AGENUS INC
Form 10-K
March 07, 2014
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

þ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2013

or

o 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: 000-29089

Agenus Inc.

(exact name of registrant as specified in its charter)

Delaware	06-1562417
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

3 Forbes Road, Lexington, Massachusetts 02421

(Address of principal executive offices, including zip code)

Registrant's telephone number, including area code:

(781) 674-4400

Securities registered pursuant to Section 12(b) of the Act:

Common Stock, $.01 Par Value	The NASDAQ Capital Market
(Title of each class)	(Name of each exchange on which registered)

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 o No þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No þ

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 þ No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulations 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). þ

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) 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. þ

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 definitions of "large accelerated filer," "accelerated filer," and "smaller reporting

company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer o Accelerated filer þ Non-accelerated filer o Smaller reporting company o (Do not check if a smaller reporting company)

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No þ

The aggregate market value of voting stock held by non-affiliates of the registrant as of June 30, 2013 was: $87.1 million. There were 62,173,299 shares of the registrant's Common Stock outstanding as of February 24, 2014.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement for the registrant's 2014 Annual Meeting of Stockholders, which definitive proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2013, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K and other written and oral statements the Company makes from time to time contain certain “forward-looking” statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. You can identify these forward-looking statements by the fact they use words such as “could,” “expect,” “anticipate,” “estimate,” “target,” “may,” “project,” “guidance,” “intend,” “plan,” “b “potential,” “opportunity,” “future” and other words and terms of similar meaning and expression in connection with any discussion of future operating or financial performance. You can also identify forward-looking statements by the fact that they do not relate strictly to historical or current facts. Such forward-looking statements are based on the Company's current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes to differ materially from current expectations. These statements are likely to relate to, among other things, our business strategy, our research and development, our product development efforts, our ability to commercialize our product candidates, the activities of our licensees, our prospects for initiating partnerships or collaborations, our ability to successfully integrate our recent acquisition of our wholly-owned subsidiary, 4-Antibody AG, the timing of the introduction of products, the effect of new accounting pronouncements, uncertainty regarding our future operating results and our profitability, anticipated sources of funds as well as our plans, objectives, expectations, and intentions.

Although we believe we have been prudent in our plans and assumptions, no assurance can be given that any goal or plan set forth in forward-looking statements can be achieved and readers are cautioned not to place undue reliance on such statements, which speak only as of the date made. We undertake no obligation to release publicly any revisions to forward-looking statements as a result of new information, future events or otherwise.

We believe that the risks identified in this Annual Report on Form 10-K, including, without limitation, the risks set forth in Part I-item 1A. "Risk Factors," could cause actual results to differ materially from any forward-looking statement contained in this Annual Report on Form 10-K. We encourage you to read those descriptions carefully. We caution investors not to place significant reliance on forward-looking statements contained in this document; such statements need to be evaluated in light of all the information contained in this document. Furthermore, the statements speak only as of the date of this document, and we undertake no obligation to update or revise these statements.

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PART I

Item 1. Business

Our Business

Agenus Inc. (including its subsidiaries, also referred to as “Agenus,” the “Company,” “we,” “us,” and “our”) is a biopharmaceutical company developing a portfolio of immuno-oncology candidates, including checkpoint modulators, heat shock protein vaccines and adjuvants. We are focused on immunotherapeutic products based on our core platform technologies with multiple product candidates advancing through the clinic, including several product candidates that have advanced into late-stage clinical trials through corporate partners. We assess the development, commercialization and/or partnering strategies with respect to each of our internal product candidates periodically based on several factors, including clinical trial results, competitive positioning, and funding requirements and resources.

Our core technology portfolio consists of our Checkpoint Antibody Program, our Heat Shock Protein ("HSP") Platform (based on our HSP technologies), and our Saponin Platform (based on our saponin adjuvant technologies).

Our Checkpoint Antibody Program became part of our portfolio with the recent acquisition of 4-Antibody AG, a private European-based biopharmaceutical company ("4-AB"). This acquisition (the "Acquisition") provided us with a technology platform for the rapid discovery and optimization of fully-human antibodies against a wide array of molecular targets. This platform has been applied to six immune checkpoint targets seeking therapeutic antibody check point modulators ("CPMs") to regulate immune response to cancers and other diseases. Our proprietary antibody discovery engine, Retrocyte Display®, is designed to generate high quality therapeutic antibody drug candidates quickly using a high-throughput approach incorporating human antibody libraries expressed in mammalian B-lineage cells. We currently have pre-clinical checkpoint antibody programs targeting GITR, OX40, CTLA-4, PD-1, TIM-3 and LAG-3 from 4-AB’s technologies. We have selected two GITR agonists and one CTLA-4 antagonist to advance into pre-clinical development. We are targeting to identify development candidates for the other four checkpoint programs during 2014, and to be in a position to file investigational new drug applications on four candidates within the next two years.

Within our HSP Platform we are developing our Prophage Series cancer vaccines. Our Prophage Series cancer vaccines are autologous therapies derived from cells extracted from the patient’s tumor. As a result, Prophage Series vaccines contain a precise antigenic ‘fingerprint’ of a patient’s particular cancer and are designed to reprogram the body’s immune system to target only cells bearing this fingerprint, reducing the risk that powerful anti-cancer agents will target healthy tissue and cause debilitating side effects often associated with chemotherapy and radiation therapy. We believe that in contrast to many other autologous vaccines that are based on cellular preparations, the Prophage Series is based on a stable protein preparation produced via a relatively simple manufacturing process. Our Prophage Series G vaccines are currently being studied in two different settings of glioblastoma multiforme, or GBM: newly diagnosed and recurrent disease.

Also within our HSP Platform, is HerpV, a recombinant, synthetic vaccine containing multiple antigens derived from the herpes simplex 2 virus. HerpV is currently in a Phase 2 clinical trial, and we believe it is one of the most clinically-advanced therapeutic vaccines for the treatment of genital herpes in clinical development. Combining our heat shock protein technology and our QS-21 Stimulon adjuvant, HerpV represents a potential new approach to the treatment of genital herpes. Rather than attempting to suppress the virus, which is what antivirals do, HerpV has the potential to enable the individual’s own immune system to stop the virus from causing and transmitting disease without chronic treatment. In November 2013, we released top line results from a Phase 2, randomized, double blind, multicenter clinical trial of HerpV in HSV-2 positive genital herpes patients, which showed that the trial met its primary endpoint. We anticipate reporting additional study results assessing the efficacy of a booster injection of HerpV during the first half of 2014.

Within our Saponin Platform is QS-21 Stimulon® adjuvant, or QS-21 Stimulon. QS-21 Stimulon is a saponin extracted from the bark of the Quillaja saponaria tree, also known as the Soapbark, an evergreen tree native to warm temperate central Chile. An adjuvant, such as QS-21 Stimulon, is a substance added to a vaccine or other immunotherapy that is intended to enhance immune response. QS-21 Stimulon has become a key component in the

development of investigational preventive vaccine formulations across a wide variety of infectious diseases, including several investigational therapeutic vaccines intended to treat cancer and degenerative disorders. QS-21 Stimulon has been widely studied and approximately 50,000 patients have received vaccines containing the adjuvant. The key licensees of QS-21 Stimulon are GlaxoSmithKline ("GSK") and JANSSEN Alzheimer Immunotherapy ("JANSSEN AI"). QS-21 Stimulon is currently being studied in 21 vaccine indications, which include GSK's Phase 3 vaccine programs for RTS,S for malaria, MAGE-A3 cancer immunotherapeutic for non-small cell lung cancer and melanoma and HZ/su for shingles. In addition, JANSSEN AI’s QS-21 Stimulon adjuvant-containing vaccine candidate is in Phase 2 trials for the treatment of Alzheimer’s disease. If any of our partners’ products containing QS-21 Stimulon successfully completes clinical development and receives approval for commercial sale, we are generally entitled to receive royalties for 10 years after commercial launch, with some exceptions.

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Our business activities have included product research and development, intellectual property prosecution, manufacturing, regulatory and clinical affairs, corporate finance and development activities, and support of our collaborations. Our product candidates require clinical trials and approvals from regulatory agencies, as well as acceptance in the marketplace. Part of our strategy is to develop and commercialize some of our product candidates by continuing our existing arrangements with academic and corporate collaborators and licensees and by entering into new collaborations.

Our common stock is currently listed on The Nasdaq Capital Market (“Nasdaq”) under the symbol “AGEN”.

Our Products and Technologies Under Development

Research and development expenses for the years ended December 31, 2013, 2012, and 2011, were $13.0 million, $10.6 million, and $11.0 million, respectively. Set forth below are the details of our research and development programs.

The Checkpoint Antibody Program

Effective February 2014, we acquired 4-AB, a private European-based biopharmaceutical company, providing us with a technology platform for the rapid discovery and optimization of fully-human antibodies against a wide array of molecular targets. We are applying this antibody platform to discover and optimize checkpoint modulators ("CPMs") that regulate immune response to cancers and other diseases. Our proprietary discovery engine within the platform, Retrocyte Display®, is designed to generate high quality therapeutic antibody drug candidates quickly using a high-throughput approach incorporating human antibody libraries expressed in mammalian B-lineage cells. We currently have pre-clinical checkpoint antibody programs targeting GITR, OX40, CTLA-4, PD-1, TIM-3 and LAG-3 from 4-AB’s technologies, and have selected two GITR agonists and one CTLA-4 antagonist to advance into pre-clinical development. We are targeting to identify development candidates for the other four checkpoint programs during 2014, and to be in a position to file investigational new drug applications on four candidates within the next two years.

Checkpoints within the body are endogenous processes that regulate immune response. These molecules serve as checks employed by the body to prevent runaway immune responses which can be debilitating, or even deadly. Unfortunately, these necessary mechanisms of control can hinder the anti-cancer immune response. They can be sabotaged by cancer cells as a defense against immune attack. Thus, while checkpoints usually function to appropriately regulate immune responses, cancers can “co-opt” check point processes to evade destruction by the immune system. CPMs are potential medicines (usually anitbodies) that bind to checkpoint proteins and either enhance or block specific checkpoint processes. CPMs, one of the most exciting new approaches to cancer therapy, are designed to make cancers more susceptible to destruction by the body’s immune responses. CPMs include compounds like Bristol Meyer Squibb’s Yervoy and Merck’s PD-1 antagonist.

It took 4-AB over seven years to build the Retrocyte Display® Antibody Platform, which we believe is one of the best ways to generate fully human monoclonals. 4-AB has institutional and corporate collaborations, including with the Ludwig Cancer Research , and Recepta Biopharma SA, and we are in active discussions for additional future collaborations. In collaboration with our partners, we will explore ways to advance the emerging portfolio of CPMs as single agents and in optimized combinations, including potential combinations with Prophage and other agents.

The Heat Shock Protein Platform

Heat shock proteins (HSP) are a group of proteins present in all cells. Their expression is increased when cells are exposed to elevated temperatures or other stresses. The immunological function of HSPs was first discovered when it was shown that HSPs purified from cancer cells produced immunity to cancer whereas HSPs purified from normal tissue did not. This discovery led to the understanding that HSPs actually chaperone (bind to and carry) the “peptide fingerprint,” which includes the antigenic peptides of the cells from which they are purified. It was further identified that immunization with HSPs work by interacting with antigen presenting cells that then express the HSP-associated antigenic peptides to cause a CD4+ and CD8+ T-cell immune response that in turn targets the cancer cells.

Collectively, these many years of research taught us the importance of targeting cancer with high specificity. In order to provide effective immunization, HSPs must be isolated from cancer cells. Since HSPs are expressed in all tumor cells, the approach of immunizing with HSPs is broadly applicable to a variety of cancer types. Agenus pioneered the use of the heat shock protein, gp96, purified from the patients' own tumor tissue, as a way to make a patient-specific vaccine.

Because cancer is a highly variable disease from one patient to another, due to rapid mutation of cancer cells, we believe that a patient-specific vaccination approach is required to generate a more robust and targeted immune response against the disease. For certain diseases, such as genital herpes, we do not believe that a personalized vaccination approach is required,

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since the pathogen does not vary as greatly from patient to patient as do cancer cells. For example, in our HerpV product candidate for the treatment of genital herpes, we complex, or bind, several defined antigenic herpes peptides to an HSP (Hsc70) that we genetically engineer, creating an HSPPC. This HSPPC, when injected into the skin, is designed to elicit a cellular immune response to the synthetic peptides carried by the HSP.

The Prophage Series Vaccines

Our Prophage Series cancer vaccines are autologous therapies derived from cells extracted from the patient's tumor. As a result, Prophage Series vaccines contain a precise antigenic 'fingerprint' of a patient's particular cancer and are designed to reprogram the body's immune system to target only cells bearing this fingerprint, reducing the risk that powerful anti-cancer agents will target healthy tissue and cause debilitating side effects often associated with chemotherapy and radiation therapy. We believe that in contrast to many other autologous vaccines that are based on cellular preparations, the Prophage Series is based on a stable protein preparation produced via a relatively simple manufacturing process. Our Prophage Series G vaccines are currently being studied in two different settings of glioblastoma multiforme, or GBM: newly diagnosed and recurrent disease.

Each Prophage Series vaccine is manufactured using a patient's own tumor which is removed through surgery. After the patient undergoes surgery to remove cancerous tumor tissue, the tumor is shipped frozen in a specially designed kit provided by the company to our Lexington, Massachusetts facility. Each Prophage Series vaccine is produced in about 10 hours, after which it undergoes extensive quality testing which takes about 2 weeks. The turnaround time from the date of surgery is about 3 to 4 weeks which generally fits well with the patient's recovery time from surgery. Once we release the vaccine, it is shipped frozen overnight to the hospital pharmacy or clinician. Prophage Series vaccines are given as a simple intradermal injection. In this effort, Agenus has established, within a single facility, well-defined, cost efficient manufacturing under Good Manufacturing Practices (GMPs) that have supported the processing of over 1,000 tumor samples from across the globe.

Since the first patient was enrolled in a clinical trial studying a Prophage Series vaccine in 1997, nearly 900 cancer patients have been treated with our vaccine in multiple cancers and across numerous clinical trials. The results of these trials have been published and/or presented at major conferences. These results indicate consistent clinical and/or immunological activity across many types of cancer.

Because our Prophage Series vaccines are derived from the patient's own tumor, they are unlike the majority of approved therapies and as such, they are experiencing a long development process and incurring high development costs, either of which could delay or prevent our commercialization efforts. For additional information regarding regulatory risks and uncertainties, please read the risks identified in Part 1-Item 1A. "Risk Factors" of this Annual Report on Form 10-K.

The Prophage Series G-100 and G-200 vaccines are currently being studied in two different settings of glioblastoma multiforme; patients who have been newly diagnosed as well as those with recurrent disease. Glioblastoma is the most common primary malignant brain tumor and accounts for the majority of diagnoses of malignant cancers of the brain. In addition, our Prophage Series vaccines are currently being studied in stage III and IV metastatic melanoma.

Glioblastoma Multiforme

GBM is a cancer affecting the central nervous system arising from glial cells which become cancerous. GBM, the most common primary malignant brain tumor, is currently a rapidly fatal disease. The American Cancer Society estimates that 23,380 new cases of the brain and other nervous system cancers will be diagnosed during 2014 in the U.S., and that 14,320 people will die from these tumors during 2014 in the U.S.

We have investigator-sponsored Phase 2 trials fully enrolled in the United States testing the Prophage Series vaccine candidates G-100 (HSPPC-96) and G-200 in newly diagnosed and recurrent GBM, respectively. In June 2011, results from the Phase 2 trial in recurrent GBM were presented at the 47th Annual Meeting of the American Society of Clinical Oncology (ASCO) showing, among other things, that measures of immune response post vaccination with G-200 demonstrated a significant tumor-specific CD8+ T-cell response as well as innate immune responses as marked by a significant increase in the levels of circulating NK cells. Subsequently, in December 2013, these Phase 2 results were published demonstrating that more than 90% of the patients treated with Prophage Series G-200 were alive at six months after surgery and 30% were alive at twelve months. Additionally, the median overall survival was approximately eleven months. This compares favorably to historical control data with expected median survival for

recurrent GBM patients of three to nine months. The primary objective of this multi-center, single arm Phase 2 trial was to assess the survival rate at six months. The data was published in a manuscript in Neuro-Oncology, the official journal of the Society of Neuro-Oncology.

In September 2013, we announced the results of a recent analysis from a multiple-center, Phase 2 clinical trial in 46 patients with newly diagnosed GBM treated with Prophage Series G-100 (HSPPC-96) in combination with the current standard of care (radiation and temozolomide) which showed that, to date, patients treated with HSPPC-96 had a median progression

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free survival (PFS) of 17.8 months, with 63% of the patients progression free at 12 months and 20% of patients progression free at 24 months. These results indicate improvement when compared to patients treated with the standard of care, for which median PFS is 6.9 months. Median overall survival (OS), the primary endpoint of the trial, is 23.3 months to date and remains durable in patients treated with HSPPC-96. In this study, the 12 month survival rate is 85%, with 50% of patients still alive and being followed, with many surviving beyond the 24 month study period. For the standard of care alone, the median OS rate is 14.6 months to date.

In addition to the Phase 2 trial in patients with newly diagnosed GBM, the Alliance for Clinical Trials in Oncology, a cooperative group of the NCI, is supporting a randomized Phase 2 clinical trial of the HSPPC-96 vaccine in combination with bevacizumab (Avastin®) in approximately 222 patients with surgically resectable, recurrent GBM. Patients have already been randomized into this trial and active recruitment is underway at multiple centers in the United States. We believe that this trial is the largest vaccine trial ever funded by the NCI in brain tumors and the largest vaccine study ever conducted in combination with Avastin. The study is designed to compare efficacy of the HSPPC-96 vaccine administered with bevacizumab either concomitantly or at progression, versus treatment with bevacizumab alone. The primary endpoint is overall survival. This study design is supported in part by previous research indicating a potential synergistic effect between the mechanisms of action behind both HSPPC-96 and bevacizumab.

Melanoma

In January 2014, we announced the initiation of an investigator-sponsored, randomized Phase 2 clinical trial of the Prophage vaccine in combination with ipilimumab in patients with stage III and IV metastatic melanoma. This study, which is an investigator-sponsored trial at the University of Texas Health Science Center in Houston, is designed to evaluate the safety, feasibility and immunogenicity of the combination of the Prophage vaccine and ipilimumab with or without low-dose cyclophosphamide in approximately 25 patients. This study represents the first time that one of our Prophage Series cancer vaccines has been evaluated in the clinic in combination with a checkpoint inhibitor antibody.

Renal Cell Carcinoma

In April 2008, the Russian Ministry of Public Health issued a registration certificate for the use of Oncophage for the treatment of kidney cancer patients at intermediate risk for disease recurrence. Because, among other things, we have limited resources and minimal sales and marketing experience, commercialization of Oncophage has been slow, and only modest sales of Oncophage in Russia have occurred. The Russian registration was our first product approval from a regulatory authority, and the first approval of a patient-specific therapeutic cancer vaccine in a major market.

In December 2011, we out-licensed this program to NewVac LLC (a subsidiary of ChemRar Ventures LLC, "NewVac"), a company focused on the development of innovative technology for cancer immunotherapy.

In December 2011, we granted NewVac an exclusive license to manufacture, market and sell Oncophage as well as pursue a development program in the Russian Federation and certain other CIS countries (“NewVac Agreement”). The NewVac Agreement may be terminated by either party upon a material breach if the breach is not cured within the time specified in the agreement. The NewVac Agreement may also be terminated by us if certain milestones are not achieved and by NewVac without cause. The NewVac Agreement has an initial term of three years and may be extended under certain terms for a period ending the later of December 2021, or the expiration of the last valid claim of the licensed patent rights, as defined in the NewVac Agreement. Upon termination of the NewVac Agreement, all activity under the agreement immediately ceases. During the term of the NewVac Agreement we are entitled to receive modest milestone payments in addition to payments for supply of Oncophage and/or royalties in the low double-digits on net sales of Oncophage.

Manufacturing

Commercial and clinical supplies of Oncophage and other vaccine candidates deriving from the Prophage Series are manufactured in our Lexington, Massachusetts facility. We estimate that this facility could support the production of up to 4,000 batches per year. On average, it takes eight to 10 hours of direct processing time to manufacture a patient batch of vaccine.

After manufacturing, Prophage Series vaccines are tested and released by our quality systems staff. The quality control organization performs a series of release assays designed to ensure that the product meets all applicable

specifications. Our quality assurance staff also reviews manufacturing and quality control records prior to batch release in an effort to assure conformance with current Good Manufacturing Practices, also known as cGMP, as mandated by the FDA and foreign regulatory agencies.

Our manufacturing staff is rigorously trained and routinely evaluated for conformance to manufacturing procedures and quality standards. This oversight is intended to ensure compliance with FDA and foreign regulations and to provide consistent

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vaccine output. Our quality control and quality assurance staff is similarly trained and evaluated as part of our effort to ensure consistency in the testing and release of the product, as well as consistency in materials, equipment, and facilities.

HerpV

HerpV, formerly known as AG-707 plus QS-21 Stimulon, is an investigational therapeutic vaccine candidate directed at the virus that causes genital herpes (herpes simplex virus-2, or HSV-2) and is the first potential recombinant (off-the-shelf) application of our HSP technology. HerpV includes our proprietary QS-21 Stimulon adjuvant. HerpV is a polyvalent “off-the-shelf” vaccine consisting of recombinant human heat shock protein-70 associated with a total of thirty-two distinct antigens representative of genital herpes virus (HSV-2) genome. This means that it may be applicable to a broader patient population and may have potential in managing outbreaks and disease transmission. We consider HerpV to be part of a platform technology, since with the integration of heat shock proteins with antigenic peptides, we could potentially create therapeutic vaccines for various infectious diseases.

Genital herpes is one of the most common ulcerating diseases of the genital mucosa. The World Health Organization currently estimates that in the U.S., approximately 40 to 60 million people are HSV-2-infected, with an incidence of 1-2 million infections and 600,000 to 800,000 clinical cases per year. Prevalence in the 30-40 year-old population is about 30%. This disease often results in recurrent painful sores in the genital area. Current therapies involve taking a daily medication that only partly suppresses the virus.

The published results of a Phase 1 study show that HerpV administered with our QS-21 Stimulon adjuvant was associated with a significant induction of both CD4+ and CD8+ cellular immune responses. We believe that this is the first instance of a herpes vaccine candidate eliciting both CD4 and CD8 cellular immunity in human subjects. In November 2013, we released top line results from a Phase 2, randomized, double blind, multicenter clinical trial of HerpV in HSV-2 positive genital herpes patients. The Phase 2 trial met its primary endpoint. The primary analysis, which looked at viral shedding after the initial three injections, shows that patients who received HerpV had a statistically significant reduction in viral shedding. This study was designed to determine the biological efficacy of HerpV on genital viral shedding after three injections of the vaccine. As of the date of this report, all subjects in the study have received a booster injection of HerpV that was given six months after the first vaccination followed by determination of genital viral shedding for an additional 45-day period. We anticipate reporting additional study results after booster injection during the first half of 2014.

The Saponin Platform & QS-21 Stimulon

QS-21 Stimulon, from our Saponin Platform, is an adjuvant, or a substance added to a vaccine or other immunotherapy that is intended to enhance immune response. It is a saponin extracted from the bark of the Quillaja saponaria tree, also known as the Soapbark, an evergreen tree native to warm temperate central Chile. QS-21 Stimulon has become a key component in the development of investigational preventive vaccine formulations across a wide variety of infectious diseases, including several investigational therapeutic vaccines intended to treat cancer and degenerative disorders. There are approximately 21 vaccines containing QS-21 Stimulon in clinical development by us and our licensees, including a total of four in Phase 3 testing by GSK for malaria, melanoma, non-small cell lung cancer and shingles, and one in Phase 2 trials with JANSSEN AI for the treatment of Alzheimer's disease. Assuming regulatory approval, the first products containing QS-21 Stimulon are anticipated to be launched in 2015. If any of our partners’ products containing QS-21 Stimulon successfully completes clinical development and receives approval for commercial sale, we are generally entitled to receive royalties for 10 years after commercial launch, with some exceptions. The pipeline of product candidates containing QS-21 Stimulon is very diverse, encompassing prophylactic as well as therapeutic vaccines for infectious diseases, multiple cancer types, and Alzheimer's disease. We do not incur clinical development costs for the product candidates of our licensees. In addition to the programs of our licensees, our internally-developed vaccine candidate HerpV, which is in a Phase 2 study for the treatment of genital herpes in Herpes Simplex Virus 2 (HSV-2) positive subjects, contains QS-21 Stimulon. See "Heat Shock Protein Technology - HerpV" above.

QS-21 Stimulon has the ability to stimulate antibody, or humoral, immune response, and has also been shown to activate cellular immunity. A natural product, QS-21 Stimulon is a triterpene glycoside, or saponin, purified from the bark of a South American tree called Quillaja saponaria. It is sufficiently characterized with a known molecular

structure, thus distinguishing it from other adjuvant candidates, which are typically emulsions, polymers, or biologicals. QS-21 Stimulon has been tested in approximately 185 clinical trials involving, in the aggregate, over 50,000 subjects in a variety of cancer indications, infectious diseases, and other disorders. These studies have been carried out by academic institutions and pharmaceutical companies in the United States and internationally. A number of these studies have shown QS-21 Stimulon to be significantly more effective in stimulating antibody responses than aluminum hydroxide or aluminum phosphate, the adjuvants most commonly used in approved vaccines in the United States today.

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Partnered QS-21 Stimulon Programs

A number of pharmaceutical and biotechnology companies have licensed QS-21 Stimulon from us for use in vaccines to treat a wide variety of human diseases. Companies with QS-21 Stimulon programs include GSK and JANSSEN AI. In return for rights to use QS-21 Stimulon, these companies have generally agreed to pay us license fees, manufacturing payments, milestone payments, and royalties on product sales for at least 10 years after commercial launch, with some exceptions. In addition to our corporate licensing arrangements, we have developed a number of academic collaborations to test new vaccine concepts and products containing QS-21 Stimulon.

GSK. In July 2006, we entered into a license agreement and a supply agreement with GSK for the use of QS-21 Stimulon (the "GSK License Agreement" and the "GSK Supply Agreement", respectively). In January 2009, we entered into an Amended and Restated Manufacturing Technology Transfer and Supply Agreement (the “Amended GSK Supply Agreement”) under which GSK has the right to manufacture all of its requirements of commercial grade QS-21 Stimulon. GSK is obligated to supply us (or our affiliates, licensees, or customers) certain quantities of commercial grade QS-21 Stimulon for a stated period of time. In March 2012 we entered into a First Right to Negotiate and Amendment Agreement amending the GSK License Agreement and the Amended GSK Supply Agreement to clarify and include additional rights for the use of QS-21 Stimulon (the "GSK First Right to Negotiate Agreement"). In addition, we granted GSK the first right to negotiate for the purchase of the Company or certain of our assets. The first right to negotiate will expire after five years. As consideration for entering into the GSK First Right to Negotiate Agreement, GSK paid us an upfront, non-refundable payment of $9.0 million, $2.5 million of which is creditable toward future royalty payments. We refer to the GSK License Agreement, the Amended GSK Supply Agreement and the GSK First Right to Negotiate Agreement, from time to time as the "GSK Agreements". As of December 31, 2013, we have received $21.3 million of a potential $24.3 million in upfront and milestone payments related to the GSK Agreements. We are generally entitled to receive low single-digit royalties on net sales for a period of 7-10 years after the first commercial sale of a resulting GSK product with some exceptions. The GSK License and Amended GSK Supply Agreements may be terminated by either party upon a material breach if the breach is not cured within the time specified in the respective agreement. The termination or expiration of the GSK License Agreement does not relieve either party from any obligation which accrued prior to the termination or expiration. Among other provisions, the milestone payment obligations survive termination or expiration of the GSK Agreements for any reason, and the license rights granted to GSK survive expiration of the GSK License Agreement. The license rights and payment obligations of GSK under the Amended GSK Supply Agreement survive termination or expiration, except that GSK's license rights and future royalty obligations do not survive if we terminate due to GSK's material breach unless we elect otherwise.

We believe QS-21 Stimulon is a key component included in several of GSK's proprietary adjuvant systems and a number of GSK's vaccine candidates currently in development are formulated using adjuvant systems containing QS-21 Stimulon. GSK has ongoing Phase 3 studies evaluating its investigational MAGE-A3 Antigen-Specific Cancer Immunotherapeutic containing QS-21 Stimulon in melanoma and non-small cell lung cancer. We anticipate data from the Phase 3 trial in non-small cell lung cancer will be reported during the first half of 2014. GSK’s DERMA study, a Phase 3 randomized, blinded, placebo-controlled MAGE-A3 trial did not meet its first co-primary endpoint in melanoma patients. In an independent analysis, the study did not significantly extend the disease-free survival period when compared to placebo in the overall MAGE-A3 positive trial population. In line with the Independent Data Monitoring Committee’s unanimous recommendation, GSK will continue the study until the second co-primary endpoint is assessed. This co-primary endpoint is based on predefined criterion that was agreed upon by regulatory authorities. This analysis, which is based on gene signature, is designed to prospectively identify patients who may have the capability to be more immunologically responsive and therefore can potentially benefit from treatment. If further analysis shows that the predefined gene signature subset data are successful, there is the potential that a regulatory filing could be considered. GSK anticipates that these data will be available in 2015. In October 2011, The New England Journal of Medicine published results of a Phase 3 trial of GSK Biologicals' RTS,S malaria vaccine candidate containing QS-21 Stimulon. Results of the study, the largest malaria vaccine efficacy and safety trial ever conducted, demonstrate that RTS,S provided young African children with significant protection against clinical and severe malaria-reducing risk by 56 percent and 47 percent, respectively, for the 12-month period following

vaccination. In November 2012, The New England Journal of Medicine published results of a second Phase 3 trial for RTS,S. In this study, infants (aged 6-12 weeks at first vaccination) receiving the RTS,S vaccine candidate experienced one-third fewer episodes of both clinical and severe malaria and experienced similar reactions to the injection when compared to those who received the control meningococcal C conjugate vaccine. Both co-primary endpoints in the large ongoing efficacy trial were met. In November 2013, additional Phase 3 data was reported that shows that RTS,S helps protect young children and infants from clinical malaria up to 18 months post vaccination. GSK plans to submit a regulatory application in Africa in 2014.

Elan/JANSSEN Alzheimer's Immunotherapy. Elan Pharmaceuticals, Inc. and/or its affiliates (“Elan”) had a commercial license for the use of QS-21 Stimulon in the research and commercialization of Elan's Alzheimer's disease vaccine candidate that contains QS-21 Stimulon (“JANSSEN Product”). Effective September 14, 2009, we entered into an Amended and Restated License Agreement with Elan, which was assigned by Elan to JANSSEN AI on September 17, 2009 (the “JANSSEN AI

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License Agreement"). Under the terms of the JANSSEN AI License Agreement, JANSSEN AI has the right to develop, make, have made, use, sell, offer for sale, import, and have sold, the JANSSEN Product. In addition, pursuant to the terms of the JANSSEN AI License Agreement, JANSSEN AI has the right to manufacture all of its requirements of QS-21 Stimulon for use in the JANSSEN Product. We have no further supply obligations to JANSSEN AI. If all benchmarks are met under the JANSSEN AI License Agreement, we could receive up to $11.5 million in future milestone payments; $1.5 million has been received as of December 31, 2013. Furthermore, under the terms of the JANSSEN AI License Agreement, we are entitled to receive mid-single-digit royalties on net sales of the JANSSEN Product for a period of at least 10 years after the first commercial sale of such product, if any. Expiration or termination of the JANSSEN AI License Agreement is without prejudice to any rights that accrued to the benefit of the parties prior to the date of such expiration or termination. Upon expiration of the JANSSEN AI License Agreement, JANSSEN AI will have a royalty-free license. JANSSEN may terminate the JANSSEN AI License Agreement by giving us written notice. If a material breach is not cured within the time specified in the JANSSEN AI License Agreement, either party may terminate. Upon early termination of the JANSSEN AI License Agreement, JANSSEN AI's license rights terminate and future payment obligations do not accrue. The termination or expiration of the JANSSEN AI License Agreement will not relieve either party from any obligation which accrued prior to the termination or expiration. However, in the event that JANSSEN elects an early termination of the JANSSEN AI License Agreement, all rights to know-how, manufacturing technology and patents covered under the JANSSEN AI License Agreement will revert back to us.

Manufacturing

Except in the case of GSK and JANSSEN AI, we have retained worldwide manufacturing rights for QS-21 Stimulon. We have the right to subcontract manufacturing for QS-21 Stimulon and we have a supply agreement with a contract manufacturer for the production of QS-21 Stimulon through September 2014. In addition, under the terms of our agreement with GSK, GSK is committed to supply certain quantities of commercial grade QS-21 Stimulon to us and our licensees for a fixed period of time.

Intellectual Property Portfolio

We seek to protect our technologies through a combination of patents, trade secrets and know-how and currently have exclusive rights, through outright ownership or through exclusive licenses, to approximately 60 issued United States patents and approximately 99 issued foreign patents. We also have exclusive rights to approximately 13 pending United States patent applications and approximately 43 pending foreign patent applications. While we have patent coverage in Russia for Oncophage, we may not have rights in other territories where we may pursue regulatory approval for Prophage Series vaccine candidates.

Our issued patents include those that cover our core technologies including HSPs for the treatment of cancers and infectious disease, and saponin adjuvants.

The issued patents that cover the Prophage Series vaccines expire at various dates between 2015 and 2024. The issued patents relating to HerpV expire at various dates between 2014 and 2029. Our patents to purified QS-21 Stimulon have expired. Additional protection for QS-21 Stimulon in combination with other agents is provided by our other issued patents which expire between 2017 and 2022. We continue to explore means of extending the life cycle of our patent portfolio.

Through our acquisition of 4-AB, we own patents and patent applications directed to various methods and compositions, including methods for identifying therapeutic antibodies and product candidates arising out of 4-AB's technology platforms. In particular, we own patents and patent applications relating to Retrocyte Display®, a high throughput antibody expression platform for the identification of fully human monoclonal antibodies. This patent family is projected to expire between 2029 and 2030. We also own patents and/or patent applications relating to methods for generating precursor lymphocytes and use thereof for production of binding proteins (projected to expire between 2021 and 2024); retroviral vector particles and uses thereof (projected to expire in 2030); and antibodies that target and neutralize human Cytomegalovirus (projected to expire in 2030). As we advance our research and development efforts with our institutional and corporate collaborators, we intend to seek patent protection for newly-identified therapeutic antibodies and product candidates.

Various patents and patent applications have been exclusively licensed to us by the following entities:

Mount Sinai School of Medicine

In November 1994, we entered into a patent license agreement with the Mount Sinai School of Medicine (the "Mount Sinai Agreement"). Through the Mount Sinai Agreement, we obtained an exclusive, worldwide license to patent rights relating to the heat shock protein technology that resulted from the research and development performed by Dr. Pramod Srivastava, our founding scientist and a former member of our Board of Directors. We agreed to pay Mount Sinai a royalty on the net sales of products covered by the licensed patent rights and also provided Mount Sinai with a 0.45% equity interest in the Company (approximately 10,300 shares) valued at approximately $90,000 at the time of issuance. The term of the Mount Sinai

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Agreement ends when the last of the licensed patents expires (2016) or becomes no longer valid. If we fail to pay royalties that are due under the agreement, Mount Sinai may issue written notice to us. If we continue to fail to pay royalties after 60 days from receipt of the written notice, Mount Sinai can terminate the agreement. The Mount Sinai Agreement requires us to use due diligence to make the products covered by the licensed patent rights commercially available, including a requirement for us to use best efforts to reach a number of developmental milestones, which have been achieved. If we fail to comply with the due diligence provisions of the agreement, Mount Sinai could take actions to convert our exclusive license to a non-exclusive license after six months written notice. The Mount Sinai Agreement does not contain any milestone payment provisions.

Fordham University

During 1995, Dr. Srivastava moved his research to Fordham University ("Fordham"). We entered into a sponsored research and technology license agreement with Fordham in March 1995 (the "Fordham Agreement") relating to the continued development of the heat shock protein technology and agreed to make payments to Fordham to sponsor Dr. Srivastava's research. Through the Fordham Agreement, we obtained an exclusive, perpetual, worldwide license to all of the intellectual property, including all the patent rights, which resulted from the research and development performed by Dr. Srivastava at Fordham. We also agreed to pay Fordham a royalty on the net sales of products covered by the Fordham Agreement through the last expiration date on the patents under the agreement (2018) or when the patents become no longer valid. The agreement does not contain any milestone payment provisions or any diligence provisions. Dr. Srivastava moved his research to the University of Connecticut Health Center ("UConn") during 1997 and, accordingly, the parts of the agreement related to payments for sponsored research at Fordham terminated in mid-1997. During the term of this agreement, we paid Fordham approximately $2.4 million.

University of Connecticut

In May 2001, we entered into a license agreement with UConn which was amended in March 2003 and June 2009. Through the license agreement, we obtained an exclusive worldwide license to patent rights resulting from inventions discovered under a research agreement that was effective from February 1998 until December 2006. The term of the license agreement ends when the last of the licensed patents expires (2024) or becomes no longer valid. UConn may terminate the agreement: (1) if, after 30 days written notice for breach, we continue to fail to make any payments due under the license agreement, or (2) we cease to carry on our business related to the patent rights or if we initiate or conduct actions in order to declare bankruptcy. We may terminate the agreement upon 90 days written notice. We are required to make royalty payments on any obligations created prior to the effective date of termination of the license agreement. Upon expiration or termination of the license agreement due to breach, we have the right to continue to manufacture and sell products covered under the license agreement which are considered to be works in progress for a period of 6 months. The license agreement contains aggregate milestone payments of approximately $1.2 million for each product we develop covered by the licensed patent rights. These milestone payments are contingent upon regulatory filings, regulatory approvals, and commercial sales of products. We have also agreed to pay UConn a royalty on the net sales of products covered by the license agreement as well as annual license maintenance fees beginning in May 2006. Royalties otherwise due on the net sales of products covered by the license agreement may be credited against the annual license maintenance fee obligations. Under the March 2003 amendment, we agreed to pay UConn an upfront payment and to make future payments for each patent or patent application with respect to which we exercised our option under the research agreement. As of December 31, 2013, we have paid approximately $535,000 to UConn under the license agreement. The license agreement gives us complete discretion over the commercialization of products covered by the licensed patent rights but also requires us to use commercially reasonable diligent efforts to introduce commercial products within and outside the United States. If we fail to meet these diligence requirements, UConn may be able to terminate the license agreement.

Regulatory Compliance

Governmental authorities in the United States and other countries extensively regulate the preclinical and clinical testing, manufacturing, labeling, storage, record keeping, advertising, promotion, export, marketing and distribution, among other things, of our investigational product candidates. In the United States, the FDA under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act and other federal statutes and regulations, subject pharmaceutical products to rigorous review.

In order to obtain approval of a new product from the FDA, we must, among other requirements, submit proof of safety and efficacy as well as detailed information on the manufacture and composition of the product. In most cases, this proof entails extensive preclinical, clinical, and laboratory tests. Before approving a new drug or marketing application, the FDA may also conduct pre-licensing inspections of the company, its contract research organizations and/or its clinical trial sites to ensure that clinical, safety, quality control, and other regulated activities are compliant with Good Clinical Practices, or GCP, or Good Laboratory Practices, or GLP, for specific non-clinical toxicology studies. The FDA may also require confirmatory trials, post-

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marketing testing, and extra surveillance to monitor the effects of approved products, or place conditions on any approvals that could restrict the commercial applications of these products. Once approved, the labeling, advertising, promotion, marketing, and distribution of a drug or biologic product must be in compliance with FDA regulatory requirements.

In Phase 1 clinical trials, the sponsor tests the product in a small number of patients or healthy volunteers, primarily for safety at one or more doses. Phase 1 trials in cancer are often conducted with patients who have end-stage or metastatic cancer. In Phase 2, in addition to safety, the sponsor evaluates the efficacy of the product in a patient population somewhat larger than Phase 1 trials. Phase 3 trials typically involve additional testing for safety and clinical efficacy in an expanded population at geographically dispersed test sites. The FDA may order the temporary or permanent discontinuation of a clinical trial at any time.

The sponsor must submit to the FDA the results of preclinical and clinical testing, together with, among other things, detailed information on the manufacture and composition of the product, in the form of a new drug application or, in the case of biologics, like the Prophage Series vaccines, a biologics license application ("BLA") . In a process that can take a year or more, the FDA reviews this application and, when and if it decides that adequate data are available to show that the new compound is both safe and effective for a particular indication and that other applicable requirements have been met, approves the drug or biologic for marketing.

Whether or not we have obtained FDA approval, we must generally obtain approval of a product by comparable regulatory authorities of international jurisdictions prior to the commencement of marketing the product in those jurisdictions. We are also subject to cGMP, GCP, and GLP compliance obligations, and are subject to inspection by international regulatory authorities. International requirements may in some circumstances be more rigorous than U.S. requirements and may require additional investment in manufacturing process development, non-clinical studies, clinical studies, and record keeping that are not required for U.S. regulatory compliance or approval. The time required to obtain this approval may be longer or shorter than that required for FDA approval and can also require significant resources in time, money, and labor.

Under the laws of the United States, the countries of the European Union, and other nations, we and the institutions where we sponsor research are subject to obligations to ensure the protection of personal information of human subjects participating in our clinical trials. We have instituted procedures that we believe will enable us to comply with these requirements and the contractual requirements of our data sources. The laws and regulations in this area are evolving, and further regulation, if adopted, could affect the timing and the cost of future clinical development activities.

We are also subject to regulation under the Occupational Safety and Health Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, and other current and potential future federal, state, or local regulations. Our research and development activities involve the controlled use of hazardous materials, chemicals, biological materials, various radioactive compounds, and for some experiments we use recombinant DNA. We believe that our procedures comply with the standards prescribed by local, state, and federal regulations; however, the risk of injury or accidental contamination cannot be completely eliminated. We conduct our activities in compliance with the National Institutes of Health Guidelines for Recombinant DNA Research.

Additionally, the U.S. Foreign Corrupt Practices Act (“FCPA”) prohibits U.S. corporations and their representatives from offering, promising, authorizing or making payments to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business abroad. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Other countries have enacted similar anti-corruption laws and/or regulations.

Competition

Competition in the pharmaceutical and biotechnology industries is intense. Many pharmaceutical or biotechnology companies have products on the market and are actively engaged in the research and development of products for the treatment of cancer and infectious diseases. In addition, many competitors focus on immunotherapy as a treatment for cancer and infectious diseases. In particular, some of these companies are developing cancer vaccines produced from a patient's own cells or tissue. Others are focusing on developing heat shock protein products. Prior to regulatory approval, we may compete for access to patients with other products in clinical development, with products approved

for use in the indications we are studying, or with off-label use of products in the indications we are studying. In addition, we compete for funding, access to licenses, personnel, and third-party collaborations. Many competitors have substantially greater financial, manufacturing, marketing, sales, distribution, and technical resources, and more experience in research and development, clinical trials, and regulatory matters, than we do. Competing companies developing or acquiring rights to more efficacious therapeutic products for the same diseases we are targeting, or which offer significantly lower costs of treatment, could render our products noncompetitive or obsolete. See Part I-Item 1A. “Risk Factors- Our competitors in the biotechnology and pharmaceutical

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industries may have superior products, manufacturing capability, selling and marketing expertise and/or financial and other resources."

Academic institutions, governmental agencies, and other public and private research institutions conduct significant amounts of research in biotechnology, medicinal chemistry, and pharmacology. These entities have become increasingly active in seeking patent protection and licensing revenues for their research results. They also compete with us in recruiting and retaining skilled scientific talent.

We are aware of compounds that claim to be comparable to QS-21 Stimulon that are being used in clinical trials. Several other vaccine adjuvants are in development and could compete with QS-21 Stimulon for inclusion in vaccines in development. These adjuvants include, but are not limited to, oligonucleotides, under development by Pfizer, Idera, Colby, and Dynavax, MF59 under development by Novartis, IC31, under development by Intercell, and MPL, under development by GSK. In the past, the Company has provided QS-21 Stimulon to other entities under materials transfer arrangements. In at least one instance, it is possible that this material was used unlawfully to develop synthetic formulations and/or derivatives of QS-21. In addition, companies such as Adjuvance Technologies, Inc., CSL Limited, and Novavax, Inc., as well as academic institutions and manufacturers of saponin extracts, are developing saponin adjuvants, including derivatives and synthetic formulations. These sources may be competitive for our ability to execute future partnering and licensing deals with QS-21 Stimulon. The existence of products developed by these and other competitors, or other products of which we are not aware or which other companies may develop in the future, may adversely affect the marketability of products we develop.