- conditions imposed on us or our collaborators by the FDA or any foreign regulatory authority regarding the scope or design of clinical trials;
- delays in obtaining, or our inability to obtain, required approvals from institutional review boards, or IRBs, or other reviewing entities at clinical sites selected for participation in our clinical trials;
- insufficient supply or deficient quality of the product candidates or other materials necessary to conduct the clinical trials;

- delays in obtaining regulatory agency approval for the conduct of the clinical trials;
- lower-than-anticipated enrollment and retention rate of subjects in clinical trials for a variety of reasons, including size of patient population, nature of trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;
- serious and unexpected drug-related side effects experienced by patients in clinical trials; or
- failure of our or our collaborators' third-party contractors to meet their contractual obligations in a timely manner.

Data obtained from pre-clinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we cannot assure you that, in the course of clinical trials, some drawbacks would not appear that reveal that it is not possible or practical to continue development efforts for the subject product candidates.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us or our collaborators, the FDA, the IRBs at the sites where the IRBs are overseeing a trial, or a data safety monitoring board, or DSMB, overseeing the clinical trial at issue, or other regulatory authorities due to a number of factors, including:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;
- unfavorable interpretations by FDA or similar foreign regulatory authorities of data, where clinical study plans call for interim data analysis;
- FDA or similar foreign regulatory authorities determine the plan or protocol for the investigation is deficient in design to meet its stated objectives;
- lack of, or failure to, demonstrate efficacy;
- unforeseen safety issues; or
- lack of adequate funding to continue the clinical trial.

In addition, changes in regulatory requirements and guidance may occur and we or our collaborators may need to amend clinical trial protocols to reflect these changes. Amendments may require us or our collaborators to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the cost, timing or successful completion of a clinical trial.

Even if a product candidate successfully completes clinical trials, those results are not necessarily predictive of results of additional trials that may be needed before regulatory approval may be obtained. Although there are a large number of drugs and biologics in development globally, only a small percentage obtain regulatory approval, even fewer are approved for commercialization, and only a small number achieve widespread physician and consumer acceptance.

If the results of our clinical trials are inconclusive or if there are safety concerns or adverse events associated with the product candidates we develop, we may:

- lose any competitive advantages that such product candidates may have;
- be delayed in obtaining marketing approval for the subject product candidates, if 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, contraindications or safety warnings;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;
- be sued;
- experience damage to our reputation; or
- not reach the milestones triggering payments from our collaborators.

Our product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and obtaining regulatory approval. Currently, only a very limited number of gene therapy products have been approved in the United States or Europe.

We have concentrated our research and development efforts on our CAR T-cell immunotherapy product development, including our gene-editing technologies, and our future success depends on the successful development of this therapeutic approach. We are in the early stages of developing our UCART product candidates' platform and there can be no assurance that any development problems we experience in the future related to our gene-editing technologies will not cause significant delays or unanticipated costs, or that such development problems can be overcome. We may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial partners, which may prevent us from completing our clinical studies or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical study requirements of the FDA, EMA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate are determined according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more complex and consequently more expensive and take longer than for other, better known or extensively studied pharmaceutical or other product candidates. Currently, two gene therapy products received marketing authorization from the EMA and have been approved in Europe, and only one gene therapy product has been approved in the United States, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either Europe or the United States. Approvals by the EMA and FDA for existing gene therapy products may not be indicative of what these regulators may require for approval of further gene therapy products. More generally, approvals by any regulatory agency may not be indicative of what any other regulatory agency may require for approval or what such regulatory agencies may require for approval in connection with new product candidates.

The regulatory landscape that will govern our product candidates is uncertain; regulations relating to more established gene therapy and cell therapy products are still developing, and changes in regulatory requirements could result in delays or discontinuation of development of our product candidates or unexpected costs in obtaining regulatory approval.

Because we are developing novel CAR T-cell immunotherapy product candidates that are unique biological entities, the regulatory requirements that we will be subject to are not entirely clear. Even with respect to more established products that fit into the categories of gene therapies or cell therapies, the regulatory landscape is still developing. For example, regulatory requirements governing gene therapy products and cell therapy products have changed frequently and may continue to change in the future. Moreover, there is substantial, and sometimes uncoordinated, overlap in those responsible for regulation of existing gene therapy products and cell therapy products. For example, in the United States, the FDA has established the Office of Tissues and Advanced Therapies (OTAT, formerly known as the Office of Cellular, Tissue and Gene Therapies, or OCTGT) within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical trials are also subject to review and oversight by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at the institution participating in the clinical trial. Gene therapy clinical studies conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health, or the NIH, are also subject to review by the NIH Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC. Although the FDA decides whether individual gene therapy protocols may proceed, review process and determinations of other reviewing bodies can impede or delay the initiation of a clinical study, even if the FDA has reviewed the study and approved its initiation. Conversely, the FDA can place an IND application on clinical hold even if such other entities have provided a favorable review. Furthermore, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which a clinical trial will be conducted. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other regulatory bodies to change the requirements for approval of any of our product candidates.

On February 6, 2017, the FDA notified us that the IND we submitted for our two Phase I UCART123 Clinical Studies could proceed. Our submissions for IRB and IBC approvals are pending at Weill Cornell and MD Anderson Cancer Center, and we may not receive their approvals. If we do not receive IRB approval for our UCART123 Clinical Studies, we will not be able to commence the studies at those institutions. Clinical trial agreements with Weill Cornell and MD Anderson Cancer Center are being negotiated and such agreements must be in place before our UCART123 Clinical Studies may be commenced.

Similarly, complex regulatory environments exist in other jurisdictions in which we might consider seeking regulatory approvals for our product candidates, further complicating the regulatory landscape. For example, in the EU a special committee called the Committee for Advanced Therapies (CAT) was established within the EMA in accordance with Regulation (EC) No 1394/2007 on advanced-therapy medicinal products (ATMPs) to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field. ATMPs include gene therapy products as well as somatic cell therapy products and tissue

engineered products. In this regard, on May 28, 2014, the EMA issued a recommendation that Cellectis' UCART19 be considered a gene therapy product under Regulation (EC) No 1394/2007 on ATMPs. We believe this recommendation is likely to be applicable to our UCART product candidates; however, this recommendation is not definitive until such products obtain regulatory approval for commercialization.

These various regulatory review committees and advisory groups and new or revised guidelines that they promulgate from time to time may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. Because the regulatory landscape for our CAR T-cell immunotherapy product candidates is new, we may face even more cumbersome and complex regulations than those emerging for gene therapy products and cell therapy products. Furthermore, even if our product candidates obtain required regulatory approvals, such approvals may later be withdrawn as a result of changes in regulations or the interpretation of regulations by applicable regulatory agencies.

As we or our collaborators advance our product candidates, we and they will be required to consult with these regulatory and advisory groups and comply with all applicable guidelines, rules and regulations. Because the UCART19 Clinical Studies are being sponsored by Servier in collaboration with Pfizer, they are directly interacting with the relevant regulatory agencies and we are not able to direct such interactions. Some of the discussions among our commercial collaborators and relevant regulatory agencies could generate additional unexpected requirements from regulatory agencies that would apply to our wholly-controlled UCART product candidates, including UCART123, and could lead to potential delays or additional requirements. For example, as a result of such interactions, regulators may require that we implement additional studies or testing with respect to our product candidates or modify our clinical studies, including the UCART123 Clinical Studies.

If we fail to do so, we may be required to delay or discontinue development of our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

Our gene-editing technology is relatively new, and if we are unable to use this technology in all of our intended applications, our revenue opportunities will be limited.

Our technology involves a relatively new approach to gene editing, using sequence-specific DNA-cutting enzymes, or nucleases, to perform precise and stable modifications in the DNA of living-cells and organisms. Although we have generated nucleases for many specific gene sequences, we have not created nucleases for all gene sequences that we may seek to target, and we may not be able do so, which could limit the usefulness of our technology.

The expected value and utility of our nucleases is, in part, based on our belief that the targeted modification of genes or specific regulation of gene expression may enable us to develop a new therapeutic approach. There is only a limited understanding of the role of specific genes in these applications. Life sciences companies have only been able to successfully develop or commercialize a few products in this biopharmaceutical space based on results from genome research or the ability to regulate gene expression. We or our collaborators may not be able to use our technology to develop commercial products in the intended diseases.

In addition, the biopharmaceutical industry is rapidly developing, and our competitors may introduce new technologies that render our technology obsolete or less attractive. New technology could emerge at any point in the development cycle of our product candidates. As competitors use or develop new technologies, we may be placed at a competitive disadvantage, and competitive pressures may force us to implement new technologies at a substantial cost. In addition, our competitors have greater financial, technical and personnel resources that allow them to enjoy technological advantages and may in the future allow them to implement new technologies before we can. We cannot be certain that we will be able to implement technologies on a timely basis or at a cost that is acceptable to us. If we are unable to maintain technological advancements consistent with industry standards, our operations and financial condition may be adversely affected.

We depend almost entirely on the successful development of our product candidates. We cannot be certain that we or our collaborators will be able to obtain regulatory approval for, or successfully commercialize, these products.

Currently, UCART123 is our only fully-controlled product candidate that has been approved by the FDA to enter into Phase I clinical studies in the United States. In addition, UCART19, which is exclusively licensed to Servier, is the subject of two Phase I clinical studies in the United Kingdom, each sponsored by Servier, and has been approved for a Phase I clinical study in the United States, to be conducted in collaboration with Pfizer. Notwithstanding the foregoing, we may never be able to develop products that will be approved or commercialized. Our business depends primarily on the successful clinical development, regulatory approval and commercialization of our CAR T-cell immunotherapy product candidates. We are also studying in pre-clinical studies, on our own or through our collaborators, other product candidates based on gene-edited CAR T-cells for cancer immunotherapy.

Our therapeutic product candidates will require substantial additional clinical development, testing, and regulatory approval before we are permitted to commence their commercialization. The clinical trials of our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market any product candidate. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate, with substantial evidence gathered in well-controlled clinical trials, and, with respect to approval in the United States, to the satisfaction of the FDA or, with respect to approval in other countries, similar regulatory authorities in those countries, that the product candidate is safe and effective for use in each target indication. In the United States, we expect that the requisite regulatory submission to seek marketing approval for our gene therapy products will be a Biologic License Application, or BLA, and the competent regulatory authority is the FDA. In the EU, the requisite approval is a Marketing Authorisation, or MA, which for products developed by the means of recombinant DNA technology, gene or cell therapy products as well as tissue engineered products, is issued through a centralized procedure involving the EMA. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. Despite our efforts, our product candidates may not:

- offer improvement over existing, comparable products;
- be proven safe and effective in clinical trials; or
- meet applicable regulatory standards.

This process can take many years and may include post-marketing studies and surveillance, which will require the expenditure of substantial resources beyond our existing cash on hand. Of the large number of drugs in development globally, only a small percentage successfully completes the regulatory approval process and even fewer are commercialized. Furthermore, we have not marketed, distributed or sold any products. Our success will, in addition to the factors discussed above, depend on the successful commercialization of the product candidates we develop on our own or on behalf of our collaborators, which may require:

- obtaining and maintain commercial manufacturing arrangements with third-party manufacturers;
- collaborating with pharmaceutical companies or contract sales organizations to market and sell any approved drug; or
- acceptance of any approved drug in the medical community and by patients and third-party payors.

Many of these factors are beyond our control. We do not expect any of the product candidates we develop on our own and those we develop on behalf of our collaborators to be commercially available for many years and some or all may never become commercially available. We may never generate revenues through the sale of products.

Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical programs, we cannot assure you that our product candidates will be successfully developed or commercialized.

We face substantial competition from companies, including biotechnology and pharmaceutical companies, many of which have considerably more resources and experience than we have, which may result in others discovering, developing, receiving approval for, or commercializing products before or more successfully than us.

The biotechnology and pharmaceutical industries are characterized by intense competition and rapid innovation, and many companies put significant resources toward developing novel and proprietary therapies for the treatment of cancer, which often incorporate novel technologies and valuable intellectual property. We compete with companies in the immunotherapy space, as well as companies developing novel targeted therapies for cancer. In addition, our product candidates, if approved, will compete with existing standards of care for the diseases that our product candidates target as well as new compounds, drugs or therapies, some of which may achieve better results than our product candidates. We anticipate that we will face intense and increasing competition from many different sources, including new and established biotechnology and pharmaceutical companies, academic research institutions, governmental agencies and public and private research institutions.

Our competitors include:

- Gene-editing space: CRISPR Therapeutics, Inc., Editas Medicine, Inc., Intellia Therapeutics, Inc., Caribou Biosciences, Precision BioSciences, Inc. and Sangamo BioSciences, Inc.

- CAR space: Bellicum Pharmaceuticals, Inc., Juno Therapeutics, Inc., Celgene Corporation (in collaboration with bluebird bio, Inc.), Ziopharm Oncology (in collaboration with Intrexon, Inc.), Kite Pharma, Inc. (in collaboration with Amgen), Novartis AG and Johnson & Johnson (in collaboration with Transposagen), and Autolus Limited.
- Cell-therapy space: Adaptimmune Ltd, Lion Biotechnologies, Inc., Unum Therapeutics, Inc., NantKwest, Inc., Celyad S.A., Atara Biotherapeutics, Inc., and Immunocore Ltd.

We also face competition from non-cell based treatments offered by companies such as Amgen Inc., AstraZeneca plc, Bristol-Myers Squibb Company, Incyte Corporation, Merck & Co., Inc., and F. Hoffman-La Roche AG. Immunotherapy is further being pursued by several biotech companies as well as by large-cap pharmaceutical companies. Many of our competitors, either alone or with their collaboration partners, have substantially greater financial, technical and other resources, such as larger research and development staff and/or greater expertise in research and development, manufacturing, pre-clinical testing and conducting clinical trials. In addition, smaller or early-stage companies may compete with us through collaborative arrangements with more established companies. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these enterprises. Mergers and acquisitions in the pharmaceutical, biotechnology and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Our competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaborators, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized, or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products.

Even if we obtain regulatory approval of our product candidates, we may not be the first to market and that may affect the price or demand for our product candidates. Additionally, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances. A competitor could obtain orphan product exclusivity from the FDA with respect to such competitor's product. If such competitor product is determined to be the same product as one of the product candidates we develop, that may prevent us or our collaborators from obtaining approval from the FDA for such product candidate for the same indication for seven years, except in limited circumstances.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is inherently unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

The FDA or other regulatory authority, as applicable, may delay, limit or deny approval of our product candidates for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials or require that additional clinical trials be conducted;
- 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 clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;

- the CROs that are retained to assist us in connection with the clinical trials of our product candidates may take actions that materially adversely impact the clinical trials;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from manufacturing, pre-clinical studies or clinical trials;
- the FDA or comparable foreign regulatory authorities may not accept data generated at the sites involved in the clinical trials for our product candidates;
- the FDA or comparable foreign regulatory authorities may not approve the production process, formulation, labeling or specifications of our product candidates;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a BLA or other submission or to obtain regulatory approval in the United States or elsewhere;
- if the marketing application, if and when submitted, is reviewed by an advisory committee, the FDA or comparable foreign regulatory authorities may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee may recommend against approval of our application or may recommend that the competent regulatory authorities require, as a condition of approval, additional pre-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA or comparable foreign regulatory authorities may require development of a Risk Evaluation and Mitigation Strategy as a condition of approval or post-approval;
- the FDA or comparable foreign regulatory authorities may restrict the use of our products to a narrow population;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; or
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market the product candidates we develop, which would significantly harm our business, results of operations and prospects. In addition, even if we or our collaborators were able to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our products, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a drug 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 materially harm the commercial prospects for the product candidates we develop.

We expect several of the product candidates we develop will initially be available as treatment for patients with advanced disease, or with a rare disease with no other treatment option, which could limit the size of the market for these product candidates.

We expect that, if approved, several of the product candidates we develop will initially receive regulatory approval as treatment for advanced or rare diseases. This could limit the initial size of the market for these product candidates, and we cannot predict when, if ever, such product candidates would receive regulatory approval for indications treating a more expansive patient population.

The manufacturing of the product candidates we develop is highly complex. Any issues that arise in the manufacturing process could have an adverse effect on our business, financial position or prospects.

The product candidates we develop undergo a complex, highly-regulated manufacturing process that is subject to multiple risks. As a result of the complexities of this process, the cost to manufacture our CAR T-cell immunotherapy products is generally higher than traditional small molecule chemical compounds, and the manufacturing process requires very minimal batch-to-batch variability, which is expensive to ensure. Our manufacturing process is susceptible to product loss or failure due to issues associated with the collection of white blood cells, or starting material, from healthy third-party donors, shipping such material to the manufacturing site, ensuring standardized production batch-to-batch in the context of mass production, freezing the manufactured product, shipping the final product globally, and infusing patients with the product. In addition, we may face manufacturing issues associated with interruptions in the manufacturing process, contamination, equipment or reagent failure, shortage of raw material and other procurement issues, improper installation or operation of equipment, vendor or operator error, inconsistency in cell growth, and variability in product characteristics. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects, and other supply disruptions. If microbial, viral, or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the

contamination. Further, as our product candidates are developed through pre-clinical to late stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials.

Currently, the product candidates we develop are manufactured using processes intended for pre-clinical and clinical stage production by a third-party contract manufacturing organization, or CMO. Although we work with CMOs to ensure that commercially viable processes will be available for mass production, there are risks associated with scaling to the level required for advanced clinical trials or commercialization, including, among others, cost overruns, potential problems with process scale-up and/or scale-out, process reproducibility, stability issues, lot consistency, and timely availability of reagents or raw materials. We may ultimately be unable to reduce the cost of goods for the product candidates to levels that will allow for an attractive return on investment if and when those product candidates are commercialized.

We expect our manufacturing strategy for the product candidates we develop will continue to involve the use of one or more CMOs as well as establishing our own capabilities and infrastructure, including a manufacturing facility. We expect that development of our own manufacturing facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in developing a manufacturing facility and may never be successful in developing our own manufacturing facility or capability. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures, regulatory issues and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

In addition, the manufacturing process for any products that we may develop is subject to FDA and foreign regulatory authority approval processes for the jurisdictions in which we or our collaborators will seek marketing approval for commercialization, and we will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements on an ongoing basis. If the manufacturing process is changed during the course of product development, FDA or foreign regulatory authorities could require us to repeat some or all previously conducted trials or conduct additional bridging trials, which could delay or impede our ability to obtain marketing approval. If we or our CMOs are unable to reliably produce product candidates or products to specifications acceptable to the FDA or other regulatory authorities, such as the FDA's cGMP standards compliance, we may not obtain or maintain the approvals we need to further develop, conduct clinical trials for, and commercialize such products in the relevant territories. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CMOs will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects.

Negative public opinion and increased regulatory scrutiny of genetic research and therapies involving gene editing may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Our gene-editing technologies are novel. Public perception may be influenced by claims that gene editing is unsafe, and products incorporating gene editing may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians specializing in our targeted diseases prescribing our product candidates as treatments in lieu of, or in addition to, existing, more familiar, treatments for which greater clinical data may be available. Any increase in negative perceptions of gene editing may result in fewer physicians prescribing our treatments or may reduce the willingness of patients to utilize our treatments or participate in clinical trials for our product candidates. Increased negative public opinion, or more restrictive government regulations in response thereto, would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for such product candidates. For example, in 2003, 20 subjects treated for X-linked severe combined immunodeficiency in two gene therapy studies using a

murine gamma-retroviral vector, a viral delivery system, showed correction of the disease, but the studies were terminated after five subjects developed leukemia. Although none of our current product candidates utilize these gamma-retroviruses, our product candidates use a viral delivery system. Additionally, there have been a number of patient deaths in recent CAR-T trials conducted in the United States by our competitiors leading to clinical trial holds. Adverse events in clinical studies for the product candidates we develop or those of our competitors, even if not ultimately attributable to our or their product candidates, respectively (such as the many adverse events that typically arise from the transplant process), and any resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stronger labeling for those product candidates that are approved and a decrease in demand for any such product candidates.

We or our collaborators may find it difficult to enroll patients in clinical studies on the product candidates we develop, which could delay or prevent clinical studies of the product candidates.

Identifying and qualifying patients to participate in clinical studies of the product candidates we develop is critical to our success. The timing of these clinical studies will depend, in part, on the speed of recruitment of patients to participate in testing such product candidates as well as completion of required follow-up periods. We or our collaborators may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete the clinical studies for our product candidates in a timely manner. If patients are unwilling to participate in such studies because of negative publicity from adverse events in the biotechnology or gene or cell therapy industries or for other reasons, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our technology or termination of the clinical studies altogether.

In addition, clinical trials for the product candidates we develop will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition may reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators is limited, we expect to conduct some of the clinical trials at the same clinical trial sites that some of our competitors use, which may reduce the number of patients who are available for our clinical trials at such clinical trial sites. Certain of our competitors may have greater success than us in enrolling patients as a result of a variety of factors. Moreover, because the product candidates we develop represent a departure from more commonly used methods for cancer treatment, potential patients and their doctors may be inclined to use conventional therapies, such as chemotherapy and stem cell transplants, rather than enroll patients in our future clinical trial or clinical trial of our collaborators.

Patient enrollment is affected by a variety of factors, including:

- severity of the disease under investigation;
- design of the clinical trial protocol;
- size and nature of the patient population;
- eligibility criteria for the trial in question;
- perceived risks and benefits of the product candidate under trial;
- proximity and availability of clinical trial sites for prospective patients;
- availability of competing therapies and clinical trials;
- clinicians’ and patients’ perceptions as to the potential advantages of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- our ability to monitor patients adequately during and after treatment.

Our competitors in the immuno-oncology space are developing products that similarly use CAR T-cells to seek out and destroy cancer cells. In addition to the factors identified above, patient enrollment in any clinical trials we may conduct may be adversely impacted by any negative outcomes our competitors may experience, including adverse side effects (including fatalities), clinical data showing inadequate efficacy or failures to obtain regulatory approval.

If we or our collaborators have difficulty enrolling a sufficient number of patients to conduct clinical studies as planned, we or our collaborators may need to delay, limit or terminate ongoing or planned clinical studies, any of which could have a material adverse effect on our business and financial condition. Even if we are able to enroll a sufficient number of patients in our clinical trials, delays in patient enrollment may result in increased costs or may affect the timing or outcome of the planned clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of the product candidates we develop.

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

Our gene-editing technologies may not be sufficiently specific for their target sites, or they may not target unique sites within the genome of interest, which may result in random DNA recombination events. For example, off-target cleavage may lead to the production of double-strand breaks that overwhelm the cell's repair machinery and, as a consequence, yield chromosomal rearrangements and/or cell death. Off-target cleavage events also may result in random integration of donor DNA. As a result, off-target cleavage in T-cells may lead to undesirable side effects for patients, and consequently could cause delays, interruptions or suspensions of clinical trials and delays or denial of regulatory approval by the FDA or other regulatory authorities. Because the products we develop have had only very limited clinical application, in connection with the UCART19 Clinical Studies, we do not yet have sufficient information to know whether any of our product candidates will cause undesirable side effects.

Any undesirable side effects could cause us, our collaborators or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other regulatory authorities. Further, if the product candidates we develop receive marketing approval and we or others identify undesirable side effects caused by the products or any other similar products after the approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of the products;
- 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 perform additional post marketing safety studies or post marketing safety registries;
- we or our collaborators may be required to change the way the products are distributed or administered or conduct additional clinical trials;
- we or our collaborators may decide to remove the products from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our products or products developed with our technologies; and
- our reputation may suffer.

Any of these events could prevent the affected products from reaching the milestones triggering payment to Cellectis or achieving or maintaining market acceptance and could substantially increase the costs of commercializing such products and significantly impact the ability of such products to generate revenues.

If the product candidates we develop do not achieve projected development and commercialization in the announced or expected timeframes, the further development or commercialization of our product candidates may be delayed, and our business will be harmed.

We sometimes estimate, or may in the future estimate, for planning purposes, the timing of the accomplishment of various scientific, clinical, manufacturing, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of scientific studies, clinical trials, the submission of regulatory filings, the receipt of marketing approval or commercialization objectives. The achievement of many of these milestones may be outside of our control. All of these milestones are based on a variety of assumptions including, assumptions regarding capital resources and constraints, progress of development activities, and the receipt of key regulatory approvals or actions, any of which may cause the timing of achievement of the milestones to vary considerably from our estimates.

If we or our collaborators fail to achieve announced milestones in the expected timeframes, the commercialization of the product candidates may be delayed, our credibility may be undermined, and our business and results of operations may be harmed.

Further development and commercialization of our own product candidates will depend, in part, on strategic alliances with our collaborators. If our collaborators do not diligently pursue product development efforts, our progress may be delayed and our revenues may be deferred.

We expect to rely, to some extent, on our collaborators to provide funding in support of our own independent research and pre-clinical and clinical testing. Our technology is broad based, and we do not currently possess the financial resources necessary to fully develop and commercialize potential products that may result from our technologies or the resources or capabilities to complete the lengthy marketing approval processes that may be required for the products. Therefore, we plan to rely on strategic alliances to financially help us develop and commercialize our own biopharmaceutical products. As a result, our success depends, in part, on our ability to collect milestone and royalty payments from our collaborators. To the extent our collaborators do not aggressively pursue product candidates for which we are entitled to such payments or pursue such product candidates ineffectively, we will fail to realize these significant revenue streams, which could have an adverse effect on our business and future prospects. For example, since Servier has obtained exclusive rights on UCART19, it controls this product candidate and its future development (including the UCART19 Clinical Studies) and commercialization. We will receive royalties on sales of the product, but will have no control over such further development and commercialization.

If collaborators with whom we currently have alliances, such as Pfizer and Servier, or future collaborators with whom we may engage, are unable or unwilling to advance our programs, or if they do not diligently pursue product development and product approval, this may slow our progress and defer or negatively impact our revenues. Such failures would have an adverse effect on our ability to collect key revenue streams and, for this reason, would adversely impact our business, financial position and prospects. Our collaborators may sublicense or abandon product candidates or we may have disagreements with our collaborators, which would cause associated product development to slow or cease. There can be no assurance that our current strategic alliances will be successful, and we may require significant time to secure new strategic alliances because we need to effectively market the benefits of our technology to these future alliance partners, which may direct the attention and resources of our research and development personnel and management away from our primary business operations. Further, each strategic alliance arrangement will involve the negotiation of terms that may be unique to each collaborator. These business development efforts may not result in a strategic alliance or may result in unfavorable arrangements.

The loss of existing or future collaboration agreements would not only delay or potentially terminate the possible development or commercialization of products we may derive from our technologies, but it may also delay or terminate our ability to test target candidates for specific genes. If any collaborator fails to conduct the collaborative activities successfully and in a timely manner, the pre-clinical or clinical development or commercialization of the affected target candidates or research programs would be delayed or could be terminated.

Under typical collaboration agreements, we would expect to receive revenue for the research and development of a CAR T-cell immunotherapy product based on achievement of specific milestones, as well as royalties based on a percentage of sales of the commercialized products. Achieving these milestones will depend, in part, on the efforts of our partner as well as, in most cases and for a limited period of time, our own. If we, or any alliance partner, fail to meet specific milestones, then the strategic alliance may be terminated, which could reduce our revenues.

Under our collaboration agreement with Pfizer, at any time after the first anniversary of the effective date of the agreement, Pfizer will have the right to terminate the agreement at will upon 60 days’ prior written notice, either in its entirety or on a target-by-target basis. Either party may terminate the agreement in its entirety upon written notice, if the other party commits a material breach that fundamentally frustrates the objectives or transactions contemplated by the agreement or affects substantially all of the research program and such breach remains uncured for 90 days from the date such written notice is provided. Either party may terminate the agreement on a target-by-target basis upon written notice, if the other party commits a material breach that relates to such target and such breach remains uncured for 90 days from the date such written notice is provided. The agreement may also be terminated upon written notice by Pfizer at any time in the event that we become bankrupt or insolvent. Further, the agreement provides Pfizer with a right to terminate any specific research project or research program under the agreement if we undergo a change of control.

Under our collaboration agreement with Servier, either party may terminate the agreement in its entirety in the event of the other party’s material breach, which continues or remains uncured for 90 days after written notice is provided to the breaching party, or 30 days after written notice is provided with respect to a payment obligation breach. The parties may also terminate the agreement by mutual written consent. Servier has the right, at its sole discretion, to terminate the agreement in its entirety or with respect to specific products or product candidates, upon three months’ prior written notice to us. Servier may also terminate the agreement at any time for product-related safety reasons. Either party may terminate the agreement in the event of the other party’s bankruptcy or insolvency. Further, the agreement provides Servier with buy-out rights with respect to our interest in products and product candidates under the agreement if we undergo a change of control.

Even if we or our collaborators successfully complete clinical trials of our product candidates, those candidates may not be commercialized successfully for other reasons.

Even if we or our collaborators successfully complete clinical trials for one or more of the product candidates, those candidates may not be commercialized for other reasons, including:

- failing to receive regulatory approvals required to market them as drugs;
- being subject to proprietary rights held by others;
- failing to comply with GMP requirements;
- being difficult or expensive to manufacture on a commercial scale;
- having adverse side effects that make their use less desirable;
- failing to compete effectively with existing or new products or treatments commercialized by competitors; or
- failing to show long-term benefits sufficient to offset associated risks.

In addition, for any product candidates we develop through our strategic alliances, we will depend entirely upon the other party for marketing and sales of that product. These partners may not devote sufficient time or resources to the marketing and commercialization, or may determine not to pursue marketing and commercialization at all. Our business and results of operations will be negatively impacted by any failure of our collaborators to effectively market and commercialize an approved product.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to ongoing regulatory requirements.

Even if we obtain regulatory approval in a jurisdiction for the product candidates we develop, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, and submission of safety and other post-market information. Any regulatory approvals received for the product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product. For example, the holder of an approved BLA in the United States is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo follow-up observations for potential adverse events for as long as 15 years. Similarly, in the EU, pharmacovigilance obligations are applicable to all medicinal products. In addition to those, holders of a marketing authorization for gene or cell therapy products must detail, in their application, the measures they envisage to ensure follow-up of the efficacy and safety of these products. In cases of particular concern, marketing authorization holders for gene or cell therapy products in the EU may be required to design a risk management system with a view to identifying, preventing or minimizing risks, and may be obliged to carry out post-marketing studies. In the United States, the holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Similar provisions apply in the EU. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws. Similarly, in the EU any promotion of medicinal products is highly regulated and, depending on the specific jurisdiction involved, may require prior vetting by the competent national regulatory authority.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory agency may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we or our collaborators fail to comply with applicable regulatory requirements following approval of any of the product candidates we develop, national competent authorities may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend or terminate any ongoing clinical trials;

- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our collaborators;
- restrict the marketing, distribution or manufacturing of the product;
- seize or detain product or otherwise require the withdrawal or recall of product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit ability to commercialize products and generate revenues. In addition, the FDA's policies, and policies of foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, marketing approval that has been obtained may be lost and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

We expect the product candidates we develop will be regulated as biological products, or biologics, and therefore they may be subject to competition sooner than anticipated.

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, was enacted as part of the 2010 Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, to establish an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as "interchangeable" based on its similarity to an approved biologic. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the reference product was approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biological products.

We believe that any of the product candidates we develop that is approved as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider the subject product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of the reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

Even if we or our collaborators obtain and maintain approval for product candidates in the United States or another jurisdiction, we or our collaborators may never obtain approval for the same product candidates in other jurisdictions, which would limit market opportunities and adversely affect our business.

Approval of a product candidate in the United States by the FDA or by the requisite regulatory agencies in any other jurisdiction does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. The approval process varies among countries and may limit our or our collaborators' ability to develop, manufacture, promote and sell our product candidates internationally. Failure to obtain marketing approval in international jurisdictions would prevent the product candidates from being marketed outside of the jurisdictions in which regulatory approvals have been received. In order to market and sell the product candidates in the EU and many other jurisdictions, we and our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and may involve additional pre-clinical studies or clinical trials both before and post approval. In many countries, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the intended price for the product is also subject to approval. Further, while regulatory approval of a product candidate in one country does not ensure approval in any other country, a failure or delay in obtaining regulatory approval in one country may have a

negative effect on the regulatory approval process in others. If we or our collaborators fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, the target market will be reduced and the ability to realize the full market potential of the subject product candidates will be harmed and our business will be adversely affected.

Depending on the results of clinical trials and the process for obtaining regulatory approvals in other countries, we or our collaborators may decide to first seek regulatory approvals of a product candidate in countries other than the United States, or we or our collaborators may simultaneously seek regulatory approvals in the United States and other countries, in which case we or our collaborators will be subject to the regulatory requirements of health authorities in each country in which we seek approvals. Obtaining regulatory approvals from health authorities in countries outside the United States is likely to subject us or our collaborators to all of the risks associated with obtaining approval in the United States or the EU described herein.

We plan to seek orphan drug status for some or all of our product candidates, but we may be unable to obtain such designations or to maintain the benefits associated with orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.

We plan to seek orphan drug designation for some or all of our product candidates in specific orphan indications in which there is a medically plausible basis for the use of these products. Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting a BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Although we intend to seek orphan product designation for some or all of our product candidates, we may never receive such designations.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a BLA, to market the same biologic for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority to the product with orphan product exclusivity or if FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Even if we obtain orphan drug designation for a product candidate, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan designated indication and may be lost if the FDA later determines that the request for designation was materially defective, the disease or condition exceeded the population threshold, or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug with the same active moiety for the same condition if the FDA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product.

Similarly, in Europe, a medicinal product may receive orphan designation under Article 3 of Regulation (EC) 141/2000. This applies to products that are intended for a life-threatening or chronically debilitating condition and either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would unlikely generate sufficient return in the EU to justify the necessary investment. Moreover, in order to obtain orphan designation in the EU it is necessary to demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition.

In the EU, orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and applicants can benefit from specific regulatory assistance and scientific advice. Products receiving orphan designation in the EU can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the EU for pediatric studies (Article 37, Regulation 1901/2006). However, the 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation—for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;

- the first applicant consents to a second orphan medicinal product application; or
- the first applicant cannot supply enough orphan medicinal product.

We may seek fast-track designation for some or all of our product candidates. There is no assurance that the FDA will grant such designation and, even if it does grant fast track designation to any of our product candidates, that designation may not actually lead to a faster development or regulatory review or approval process and it does not increase the likelihood that our product candidates will receive marketing approval in the United States.

We may seek fast-track designation and review for some or all of our other product candidates. If a drug is intended for the treatment of a serious or life-threatening condition or disease, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant this designation. Thus, even if we believe a particular product candidate is eligible for this designation, we cannot assure that the FDA would decide to grant it. Moreover, even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

We may seek a regenerative advanced therapy (RAT) designation and/or a breakthrough therapy designation for our product candidates. Even if we achieve a RAT designation or a breakthrough designation from the FDA for the product candidates we develop, or, if applicable, by other national or international regulatory agencies, such designation may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek a RAT designation or a breakthrough therapy designation for our product candidates in the future.

A drug is eligible for RAT designation if, (i) the drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations; (ii) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (iii) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.

A breakthrough therapy is defined as a product that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

For product candidates that have been designated as a RAT or a breakthrough therapy, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Designation as a RAT or breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe that our product candidates meet the criteria for designation as a RAT or a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a RAT designation or a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as RAT or a breakthrough therapy, the FDA may later decide that such product no longer meet the conditions for qualification.

Even if any of our product candidates are commercialized, they may not be accepted by physicians, patients, or the medical community in general, and may also become subject to market conditions that could harm our business.

Even if any of our product candidates receive marketing approval, the medical community may not accept such products as adequately safe and efficacious for their indicated use. Moreover, physicians may choose to restrict the use of the product, if, based on experience, clinical data, side-effect profiles and other factors, they are not convinced that the product is preferable to existing drugs or treatments. We cannot predict the degree of market acceptance of any product candidate that receives marketing approval, which will depend on a number of factors, including, but not limited to:

- the demonstration of the clinical efficacy and safety of the product;
- the approved labeling for the product and any required warnings;
- the advantages and disadvantages of the product compared to alternative treatments;
- our and any collaborator’s ability to educate the medical community about the safety and effectiveness of the product;
- the coverage and reimbursement policies of government and commercial third-party payors pertaining to the product; and
- the market price of the product relative to competing treatments.

Product liability lawsuits could divert our resources, result in substantial liabilities and reduce the commercial potential of our product candidates.

The risk that we may be sued on product liability claims is inherent in the development and commercialization of biopharmaceutical products. Side effects of, or manufacturing defects in, products that we develop could result in the deterioration of a patient’s condition, injury or even death. For example, our liability could be sought by patients participating in the clinical trials for our product candidates as a result of unexpected side effects resulting from the administration of these products. Once a product is approved for sale and commercialized, the likelihood of product liability lawsuits increases. Criminal or civil proceedings might be filed against us by patients, regulatory authorities, biopharmaceutical companies and any other third party using or marketing our products. These actions could include claims resulting from acts by our partners, licensees and subcontractors, over which we have little or no control. These lawsuits may divert our management from pursuing our business strategy and may be costly to defend. In addition, if we are held liable in any of these lawsuits, we may incur substantial liabilities and may be forced to limit or forgo further commercialization of the affected products.

In addition, regardless of merit or eventual outcome, product liability claims may result in: impairment of our business reputation; withdrawal of clinical trial participants; initiation of investigations by regulators; costs due to related litigation; distraction of management's attention from our primary business; substantial monetary awards to trial participants, patients or other claimants; loss of revenue; exhaustion of any available insurance and our capital resources; the inability by us and our collaborators to commercialize our product candidates; and decreased demand for our product candidates, if approved for commercial sale.

We maintain product liability insurance coverage for damages caused by our product candidates with coverage limits that , we believe are customary for companies in our industry. This coverage may be insufficient to reimburse us for any expenses or losses we may suffer. Because all of our fully-controlled product candidates are in pre-clinical development stages, we currently do not carry clinical trial insurance for our product candidates. In addition, in the future, we may not be able to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product or other legal or administrative liability claims by us or our partners, licensees or subcontractors, which could prevent or inhibit the commercial production and sale of any of our product candidates that receive regulatory approval, which could adversely affect our business.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.

Successful sales of our product candidates, if approved, depend, in part, on the availability of adequate coverage and reimbursement from third-party payors.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid in the United States, and commercial payors are critical to new product acceptance.

Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Policies for coverage and reimbursement for products vary among third-party payors. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us or our collaborators to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of our product candidates.

Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates. Because our product candidates represent new approaches to the treatment of cancer and accordingly, may have a higher cost than conventional therapies and may require long-term follow up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be elevated.

Government restrictions on pricing and reimbursement, as well as other healthcare payor cost-containment initiatives, may negatively impact our ability to generate revenues if we obtain regulatory approval for any of our product candidates.

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. The continuing efforts of various governments, insurance companies, managed care organizations and other payors to contain or reduce healthcare costs may adversely affect one or more of the following:

- our ability or our collaborators' ability to set a price we believe is fair for our products, if approved;
- our ability or our collaborators' ability to obtain and maintain market acceptance by the medical community and patients;

- our ability to generate revenues and achieve profitability; and
- the availability of capital.

In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our or our collaborators' ability to sell our products profitably. By way of example, in the United States, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, the ACA) was enacted in March 2010. The ACA has been expected to have a significant impact on the provision of, and payment for, health care in the United States. The ACA was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law which, among other things, further reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additional legislative proposals to reform healthcare and government insurance programs, along with the trend toward managed healthcare in the United States, could influence the purchase of medicines and reduce demand and prices for our products, if approved. This could harm our or our collaborators' ability to market any products and generate revenues. Cost containment measures that healthcare payors and providers are instituting and the effect of further healthcare reform could significantly reduce potential revenues from the sale of any of our product candidates approved in the future, and could cause an increase in our compliance, manufacturing, or other operating expenses.

In some countries, the proposed pricing for a biopharmaceutical product must be approved before it may be lawfully marketed. In addition, in certain foreign markets, the pricing of biopharmaceutical product is subject to government control and reimbursement may in some cases be unavailable. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its Member States to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. An EU Member State may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for biopharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, biopharmaceutical products launched in the EU do not follow price structures of the United States and generally tend to have significantly lower prices.

We believe that pricing pressures will continue and may increase, which may make it difficult for us to sell our potential products that may be approved in the future at a price acceptable to us or any of our future collaborators.

Our future profitability, if any, depends, in part, on our ability to penetrate global markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability, if any, will depend, in part, on our ability and the ability of our collaborators to commercialize the product candidates we develop in markets throughout the world. Commercialization of our product candidates in various markets could subject us to risks and uncertainties, including:

- obtaining, on a country-by-country basis, the applicable marketing authorization from the competent regulatory authority;
- the burden of complying with complex and changing regulatory, tax, accounting and legal requirements in each jurisdiction that we pursue;
- differing medical practices and customs affecting acceptance in the marketplace;
- import or export licensing requirements;
- country specific requirements related to the cells used as starting material for manufacturing
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training, healthcare professionals and patients documents;
- reduced protection of intellectual property rights in some foreign countries;
- foreign currency exchange rate fluctuations;
- patients' ability to obtain reimbursement for products in various markets; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Sales of the products could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

We are subject to healthcare laws and regulations, which could expose us to the potential for criminal sanctions, civil penalties, exclusion from government healthcare programs, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and others will play a primary role in the recommendation and prescription of our products, if approved. Our arrangements with such persons and third-party payors must be structured in accordance with the 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, market, sell and distribute our products, if we obtain marketing approval. Restrictions under applicable federal, state and foreign healthcare laws and regulations include but are not limited to the following:

- The federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration (including any kickback, bribe or rebate), directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase or lease, order or recommendation of, any item, good, facility or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid.
- The federal civil and criminal false claims laws and civil monetary penalties laws, which impose criminal and civil penalties, including those from civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, 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.
- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program or knowingly and willingly falsifying, concealing or covering up a material fact or making false statements relating to healthcare matters.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, which impose certain requirements on covered entities and their business associates, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.
- The federal transparency requirements under the Physician Payments Sunshine Act, enacted as part of the ACA, that require applicable manufacturers of covered drugs, devices, biologics and medical supplies to track and annually report to CMS payments and other transfers of value provided to physicians and teaching hospitals and certain ownership and investment interests held by physicians or their immediate family members.

- Analogous laws and regulations in various U.S. states, such as state anti-kickback and false claims laws, which may apply to items or services reimbursed by any third-party payor, including commercial insurers, state marketing and/or transparency laws applicable to manufacturers that may be broader in scope than
- U.S. federal requirements, state laws that require biopharmaceutical companies to comply with the biopharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. government, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect as HIPAA.
- Similar legislation is applicable in EU Member States, including by way of example and without limitation: the UK's Bribery Act 2010 or the French Decree No 3013-414 on Transparency of Benefits Given by Companies Manufacturing or Marketing Health and Cosmetic Products for Human Use (*Décret n° 2013-414 du 21 mai 2013 relatif à la transparence des avantages accordés par les entreprises produisant ou commercialisant des produits à finalité sanitaire et cosmétique destinés à l'homme*).

Ensuring that our business arrangements with third parties comply with applicable healthcare laws and regulations could be costly. It is possible that governmental authorities will conclude that our business practices do 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 were 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, individual imprisonment and exclusion from government funded healthcare programs, such as Medicare and Medicaid, any of which could substantially disrupt our operations. If the physicians or other providers or entities with whom we expect to do business are found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Risks Related to Our Reliance on Third Parties

We expect to rely on third parties to conduct some or all aspects of our product manufacturing, quality control, protocol development, material supply, research and pre-clinical development, clinical testing and distribution, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our product manufacturing, quality control, protocol development, material supply, research and pre-clinical development and clinical testing as well as distribution and will rely on third parties for some of these activities. Under certain circumstances, these third parties may be entitled to terminate their engagements with us. If we need to enter into alternative arrangements, it could delay our product development activities.

In addition, in connection with our engagement of third parties, we expect to control only certain aspects of their activities. Our reliance on these third parties for product manufacturing, quality control, protocol development, material supply, research and pre-clinical development and clinical testing and distribution activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study and trial protocols. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study and trial plans and protocols, or if there are disagreements between us and these third parties, we may not be able to complete, or may be delayed in completing, the pre-clinical studies and clinical trials required to support future regulatory submissions and approval of the product candidates we develop. In some such cases we may need to locate an appropriate replacement third-party relationship, which may not be readily available or on acceptable terms, which would cause additional delay with respect to the approval of our product candidates and would thereby have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, reliance on third-party manufacturers, suppliers, research organizations and/or distributors entails risks to which we would not be subject if we conducted the above-mentioned activities ourselves, including:

- the inability to negotiate supply, manufacturing, research and/or distribution agreements with third parties under commercially reasonable terms or at all, because the number of potential suppliers, manufacturers, research organizations and distributors is limited and each must be approved by the FDA or comparable foreign regulatory authorities and would need to develop approved or validated processes for production, testing or distribution of material we use or of our products;

- that our third-party manufacturers, research organizations or distributors may have little or no experience with our products and may therefore require a significant amount of support from us in order to implement and maintain the infrastructure and processes required to manufacture, test or distribute our product candidates;
- reduced control over manufacturing and distribution activities and quality control processes and the possibility that our contract manufacturers, research organizations and distributors are not able to execute our manufacturing, testing or distribution procedures and other logistical support requirements appropriately;
- that our contract manufacturers may not perform as agreed, may not devote sufficient resources to our products or may not remain in the contract manufacturing business for the time required to supply investigational products for our clinical trials or to successfully produce, store and supply our products once approved;
- that we may not own, have equivalent necessary rights in, or access to the intellectual property rights to, or know how residing in any improvements or developments made by our third-party manufacturers or research organizations in the manufacturing process or testing of our products;
- breach, termination or nonrenewal of our agreements by third-party manufacturers, suppliers, research organizations or distributors in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our subcontractors, suppliers, research organizations or distributors caused by conditions unrelated to our business or operations, including the bankruptcy of any such third-party provider.

Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

All entities involved in the preparation of products for clinical studies or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. For example, in the United States, components of a finished CAR T-cell immunotherapy product approved for commercial sale or used in clinical studies must be manufactured in accordance with the current Good Manufacturing Practices (cGMP) requirements. Similarly, all investigational medicinal products in the EU must be manufactured in compliance with Good Manufacturing Practices, or GMP. The FDA's cGMP regulations and comparable regulations in other jurisdictions govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of the product candidates we develop that may not be detectable in final product testing. In the United States, we or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's cGMP requirements enforced by the FDA through its facilities inspection program. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates. In addition, the regulatory authorities may, at any time, inspect a manufacturing facility involved with the preparation and/or control of our product candidates, including starting and raw material, excipients, equipment and consumables, as well as the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval inspection, FDA approval of the products will not be granted.

Similarly, in the EU, Directive 2003/94/EC lays down the principles and guidelines of GMP in respect of medicinal products and investigational medicinal products and requires that products are consistently produced and controlled in accordance with the applicable quality standards. It also requires that medicinal products and investigational medicinal products that are imported from third countries are manufactured in accordance with standards at least equivalent to the GMP standards laid down in the EU. Directive 2003/94/EC, together with the detailed EU Guidelines on GMP, govern the quality management, personnel, premises, documentation, production operations, quality control, outsources activities, complaints and product recall and self-inspection. GMP inspections are performed by the competent authorities of the EU Member States, and are coordinated by the EMA in the case of medicinal products that are authorized through the EU centralized procedure.

If any of our third-party manufacturers, directly or indirectly (due to failure of their own sub-contractors), fail to maintain regulatory compliance, the regulator can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product, revocation or non-renewal of a pre-existing approval, refusal to accept some non-clinical and/or clinical data generated with material for which that third-party was responsible, or imposition of a hold on or refusal to commence, clinical investigations. As a result, our business, financial condition and results of operations may be materially harmed.

In addition, if supply from one approved manufacturer or supplier is interrupted, there could be a significant disruption in commercial and/or clinical supply of our products. Identifying and engaging an alternative manufacturer or supplier that complies with applicable regulatory requirements could result in further delay. Applicable regulatory agencies may also require additional studies if a new manufacturer or supplier is relied upon in connection with commercial production. Switching manufacturers or suppliers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of some non-clinical and clinical studies, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical studies may be delayed or we could lose potential revenue.

Access to raw materials and products necessary for the conduct of clinical trials and manufacturing of our product candidates is not guaranteed.

We are dependent on third parties for the supply of various biological materials—such as cells, cell culture media, cytokines, vectors, nucleic acids or antibodies—that are necessary to produce our product candidates. The supply of these materials could be reduced or interrupted at any time. In such case, we may not be able to find other acceptable suppliers or on acceptable terms. If key suppliers or manufacturers are lost or the supply of the materials is diminished or discontinued, we may not be able to develop, manufacture, and market our product candidates in a timely and competitive manner. In addition, these materials are subject to stringent manufacturing process and rigorous testing. Delays in the completion and validation of facilities and manufacturing processes of these materials could adversely affect the ability to complete trials and commercialize our products candidates. In addition, our suppliers or manufacturers may, from time to time, change their internal manufacturing or testing processes and procedures. Such changes may require us to perform or have performed studies to demonstrate equivalence of the materials produced or tested under such new procedures. Such equivalence testing may impose significant delays in the development of our product candidates. Furthermore, our suppliers may face quality issues or findings from regulatory authorities' inspections that could lead to delays or interruption of the supply of our product candidates.

We or our collaborators rely on third parties to conduct, supervise and monitor our or their clinical studies, and if these third parties perform in an unsatisfactory manner, it may harm our business.

We or our collaborators rely on medical institutions, clinical investigators, contract research organizations, or CROs, contract laboratories, and collaborators to carry out or otherwise assist us in connection with our or their clinical trials and to perform data collection and analysis. While we will have agreements governing their activities, we will have limited influence over their actual performance and will control only certain aspects of such third parties' activities. Nevertheless, we will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory, ethical and scientific standards, and our reliance on the third party does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's and other regulatory authorities' good clinical practices, or GCP, cGMP, good laboratory practices, or GLP, and other applicable requirements for conducting, recording and reporting the results of our pre-clinical studies and clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. Regulatory authorities around the world, including the FDA and European authorities, enforce these requirements through periodic inspections of study sponsors, CROs, principal investigators and clinical trial sites. If we, our CROs, our investigators or trial sites fail to comply with applicable GCP, GLP, GMP or other applicable regulatory requirements, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA, EMA or other regulatory authorities around the world may require us to perform additional clinical trials before issuing any marketing authorizations for our product candidates. Upon inspection, the FDA or EMA may determine that our clinical trials did not comply with GCP, GLP and GMP requirements, which may render the data generated in those trials unreliable or otherwise not usable for the purpose of supporting the marketing authorization applications for our products. In addition, our future clinical trials will require a sufficient number of study subjects to evaluate the safety and efficacy of our product candidates. Accordingly, if, for example, our CROs fail to comply with these regulations or if trial sites fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, or anyway incur delays in the performance of such trials, which would delay the regulatory approval process for the approval of our product candidates.

Clinical trials conducted in reliance on third parties may be delayed, suspended, or terminated if:

- we are unable to negotiate agreements with third parties under reasonable terms;
- termination or nonrenewal of agreements with third parties occurs in a manner or at a time that is costly or damaging to us;
- the third parties do not successfully carry out their contractual duties or fail to meet regulatory obligations or expected deadlines; or
- the quality or accuracy of the data obtained by third parties is compromised due to their failure to adhere to clinical protocols, regulatory or ethical requirements, or for other reasons.

Third party performance failures may increase our costs, delay our ability to obtain regulatory approval, and delay or prevent starting or completion of clinical trials and delay or prevent commercialization of our product candidates. While we believe that there are numerous alternative sources to provide these services, in the event that we seek such alternative sources, we may not be able to enter into replacement arrangements without incurring delays or additional costs.

We may enter into agreements with third parties to sell and market any of the products candidates we develop on our own and for which we obtain regulatory approval, which may affect the sales of our own products and our ability to generate revenues.

Given our early development stage, we have no experience in sales, marketing and distribution of biopharmaceutical products. However, if any of our product candidates obtain marketing approval, we intend to develop sales and marketing capacity, either alone or with partners, by contracting with, or licensing, them to market any of our own products. Outsourcing sales and marketing in this manner may subject us to a variety of risks, including:

- our inability to exercise direct control over sales and marketing activities and personnel;
- failure or inability of contracted sales personnel to obtain access to or persuade adequate numbers of physicians to prescribe our products;
- potential disputes with third parties concerning sales and marketing expenses, calculation of royalties, and sales and marketing strategies; and
- unforeseen costs and expenses associated with sales and marketing.

If we are unable to partner with a third party that has adequate sales, marketing, and distribution capabilities, we may have difficulty commercializing our product candidates, which would adversely affect our business, financial condition, and ability to generate product revenues.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties for the advancement of our products platform, pre-clinical testing, quality control, clinical trials, and manufacturing activities, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor’s discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, agreements with third parties typically restrict the ability of such third parties to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the strategic alliance. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and product development that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements.

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor’s discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks Related to Our Plant Products Business

Our plant product development efforts use complex integrated technology platforms and require substantial time and resources; these efforts may not be successful, or the rate of product improvement may be slower than expected.

The development of successful agricultural products using complex technology platforms such as ours requires significant levels of investment in research and development, including field testing, to demonstrate their effectiveness and can take several years or more. For the years ended December 31, 2015 and 2016, we spent €2.6 million and €3.7 million, respectively, on plant sciences research and development and royalty expenses. We intend to continue to invest in research and development, including additional and expanded field testing, to continue to improve the performance of our plant products. Our investment in research and development may not result in significant plant product revenues over the next several years, if ever.

Development of new or improved agricultural products involves risks of failure inherent in the development of products based on innovative and complex technologies. These risks include the possibility that:

- our plant products will fail to perform as expected in the field;
- our plant products will not receive necessary regulatory permits and governmental clearances in the markets in which we intend to sell them;
- our plant products may have poisonous effects on consumers;
- our plant products will be viewed as too expensive by our potential customers compared to competitive products;
- our plant products will be difficult to produce on a large scale or will not be economical to grow;
- proprietary rights of third parties will prevent us, our collaborators, or our licensees from marketing our plant products;
- we may be unable to patent our discoveries in the necessary jurisdictions,
- we or our collaborators may be unable to fully develop or commercialize products containing our plant products or, if developed, to commercialize such products or to do so in a timely manner; and
- third parties may develop superior or equivalent plant products.

Our plant products are not yet available for commercial use.

Our plant products are in the early stages of development, and there is no established market for them. Completion of product development could be protracted. Such products are not yet ready for commercial launch and may not be ready for commercial launch for numerous years, if ever. If we are not able to commercialize our existing products or new products on a significant scale, then we may not be successful in building a sustainable or profitable plant sciences business. Moreover, we expect to price our products based on our assessment of the value that we believe they provide to the customer, rather than on the cost of production. If our customers attribute a lower value to our products than we do, they may not be willing to pay the premium prices that we expect to charge. Pricing levels may also be negatively affected if our products are unsuccessful in producing the yields we expect.

We rely on third parties to conduct, monitor, support, and oversee field trials and other research services for product candidates in development, and any performance issues by third parties, or our inability to engage third parties on acceptable terms, may impact our ability to successfully commercialize such product candidates.

We currently conduct field trials, and plan to conduct further field trials, of our plant product candidates in various geographies. We currently rely on third parties to conduct, monitor, support, and oversee these field trials. In some cases, these field trials are conducted outside of the United States, making it difficult for us to monitor the daily activity of the work being conducted by the third parties that we engage. Although we provide our third-party contractors with extensive protocols regarding the establishment, management, harvest, transportation and storage of our product candidates, we have limited control over the execution of field trials. Consequently, the success of these field trials depends upon the ability of these third parties to correctly follow our suggested protocols. However, there is no guarantee that third parties will devote adequate time and resources to our field trials or conduct the field trials in accordance with our protocols, including maintenance of all required field trial information. Any such failures may result in delays in the development of our product candidates or the incurrence of additional costs. Even if our third-party contractors adhere to our suggested protocols, field trials may fail to succeed for a variety of other reasons, including weather, disease or pests, improper timing of planting our seeds, or incorrect fertilizer use. Ultimately, we remain responsible for ensuring that each of our field trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our responsibilities.

Additionally, if we are unable to maintain or enter into agreements with third-party contractors on acceptable terms, or if any such engagement is terminated prematurely, we may be unable to conduct or complete our field trials in the manner we anticipate. If our relationship with any of these third-party contractors is terminated, we may be unable to enter into arrangements with alternative contractors on commercially reasonable terms, or at all. Switching or adding third party contractors can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when any new third party commences field trial work. As a result, delays may occur, which could materially impact our ability to meet our desired development timelines.

Our crops are new, and producers may require instruction to successfully establish, grow and harvest our crops.

As part of our customer support, we plan to provide agricultural producers with information and protocols regarding the establishment, management, harvest, transportation and storage of our crops. Such crop management recommendations may include equipment selection, planting and harvest timing, application of crop protection chemicals or herbicides and storage systems and protocols. Our general or specific protocols may not apply in all circumstances, may be improperly implemented, may not be sufficient, or may be incorrect, leading to reduced yields, crop failures or other production problems or losses by our customers. Such failures may harm our customer relationships, our reputation and our ability to successfully market our products, and may lead to liability claims against us. Further, the use of our seeds may require a change in current planting, rotation or agronomic practices, which may be difficult to implement or may discourage the use of our plant products by agricultural producers.

There are various reasons why our crops of our products, once available, may fail to succeed, including weather, disease or pests, improper timing of planting our seeds, or incorrect fertilizer use. Statements by potential customers about negative experiences with our products could harm our reputation, and the decision by these parties not to proceed with large-scale seed purchases could harm our business, revenue and profitability.

The successful commercialization of our plant products depends on our ability to produce high-quality plants and seeds cost-effectively on a large scale and to accurately forecast demand for our plant products and we may be unable to do so.

The production of commercial-scale quantities of seeds requires the multiplication of the plants or seeds through a succession of plantings and seed harvests. The cost-effective production of high-quality, high-volume quantities of some of our plant products depends on our ability to scale our production processes to produce plants and seeds in sufficient quantity to meet demand. For example, food products such as soybean oil and wheat flour, and feed ingredients such as soybean meal, will require optimized production and commercialization of the underlying plant and seed harvests. We cannot assure you that our existing or future seed production techniques will enable us to meet our large-scale production goals cost-effectively for the plant products in our pipeline. Even if we are successful in developing ways to increase yields and enhance quality, we may not be able to do so cost-effectively or on a timely basis, which could adversely affect our ability to achieve profitability. If we are unable to maintain or enhance the quality of our plants and seeds as we increase our production capacity, including through the expected use of third parties, we may experience reductions in customer demand, higher costs and increased inventory write-offs.

In addition, because of the length of time it takes to produce commercial quantities of marketable plants and seeds, we will need to make seed production decisions well in advance of plant product sales. Our ability to accurately forecast demand can be adversely affected by a number of factors outside of our control, including changes in market conditions, environmental factors, such as pests and diseases, and adverse weather conditions. A shortfall in the supply of our products may reduce product sales revenue, damage our reputation in the market and adversely affect customer relationships. Any surplus in the amount of plant products we have on hand may negatively impact cash flows, reduce the quality of our inventory and ultimately result in write-offs of inventory. Any failure on our part to produce sufficient inventory, or overproduction of a particular product, could harm our business, results of operations and financial condition. In addition, customers may cancel orders or request a decrease in quantity at any time prior to delivery of the plants or seeds, which may lead to a surplus of our plant products.

We face significant competition in plant biotechnology and many of our competitors have substantially greater financial, technical and other resources than we do.

The market for agricultural biotechnology products, such as seeds and seed traits, are intensely competitive and change rapidly. The agricultural biotechnology market is characterized by a small number of large companies, which control the vast majority of patented seeds and technology. The majority of these competitors have substantially greater financial, technical, marketing, sales, distribution and other resources than we do, such as larger research and development staff, more experienced marketing and manufacturing organizations and more well-established sales forces. As a result, we may be unable to compete successfully against our current or future competitors, which may result in price reductions, reduced margins and the inability to achieve market acceptance for products containing our discoveries. We expect to continue to face significant competition in the markets in which we intend to commercialize our plant products. Our competitors in the agricultural biotechnology space include:

- Companies developing plants with enhanced properties: Arcadia Biosciences, Inc., Chromatin Inc., Cibus Global, Ltd., Evogene Ltd., Danzinger Innovation Ltd., Keygene N.V. and Precision Plant Sciences, Inc.
- Major seed/agrochemical companies: BASF SE, Bayer AG, DuPont Pioneer, Groupe Limagrain Holding SA, Monsanto Co., Syngenta AG, Takii & Company, LTD, The Dow Chemical Co. and The J.R. Simplot Co.

Many of our competitors engage in ongoing research and development and have a competitive advantage in their ability to bring new products to market quickly. Technological developments by our competitors could render our products less competitive, resulting in reduced sales compared to our expectations. Our ability to compete effectively and to achieve commercial success depends, in part, on our ability to: control manufacturing and marketing costs; effectively price and market our plant products; successfully develop an effective marketing program, and an efficient distribution system; develop of new products with properties attractive to our customers, and commercialize of our products quickly without incurring major regulatory costs. We may not be successful in achieving these factors and any such failure may adversely affect our plant sciences business and its results of operations and financial condition.

We also anticipate increased competition in the future as new companies enter the market and new technologies become available, particularly in the areas of gene editing. Our technology may be rendered obsolete or uneconomical by technological advances or entirely different approaches developed by one or more of our competitors, which will prevent or limit our ability to generate revenues from the commercialization of our technology.

Our plant sciences business is highly seasonal and subject to weather conditions and other factors beyond our control, which may cause our sales and operating results to fluctuate significantly.

The sale of plant products is dependent upon planting and growing seasons, which vary from year to year, and are expected to result in both highly seasonal patterns and substantial fluctuations in quarterly sales and profitability. As we have not yet made any sales of our plant products, we have not yet experienced the full nature or extent to which this business may be seasonal. Weather conditions and natural disasters, such as heavy rains, hurricanes, hail, floods, tornadoes, freezing conditions, drought or fire, also affect decisions by our customers about the types and amounts of seeds to plant and the timing of harvesting and planting such seeds. Disruptions that cause delays by our customers in harvesting or planting can result in the movement of orders to a future quarter, which would negatively affect the quarter and cause fluctuations in our operating results.

The successful commercialization of our plant products may face challenges from public perceptions of genetically engineered products and ethical, legal, environmental and social concerns. In addition, our products may become subject to government regulation.

The successful commercialization of our plant products depends, in part, on public acceptance of genetically engineered agricultural products. Any increase in negative perceptions of gene editing may result in decreased market acceptance of our plant products. Increased negative public opinion, or more restrictive government regulations in response thereto, would have a negative effect on our plant sciences business and may delay or impair the development and commercialization of our plant products.

The commercial success of our plant products may be adversely affected by claims that biotechnology plant products are unsafe for consumption or use, pose risks of damage to the environment, or create legal, social and ethical dilemmas. If we are not able to overcome these concerns, our products may not achieve market acceptance. Any of the risks discussed below could result in expenses, delays or other impediments to our plant development programs or the market acceptance and commercialization of our plant products:

- public attitudes about the safety and environmental hazards of, and ethical concerns over, genetic research and biotechnology plant products, which could influence public acceptance of our technologies and plant products;
- public attitudes regarding, and potential changes to laws governing, ownership of genetic material, which could weaken our intellectual property rights with respect to our genetic material and discourage collaborators from supporting, developing or commercializing our products and technologies; and
- failure to maintain or secure consumer confidence in, or to maintain or receive governmental approvals for, our plant products.

In addition, changes in regulatory requirements could result in a substantial increase in the time and costs associated with developing our plant products and negatively impact our operating results.

In the United States, the United States Department of Agriculture, or USDA, regulates, among other things, the introduction (including the importation, interstate movement, or release into the environment) of organisms and products altered or produced through genetic engineering that are plant pests or that there is reason to believe are plant pests. Such organisms and products are considered “regulated articles.” However, a petitioner may submit a request for a determination by the USDA of “nonregulated status” for a particular article. A petition for determination of nonregulated status must include detailed information, including relevant experimental data and publications, and a description of the genotypic differences between the regulated article and the nonmodified recipient organism, among other things. We previously submitted a request for a determination of “nonregulated status” to the USDA for our potato product candidates, our high oleic and low linolineic soybean product candidates and our powdery mildew-resistant wheat product candidate. The USDA confirmed in writing that each of these product candidates is not

deemed to be a “regulated article” under the Plant Protection Act because it does not contain genetic material from plant pests. While we believe that the USDA’s reasoning will continue to extend to our other product candidates, we have not obtained a determination from USDA that any of our other product candidates are not “regulated articles” under these regulations. USDA’s regulations also require that companies obtain a permit or file a notification before engaging in the introduction (including the importation, interstate movement, or release into the environment such as field testing) of “regulated articles.” We cannot predict whether the USDA or advocacy groups will challenge our interpretation, or whether the USDA will alter the manner in which it interprets its own regulations or institutes new regulation, or otherwise modifies regulations in a way that will subject our products to more burdensome standards, thereby substantially increasing the time and costs associated with developing our plant products. Moreover, we cannot assure you that the USDA will apply this same analysis to any of our other plant products in development. Complying with USDA’s plant pest regulations, including permitting requirements, is a costly, time-consuming process and could delay or prevent the commercialization of our plant products.

Our plant products may also be subject to extensive FDA food product regulations. Under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act, any substance that is intentionally added to food is a food additive, and is therefore subject to FDA premarket review and approval, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use (generally recognized as safe, or GRAS), or unless the use of the substance is otherwise excluded from the definition of a food additive. The FDA may classify some or all of our product candidates as containing a food additive that is not GRAS or otherwise determine that our plant products contain significant compositional differences from existing plant products that require further review. Such classification would cause these product candidates to require pre-market approval, which could delay the commercialization of these products.

In the EU, genetically modified foods, or GM foods, can only be allowed on the market once they have been authorized subject to rigorous safety assessments. The procedures for evaluation and authorization of GM foods are governed by Regulation (EC) 1829/2003 on GM food and feed and Directive 2001/18/EC on the release of genetically modified organisms, or GMOs, into the environment. If the GMO is not to be used in food or feed, then an application must be made under Directive 2001/18/EC. If the GMO is to be used in food or feed (but it is not grown in the EU) then a single application for both food and feed purposes under Regulation 1829/2003 should be made. If the GMO is used in feed or food and it is also grown in the EU, an application for both cultivation and food/feed purposes needs to be carried out under Regulation (EC) 1829/2003. A different EU regulation, Regulation (EC) 1830/2003, regulates the labeling of products that contain GMOs that are placed on the EU market. There are currently legislative proposals in the EU that would allow EU Member States to restrict or prohibit growing GMOs in their territory, on a range of environmental grounds, even if such crops were previously authorized at EU level. Should these proposals become law, growing GMOs may become more difficult in individual EU Member States.

We cannot predict whether or when any jurisdiction will change its regulations with respect to our plant products. Advocacy groups have engaged in publicity campaigns and filed lawsuits in various countries against companies and regulatory authorities, seeking to halt biotechnology approval activities or influence public opinion against genetically engineered products. In addition, governmental reaction to negative publicity concerning our plant products could result in greater regulation of genetic research and derivative products or regulatory costs that render our plant products cost prohibitive.

We may be sued for product liability and if such lawsuits were determined adversely, we could be subject to substantial damages, for which insurance coverage is not available.

We may be held liable if any plant product we develop, or any product that uses or incorporates, any of our technologies, causes injury or is found otherwise unsuitable during product testing, production, marketing or sale. For example, the detection of unintended biotechnology material in pre-commercial seed, commercial seed varieties or the crops and products produced may result in the inability to market the crops grown or physical injury to consumers resulting in potential liability for us as the seed producer or technology provider. If this were to occur, we could be subject to claims by multiple parties based not only on the cost of our plant products but also on their lost profits and business opportunities, including but not limited to trade disruption. Courts have levied substantial damages in the U.S. and elsewhere against a number of companies in the agricultural industry over the past several years in connection with claims for injuries allegedly caused by use of their products. Calyxt does not currently have product liabilities coverage for such claims. In addition, the detection of unintended biotechnology material in our seeds or in the environment could result in governmental actions such as mandated crop destruction, product recalls or environmental cleanup or monitoring. Concerns about seed quality related to biotechnology could also lead to additional regulations being imposed on our business, such as regulations related to testing procedures, mandatory governmental reviews of biotechnology advances, or the integrity of the food supply chain from the farm to the finished product.

Some of our plant products may end up in markets or countries in which they have not received regulatory approval, which may result regulatory challenges or lawsuits.

The scale of the commodity food industry may make it difficult to monitor and control the distribution of our plant products. As a result, our plant products may be sold inadvertently within jurisdictions where they are not approved for distribution. Such sales may lead to regulatory challenges or lawsuits against us, which could result in significant expenses and management attention.

Our plant sciences activities are currently conducted at a limited number of locations, which makes us susceptible to damage or business disruptions caused by natural disasters or acts of vandalism.

Calyxt's current headquarters and certain research and development operations are located in New Brighton, Minnesota and Calyxt's new headquarters facility is located in Roseville, Minnesota. The greenhouse for the new headquarters is operational and the remainder of the new facility which includes an office, labs and demonstration kitchen are expected to be operational in late 2017 or early 2018. Our seed production takes place primarily in the United States and Argentina. Warehousing for seed storage, which is conducted by a third-party contractor, is located primarily in Minnesota and Wisconsin. We take precautions to safeguard our facilities, including insurance, health and safety protocols, and offsite storage of critical research results and computer data. However, a natural disaster, such as a hurricane, drought, fire, flood, tornado, earthquake, or acts of vandalism, could cause substantial delays in our operations, damage or destroy our equipment, inventory or development projects, and cause us to incur additional expenses.

Risks Related to Intellectual Property

Our ability to compete may decline if we do not adequately protect our proprietary rights.

Our commercial success depends, in part, on obtaining and maintaining proprietary rights to our intellectual property estate, including our product candidates, as well as successfully defending these rights against third-party challenges. We will only be able to protect our product candidates from unauthorized use by third parties to the extent that valid and enforceable patents, or effectively protected trade secrets, cover them. Our ability to obtain patent protection for our product candidates is uncertain due to a number of factors, including:

- we may not have been the first to invent the technology covered by our pending patent applications or issued patents;
- we cannot be certain that we were the first to file patent applications covering our product candidates, including their compositions or methods of use, as patent applications in the United States and most other countries are confidential for a period of time after filing;
- others may independently develop identical, similar or alternative products or compositions or methods of use thereof;
- our disclosures in patent applications may not be sufficient to meet the statutory requirements for patentability;
- any or all of our pending patent applications may not result in issued patents;
- we may not seek or obtain patent protection in countries that may eventually provide us a significant business opportunity;
- any patents issued to us may not provide a basis for commercially viable products, may not provide any competitive advantages, or may be successfully challenged by third parties;
- our compositions and methods may not be patentable;
- others may design around our patent claims to produce competitive products that fall outside of the scope of our patents; and
- others may identify prior art or other bases upon which to challenge and ultimately invalidate our patents or otherwise render them unenforceable.

Even if we have or obtain patents covering our product candidates or compositions, we may still be barred from making, using and selling our product candidates or technologies because of the patent rights of others. Others may have filed, and in the future may file, patent applications covering compositions, products or methods that are similar or identical to ours, which could materially affect our ability to develop successfully our product candidates or to commercialize successfully our products if approved. In addition, because patent applications can take many years to issue, there may be currently pending applications unknown to us that may later result in issued patents that our product candidates or compositions may infringe. These patent applications may have priority over patent applications filed by us.

Obtaining and maintaining a patent portfolio entails significant expense of resources. Part of such expense includes periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications due over the course of several stages of prosecuting patent applications, and over the lifetime of maintaining and enforcing issued patents. We may or may not choose to pursue or maintain protection for particular intellectual property in our portfolio. If we choose to forgo patent protection or to allow a patent application or patent to lapse purposefully or inadvertently, our competitive position could suffer. Furthermore, we employ reputable law firms and other professionals to help us comply with the various procedural, documentary, fee payment and other similar provisions we are subject to 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. There are situations, however, in which failure to make certain payments or noncompliance with certain requirements in the patent process can result in abandonment or lapse of a 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 would have a material adverse effect on our business.

Legal action that may be required to enforce our patent rights can be expensive and may involve the diversion of significant management time. In addition, these legal actions could be unsuccessful and could also result in the invalidation of our patents or a finding that they are unenforceable. We may or may not choose to pursue litigation or other actions against those that have infringed on our patents, or have used them without authorization, due to the associated expense and time commitment of monitoring these activities. If we fail to protect or to enforce our intellectual property rights successfully, our competitive position could suffer, which could harm our results of operations.

Patents and patent applications involve highly complex legal and factual questions, which, if determined adversely to us, could negatively impact our position.

The patent positions of biopharmaceutical companies and other actors in our fields of business can be highly uncertain and typically involve complex scientific, legal and factual analyses. In particular, the interpretation and breadth of claims allowed in some patents covering biopharmaceutical compositions may be uncertain and difficult to determine, and are often affected materially by the facts and circumstances that pertain to the patented compositions and the related patent claims. The standards of the United States Patent and Trademark Office, or USPTO, are sometimes uncertain and could change in the future. Consequently, the issuance and scope of patents cannot be predicted with certainty. Patents, if issued, may be challenged, invalidated or circumvented. U.S. patents and patent applications may also be subject to interference proceedings, and U.S. patents may be subject to reexamination proceedings, post-grant review and/or *inter partes* review in the USPTO. Foreign patents as well may be subject to opposition or comparable proceedings in the corresponding foreign patent office. For example, one of the patents relating to our TALEN technology is currently under opposition before the European Patent Office. Challenges to our patents could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such interference, reexamination, post-grant review, *inter partes* review and opposition proceedings may be costly. Accordingly, rights under any issued patents may not provide us with sufficient protection against competitive products or processes.

Furthermore, even if not challenged, our patents and patent applications may not adequately protect our products or prevent others from designing their products to avoid being covered by our claims. If the breadth or strength of protection provided by the patent applications we hold with respect to our product candidates is threatened, it could dissuade companies from collaborating with us to develop, and could threaten our ability to successfully commercialize, our product candidates. Furthermore, for U.S. applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third party or instituted by the USPTO in order to determine who was the first to invent any of the subject matter covered by such patent claims.

In addition, changes in, or different interpretations of, patent laws in the United States and other countries may permit others to use our discoveries or to develop and commercialize our technology and products without providing any compensation to us, or may limit the scope of patent protection that we are able to obtain. The laws of some countries do not protect intellectual property rights to the same extent as U.S. laws and those countries may lack adequate rules and procedures for defending our intellectual property rights.

If we fail to obtain and maintain patent protection and trade secret protection of our product candidates, we could lose our competitive advantage and competition we face would increase, reducing any potential revenues and adversely affecting our ability to attain or maintain profitability.

Developments in patent law could have a negative impact on our business.

From time to time, the United States Supreme Court, or the Supreme Court, other federal courts, the United States Congress, the USPTO and similar foreign authorities may change the standards of patentability and any such changes could have a negative impact on our business.

The Leahy-Smith America Invents Act, or the America Invents Act, which was signed into law in 2011, includes a number of significant changes to U.S. patent law. These changes include a transition from a “first-to-invent” system to a “first-to-file” system, changes to the way issued patents are challenged, and changes to the way patent applications are disputed during the examination process. As a result of these changes, the patent law in the United States may favor larger and more established companies that have greater resources to devote to patent application filing and prosecution. The USPTO has developed new and untested regulations and procedures to govern the full implementation of the America Invents Act, and many of the substantive changes to patent law associated with the America Invents Act, and, in particular, the first-to-file provisions became effective on March 16, 2013. Substantive changes to patent law associated with the America Invents Act may affect our ability to obtain patents, and if obtained, to enforce or defend them. Accordingly, it is not clear what, if any, impact the America Invents Act will have on the cost of prosecuting our patent applications and our ability to obtain patents based on our discoveries and to enforce or defend any patents that may issue from our patent applications, all of which could have a material adverse effect on our business.

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

In addition to patent protection, because we operate in the highly technical field of development of therapies, we rely in part on trade secret protection in order to protect our proprietary technology and processes. However, trade secrets are difficult to protect. We expect to enter into confidentiality and intellectual property assignment agreements with our employees, consultants, outside scientific collaborators, sponsored researchers, and other advisors. These agreements generally require that the other party keep confidential and not disclose to third parties all confidential information developed by the party or made known to the party by us during the course of the party’s relationship with us. These agreements also generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may be breached or held unenforceable and may not effectively assign intellectual property rights to us.

In addition to contractual measures, we try to protect the confidential nature of our proprietary information using physical and technological security measures. Such measures may not provide adequate protection for our proprietary information. For example, our security measures may not prevent an employee or consultant with authorized access from misappropriating our trade secrets and providing them to a competitor, and the recourse we have available against such misconduct may not provide an adequate remedy to protect our interests fully. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret can be difficult, expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secrets. Furthermore, our proprietary information may be independently developed by others in a manner that could prevent legal recourse by us. If any of our confidential or proprietary information, including our trade secrets, were to be disclosed or misappropriated, or if any such information was independently developed by a competitor, our competitive position could be harmed.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on our product candidates in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States, assuming that rights are obtained in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but where our ability to enforce our patent rights is not as strong as in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent such competition.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries. In addition, the legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biopharmaceuticals or biotechnologies. As a result, many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. Such issues may make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of our other intellectual property rights. For example, many foreign countries, including the EU countries, have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. In those countries, we and our licensors may

have limited remedies if patents are infringed or if we or our licensors are compelled to grant a license to a third party, which could materially diminish the value of those patents. This could limit our potential revenue opportunities. Accordingly, our and our licensors' efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license.

Furthermore, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded to us, if any, may not be commercially meaningful, while the damages and other remedies we may be ordered to pay such third parties may be significant. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Third parties may assert rights to inventions we develop or otherwise regard as our own.

Third parties may in the future make claims challenging the inventorship or ownership of our intellectual property. We have written agreements with collaborators that provide for the ownership of intellectual property arising from our strategic alliances. These agreements provide that we must negotiate certain commercial rights with such collaborators with respect to joint inventions or inventions made by our collaborators that arise from the results of the strategic alliance. In some instances, there may not be adequate written provisions to address clearly the allocation of intellectual property rights that may arise from the respective alliance. If we cannot successfully negotiate sufficient ownership and commercial rights to the inventions that result from our use of a third-party collaborator's materials when required, or if disputes otherwise arise with respect to the intellectual property developed through the use of a collaborator's samples, we may be limited in our ability to capitalize on the full market potential of these inventions. In addition, we may face claims by third parties that our agreements with employees, contractors, or consultants obligating them to assign intellectual property to us are ineffective, or are in conflict with prior or competing contractual obligations of assignment, which could result in ownership disputes regarding intellectual property we have developed or will develop and could interfere with our ability to capture the full commercial value of such inventions. Litigation may be necessary to resolve an ownership dispute, and if we are not successful, we may be precluded from using certain intellectual property, or may lose our rights in that intellectual property. Either outcome could have a material adverse impact on our business.

Third parties may assert that our employees or consultants have wrongfully used or disclosed confidential information or misappropriated trade secrets.

We may employ individuals who were previously employed at universities or other biopharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees and consultants do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in 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 defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

A dispute concerning the infringement or misappropriation of our proprietary rights or the proprietary rights of others could be time consuming and costly, and an unfavorable outcome could harm our business.

There is significant litigation in the biopharmaceutical industry regarding patent and other intellectual property rights. Although we are not currently subject to any material pending intellectual property litigation, and are not aware of any such threatened litigation, we may be exposed to future litigation by third parties based on claims that our product candidates, technologies or activities infringe the intellectual property rights of others. If our development activities are found to infringe any such patents, we may have to pay significant damages or seek licenses to such patents. A patentee could prevent us from using the patented drugs or compositions. We may need to resort to litigation to enforce a patent issued to us, to protect our trade secrets, or to determine the scope and validity of third-party proprietary rights.

From time to time, we may hire scientific personnel or consultants formerly employed by other companies involved in one or more areas similar to the activities conducted by us. Either we or these individuals may be subject to allegations of trade secret misappropriation or other similar claims as a result of prior affiliations. If we become involved in litigation, it could consume a substantial portion of our managerial and financial resources, regardless of whether we win or lose. We may not be able to afford the costs of litigation. Any adverse ruling or perception of an adverse ruling in defending ourselves against these claims could have a material adverse impact on our cash position. Any legal action against us or our collaborators could lead to:

- payment of damages, potentially including treble damages if we are found to have willfully infringed a party's patent rights;
- injunctive or other equitable relief that may effectively block our ability to further develop, commercialize, and sell products; or
- our or our collaborators' being required to obtain a license under third-party intellectual property, and such license may not be available on commercially acceptable terms, if at all, all of which could have a material adverse impact on our cash position and business and financial condition. As a result, we could be prevented from commercializing current or future product candidates.

We may infringe intellectual property rights of others, which may prevent or delay our product development efforts and may prevent or increase the costs of our successfully commercializing our product candidates, if approved.

Our success will depend in part on our ability to operate without infringing the intellectual property and proprietary rights of third parties. We cannot assure you that our business operations, products and methods and the business operations, products and methods of our collaborators do not or will not infringe the patents or other intellectual property rights of third parties.

The biopharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that our product candidates or the use of our technologies infringe patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. Any claim relating to intellectual property infringement that is successfully asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we or our collaborators are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we or our collaborators may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing our products or the products we developed with our collaborators.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our products. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, intellectual property litigation or claims could force us to do one or more of the following:

- cease developing, selling or otherwise commercializing our product candidates;
- pay substantial damages for past use of the asserted intellectual property;
- obtain a license from the holder of the asserted intellectual property, which license may not be available on reasonable terms, if at all; and
- in the case of trademark claims, redesign, or rename trademarks we may own, to avoid infringing the intellectual property rights of third parties, which may not be possible and, even if possible, could be costly and time-consuming.

Any of these risks coming to fruition could have a material adverse effect on our business, results of operations, financial condition and prospects.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent covering our product candidate, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Furthermore, third parties may petition courts for declarations of invalidity or unenforceability with respect to our patents or individual claims there. If successful, such claims could narrow the scope of protection afforded our product candidates and future products, if any. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review and equivalent proceedings in foreign jurisdictions, e.g., opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover our product candidates or competitive products. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

We may not be successful in obtaining or maintaining necessary rights to product components and processes for our development pipeline through acquisitions and in-licenses.

We have rights, through licenses from third parties and under patents that we own, to the intellectual property to develop our product candidates. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently, and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size and greater cash resources and clinical development and commercialization capabilities.

For example, we sometimes collaborate with academic institutions to accelerate our pre-clinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution’s rights in technology resulting from the strategic alliance. Regardless of such right of first negotiation, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us, and the institution may license such intellectual property rights to third parties, potentially blocking our ability to pursue our development and commercialization plans.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license to us intellectual property rights that we require in order to successfully develop and commercialize our products. We also may be unable to obtain such a license or assignment on terms that would allow us to make an appropriate return on our investment. In either event, our business, financial condition and prospects for growth could suffer.

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 are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, our licensors may have the right to terminate the license, in which event we would not be able to market products covered by the license.

In addition, disputes may arise regarding the payment of the royalties due to licensors in connection with our exploitation of the rights we license from them. Licensors may contest the basis of royalties we retained and claim that we are obligated to make payments under a broader basis. In addition to the costs of any litigation we may face as a result, any legal action against us could increase our payment obligations under the respective agreement and require us to pay interest and potentially damages to such licensors.

In some cases, patent prosecution of our licensed technology is controlled solely by the licensor. If such licensor fails to obtain and maintain patent or other protection for the proprietary intellectual property we license from such licensor, we could lose our rights to such intellectual property or the exclusivity of such rights, and our competitors could market competing products using such intellectual property. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. In other cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners.

Under each of the material exclusive licenses granted to us, the licensor controls the prosecution of patents covered by the license. Under our collaboration agreement with Pfizer, we and Pfizer each generally control the prosecution of our respective owned patents, and Pfizer has the first right to elect to control the prosecution of certain jointly-developed intellectual property. Under our collaboration agreement with Servier, we and Servier each generally control the prosecution of our respective owned patents, and we generally control the prosecution of joint patents, unless Servier exercises its option under the agreement to obtain an exclusive license to further develop, manufacture and commercialize a product candidate, in which case Servier will control prosecution of the joint patents. In addition, Servier currently controls prosecution of those patent rights covering solely UCART19. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. 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 basis of royalties due to our licensors;
- 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 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 from third parties prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

Risks Related to Our Organization, Structure and Operation

We will need to develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.

As of December 31, 2016, we had 122 full-time employees and we expect to increase our number of employees and the scope and location of our operations. To manage our anticipated development and expansion, including the development and the commercialization of our product candidates, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

We depend on key management personnel and attracting and retaining other qualified personnel, and our business could be harmed if we lose key management personnel or cannot attract and retain other qualified personnel.

Our success depends to a significant degree upon the technical skills and continued service of certain members of our management team, including Dr. André Choulika, our co-founder and Chief Executive Officer; Dr. David Sourdive, our co-founder and Executive Vice President, Technical Operations; Dr. Mathieu Simon, our Chief Operating Officer; Dr. Philippe Duchateau, our Chief Scientific Officer; and Dr. Dan Voytas, the Chief Scientific Officer of Calyxt, Inc. The loss of the services of these key executive officers could have a material adverse effect on us. Our success also will depend upon our ability to attract and retain additional qualified management, regulatory, medical, technical, and sales and marketing executives and personnel. The failure to attract, integrate, motivate, and retain additional skilled and qualified personnel could have a material adverse effect on our business.

We compete for such personnel against numerous companies, including larger, more established companies with significantly greater financial resources than we possess. In addition, failure to succeed in our product candidates' development may make it more challenging to recruit and retain qualified personnel. There can be no assurance that we will be successful in attracting or retaining such personnel and the failure to do so could have a material adverse effect on our business, financial condition, and results of operations.

In order to induce valuable employees to remain at Cellectis, we have provided over the last years free shares and stock options to purchase ordinary shares that vest over time. The value to employees of free shares and stock options that vest over time may be significantly affected by movements in the price of our ordinary shares that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us. The loss of the services of any of our key executive officers or other officers or senior employees within a short timeframe, and our inability to find suitable replacements could potentially harm our business, prospects, financial condition or results of operations. We do not maintain "key man" insurance policies on the lives of any of our employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior scientific and medical personnel.

The requirements of being a U.S. public company require significant resources and management attention and affect our ability to attract and retain executive management and qualified board members.

As a U.S. public company, we incur significant legal, accounting, and other expenses. We are subject to the Exchange Act, including the reporting requirements thereunder, the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the Nasdaq listing requirements and other applicable securities rules and regulations. Compliance with these rules and regulations results in substantial legal and financial compliance costs and makes some activities more difficult, time-consuming or costly and increases demand on our systems and resources. These costs and other impacts would increase if we ceased to qualify as a foreign private issuer, in which case we would be required to comply with the enhanced reporting and governance requirements applicable to U.S. domestic reporting companies.

Further, being a U.S. public company and a French public company has impacted the disclosure of information and required compliance with two sets of applicable rules. From time to time, this may result in uncertainty regarding compliance matters and has resulted in higher costs necessitated by legal analysis of dual legal regimes, ongoing revisions to disclosure and adherence to heightened governance practices. As a result of the enhanced disclosure requirements of the U.S. securities laws, business and financial information that we report is broadly disseminated and highly visible to investors, which we believe may increase the likelihood of threatened or actual litigation, including by competitors and other third parties, which could, even if unsuccessful, divert financial resources and the attention of our management from our operations.

We must maintain effective internal control over financial reporting, and if we are unable to do so, the accuracy and timeliness of our financial reporting may be adversely affected, which could have a material adverse effect on our business, investor confidence and market price.

We must maintain effective internal control over financial reporting in order to accurately and timely report our results of operations and financial condition. In addition, as a public company, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, requires, among other things, that we assess the effectiveness of our disclosure controls and procedures and the effectiveness of our internal control over financial reporting at the end of each fiscal year. Pursuant to Section 404 of the Sarbanes-Oxley Act, we are required to furnish a report by our management on our internal control over financial reporting, and we are required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. The rules governing the standards that must be met for our management to assess our internal control over financial reporting pursuant to Section 404 of the Sarbanes-Oxley Act are complex and require significant documentation, testing and possible remediation. These stringent standards require that our audit and finance committee be advised and regularly updated on management’s review of internal control over financial reporting.

Our compliance with applicable provisions of Section 404 requires that we incur substantial accounting expense and expend significant management attention and time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements.

If we fail to staff our accounting and finance function adequately or maintain internal control over financial reporting adequate to meet the requirements of the Sarbanes-Oxley Act, our business and reputation may be harmed. Moreover, if we are not able to comply with the applicable requirements of Section 404 in a timely manner, we may be subject to sanctions or investigations by regulatory authorities, including the SEC and Nasdaq. Furthermore, if we are unable to conclude that our internal control over financial reporting is effective or if our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our stock could decline, and we could be subject to sanctions or investigations by the SEC, Nasdaq or other regulatory authorities. Failure to implement or maintain effective internal control systems required of public companies could also restrict our access to the capital markets. The occurrence of any of the foregoing would also require additional financial and management resources.

Our failure to maintain certain tax benefits applicable to French technology companies may adversely affect our results of operations.

As a French technology company, we have benefited from certain tax advantages, including, for example, the research tax credit (*Crédit d’Impôt Recherche*), or CIR. The CIR is a French tax credit aimed at stimulating research and development. The CIR can be offset against French corporate income tax due and the portion in excess (if any) may be refunded at the end of a three fiscal-year period (or, sooner, for smaller companies such as ours). The CIR receivable of €7.2 million as of December 31, 2016, is calculated based on our claimed amount of eligible research and development expenditures in France. The French tax authority with the assistance of the Research and Technology Ministry may audit each research and development program in respect of which a CIR benefit has been claimed and assess whether such program qualifies in its view for the CIR benefit. The French tax authorities may challenge our eligibility to, or our calculation of certain tax reductions and/or deductions in respect of our research and development activities and, should the French tax authorities be successful, we may be liable for additional corporate income tax, and penalties and interest related thereto, or we may not obtain the refunds for which we have applied, which could have a significant impact on our results of operations and future cash flows. Furthermore, if the French Parliament decides to eliminate, or reduce the scope or the rate of, the CIR benefit, either of which it could decide to do at any time, our results of operations could be adversely affected.

We may be exposed to significant foreign exchange risk, which may adversely affect our financial condition, results of operations and cash flows.

We incur portions of our expenses and may in the future derive revenues in currencies other than the euro, in particular, the U.S. dollar. As a result, we are exposed to foreign currency exchange risk as our results of operations and cash flows are subject to fluctuations in foreign currency exchange rates. While we are engaged in hedging transactions to minimize the impact of

uncertainty in future exchange rates on cash flows, we may not hedge all of our foreign currency exchange rate risk. In addition, hedging transactions carry their own risks and costs, including the possibility of a default by the counterpart to the hedge transaction. We cannot predict the impact of foreign currency fluctuations, and foreign currency fluctuations in the future may adversely affect our financial condition, results of operations and cash flows.

We may use hazardous chemicals and biological materials in our business. Any claims relating to improper handling, storage or disposal of these materials could be time consuming and costly.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment, manufacture and disposal of hazardous materials and wastes. Our research and development processes may involve the controlled use of hazardous materials, including chemicals and biological materials. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from these materials. We may be sued for any injury or contamination that results from our use or the use by third parties of these materials, and our liability may exceed any insurance coverage and our total assets. Federal, state, local or foreign laws and regulations govern the use, manufacture, storage, handling and disposal of these hazardous materials and specified waste products, as well as the discharge of pollutants into the environment and human health and safety matters. Compliance with environmental laws and regulations may be expensive and may impair our research and development efforts. If we fail to comply with these requirements, we could incur delays, substantial costs, including civil or criminal fines and penalties, clean-up costs or capital expenditures for control equipment or operational changes necessary to achieve and maintain compliance. In addition, we cannot predict the impact on our business of new or amended environmental laws or regulations or any changes in the way existing and future laws and regulations are interpreted and enforced. These current or future laws and regulations may impair our research, development or production efforts.

Our internal computer systems, or those of our third-party contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of our third-party contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we do not believe that we have 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 regulatory 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.

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

Our current strategy does not involve plans to acquire companies or technologies facilitating or enabling us to access to new medicines, new technologies, new research projects, or new geographical areas, or enabling us to express synergies with our existing operations. However, if such acquisitions were to become necessary or attractive in the future, we may not be able to identify appropriate targets or make acquisitions under satisfactory conditions, in particular, satisfactory price conditions. In addition, we may be unable to obtain the financing for these acquisitions under favorable conditions, and could be led to finance these acquisitions using cash that could be allocated to other purposes in the context of existing operations. 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 company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new products 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, which could have a material adverse effect on our business, financial conditions, earnings and prospects.

Risks Related to Ownership of Our Ordinary Shares and ADSs

We believe we were a "passive foreign investment company," or PFIC, for U.S. federal income tax purposes for 2016, and expect to continue to be a PFIC for the current taxable year, and potentially future taxable years, which could result in adverse U.S. federal income tax consequences to U.S. investors.

A non-U.S. corporation will be considered a PFIC for any taxable year if either (1) at least 75% of its gross income for such year is passive income or (2) at least 50% of the value of its assets (based on an average of the quarterly values of the assets during such year) is attributable to assets that produce or are held for the production of passive income. Based on the value and composition of our assets, although not free from doubt, we believe that we were a PFIC for U.S. federal income tax purposes for the 2016 taxable year and we expect to continue to be a PFIC for the current taxable year and potentially future taxable years. The determination of PFIC status is fact-specific, and a separate determination must be made each taxable year as to whether we are a PFIC (after the close of each such taxable year). If we are a PFIC for any taxable year during which a U.S. holder (as defined in the section titled "Taxation—Material U.S. Federal Income Tax Considerations" in this Annual Report) holds ADSs, the U.S. holder may be subject to adverse tax consequences, including (1) the treatment of all or a portion of any gain on disposition as ordinary income, (2) the application of an interest charge with respect to such gain and certain dividends and (3) compliance with certain reporting requirements. Each U.S. holder is strongly urged to consult its tax advisor regarding these issues and any available elections to mitigate such tax consequences. See the section titled "Taxation—Material U.S. Federal Income Tax Considerations" in this Annual Report.

The market price for our ADSs may be volatile or may decline regardless of our operating performance.

The trading price of the ADSs has fluctuated, and is likely to continue to fluctuate, substantially. The trading price of our ADSs 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.

Since the ADSs were sold in our initial public offering in March 2015 at a price of $41.50 per share, the price per ADS has ranged as low as $16.09 and as high as $50.00 through March 22, 2017. The market price of the ADSs may fluctuate significant in response to numerous factors, many of which are beyond our control, including:

- actual or anticipated fluctuations in our financial condition and operating results;
- our failure to develop and commercialize our product candidates;
- adverse results of delays in our or any of our competitors' pre-clinical studies or clinical trials;
- actual or anticipated changes in our growth rate relative to our competitors;
- competition from existing products or new products that may emerge;
- announcements by us, our collaborators or our competitors of significant acquisitions, strategic partnerships, joint ventures, strategic alliances, or capital commitments;
- adverse regulatory decisions, including failure to receive regulatory approval for any of our product candidates;
- the termination of a strategic alliance or the inability to establish additional strategic alliances;
- unanticipated serious safety concerns related to the use of any of our product candidates;
- failure to meet or exceed financial estimates and projections of the investment community or that we provide to the public;
- issuance of new or updated research or reports by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- inconsistent trading volume levels of our ADSs;
- price and volume fluctuations in trading of our ordinary shares on the Alternext market of the Euronext in Paris;
- additions or departures of key management or scientific personnel;
- disputes or other developments related to proprietary rights, including patents, litigation matters, and our ability to obtain patent protection for our technologies;
- our inability to obtain reimbursement by commercial third-party payors and government payors and any announcements relating to coverage policies or reimbursement levels;
- announcement or expectation of additional debt or equity financing efforts;

- sales of our ordinary shares or ADSs by us, our insiders or our other shareholders; and
- general economic and market conditions.

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 holders from readily selling their ADSs and may otherwise negatively affect the liquidity of our capital shares. 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.

Share ownership is concentrated in the hands of our principal shareholders and management, who will continue to be able to exercise a direct or indirect controlling influence on us.

Our executive officers, directors, current 5% or greater shareholders and affiliated entities beneficially own approximately 45.06% of our ordinary shares outstanding (including those underlying our ADSs) as of February 28, 2017. As a result, these shareholders, acting together, have significant influence over all matters that require approval by our shareholders, including the election of directors and approval of significant corporate transactions. Corporate action might be taken even if other shareholders oppose them. This concentration of ownership might also have the effect of delaying or preventing a change of control of our company that other shareholders may view as beneficial.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, the price of our ADSs and 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. If few or no securities or industry analysts cover us, the trading price for our ADSs would be negatively impacted. If one or more of the analysts who covers us downgrades our ADSs or publishes incorrect or unfavorable research about our business, the price of our ADSs would likely decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, or downgrades our ADSs, could also cause the price of our ADSs or trading volume to decline.

We do not currently intend to pay dividends on our securities. In addition, French law may limit the amount of dividends we are able to distribute.

We have never declared or paid any cash dividends on our share capital and do not currently intend to do so for the foreseeable future. We currently intend to invest our future earnings, if any, to fund our growth. Therefore, holders of our ordinary shares and ADSs are not likely to receive any dividends for the foreseeable future and any increase in value will depend solely upon any future appreciation. Consequently, holders of our equity securities may need to sell all or part of their holdings after price appreciation, which may never occur, as the only way to realize any future gains.

Further, under French law, the determination of whether we have been sufficiently profitable to pay dividends is made on the basis of our statutory financial statements prepared and presented in accordance with French generally accepted accounting principles called *“Plan Comptable Général”* defined by the regulation 99-03 from the Committee of the French Accountancy Regulation. In addition, payment of dividends may subject us to additional taxes under French law. Please see the section of this Annual Report titled “Memorandum and Articles of Association” for further details on the limitations on our ability to declare and pay dividends and the taxes that may become payable by us if we elect to pay a dividend. Therefore, we may be more restricted in our ability to declare dividends than companies not based in France.

In addition, exchange rate fluctuations may affect the amount of euros that we are able to distribute, and the amount in U.S. dollars that our shareholders receive upon the payment of cash dividends or other distributions we declare and pay in euros, if any. These factors could harm the value of our equity securities, and, in turn, the U.S. dollar proceeds that holders receive from the sale of ADSs.

Future sales of ordinary shares or ADSs by existing shareholders could depress the market price of the ADSs.

If our existing shareholders sell, or indicate an intent to sell, substantial amounts of ordinary shares or ADSs in the public market, the trading price of our ordinary shares and/or ADSs could decline significantly. In addition, the sale of these securities could impair our ability to raise capital through the sale of additional securities. As of February 28, 2017, we had 27,264,624 outstanding ordinary shares (excluding those underlying ADSs). As of February 28, 2017, approximately 8,261,560 of our outstanding ordinary shares (excluding those underlying ADSs) are held by directors, executive officers and other affiliates and continue to be subject to resale limitations under Rule 144 under the Securities Act. In addition, as of February 28, 2017, options and warrants to purchase an aggregate of 9,924,108 ordinary shares issued under our equity incentive plans were exercisable, subject to compliance with Rule 144 under the Securities Act in the case of our affiliates.

If these additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares and/or our ADSs could decline substantially.

Our By-laws and French corporate law contain provisions that may delay or discourage a takeover attempt.

Provisions contained in our By-laws and the corporate laws of France, the country in which we are incorporated, could make it more difficult for a third-party to acquire us, even if doing so might be beneficial to our shareholders. In addition, provisions of our By-laws impose various procedural and other requirements, which could make it more difficult for shareholders to effect certain corporate actions. These provisions include the following:

- under French law, a non-resident of France may have to file an administrative notice with French authorities in connection with a direct or indirect investment in us, as defined by administrative rulings; see the section of this Annual Report titled “Memorandum and Articles of Association”;
- a merger (i.e., in a French law context, a share for share exchange following which our company would be dissolved without being liquidated into the acquiring entity and our shareholders would become shareholders of the acquiring entity) of our company into a company incorporated in the EU would require the approval of our board of directors as well as a two-thirds majority of the votes held by the shareholders present, represented by proxy or voting by mail at the relevant meeting;
- a merger of our company into a company incorporated outside of the EU would require the unanimous approval of our shareholders;
- under French law, a cash merger is treated as a share purchase and would require the consent of each participating shareholder;
- our shareholders have granted and may grant in the future our board of directors broad authorizations to increase our share capital or to issue additional ordinary shares or other securities (for example, warrants) to our shareholders, the public or qualified investors, including as a possible defense following the launching of a tender offer for our shares;
- our shareholders have preferential subscription rights proportionally to their shareholding in our company on the issuance by us of any additional securities as part of a cash capital increase or a capital increase by way of debt set-off. Such rights may only be waived by the extraordinary general meeting (by a two-thirds majority vote) of our shareholders or on an individual basis by each shareholder;
- our board of directors has the right to appoint directors to fill a vacancy created by the resignation or death of a director, subject to the approval by the shareholders of such appointment at the next shareholders’ meeting, which prevents shareholders from having the sole right to fill vacancies on our board of directors;
- our board of directors can only be convened by our chairman or our managing director, if any, or, when no board meeting has been held for more than two consecutive months, by directors representing at least one third of the total number of directors;
- our board of directors meetings can only be regularly held if at least half of the directors attend either physically or by way of videoconference or teleconference enabling the directors’ identification and ensuring their effective participation in the board’s decisions;
- our shares take the form of bearer securities or registered securities, if applicable legislation so permits, according to the shareholder’s choice. Issued shares are registered in individual accounts opened by us or any authorized intermediary (depending on the form of such shares), in the name of each shareholder and kept according to the terms and conditions laid down by the legal and regulatory provisions;
- approval of at least a majority of the votes held by shareholders present, represented by a proxy, or voting by mail at the relevant ordinary shareholders’ general meeting is required to remove directors with or without cause;
- advance notice is required for nominations to the board of directors or for proposing matters to be acted upon at a shareholders’ meeting, except that a vote to remove and replace a director can be proposed at any shareholders’ meeting without notice;
- transfers of shares shall comply with applicable insider trading rules;
- the crossing of certain ownership thresholds has to be disclosed and can impose certain obligations; see the section of this Annual Report titled “Item 10.B—Memorandum and Articles of Association;” and
- pursuant to French law, the sections of the By-laws relating to the number of directors and election and removal of a director from office may only be modified by a resolution adopted by a two-thirds majority vote of our shareholders present, represented by a proxy or voting by mail at the meeting.

Holders of our ADSs may not be able to exercise their right to vote the ordinary shares underlying such ADSs.

Holders of ADSs may exercise voting rights with respect to the ordinary shares represented by the ADSs only in accordance with the provisions of the deposit agreement. The deposit agreement provides that, upon receipt of notice of any meeting of holders of our ordinary shares, the depositary will fix a record date for the determination of ADS holders who shall be entitled to give instructions for the exercise of voting rights. Upon timely receipt of notice from us, if we so request, the depositary shall distribute to the holders as of the record date (1) the notice of the meeting or solicitation of consent or proxy sent by us and (2) a statement as to the manner in which instructions may be given by the holders.

Holders of ADSs may instruct the depositary of the ADSs to vote the ordinary shares underlying such ADSs. Otherwise, holders of our ADSs will not be able to exercise their right to vote, unless they withdraw the ordinary shares underlying such ADSs. However, holders of our ADSs may not know about the meeting far enough in advance to withdraw those ordinary shares. If we ask for instructions, the depositary, upon timely notice from us, will notify holders of our ADSs of the upcoming vote and arrange to deliver our voting materials to such holders. We cannot guarantee that holders of our ADSs will receive the voting materials in time to ensure that they can instruct the depositary to vote such ordinary shares or to withdraw such ordinary shares so as to vote them directly. If the depositary does not receive timely voting instructions from holders of our ADSs, it may give a proxy to a person designated by us to vote the ordinary shares underlying such ADSs in accordance with the recommendation of our board of directors. In addition, the depositary and its agents are not responsible for failing to carry out voting instructions or for the manner of carrying out voting instructions. This means that holders of our ADSs may not be able to exercise their right to vote, and there may be nothing such holders can do if the ordinary shares underlying such ADSs are not voted as requested.

The right of holders of our ADSs to participate in any future preferential subscription rights or to elect to receive dividends in shares may be limited, which may cause dilution to holders of ADSs.

Under French Law, if we issue additional securities for cash, current shareholders will have preferential subscription rights for these securities proportionally to their shareholding in our company unless they waive those rights at an extraordinary meeting of our shareholders (by a two-thirds majority vote) or individually by each shareholder. However, our ADS holders in the United States will not be entitled to exercise or sell such rights unless we register the rights and the securities to which the rights relate under the Securities Act or an exemption from the registration requirements is available. In addition, the deposit agreement for our ADSs provides that the depositary will not make rights available to holders of our ADSs unless the distribution to ADS holders of both the rights and any related securities are either registered under the Securities Act or exempted from registration under the Securities Act. Further, if we offer holders of our ordinary shares the option to receive dividends in either cash or shares, under the deposit agreement the depositary may require satisfactory assurances from us that extending the offer to holders of ADSs does not require registration of any securities under the Securities Act before making the option available to holders of ADSs. We are under no obligation to file a registration statement with respect to any such rights or securities or to endeavor to cause such a registration statement to be declared effective. Moreover, we may not be able to establish an exemption from registration under the Securities Act. Accordingly, ADS holders may be unable to participate in our rights offerings or to elect to receive dividends in shares and may experience dilution in their holdings. In addition, if the depositary is unable to sell rights that are not exercised or not distributed or if the sale is not lawful or reasonably practicable, it will allow the rights to lapse, in which case holders of our ADSs will receive no value for these rights.

Holders of our ADSs may be subject to limitations on the transfer of such ADSs and the withdrawal of the underlying ordinary shares.

ADSs are transferable on the books of the depositary. However, the depositary may close its books at any time or from time to time when it deems expedient in connection with the performance of its duties. 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 think it is advisable to do so because of any requirement of law, government or governmental body, or under any provision of the deposit agreement, or for any other reason subject to an ADS holders' right to cancel such ADSs and withdraw the underlying ordinary shares. Temporary delays in the cancellation of such ADSs and withdrawal of the underlying ordinary shares may arise because the depositary has closed its transfer books or we have closed our transfer books, the transfer of ordinary shares is blocked to permit voting at a shareholders' meeting or we are paying a dividend on our ordinary shares. In addition, holders of our ADSs may not be able to cancel such ADSs and withdraw the underlying ordinary shares when such holders owe money for fees, taxes and similar charges and when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to ADSs or to the withdrawal of ordinary shares or other deposited securities.

As a foreign private issuer, we are exempt from a number of rules under the U.S. securities laws and are permitted to file less information with the SEC than a U.S. company. This may limit the information available to holders of ADSs.

We are a "foreign private issuer," as defined in the SEC's rules and regulations and, consequently, we are not subject to all of the disclosure requirements applicable to public companies organized within the United States. For example, we are exempt from certain rules under the Exchange Act that regulate disclosure obligations and procedural requirements related to the solicitation of proxies, consents or authorizations applicable to a security registered under the Exchange Act, including the U.S. proxy rules under Section 14 of the Exchange Act. In addition, our officers and directors are exempt from the reporting and "short-swing" profit recovery provisions of Section 16 of the Exchange Act and related rules with respect to their purchases and sales of our securities. Moreover, while we currently make annual and quarterly filings with the SEC, we are not required to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. domestic public companies and are not required to file quarterly reports on Form 10-Q or current reports on Form 8-K under the Exchange Act. Accordingly, there may be less publicly available information concerning our company than there would be if we were a U.S. domestic issuer.

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

As a foreign private issuer listed on the Nasdaq Global Market, we are subject to corporate governance standards. However, Nasdaq's rules permit a foreign private issuer like us to follow the corporate governance practices of its home country. Certain corporate governance practices in France, which is our home country, may differ significantly from corporate governance standards of the Nasdaq. For example, neither the corporate laws of France nor our By-laws require a majority of our directors to be independent and our independent directors are not required to hold regularly scheduled meetings at which only independent directors are present. In addition, home country practice in France does not require us to maintain a nominating and corporate governance committee or to maintain a compensation committee composed entirely of independent directors. Currently, we follow home country practice in certain key respects. Therefore, our shareholders may be afforded less protection than they otherwise would have under corporate governance listing standards applicable to U.S. domestic issuers. A discussion of our corporate governance practices is set forth in the section titled "Management—Corporate Governance Practices."

We may lose our foreign private issuer status in the future, which could result in significant additional cost and expense.

While we currently qualify as a foreign private issuer, the determination of foreign private issuer status is made annually on the last business day of our most recently completed second fiscal quarter and, accordingly, the next determination will be made with respect to us on June 30, 2017.

In the future, we would lose our foreign private issuer status if we to fail to meet the requirements necessary to maintain our foreign private issuer status as of the relevant determination date. For example, if more than 50% of our securities are held by U.S. residents and more than 50% of our executive officers or members of our board of directors are residents or citizens of the United States, we could lose our foreign private issuer status.

The regulatory and compliance costs to us under U.S. securities laws as a U.S. domestic public company would be significantly more than costs we currently incur as a foreign private issuer. If we lost our foreign private issuer status, we would be required to file periodic reports on Form 10-Q and current reports on Form 8-K, to file periodic reports and registration statements on U.S. domestic issuer forms with the SEC, which are more detailed and extensive in certain respects than the forms available to a foreign private issuer. We would be required under current SEC rules to prepare our financial statements in accordance with U.S. GAAP, rather than IFRS, in U.S. dollars rather than euros. Such conversion of our financial statements to U.S. GAAP would involve significant time and cost. In addition, we would lose our ability to rely upon exemptions from certain corporate governance requirements of the Nasdaq that are available to foreign private issuers, such as the ones described above, and we would be required to modify certain of our policies to comply with corporate governance practices associated with U.S. domestic issuers. Moreover, we would lose our ability to rely upon exemptions from procedural requirements related to the solicitation of proxies.

It may be difficult to enforce civil liabilities against our company and directors and senior management and the experts named in this Annual Report.

Certain members of our board of directors and senior management and those of our subsidiaries, are non-residents of the United States, and all or a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. Additionally, it may be