Atara Biotherapeutics, Inc.
Form 10-K
March 09, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number 001-36548

ATARA BIOTHERAPEUTICS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware (State or other jurisdiction of incorporation or organization)	46-0920988 (I.R.S. Employer Identification No.)
611 Gateway Blvd., Suite 900 South San Francisco, CA (Address of principal executive offices)	94080 (Zip Code)

Registrant’s telephone number, including area code: (650) 278-8930

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001 per share, traded on The Nasdaq Stock Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES NO

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES NO

Indicate by check mark whether the Registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES NO

Indicate by check mark whether the Registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit and post such files). YES NO

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definition of "large accelerated filer", "accelerated filer", and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer Accelerated filer

Non-accelerated filer (Do not check if a small reporting company) Small reporting company

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES NO

The aggregate market value of common stock held by non-affiliates of the Registrant, based on the closing sales price for such stock on June 30, 2016 as reported by The Nasdaq Stock Market, was $457,200,160. This calculation excludes 8,485,039 shares held by executive officers, directors and stockholders that the Registrant has concluded are affiliates of the Registrant. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the Registrant.

The number of outstanding shares of the Registrant's Common Stock as of February 15, 2017 was 29,089,911.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive proxy statement relating to its 2017 Annual Meeting of Stockholders are incorporated by reference into Part III of this Report where indicated. Such proxy statement will be filed with the U.S.

Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

ATARA BIOTHERAPEUTICS, INC.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Such forward-looking statements, which represent our intent, belief or current expectations, involve risks and uncertainties and other factors that could cause actual results and the timing of certain events to differ materially from future results expressed or implied by such forward-looking statements. In some cases you can identify these statements by forward-looking words such as "believe," "may," "will," "estimate," "continue," "anticipa "intend," "could," "would," "project," "plan," "expect" or the negative or plural of these words or similar expressions. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- our expectations regarding the timing of initiating clinical trials, enrolling clinical trials and reporting results of clinical trials for our T-cell programs;
- the likelihood and timing of regulatory submissions or related approvals for our product candidates;
- the potential market opportunities for commercializing our product candidates;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use;
- estimates of our expenses, capital requirements and need for additional financing;
- our expectation that our existing capital resources will be sufficient to enable us to fund our planned operations into the first quarter of 2019;
- our ability to develop, acquire and advance product candidates into, and successfully complete, clinical trials;
- the initiation, timing, progress and results of future preclinical studies and clinical trials and our research and development programs;
- the scope of protection we are able to obtain and maintain for our intellectual property rights covering our product candidates;
- our financial performance;
- developments and projections relating to our competitors and our industry;
- our ability to manufacture our product candidates for our clinical trials, including our Phase 3 trials;
- our ability to sell or manufacture approved products at commercially reasonable values; and
- timing and costs related to building our manufacturing plant.

These statements are only current predictions and are subject to known and unknown risks, uncertainties and other factors that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from those anticipated by the forward-looking statements. We discuss many of these risks in this report in greater detail under the heading "1A. Risk Factors" and elsewhere in this report. You should not rely upon forward-looking statements as predictions of future events. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risks and uncertainties.

In this Annual Report on Form 10-K, unless the context requires otherwise, "Atara," "Atara Biotherapeutics," "Company," "we," "our," and "us" means Atara Biotherapeutics, Inc. and, where appropriate, its subsidiaries.

PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company focused on developing meaningful therapies for patients with severe and life-threatening diseases that have been underserved by scientific innovation. We are focused on developing allogeneic or third-party derived antigen-specific T-cells. T-cells are a type of white blood cell. Cytotoxic T-cells, otherwise known as cytotoxic T lymphocytes, or CTLs, can mount an immune response against an antigen or antigens in order to combat viral infection or disease.

Our cellular therapy platform is designed to provide a healthy immune capability to a patient whose immune system is compromised or is unable to identify the disease targets. Our product candidates are derived from cells donated by healthy individuals. These cells are trained to recognize an antigen, expanded, characterized, banked and held as inventory. These cells are ready to infuse in a partially human leukocyte antigen, or HLA, matched patient in approximately 3-5 days. Once administered, the cells home to their target, expand in-vivo to eliminate diseased cells, and eventually recede. This versatile platform can be directed towards a broad array of disease causing targets and has demonstrated clinical proof of concept across both viral and non-viral targets in conditions ranging from liquid and solid tumors to infectious and autoimmune diseases. We licensed rights to T-cell product candidates from Memorial Sloan Kettering Cancer Center, or MSK, in June 2015 and to know how and technology from QIMR Berghofer Medical Research Institute, or QIMR Berghofer, in October 2015 and September 2016. Our relationship with QIMR Berghofer provides rights to know how and a technology that is complementary to that which was licensed from MSK. This know-how and technology is enabling the development of EBV and other virally targeted CTLs for other indications such as multiple sclerosis, or MS. We are working with QIMR Berghofer on the development of product candidates for these new indications.

ATA129

Our most advanced T-cell product candidate, ATA129 (previously referred to as EBV-CTL), which is a third-party derived Epstein-Barr virus CTL, is currently being investigated for the treatment of Epstein-Barr virus, or EBV, associated post-transplant lymphoproliferative disorder, or EBV-PTLD. In immunocompromised patients, EBV causes lymphomas and other lymphoproliferative disorders, collectively called EBV-PTLD. EBV-PTLD most commonly affects patients after hematopoietic cell transplant, or HCT, or after solid organ transplant, or SOT. In December 2016, we announced that we had reached agreement with the U.S. Food and Drug Administration, or FDA, on the designs of two Phase 3 trials for ATA129 intended to support approval in two separate indications, the treatment of rituximab-refractory EBV-PTLD after HCT and after SOT.

The MATCH trial (EBV-PTLD after HCT) is designed to be a multicenter, open label, single arm trial designed to enroll approximately 35 patents with rituximab refractory EBV-PTLD after HCT. The ALLELE trial (EBV-PTLD after SOT) is designed to be a multicenter, open label trial with two non-comparative cohorts. Each cohort is designed to enroll approximately 35 patients. The first cohort will include patients who previously received rituximab monotherapy, and the second cohort will include patients who previously received rituximab plus chemotherapy. Both cohorts are planned to enroll concurrently.

The primary endpoint of both the MATCH and ALLELE trials is objective response rate, defined as the percent of patients achieving either a complete or partial response to treatment with ATA129. Secondary endpoints for both trials include duration of response, overall survival, safety, quality of life metrics, and other data in support of potential health economic benefits. The trials are expected to open initially in the United States and later expand to include ex-U.S. sites.

In addition, in June 2016, we opened a multicenter expanded access protocol, or EAP, trial to provide access to ATA129 treatment and collect additional safety data while the medication is not commercially available or available to patients through another protocol. The trial is open to patients with EBV-associated viremia or certain malignancies for whom there are no appropriate alternative treatment options.

We generated and evaluated data from new material manufactured by our contract manufacturing organization, or CMO, and initiated discussions with the FDA. We have been successful in producing ATA129 drug product and identified certain assays that need refinement prior to initiating the Phase 3 trials. We are refining these assays within our laboratories, manufacturing lots to further support comparability evaluations and the Phase 3 trials, and expect to review these data in ongoing discussions with the FDA.

In clinical trials that enrolled patients with EBV-PTLD following HCT or SOT, efficacy following treatment with ATA129 compared favorably with historical data in these patient populations. In rituximab-refractory patients with EBV-PTLD after HCT, treatment with ATA129 resulted in one-year overall survival of approximately 60% in two separate clinical trials in comparison with historical data where median survival, or the time by which 50% of patients had died, was 16-56 days. In the setting of rituximab-refractory EBV-PTLD after SOT, similar results were observed, with one-year overall survival of approximately 60% in ATA129-treated patients in comparison with an expected historical one-year survival of 36% in patients with high risk disease similar to the

patients treated in the trials. In February 2015, the FDA granted breakthrough therapy designation for ATA129 in the treatment of rituximab-refractory EBV-PTLD after HCT. Breakthrough therapy designation is an FDA process designed to accelerate the development and review of drugs intended to treat a serious condition when early trials show that the drug may be substantially better than current treatment. In February 2016, the FDA granted orphan drug designation for ATA129 for the treatment of patients with EBV-PTLD after HCT or SOT.

We are also pursing marketing approval of ATA129 in the European Union, or EU. In March 2016, the European Medicines Agency, or EMA, issued a positive opinion for orphan drug designation for ATA129 for the treatment of patients with EBV-PTLD. In October 2016, the EMA Committee for Medicinal Products for Human Use, or CHMP, and Committee for Advanced Therapies, or CAT, granted access to the EMA's newly established Priority Medicines, or PRIME, regulatory initiative for ATA129 for the treatment of patients with rituximab refractory EBV-PTLD following HCT. PRIME provides early enhanced regulatory support to facilitate regulatory applications and accelerate the review of medicines that address a high unmet need. In January 2017, we announced that pursuant to parallel scientific advice from the EMA's Scientific Advice Working Group and several national Health Technology Assessment, or HTA, agencies in the EU, in 2018 we plan to submit an application for Conditional Marketing Authorization, or CMA, of ATA129 in the treatment of patients with rituximab refractory EBV-PTLD following HCT. The CMA will be based on clinical data from Phase 1 and 2 trials conducted at MSK and supported by available data from our Phase 3 trials in rituximab refractory EBV-PTLD after HCT and SOT, which will be ongoing at the time of filing.

ATA188

Our second T-cell product candidate, ATA188, is in development for the treatment of multiple sclerosis, or MS. ATA188 is a third-party derived EBV-CTL that is targeted to specific antigens that we believe are important for the treatment of MS. We expect to initiate a Phase 1 trial in patients with MS in the second half of 2017. In addition, our partner, QIMR Berghofer, is currently conducting a Phase 1 study utilizing the autologous version of ATA188 for the treatment of patients with either secondary or progressive MS. The trial is currently enrolling. We have an exclusive option to license this program from QIMR Berghofer.

ATA520

Our third T-cell product candidate, ATA520, which is a third-party donor derived WT1-CTL, targets cancers expressing the antigen Wilms Tumor 1, or WT1, and is currently in Phase 1 clinical trials. WT1 is an intracellular protein that is overexpressed in a number of cancers, including multiple myeloma, or MM. MSK has two ongoing Phase 1 clinical trials evaluating ATA520. The first trial is a dose escalation trial of ATA520 for residual or relapsed leukemia after HCT. The second trial is a dose escalation trial of ATA520 following T-cell depleted HCT for patients with relapsed or refractory MM, including plasma cell leukemia, or PCL. Based on data from these trials, we intend to develop ATA520 in hematologic malignancies, including PCL. We expect to initiate a Phase 1/2 clinical trial in patients with hematologic malignancies in 2018.

ATA230

Our fourth T-cell product candidate, ATA230, which is a third-party derived cytomegalovirus-CTL, or CMV-CTL, is in Phase 2 clinical trials for refractory CMV, an infection that occurs in some patients who have received an HCT or SOT or are otherwise immunocompromised. We met with the FDA for an end of Phase 2 meeting to discuss late stage development of ATA230 for the treatment of anti-viral refractory or resistant CMV infection following either HCT or SOT. Given the opportunity to pursue a conditional marketing authorization in the EU for ATA129, we have decided to prioritize at this time our EBV related programs ahead of ATA230. Therefore, we intend to further evaluate ATA230 Phase 3 trial designs following the initiation of our ATA129 Phase 3 trials.

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Our pipeline of product candidates is highlighted in the figure below.

T-cell Technology Platform

Our T-cell product candidates share a common technology under which cells are collected from the blood of third-party donors and then exposed to selected viral or cancer antigens in order to activate them against that particular virus. The resulting activated T-cells are expanded in number, characterized and stored for future therapeutic use in an appropriate partially HLA matched patient, providing a readily available, cellular therapeutic option for patients. Because these T-cells are readily available, patients often only need to wait 3-5 days until they receive treatment. In addition to expanding the activated T-cells, during the course of the manufacturing process, the number of potentially alloreactive cells, which can cause graft versus host disease, or GvHD, diminish. We believe this may reduce the risk of GvHD, a potentially serious complication.

The process through which ATA129 is generated is shown in the diagram below. First, B-cells derived from the blood of a third-party donor are exposed to a specific strain of the EBV virus to create EBV transformed B lymphoblastoid cell lines, or EBV BLCLs. The BLCLs are irradiated to prevent the BLCLs from growing and then co-cultured with T-cells derived from the blood of the same third-party donor. In this co-culture process, the BLCLs present EBV antigen to the T-cells to activate the T-cells against the EBV virus. These activated EBV-specific T-cells are then sensitized and expanded, while the potentially alloreactive cells contained in the same culture are not expanded and subsequently die. When complete, the cultures are assessed for a number of attributes, including cytotoxicity, HLA restriction, alloreactivity and microbial sterility. Once fully characterized in this way, the cell lines are cryopreserved and stored for future therapeutic use as a readily available therapy.

The donor's blood contains a mix of T-cells, some that have the potential to target EBV-infected cancer cells, and others called alloreactive or allospecific T-cells, which have the potential to target cells recognized as foreign. Administration of bulk third-party lymphocytes that contain a relatively high proportion of allospecific T-cells has the potential to cause severe and life-threatening toxicities such as GvHD when these allospecific T-cells recognize the recipient's native cells as foreign. Our manufacturing process enriches the product for the desired EBV specific T-cells while depleting the undesirable allospecific T-cells as they are not stimulated to expand and eventually die.

In addition to being evaluated for expansion before release for use in clinical trials, cells are also evaluated for HLA restriction. HLA restriction refers to the fact that any given T-cell line will only recognize such T-cell line's target—in this case an EBV protein—when it is bound to a particular HLA. For example, an EBV-CTL restricted by a particular HLA known as HLA A*02:01 will only kill EBV-infected cells that show that same EBV protein when bound to HLA A*02:01. This process identifies EBV-CTLs that are specific to the desired target, limiting undesirable off-target killing of other cells.

An appropriate cell line for use in a particular patient is typically defined as being matched with at least two of ten HLA alleles and restricted through a shared HLA allele. In an analysis conducted by MSK and reported at the 2015 American Association for Cancer Research, or AACR, annual meeting, an appropriate cell line was determined to be available for all but one of 200 consecutive unrelated transplant recipients and 100 cord blood transplant recipients. This analysis was based on evaluating these potential patients against a bank of approximately 330 HLA characterized EBV-CTL lines that MSK had generated to date. MSK's clinical experience has yielded an empirically derived, proprietary approach to selecting the appropriate cell line for use in individual patients. We believe this algorithm will ultimately allow us to deliver the therapy efficiently by focusing on a more limited set of cell lines without compromising our ability to treat a wide range of patients with diverse HLA types.

A similar process is used to generate and characterize WT1 specific and CMV specific T-cells, and we also plan to utilize this process to generate diverse banks of targeted cytotoxic T-cell lines against other antigens of interest.

EBV-Targeted T-Cells for EBV-PTLD and Other EBV Associated Diseases

EBV is a member of the Herpes virus family and is one of the most common viruses in humans. It is present in all populations, infecting more than 95% of all individuals within the first four decades of life. In healthy individuals, EBV causes infectious

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mononucleosis, a generally benign self-limiting condition. Following the acute phase of EBV infection, the virus remains present in a small number of B-cells throughout the body; however, it is kept in check by the intact immune system. Though benign in the vast majority of people, EBV has been demonstrated to be involved in the development of many malignancies. In immunocompromised patients, EBV causes lymphomas and other lymphoproliferative disorders, collectively called EBV-PTLD. EBV-PTLD most commonly affects patients after HCT or after SOT. Even in patients with intact immune systems, EBV is associated with various hematologic malignancies and solid tumors including Hodgkin lymphoma, Burkitt lymphoma, other B-cell malignancies, nasopharyngeal carcinoma and gastric cancer. EBV is also associated with certain autoimmune diseases, including multiple sclerosis.

The approximate estimated number of patients per year in the United States and European Union with EBV associated diseases is highlighted in the figure below.

Indication	Estimated Number of Patients
EBV-PTLD after HCT	1,400
EBV-PTLD after SOT	1,700
EBV positive Diffuse Large B cell lymphoma	5,800
EBV positive chemotherapy refractory Hodgkin lymphoma	2,100
EBV positive nasopharyngeal carcinoma	6,000
EBV positive gastric cancer	16,500
Primary and secondary progressive multiple sclerosis	>400,000

EBV-PTLD is a rare but serious complication in recipients of HCT or SOT. EBV-PTLD is often severe and sudden in onset and results in death in the majority of HCT patients who develop the disease. A study conducted by the Karolinska Institute that was reported in the journal Haematologica noted a three-year survival rate of just 20%. According to the U.S. Department of Health and Human Services, there were 8,338 allogeneic transplants in the United States in 2013, and according to the European Society for Blood and Marrow Transplantation, there were 14,950 allogeneic transplants in the European Union. The incidence of EBV-PTLD varies between transplant centers, and in some cases can be as high as 6%. While autologous transplants, or those obtained from the same individual, still comprise the majority of all transplants in the United States and European Union, the relative proportion of allogeneic transplants, or those obtained from a third-party donor, has increased over time, and we believe this trend will continue due to the increasing utilization of haploidentical transplants and reduced intensity transplants.

The monoclonal antibody, rituximab, is typically used off-label to treat EBV-PTLD, producing initial responses in approximately 60% of treated allogeneic, or third-party derived, HCT patients, resulting in three year overall survival in approximately 20% of treated patients. However, for those who relapse after rituximab therapy or fail to respond to rituximab, or for those with CD20 negative lymphoma (which is known to be unlikely to respond to rituximab), EBV-PTLD is frequently lethal. For example, it was reported in 2014 in the journal Bone Marrow Transplantation that the median survival period from diagnosis of rituximab-refractory EBV-PTLD in adult HCT patients was 33 days, and in 2014 it was reported in the journal Haematologica that median survival was 16 days. In 2008, it was reported in the journal Bone Marrow Transplantation that the median survival period from the time of diagnosis in a group of EBV-PTLD patients who received rituximab was 56 days. Taken together, these studies suggest a range of median overall survival, or OS, in the setting of rituximab failure of 16-56 days.

MSK has conducted two separate clinical trials of ATA129 that enrolled a heterogeneous group of patients with a variety of EBV-associated malignancies, including, but not limited to, EBV-PTLD after HCT and EBV-PTLD after SOT. These trials are referred to as Study 95-024, initiated in 1995, and Study 11-130, initiated in 2011. Since licensing our T-cell product candidates, the IND under which Studies 95-024 and 11-130 were conducted has been transferred from MSK to us. Results from these two trials supported the granting of breakthrough therapy designation by the FDA for ATA129 in February 2015 for the treatment of rituximab-refractory EBV-PTLD after HCT. Data from these trials was presented at a clinical trials plenary session at the April 2015 AACR Annual Meeting and was subsequently updated at an oral presentation at the June 2015 American Society of Clinical Oncology, or ASCO, Annual Meeting.

In Study 95-024, patients with EBV-PTLD following HCT were treated with ATA129 manufactured from T-cells derived from either the primary HCT donor or an unrelated third-party donor. The term primary HCT donor refers to the donor who provided hematopoietic stem cells for the HCT. As one measure of efficacy, response rate was evaluated in these patients. The response rate refers to the proportion of patients treated with ATA129 who had either a complete or partial response as best response to treatment when measured by radiographic imaging of the tumor. In a complete response, no visible evidence of tumor following treatment was observed. In a partial response, the tumor was reduced in size by more than 50% but less than 100%.

In both the primary HCT donor and third-party donor cohorts, similar response rates of approximately 60% were achieved. Such response rates suggest that the efficacy of treatment with primary donor derived and third-party donor derived ATA129 are

comparable. The similarity in efficacy observed following treatment with third party and primary donor derived EBV-CTL is important, as there are significant limitations associated with a therapy derived from the primary transplant donor. First, it can take approximately eight weeks to generate an ATA129 line from blood remaining from the primary HCT donor. In this amount of time and based on historical data, approximately half of those patients who had either failed to respond or who had relapsed after rituximab would likely have succumbed to their EBV-PTLD and died before the cell line was available for therapeutic use. Second, due to the limited quantities of certain HCT donor materials such as umbilical cord blood, it is not possible to make a primary donor derived EBV-CTL line for all patients. Additionally, if the EBV-PTLD is of host rather than donor origin, T-cells derived from the primary HCT donor may not be able to recognize this host tumor, and therefore would not be expected to be effective in combatting the disease. Thus, we believe that the availability of readily available third-party derived ATA129 provides significant practical and therapeutic advantages in the treatment of rituximab-refractory EBV-PTLD. A median of two cycles of third-party derived ATA129 were administered in these trials. In each cycle, ATA129 is administered weekly for 3 weeks followed by 2 weeks of rest. In addition, a number of patients with disease located in the central nervous system, or CNS, responded to treatment with ATA129, suggesting that these cells are capable of passing through the blood-brain barrier.

The time course of a complete response following multiple cycles of ATA129 in a patient with rituximab-refractory EBV-PTLD is shown below using sequential positron emission tomography, or PET, scans. Also shown are the timing of rituximab and ATA129 (EBV-CTL) therapy depicted by the corresponding set of arrows, the levels of EBV DNA in the blood as measured by EBV polymerase chain reaction, or EBV PCR, a sensitive and specific technique to detect viral DNA depicted in the corresponding line, as well as the levels of CTL precursors per milliliter of blood, or CTLp/ml, depicted in the corresponding line. CTLp/ml identifies and enumerates activated T-cells.

This patient developed EBV viremia, or high levels of virus in the blood, early post-HCT as noted in the line labeled EBV PCR. Her viremia responded to rituximab, but recurred and it again responded to a second cycle of rituximab. In the interim, she developed a rapidly progressive diffuse large B-cell lymphoma, or DLBCL, that was EBV positive. By week 0, defined as the start of ATA129 therapy, the lymphoma is visible in the lymph nodes as well as in the liver and spleen. She received a first cycle of ATA129 after which she had a partial response. The patient received three subsequent cycles of ATA129 after which she achieved a complete response. In conjunction with each cycle of ATA129, expansion of EBV-specific CTLs was detected, as shown in the line labeled CTLp/ml. While these expansions were not durable, they mediated her complete response. The PET scans, in which dark areas correspond to areas of high metabolic activity, show both normal metabolism of organs such as the heart and abnormal metabolism in areas of lymphoma. After treatment with T-cells, the abnormal areas of metabolism recede, indicating eradication of tumor cells. In the final image, no abnormal metabolic activity is observed, reflecting a complete response to ATA129 therapy.

The ability to switch from one cell line to another led to the discovery of a hierarchy of HLA restriction. This is highlighted by the example below, in which a patient received three ATA129 lines (A, B and C) with different HLA restrictions, but only went into complete response upon administration of a fourth unique ATA129 line (D) with a different HLA restriction. We believe that future patients can be treated using a cell line selection algorithm based in part on the hierarchy elucidated in this manner that enables a more efficient choice of ATA129.

Treatment with EBV specific T-cells is recognized as a recommended treatment for persistent or progressive EBV-PTLD as set forth in the 2017 National Comprehensive Cancer Network Guidelines.

EBV-PTLD after HCT

To date, in the Phase 2 trial 11-130, 23 patients with rituximab-refractory EBV-PTLD after HCT have been treated with ATA129. Treatment with ATA129 resulted in one-year overall survival of approximately 65%. Greater than 60% of the patients treated responded to ATA129 which was defined as achieving either a complete response or partial response. Responses were durable. Among responders, no patients had a recurrence of EBV-PTLD after HCT. Since these trials are ongoing, we expect that these Kaplan-Meyer, or K-M, estimates of survival will evolve with ongoing follow-up of the patients and that a median OS may be reached in Study 11-130.

In 129 patients, in both 11-130 and 95-024, there were 9 possibly related serious adverse events, or SAEs. There were no infusion related toxicities, no cytokine release syndrome and one treatment related grade 1 graft versus host disease, or GvHD, which resolved without systemic therapy.

In December 2016, we announced that we had reached agreement with the FDA on the design of the Phase 3 trial for ATA129 intended to support approval for the treatment of rituximab-refractory EBV-PTLD, after HCT. The MATCH trial (EBV-PTLD after HCT) is designed to be a multicenter, open label, single arm trial designed to enroll approximately 35 patents with rituximab refractory EBV-PTLD after HCT. The primary endpoint of the MATCH trial is objective response rate, defined as the percent of patients achieving either a complete or partial response to treatment with ATA 129. Secondary endpoints include duration of response, overall survival, safety, quality of life metrics, and other data in support of potential health economic benefits.

EBV-PTLD after SOT

EBV-PTLD after SOT is a spectrum of lymphoid malignant disease associated with the use of immunosuppressive drugs after SOT. Patients with EBV-PTLD, one of the most common neoplastic diseases after SOT, commonly present with stage 3 or 4 disease. Reduction in immunosuppression, antiviral therapy, or surgical resection are common treatments, but many patients with PTLD require systemic therapy, especially those with aggressive lymphoma morphology such as DLBCL. Chemotherapy remains undesirable in PTLD because of myelotoxic side effects of cytotoxic therapy and associated infections and toxic deaths. In addition, recipients of chemotherapy face the prospect of secondary malignancies in the future. Rituximab with or without chemotherapy is often used off-label after reduction in immunosuppressive therapy with a response rate of approximately 44% to 68%. In the setting of rituximab-refractory EBV-PTLD after SOT, historical one-year survival of 36% is observed in patients with high risk disease. The rates of EBV-PTLD after SOT vary by organ transplant type, age at transplant and degree of immunosuppression with higher rates

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occurring in children than in adults. One of the unique features of EBV-PTLD after SOT in comparison with the post-HCT setting is that the immunosuppression that ultimately gives rise to the lymphoma is in many cases required chronically and, as a result, the period of time during which an EBV-associated lymphoma may arise extends for the duration of immunosuppression. Although some cases of EBV-PTLD in SOT occur within the first year, many occur years after transplant.

In trials 95-024 and 11-130, patients with EBV-PTLD after SOT were treated with ATA129. All patients had failed to respond to or relapsed following rituximab treatment. Most had also progressed after receiving chemotherapy. Additionally, nearly all patients had high risk disease defined as those with age greater than or equal to 60 years, poor performance status, elevated LDH, or presence of disease in the central nervous system, or CNS. Response rate and OS results for these patients were also evaluated by MSK.

The response rate observed in the 95-024 and 11-130 trials for rituximab-refractory post SOT setting was greater than 50% and the one-year OS was approximately 60%. Responses were durable. Among responders, no patients have had a recurrence of EBV-PTLD after SOT. Since these trials are ongoing, we expect that these K-M estimates of survival may evolve with ongoing follow-up of the patients.

In 129 patients, in both 95-024 and 11-130, there were 9 possibly related SAEs. There were no infusion related toxicities, no cytokine release syndrome and one treatment related grade 1 GvHD.

In December 2016, we announced that we had reached agreement with the FDA on the design of the Phase 3 trial for ATA129 intended to support approval for the treatment of rituximab-refractory EBV-PTLD after SOT. The ALLELE trial (EBV-PTLD after SOT) is designed to be a multicenter, open label trial with two non-comparative cohorts. Each cohort is designed to enroll approximately 35 patients. The first cohort will include patients who previously received rituximab monotherapy, and the second cohort will include patients who previously received rituximab plus chemotherapy. Both cohorts will enroll concurrently.

The primary endpoint of the ALLELE trial is objective response rate, defined as the percent of patients achieving either a complete or partial response to treatment with ATA 129. Secondary endpoints for the trial include duration of response, overall survival, safety, quality of life metrics, and other data in support of potential health economic benefits.

Multiple Sclerosis

A number of observations implicate EBV in the pathogenesis of MS. For example, MS patients are universally EBV seropositive, there are high levels of anti-EBV antibodies, their T-cells have altered immune function, there is an increase in spontaneous EBV-induced peripheral blood B-cell transformation, there is increased shedding of EBV from saliva of children, and accumulation of EBV-infected B-cells and plasma cells in the brain. The opportunity for EBV-targeted cellular therapy in MS is further supported by a case report from 2014 published in the Multiple Sclerosis Journal of a secondary progressive MS patient treated with the autologous version of our ATA188 product candidate with encouraging results. In this patient and as demonstrated in the images below, MS lesions in the brain visible through gadolinium-enhanced magnetic resonance imaging before treatment with autologous ATA188 had resolved completely upon further imaging nine weeks after the completion of the last dose of autologous ATA188 therapy. There were no significant adverse effects.

Based on this result, in early 2016, QIMR Berghofer initiated a Phase 1 clinical trial in ten patients, five with primary progressive MS and five with secondary progressive MS. The trial is currently enrolling. We have an exclusive option to license this autologous program from QIMR Berghofer. We are also developing ATA188, a third party

derived EBV-CTL, which is targeted to

certain epitopes of EBV that we believe to be important in the treatment of MS. We expect to initiate a Phase 1 trial for ATA188 in patients with MS in the second half of 2017.

Other EBV-Associated Malignancies

EBV-associated malignancies can occur even in immunocompetent patients, and include: Burkitt lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma such as DLBCL, nasopharyngeal carcinoma, or NPC, and gastric cancer. Typically, these malignancies occur many years after primary EBV infection. For Burkitt lymphoma, approximately 15% to 30% of cases in the United States and European Union are associated with EBV. For Hodgkin lymphoma, approximately 20% to 50% of cases in the United States and European Union are associated with EBV; however, many of these are responsive to chemotherapy. Nearly 100% of natural killer, or NK, T-cell lymphomas are associated with EBV. In NPC, the association with EBV is such that regardless of geography nearly 100% of the nonkeratinising tumors and all the tumor cells have been demonstrated to be monoclonally EBV-positive. EBV-positive gastric cancer can make up approximately 10% of all gastric cancers. In some of these tumor types, multiple EBV proteins are associated with the disease and in others, a smaller subset are made.

In addition, we intend to explore the therapeutic utility of EBV-targeted cellular therapy in other EBV-malignancies. In June 2016, we opened a multicenter expanded access protocol, or EAP, trial to provide access to ATA129 treatment and collect additional safety data while the medication is not commercially available or available to patients through another protocol. The trial is open to patients with EBV-associated viremia or malignancies for whom there are no appropriate alternative treatment options. We would expect to generate data in a number of these EBV-malignancies.

We have also begun to generate data utilizing ATA129 to treat NPC. Our collaborating investigator, MSK, presented clinical results at the June 2016 American Society of Clinical Oncology, or ASCO, meeting on the use of ATA129 in patients with NPC. The data included one complete response and two partial responses among 14 patients with recurrent metastatic NPC. Furthermore, 11 of 14 patients on the study were alive at a median follow up of 18.1 months. This result is encouraging when compared to historical median survival rates that range from five to eleven months for patients with metastatic disease after progression following standard chemotherapy. Of note, CTLs expanded in vivo and had sufficient persistence to drive clinical responses despite the absence of lympho-depleting chemotherapy in advance. We intend to continue to evaluate this product candidate in the treatment of NPC, and expect to initiate a Phase1/2 clinical trial evaluating ATA129 in combination with a checkpoint inhibitor for the treatment of NPC following the initiation of our ATA129 Phase 3 trials.

ATA520, WT1 Targeted T-Cells for Hematologic Malignancies and Solid Tumors

WT1 is an intracellular protein that is overexpressed in a number of cancers, including multiple myeloma, or MM, and non-small cell lung, breast, pancreatic, ovarian, and colorectal cancers. MSK has two ongoing Phase 1 clinical trials evaluating primary donor derived WT1-CTLs. The first trial is a dose escalation trial of ATA520 for residual or relapsed leukemia after HCT. The second trial is a dose escalation trial of ATA520 following T-cell depleted HCT for patients with relapsed or refractory MM, including plasma cell leukemia, or PCL. In 2011, it was reported in the journal Blood that the prognosis of PCL is poor, with a median survival of seven to eleven months and that survival is even shorter, two to seven months, when PCL occurs in the context of refractory or relapsing MM. At the ASH 2015 Annual Meeting, MSK presented results from this Phase 1 clinical trial of primary donor-derived ATA520. In this trial, response assessments were conducted utilizing criteria consistent with those defined by the International

Myeloma Working Group.

- Patients with relapsed-refractory MM, including PCL were treated with allogeneic HCT followed by WT1-CTLs.
- At one year, a response rate of greater than 50% was observed in these patients. For these data, the response rate was determined by adding the complete responses to the partial responses and then dividing by the number of patients.
- Two patients who developed a complete response remained in remission for more than one year.
- There were no treatment-related SAEs with WT1-CTLs.

Based on data from these trials, we intend to develop ATA520, which is a third-party donor-derived WT1-CTL, in hematologic malignancies, including PCL. We expect to initiate a Phase 1/2 clinical trial in patients with hematologic malignancies in 2018.

ATA230, CMV-Targeted T-cells for CMV Infection and Other CMV Associated Malignancies

CMV, also known as HHV-5, is a member of the Herpes virus family. CMV infection rate gradually increases throughout childhood, and, once infected, an individual carries the virus for life due to the ability of CMV to establish a latent state of infection. It is estimated that CMV infection affects 50% to 90% of the global adult population. Immunocompromised patients, including HCT and SOT patients, human immunodeficiency virus, or HIV, patients, and to a lesser extent cancer patients, are at highest risk for

developing significant disease syndromes caused by CMV, including interstitial pneumonia, gastrointestinal infection, central nervous system disease, hepatitis, retinitis, and encephalitis.

Antiviral drugs in the form of prophylaxis or preemptive treatment strategies have reduced morbidity and mortality, though adverse effects such as neutropenia and renal toxicity remain a challenge. The emergence of resistance to antiviral drugs also presents challenges to patient care.

CMV Viremia and Disease after HCT

Despite the use of prophylactic and preemptive therapy using small molecule antivirals, many post-HCT patients progress to develop overt, symptomatic CMV viral diseases such as retinal infections that risk permanent blindness, encephalopathy with the risk of permanent brain damage and other serious morbidities. However, the antiviral drugs used to treat CMV have significant toxicities, including marrow toxicity for ganciclovir, valganciclovir and cidofovir, and renal toxicity for foscarnet and cidofovir. In addition, CMV drug resistance mutations arise during this antiviral therapy.

MSK has conducted one Phase 1 clinical trial and is conducting two Phase 2 clinical trials of ATA230 that included patients with CMV viremia and CMV disease, in each case refractory to antiviral drug treatment. An interim summary of MSK's clinical experience was reported at the December 2014 American Society of Hematology, or ASH, Annual Meeting. This analysis evaluated outcomes in patients who were treated with ATA230 after failing a median of four different antiviral drugs and demonstrated response rates of approximately 60% in patients with refractory CMV viremia or disease. Responses in patients treated for viremia alone with ATA230 were considered to be complete responses if the viremia resolved completely and partial responses if the viral load fell 100-fold or more. Responses in patients treated for overt disease were considered to be complete responses if all detectable CMV viremia and disease resolved and partial responses if patients became asymptomatic.

An additional subset analysis of MSK's clinical experience from the ongoing Phase 2 clinical trial and including patients treated under compassionate use was reported at the December 2015 ASH Annual Meeting. This analysis included patients with refractory CMV disease in the central nervous system, or CNS, who were treated with either primary donor derived or third-party derived ATA230. Nearly all of these patients were treated with third-party derived ATA230 and one was treated with a primary donor derived ATA230. Patients had received a range of three to six prior therapies before treatment with ATA230. The overall response rate was more than 70%, including seven complete responses and one partial response. Responses in these patients treated for CMV disease in the CNS were considered to be complete responses if all detectable CMV viremia and disease resolved and partial responses if patients became asymptomatic.

At the December 2016, ASH Annual Meeting, our collaborating investigators at MSK reported Phase 2 results for our third-party derived T-cell product candidate, ATA230. Data from the Phase 2 trial described efficacy and safety of ATA230 in the treatment of 15 patients with documented CMV mutations conferring resistance to anti-viral therapies. Patients had received a median of 3 prior therapies before receiving ATA230. Dr. Susan Prockop, M.D. and colleagues reported a response rate of approximately 70% with 6 complete responses (CR) and 5 partial responses (PR). An analysis of overall survival (OS) at 6 months in responders versus non responders demonstrated an OS of approximately 70% in responders (CR+PR) versus 25% in non-responders. There were 16 SAEs possibly related to CMV-CTL among 66 patients.

We believe this data suggests a high response rate among patients with otherwise refractory CMV viremia and disease. Since these trials are ongoing, we expect that survival data may evolve with ongoing follow-up of the patients. Overall, ATA230 therapy was well tolerated. One patient developed possibly related de novo GvHD, or a flare-up of prior GvHD, in association with infusion of ATA230.

We met with the FDA for an end of Phase 2 meeting to discuss late stage development of ATA230 for the treatment of anti-viral refractory or resistant CMV infection following either HCT or SOT. Given the opportunity to pursue a conditional marketing authorization in the EU for ATA129, we have decided to prioritize at this time our EBV related programs ahead of ATA230. Therefore, we intend to further evaluate ATA230 Phase 3 trial designs following the initiation of our ATA129 Phase 3 trials.

Additional Platform Expansion Activities

We believe our T-cell technology platform will have utility beyond the current set of targets to which it has been directed. We and MSK have agreed to collaborate on further research to develop additional cellular therapies, which may include T-cell programs targeted against other antigens and chimeric antigen receptor, or CAR-T, cell programs. Pursuant to the existing agreements with MSK, we have an option to license these additional cellular therapies, and in 2016, we expanded our relationship with QIMR Berghofer to include development of CTLs targeting human papillomavirus and BK virus. We believe that viral antigens are well suited to adoptive immunotherapy given that people with normal immune systems are able to mount robust responses to these viral

targets, but immunocompromised patients and some cancer patients are not. We also intend to license or acquire additional product candidates or technologies to enhance our existing T-cell technology platform.

Our Molecularly-Targeted Product Candidates

STM434, a Targeted Therapy for Ovarian Cancer and Other Solid Tumors

STM434 is a soluble modified ActR2B receptor-IgGFc fusion protein that binds the signaling molecule human activin. We recently completed the dose escalation portion of the Phase 1 clinical trial of STM434 in ovarian cancer and other solid tumors. Based on the results of the dose escalation and the development progress of our other product candidates, we have determined not to prioritize at this time the further development of STM434 in these indications. We are investigating its potential to be used in other indications or applications.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our innovative technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and public and private research institutions. Some of these potential competitors may have a more established presence in the market and significantly greater financial, technical and human resources than we have. Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects or are less expensive than any products that we may develop.

T-Cell Product Candidates

Should our T-cell product candidates be approved for use, we will face substantial competition. In addition to the current standard of care for patients, commercial and academic clinical trials are being pursued by a number of parties in the field of immunotherapy. Early results from these trials have fueled continued interest in immunotherapy. In addition, if approved, our T-cell programs would compete with currently marketed drugs and therapies used for treatment of the following indications, and potentially with drug candidates currently in development for the same indications.

EBV-PTLD

There are currently no FDA or EMA approved products for the treatment of EBV-PTLD. However, some approved products and therapies are currently used off-label in this setting, and a number of companies and academic institutions that may license therapies to companies in the future are or may be developing new treatments. These therapies, as well as promotional efforts by competitors and clinical trial results of competitive products, could significantly diminish any ability to market and sell ATA129. The current treatment for EBV-PTLD involves administration of rituximab as a single agent or in the SOT setting, in combination with chemotherapy regimens. Additionally, a number of companies and academic institutions are developing drug candidates for EBV-PTLD and other EBV associated diseases, including Cell Medica Ltd., or Cell Medica, which is conducting Phase 1 clinical trials for baltaleucel-T, an autologous EBV specific T-cell therapy in post-transplant lymphoproliferative disorder.

Multiple Sclerosis

Competition in the MS market is expected to increase with the development of new therapies and approval of additional novel agents. There are many U.S. and international competitors in the relapsing-remitting multiple sclerosis (RRMS) market, including major multi-national fully-integrated pharmaceutical companies and established biotechnology companies.

A number of therapies are approved in the U.S. and European Union to treat RRMS. The branded RRMS treatment market includes Avonex®, marketed by Biogen Inc., or Biogen; Betaseron®, marketed by Bayer AG; Copaxone®, marketed by Teva Pharmaceutical Industries Ltd.; Rebif®, marketed by Merck KGaA; Tysabri® marketed by Biogen; Aubagio® marketed by Sanofi Aventis, or Sanofi and Genzyme Corporation; Gilenya® marketed by Novartis International AG, or Novartis; Lemtrada® marketed by Sanofi; Zinbryta® marketed by Biogen and Tecfidera® marketed by Biogen. In 2016, F. Hoffmann-La Roche Ltd Roche submitted marketing applications to the FDA and EMA for Ocrevus®, a monoclonal antibody targeting CD20, for the treatment of RRMS and primary progressive MS. There are numerous other development candidates in Phase 3 trials for RRMS including three next-generation sphingosine 1-phosphate receptor (S1PR) agonists (Celgene's ozanimod, Novartis' siponimod and Actelion's ponesimod), Novartis' anti-CD20 monoclonal antibody ofatumumab, as well as Teva's laquinimod.

In the U.S. there is one drug (mitoxantrone) approved to treat secondary progressive MS and no approved drugs for the treatment of primary progressive MS. In Europe, Betaseron® (marketed by Bayer AG) and Extavia® (marketed by Novartis) are approved drugs for the treatment of secondary progressive MS. There are currently no approved drugs for primary progressive MS. In addition to Ocrevus®, MedDay SA is developing MD-1003, a concentrated form of biotin, which is currently being tested in Phase 3 trials for progressive MS. AB Science is developing masitinib, a tyrosine kinase inhibitor, which is being tested in Phase 3 trials as a treatment for progressive MS and Novartis is developing siponimod, which is currently being tested in Phase 3 trials for secondary progressive MS.

Multiple Myeloma including Plasma Cell Leukemia

Several products are approved for the treatment of relapsed or refractory multiple myeloma, including Kyprolis (marketed by Amgen Inc.), Revlimid and Pomalyst (marketed by Celgene Corporation), Velcade (marketed by Millennium Pharmaceuticals, Inc.) and Darzalex (marketed by Janssen Research & Development, LLC). In addition, a number of companies and institutions are developing drug candidates for relapsed or refractory multiple myeloma including: AB Science SA, which is conducting a Phase 3 clinical trial for masitinib, a tyrosine kinase inhibitor; Array Biopharma Inc., which is conducting Phase 2 clinical trials for filanesib, a kinesin spindle protein inhibitor; Karyopharm Therapeutics, which is conducting Phase 2 clinical trials for Selinxor and Phase 1/2 trials for KPT-8602, both small-molecule nuclear transport inhibitors; Sanofi, which is conducting Phase 1/2 clinical trials for SAR-650984, an anti-CD38 monoclonal antibody; Altor Bioscience Corporation, which is conducting Phase 1/2 studies for ALT-803, an IL-15 super agonist; Celgene Corporation, which is conducting Phase 1/2 clinical trials for CC-220, a small molecule immunomodulatory drug; Morphosys AG, which is conducting Phase 1/2 clinical trials for MOR202, an anti-CD38 antibody; bluebird bio, Inc., which is conducting Phase1/2 clinical trials for bb2121, a CART candidate targeting BCMA; and Adaptimmune Therapeutics PLC, which is conducting Phase 1/2 clinical trials for a TCR candidate targeting NY-ESO-1 and Actinium Pharmaceuticals Inc., which is conducting Phase 1 clinical trials for 225Ac-Lintuzumab, a monoclonal antibody targeting CD33.

CMV Infection

There are numerous approved products and therapies for the treatment of CMV infection, and a number of companies and academic institutions that may license therapies to companies in the future are or may be developing new treatments for CMV infection. These therapies, as well as promotional efforts by competitors and clinical trial results of competitive products, could significantly diminish any ability to market and sell the CMV-CTL. Drug therapies approved or commonly used for CMV infection include antiviral compounds such as ganciclovir, valganciclovir, cidofovir or foscarnet.

Additionally, a number of companies and academic institutions are developing drug candidates for CMV infection and other CMV-associated diseases, including Shire Plc which initiated Phase 3 clinical trials of maribavir, a UL97 protein kinase inhibitor; Merck & Co. Inc., or Merck, which recently announced the Phase 3 clinical trials of letermovir, a CMV terminase inhibitor met the primary endpoint; and Vical Inc., which is conducting Phase 3 clinical trials in patients undergoing an allogeneic stem cell transplant evaluating ASP0113, a therapeutic bivalent plasma DNA CMV vaccine. In addition, Helocyte, Inc., is conducting two Phase 2 clinical trials for a CMV MVA-vaccine and a CMV peptide vaccine in patients undergoing an allogeneic hematopoietic stem cell transplant; Novartis AG, has completed Phase 1/2 clinical trials for CSJ-148, a monoclonal antibody combination therapy; Merck is conducting Phase 1 clinical trials for V160, a CMV DNA vaccine; VBI Vaccines Inc., is conducting Phase 1 clinical trials for VBI-1501A, an eVLP vaccine; Hookipa Biotech, is conducting Phase 1 clinical trials for HB101, a bivalent vaccine and ViraCyte, is conducting Phase 1 clinical trials for Viralym-C, a CMV-specific allogeneic cell therapy product.

License Agreements

MSK Option and License Agreement

In September 2014, we entered into an exclusive option agreement with MSK under which we acquired the right to exclusively license from MSK the worldwide rights to three clinical stage T-cell programs. The initial option period was for 12 months. In exchange for the exclusive option, we paid MSK $1.25 million in cash and issued 59,761 shares of our common stock to MSK. We and MSK also agreed to collaborate on further research to develop additional cellular therapies, which may include T-cell programs targeted against other antigens and/or CAR-T, and which we also would hold an option to license, if developed.

In June 2015, we exercised the option and entered into a license agreement with MSK. Under the terms of the license agreement, MSK granted us a worldwide, exclusive license under certain patent rights, know-how and a library of T-cells and cell lines, to research, develop, manufacture and commercialize T-cell products specific to CMV, EBV or WT1 that comprise or are based on or made using such licensed rights. MSK also agreed to transfer certain INDs related to the licensed products to us. We have agreed to use commercially reasonable efforts to commercialize the licensed products and, if commercialized, continue active marketing efforts for any commercialized licensed product through the term of the license agreement.

In connection with the option exercise and the execution of the license agreement, we made an upfront cash payment to MSK of $4.5 million. We are obligated to make additional milestone payments of up to $33.0 million with respect to the three licensed clinical stage T-cell programs based on achievement of specified development, regulatory and sales-related milestones. We are also required to make escalating mid to high single-digit royalty payments to MSK based on sales of any licensed products. In addition, under certain circumstances, we must make certain minimum annual royalty payments to MSK, which are creditable against earned royalties owed for the same annual period. We are also obligated to pay a low double-digit percentage of consideration we receive for sublicensing the licensed rights.

The license agreement expires for each licensed T-cell product on a licensed product-by-licensed product basis and a country-by-country basis, on the latest of: (i) expiration of the last licensed patent rights related to such licensed product in such country, (ii) expiration of any market exclusivity period granted by law with respect to such licensed product in such country, and (iii) a specified number of years after the first commercial sale of the licensed product in such country. Upon expiration of the license agreement, the licenses granted to us will become non-exclusive royalty-free, perpetual and irrevocable. MSK may terminate the license agreement if we materially breach the agreement and does not cure such breach within a specified period or if we experience certain insolvency events.

Intellectual Property

Patents

Our commercial success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, to operate without infringing on the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and non-U.S. patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position. Additionally, we expect to benefit from a variety of statutory frameworks in the United States, Europe and other countries that relate to the regulation of biosimilar molecules and orphan drug status. These statutory frameworks provide certain periods of regulatory exclusivity for qualifying molecules. See “Government Regulation.”

We seek composition-of-matter and/or method-of-treatment patents for each of our product candidates in key therapeutic areas.

Our in-licensed and proprietary patent estate, on a worldwide basis, is very large and consists of over 100 issued patents and 200 pending patent applications. These figures include in-licensed patents and patent applications to which we generally hold exclusive commercial rights, except in the case of three pending patent applications relating to our ATA230 product candidate for a particular indication in specific patient populations.

Individual patents extend for varying periods of time depending on the date of filing of the patent application, the priority date claimed and the legal term of patents as determined by the applicable law in the countries in which those patents are obtained.

Generally, patents issued from applications filed in the United States are effective for 20 years from the earliest non-provisional filing date. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of the FDA regulatory review period; however, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. In addition, patent term adjustments can extend term to account for certain delays by the U.S. Patent and Trademark Office, or USPTO, during prosecution before that office. The duration of non-U.S. patents varies in

accordance with provisions of applicable local law, but typically, a patent's life is 20 years from the earliest international filing date. Our licensed, issued U.S. patents are expected to expire on dates ranging from 2027 to 2029, and our licensed issued non-U.S. patents are expected to expire on dates ranging from 2023 to 2029, exclusive of possible patent term extensions. Our pending owned and licensed applications with respect to our product candidates, if issued, are expected to expire, as to applications filed in the United States, on dates ranging from 2023 to 2036, and, as to applications filed in jurisdictions outside the United States, on dates ranging from 2023 to 2036, exclusive of possible patent term extensions or adjustments. However, the actual protection afforded by a patent varies on a product- by-product basis, from country to country and depends upon many factors, including the type of patent, the scope of its coverage, the availability of extensions of patent term, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

National and international patent laws concerning protein-based biologics such as our products remain highly unsettled. No consistent policy regarding the patent-eligibility or the breadth of claims allowed in such patents has emerged to date among the United States, Europe and other countries. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries can diminish our ability to protect our inventions and enforce our intellectual property rights. Accordingly, we cannot predict the breadth or enforceability of claims that may be granted in our patents or in third-party patents. The biotechnology and pharmaceutical industries are characterized by extensive intellectual property litigation. Our ability to maintain and solidify our

proprietary position for our product candidates and technology will depend on our success in obtaining effective claims for any patent and enforcing those claims once a patent is granted. We do not know whether any of the patent applications that we may file or license from third parties will result in the issuance of any patents. The issued patents that we own or may receive in the future may be challenged, invalidated or circumvented, and the rights granted under any issued patents may not provide us with sufficient protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop and commercialize similar drugs or duplicate our technology, business model or strategy without infringing our patents. Because of the extensive time required for clinical development and regulatory review of any drug we may develop from our product candidates, it is possible that, before any of our drugs can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent. The patent positions for our product candidates are summarized below:

T-cell Technology Patent Portfolio

We hold exclusive rights to one international patent application, one Argentine patent application, and one Taiwanese patent application, all directed to ATA520 method of use claims. In addition, we have exclusively licensed MSK's rights under one US non-provisional patent application, one international patent application, and one Argentine patent application, all directed to ATA230 method of use claims for treatment of CMV retinitis in HIV-infected patients and SOT recipients, which are co-owned by MSK and another entity from which we have not licensed rights. We also hold exclusive rights to one international patent application, one Argentine patent application, and one Taiwanese patent application, all directed to methods of identifying and selecting allogeneic T-cell lines for therapeutic use. We also hold exclusive rights to one US provisional patent application directed to methods of generating antigen-specific T-cells using a CD34-negative cell population, methods of treating a human patient using antigen-specific T-cells generated by such methods, and methods of assessing antigen-specific T-cells for suitability for therapeutic use. We also hold exclusive rights to one U.S. provisional patent application directed to methods of generating antigen-specific T-cells using stem cell-like memory T-cells, antigen-specific T-cells generated by such methods, and methods of treating a human patient using such antigen-specific T-cells. The United States patent system permits the filing of provisional and non-provisional patent applications. A provisional patent application is not examined for patentability by the USPTO and automatically expires 12 months after its filing date. As a result, a provisional patent application cannot mature into a patent. Provisional patent applications are often used, among other things, to establish an early effective filing date for a later-filed non-provisional patent application. A non-provisional patent application is examined by the USPTO and can mature into a patent once the USPTO determines that the claimed invention meets the standards for patentability.

Trade Secrets

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our commercial partners, collaborators, employees and consultants and invention assignment agreements with our employees. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed by an employee. These agreements may be breached, and we may not have adequate remedies for any such breach or any unauthorized disclosure of our proprietary information. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Government Regulation

Overview of U.S. Government Regulation

The preclinical studies and clinical testing, manufacture, labeling, storage, recordkeeping, advertising, promotion, export, marketing and sales, among other things, of our product candidates are subject to extensive regulation by governmental authorities in the United States and other countries. In the United States, pharmaceutical products are regulated by the FDA under the Federal Food, Drug, and Cosmetic Act and other laws, including, in the case of biologics, the Public Health Service Act.

Our T-cell product candidates, including ATA129, are regulated by the FDA as biologics, reviewed by the Center for Biological Evaluation and Research, and will require the submission of BLAs and approval by the FDA prior to being marketed in the United States. For CTL trials conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documents must be submitted to, and the study registered with, the NIH Office of Biotechnology Activities, or the OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or the NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA. However, many companies and other institutions, not otherwise subject to the NIH Guidelines, voluntarily follow them. The NIH is responsible for convening the recombinant DNA advisory committee, or RAC, that

discusses protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a protocol. RAC proceedings and reports are posted to the OBA website and may be accessed by the public.

Failure to comply with FDA requirements, both before and after product approval, may subject us or our partners, contract manufacturers, and suppliers to administrative or judicial sanctions, including FDA refusal to approve applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, fines and/or criminal prosecution.

The steps required before a biologic may be approved for marketing of an indication in the United States generally include:

- completion of preclinical laboratory tests, animal studies and formulation studies conducted according to good laboratory practices, or GLP, and other applicable regulations;
- submission to the FDA of an investigational new drug, or IND, application, which must become effective before human clinical trials may commence;
- completion of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish that the biological product is "safe, pure and potent", which is analogous to the safety and efficacy approval standard for a chemical drug product for its intended use;
- submission to the FDA of a BLA;
- satisfactory completion of an FDA preapproval inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with applicable current good manufacturing practices, or cGMP and in the case of our T-cell product candidates, good tissue practices, or GTP; and
- FDA review of the BLA and issuance of a biologics license.

Before conducting studies in humans, laboratory evaluation of product chemistry, toxicity and formulation as well as animal studies to assess the potential safety and efficacy of the biologic candidate must be conducted. Preclinical toxicology studies in animals must be conducted in compliance with FDA regulations. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. In addition to including the results of the preclinical testing, the IND will also include a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the first phase or phases of the clinical trial lend themselves to an efficacy determination. The IND will automatically become effective 30 days after receipt by the FDA, unless the FDA within the 30-day time period places the IND on clinical hold because of safety concerns about the product candidate or the conduct of the trial described in the clinical protocol included in the IND. The IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed.

All clinical trials for new drugs and biologics must be conducted under the supervision of one or more qualified principal investigators in accordance with GCP. They must be conducted under protocols detailing the objectives of the applicable phase of the trial, dosing procedures, research subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND, and progress reports detailing the status of the clinical trials must be submitted to the FDA annually. Sponsors must also report to the FDA, within certain timeframes, serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator's brochure, or any findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product candidate. An institutional review board, or IRB, at each institution participating in the clinical trial must review and approve the protocol before a clinical trial commences at that institution, approve the information regarding the trial and the consent form that must be provided to each research subject or the subject's legal representative, and monitor the trial until completed.

Clinical trials are typically conducted in three sequential phases, but the phases may overlap and different trials may be initiated with the same product candidate within the same phase of development in similar or differing patient populations.

Phase 1 clinical studies may be conducted in a limited number of patients or healthy volunteers, as appropriate. The product candidate is initially tested for safety and, as appropriate, for absorption, metabolism, distribution, excretion, pharmacodynamics and pharmacokinetics.

Phase 2 usually involves trials in a larger, but still limited, patient population to evaluate preliminarily the efficacy of the product candidate for specific, targeted indications to determine dosage tolerance and optimal dosage and to identify possible short-term adverse effects and safety risks.

Phase 3 trials are undertaken to further evaluate clinical efficacy of a specific endpoint and to test further for safety within an expanded patient population at geographically dispersed clinical trial sites. Phase 1, Phase 2 or Phase 3 testing might not be completed successfully within any specific time period, if at all, with respect to any of our product candidates. Results from one trial are not necessarily predictive of results from later trials. Furthermore, the FDA or the sponsor may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

The results of the preclinical studies and clinical trials, together with other detailed information, including information on the manufacture and composition of the product, are submitted to the FDA as part of a BLA requesting approval to market the product candidate for a proposed indication. Under the Prescription Drug User Fee Act the fees payable to the FDA for reviewing a BLA, as well as annual fees for commercial manufacturing establishments and for approved products, can be substantial but are subject to certain limited deferrals, waivers and reductions that may be available. The fees typically increase each year. Each BLA submitted to the FDA for approval is reviewed for administrative completeness and reviewability within 60 days following receipt by the FDA of the application. If the BLA is found complete, the FDA will file the BLA, triggering a full review of the application. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission. The FDA's established goal is to review 90% of priority BLA applications within six months after the application is accepted for filing and 90% of standard BLA applications within 10 months of the acceptance date, whereupon a review decision is to be made. The FDA, however, may not approve a product candidate within these established goals and its review goals are subject to change from time to time. Further, the outcome of the review, even if generally favorable, may not be an actual approval but a "complete response letter" that describes additional work that must be done before the application can be approved. Before approving a BLA, the FDA may inspect the facility or facilities at which the product is manufactured and will not approve the product unless the facility complies with cGMP. The FDA may deny approval of a BLA if applicable statutory or regulatory criteria are not satisfied, or may require additional testing or information, which can extend the review process. FDA approval of any application may include many delays or never be granted. If a product is approved, the approval may impose limitations on the uses for which the product may be marketed, may require that warning statements be included in the product labeling, may require that additional studies be conducted following approval as a condition of the approval, and may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a Risk Evaluation and Mitigation Strategy, or REMS, or otherwise limit the scope of any approval. The FDA must approve a BLA supplement or a new BLA before a product may be marketed for other uses or before certain manufacturing or other changes may be made. Further post-marketing testing and surveillance to monitor the safety or efficacy of a product is required. Also, product approvals may be withdrawn if compliance with regulatory standards is not maintained or if safety or manufacturing problems occur following initial marketing. In addition, new government requirements may be established that could delay or prevent regulatory approval of our product candidates under development.

Under the Biologics Price Competition and Innovation Act of 2009, or the BPCIA, a statutory pathway has been created for licensure, or approval, of biological products that are biosimilar to, and possibly interchangeable with, earlier biological products licensed under the Public Health Service Act. Also under the BPCIA, innovator manufacturers of original reference biological products are granted 12 years of exclusivity before biosimilars can be approved for marketing in the United States. The approval of a biologic product biosimilar to one of our products could have a material adverse impact on our business as it may be significantly less costly to bring to market and may be priced significantly lower than our products.

Both before and after the FDA approves a product, the manufacturer and the holder or holders of the BLA for the product are subject to comprehensive regulatory oversight. For example, quality control and manufacturing procedures must conform, on an ongoing basis, to cGMP and GTP requirements, as applicable and the FDA

periodically inspects manufacturing facilities to assess compliance with these standards. Accordingly, manufacturers must continue to spend time, money and effort to maintain compliance.

Orphan Drug Act

The Orphan Drug Act provides incentives to manufacturers to develop and market drugs for rare diseases and conditions affecting fewer than 200,000 persons in the United States at the time of application for orphan drug designation. Orphan drug designation must be requested before submitting a BLA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the holder of the approval is entitled to a seven-year exclusive marketing period in the United States for that product except in very limited circumstances. For example, a drug that the FDA considers to be clinically superior to, or different from, another approved orphan drug, even though for the same indication, may also obtain approval in the United States during the seven-year exclusive marketing period. In addition, holders of exclusivity for orphan drugs are expected to assure the availability of sufficient quantities of their orphan drugs to meet the needs of patients. Failure to do so could result in the withdrawal of marketing exclusivity for the drug.

Legislation similar to the Orphan Drug Act has been enacted outside the United States, including in the EU. The orphan legislation in the EU is available for therapies addressing chronic debilitating or life-threatening conditions that affect five or fewer out of 10,000 persons or are financially not viable to develop. The market exclusivity period is for ten years, although that period can be reduced to six years if, at the end of the fifth year, available evidence establishes that the product is sufficiently profitable not to justify maintenance of market exclusivity. The market exclusivity may be extended to 12 years if the sponsor completes a pediatric investigation plan agreed upon with the relevant committee of the EMA.

Expedited Review and Approval

The FDA has various programs, including Fast Track, priority review and accelerated approval, which are intended to expedite or simplify the process for developing and reviewing promising drugs, or to provide for the approval of a drug on the basis of a surrogate endpoint. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will be shortened. Generally, drugs that are eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases or conditions and fill unmet medical needs. Priority review is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists an initial review within six months as compared to a standard review time of 10 months. Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review. Accelerated approval provides for an earlier approval for a new drug that is intended to treat a serious or life-threatening disease or condition and that fills an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a laboratory measurement or physical sign used as an indirect or substitute measurement representing a clinically meaningful outcome. As a condition of approval, the FDA may require that a sponsor of a product candidate receiving accelerated approval perform post-marketing clinical trials to confirm the clinically meaningful outcome as predicted by the surrogate marker trial.

In addition to the Fast Track, accelerated approval and priority review programs discussed above, breakthrough therapy designation may be pursued. A breakthrough therapy is defined as a drug 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 drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives: intensive guidance on an efficient drug development program; intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and rolling review.

Reimbursement

In both domestic and foreign markets, sales and reimbursement of any approved products will depend, in part, on the extent to which the costs of such products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services and imposing controls to manage costs. The containment of healthcare costs has become a priority of federal and state governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing

controls and measures, could further limit our net revenue and results. In addition, there is significant uncertainty regarding the reimbursement status of newly approved healthcare products. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our products. If third-party payors do not consider our products to be cost-effective compared to other therapies, the payors may not cover our products after approved as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

Within the United States, if we obtain appropriate approval in the future to market any of our current product candidates, we may seek approval and coverage for those products under Medicaid, Medicare and the Public Health Service, or PHS, pharmaceutical pricing program and also seek to sell the products to federal agencies.

Medicaid is a joint federal and state program that is administered by the states for low income and disabled beneficiaries. Under the Medicaid Drug Rebate Program, manufacturers are required to pay a rebate for each unit of product reimbursed by the state Medicaid programs. The amount of the rebate for each product is set by law and may be subject to an additional discount if certain pricing increases more than inflation.

Medicare is a federal program administered by the federal government that covers individuals age 65 and over as well as those with certain disabilities. Medicare Part D provides coverage to enrolled Medicare patients for self-administered drugs (i.e., drugs that do not need to be administered by a physician). Medicare Part D is administered by private prescription drug plans approved by the U.S. government and each drug plan establishes its own Medicare Part D formulary for prescription drug coverage and pricing, which the drug plan may modify from time-to-time.

Medicare Part B covers most injectable drugs given in an in-patient setting, and some drugs administered by a licensed medical provider in hospital outpatient departments and doctors' offices. Medicare Part B is administered by Medicare Administrative Contractors, which generally have the responsibility of making coverage decisions. Subject to certain payment adjustments and limits, Medicare generally pays for Part B covered drugs based on a percentage of manufacturer-reported average sales price.

Drug products are subject to discounted pricing when purchased by federal agencies via the Federal Supply Schedule, or FSS.

FFS participation is required for a drug product to be covered and paid for by certain federal agencies and for coverage under Medicaid, Medicare Part B and the PHS pharmaceutical pricing program. FSS pricing is negotiated periodically with the Department of Veterans Affairs. FSS pricing is intended to not exceed the price that a manufacturer charges its most-favored non-federal customer for its product. In addition, prices for drugs purchased by the Veterans Administration, Department of Defense (including drugs purchased by military personnel and dependents through the TRICARE retail pharmacy program), Coast Guard, and PHS are subject to a cap on pricing (known as the "federal ceiling price") and may be subject to an additional discount if pricing increases more than inflation.

To maintain coverage of drugs under the Medicaid Drug Rebate Program, manufacturers are required to extend discounts to certain purchasers under the PHS pharmaceutical pricing program. Purchasers eligible for discounts include hospitals that serve a disproportionate share of financially needy patients, community health clinics and other entities that receive health services grants from the PHS.

The United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act, or the Affordable Care Act, which included changes to the coverage and payment for drug products under government health care programs. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the Affordable Care Act. The Budget Resolution is not a law, but it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the Affordable Care Act. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the Affordable Care Act that are repealed. Outside the United States, ensuring adequate coverage and payment for our products will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts. Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly-approved health care products. Recent budgetary pressures in many European Union

countries are also causing governments to consider or implement various cost-containment measures, such as price freezes, increased price cuts and rebates. If budget pressures continue, governments may implement additional cost-containment measures. Cost-control initiatives could decrease the price we might establish for products that we may develop or sell, which would result in lower product revenues or royalties payable to us. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products.

Foreign Regulation

In addition to regulations in the United States, we expect to be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our product candidates. Whether or not we obtain FDA approval for a product candidate, we must obtain approval from the comparable regulatory authorities of foreign countries or economic areas, such as the European Union, before we may commence clinical trials or market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Certain countries outside of the United States have a process that requires the submission of a clinical trial application, or CTA, much like an IND prior to the commencement of human clinical trials. In Europe, for example, a CTA must be submitted to the

competent national health authority and to independent ethics committees in each country in which a company intends to conduct clinical trials. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed in that country. In all cases, the clinical trials must be conducted in accordance with GCP and other applicable regulatory requirements.

Under European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure is compulsory for medicinal products produced by biotechnology or those medicinal products containing new active substances for specific indications such as the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, viral diseases and designated orphan medicines, and optional for other medicines which are highly innovative. Under the centralized procedure, a marketing application is submitted to the European Medicines Agency, or EMA, where it will be evaluated by the Committee for Medicinal Products for Human Use and a favorable opinion typically results in the grant by the European Commission of a single marketing authorization that is valid for all European Union member states within 67 days of receipt of the opinion. The initial marketing authorization is valid for five years, but once renewed is usually valid for an unlimited period. As with accelerated approval in the U.S., conditional marketing authorization in the European Union is permitted based on incomplete clinical data for a limited number of medicinal products for human use, including products designated as orphan medicinal products under EU law, if (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) unmet medical needs will be fulfilled and (4) the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required. Specific obligations, including with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data, may be specified in the conditional marketing authorization. Conditional marketing authorizations are valid for one year and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions.

As in the United States, we may apply for designation of a product as an orphan drug for the treatment of a specific indication in the European Union before the application for marketing authorization is made. Orphan drugs in Europe enjoy economic and marketing benefits, including up to 11 years of exclusivity for the approved indication unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan designated product. The PRIority MEdicines, or PRIME, initiative was established by the EMA to help promote and foster the development of new medicines in the European Union that demonstrate potential for a major therapeutic advantage in areas of unmet medical need. Benefits from the PRIME designation include early confirmation of potential for accelerated assessment, early dialogue and increased interaction with relevant regulatory committees to discuss development options, scientific advice at key development milestones, and proactive regulatory support from the EMA.

Additional Regulation

We are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential federal, state or local regulations. These and other laws govern our use, handling and disposal of various biological and chemical substances used in, and waste generated by, our operations. Our research and development involves the controlled use of hazardous materials, chemicals and viruses. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by state and federal regulations, the risk of accidental contamination or injury from these materials cannot be completely eliminated. In the event of such an accident, we could be held liable for any damages that result and any such liability could exceed our resources.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biological products, government control and other changes to the healthcare system of the United

States. It is uncertain what legislative proposals will be adopted or what actions federal, state or private payers for medical goods and services may take in response to any healthcare reform proposals or legislation. We cannot predict the effect medical or healthcare reforms may have on our business, and no assurance can be given that any such reforms will not have a material adverse effect.

Manufacturing

Our initial strategy is to outsource the manufacturing of drug substance and drug product for our preclinical studies and clinical trials. We also outsource fill-finish, packaging, labeling, storage, shipping and distribution. In selecting contract manufacturing organizations, or CMOs, to manufacture our product candidates, we generally strive to select the CMO based on the particular technical needs of the product candidate. In addition, we aim to work with CMOs that possess the requisite scale, expertise and experience to support clinical as well as commercial product manufacturing. We are currently in the final stages of transferring the manufacturing processes from MSK to our CMO. The transfer of manufacturing processes to our CMO includes modifications to the processes, improvements in the manufacturing process as well as product testing. Moreover, we are currently developing commercial-s