DYNAVAX TECHNOLOGIES CORP
Form 10-K/A
August 04, 2006

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SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K/A
Amendment No. 1

(Mark One)

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

For the fiscal year ended December 31, 2005

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: 000-24647

Dynavax Technologies Corporation
(Exact name of registrant as specified in its charter)

Delaware	**33-0728374**
(State or other jurisdiction of incorporation or organization)	*(IRS Employer Identification No.)*

2929 Seventh Street, Suite 100
Berkeley, CA 94710-2753
(510) 848-5100
(Address, including Zip Code, and telephone number, including area code, of the registrant s principal executive offices)

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

Title of Each Class:	Name of Each Exchange on Which Registered:
None	None

Securities Registered Pursuant to Section 12(g) of the Act:
Common Stock, par value $0.001 per share
(Title of Class)

Indicate by check mark if the registrant is a Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes £ No R

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 £ No R

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 R No £

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the 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. R

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

Large accelerated filer £ Accelerated filer R Non-accelerated filer £

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

The aggregate market value of the voting stock held by non-affiliates of the registrant, based upon the closing sale price of the common stock on June 30, 2005 as reported on the Nasdaq National Market, was approximately $96,686,827. Shares of common stock held by each officer and director and by each person known to the Company who owns 5% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 31, 2006, the registrant had outstanding 30,493,501 shares of common stock.

DOCUMENTS INCORPORATED BY REFERENCE: Not applicable.

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EXPLANATORY NOTE

The purpose of this Amendment No. 1 to our Form 10-K is to correct Exhibits 31.1 and 31.2, which contained inadvertent omissions of a portion of paragraph 4 at the time they were filed with the original Form 10-K on March 16, 2006. No other items of the original Form 10-K are being amended.

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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 and Section 21E of the Securities Exchange Act of 1934 which are subject to a number of risks and uncertainties. All statements that are not historical facts are forward-looking statements, including statements about our business strategy, our future research and development, our preclinical and clinical product development efforts, our ability to commercialize our product candidates, the timing of the introduction of our products, the effect of GAAP accounting pronouncements, uncertainty regarding our future operating results and our profitability, anticipated sources of funds and all plans, objectives, expectations and intentions. These statements appear in a number of places and can be identified by the use of forward-looking terminology such as may, will, should, expect, plan, anticipate, believe, estimate, predict, future, intend, or certain or the negative of these terms or ot or comparable terminology, or by discussions of strategy.

Actual results may vary materially from those in such forward-looking statements as a result of various factors that are identified in Item 7 Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere in this document. No assurance can be given that the risk factors described in this Annual Report on Form 10-K are all of the factors that could cause actual results to vary materially from the forward-looking statements. All forward-looking statements speak only as of the date of this Annual Report on Form 10-K. Readers should not place undue reliance on these forward-looking statements and are cautioned that any such forward-looking statements are not guarantees of future performance. We assume no obligation to update any forward-looking statements.

This Annual Report on Form 10-K includes trademarks and registered trademarks of Dynavax Technologies Corporation. Products or service names of other companies mentioned in this Annual Report on Form 10-K may be trademarks or registered trademarks of their respective owners. Investors and security holders may obtain a free copy of the Annual Report on Form 10-K and other documents filed by Dynavax with the Securities and Exchange Commission (SEC) at the SEC s website at http://www.sec.gov. Free copies of the Annual Report on Form 10-K and other documents filed by Dynavax with the SEC may also be obtained from Dynavax by directing a request to Dynavax, Attention: Jane M. Green, Ph.D., Vice President, Corporate Communications, 2929 Seventh Street, Suite 100, Berkeley, CA 94710-2753, (510) 848-5100.

PART I

ITEM 1. BUSINESS

Overview

Dynavax Technologies Corporation (the Company) discovers, develops and intends to commercialize innovative products to treat and prevent allergies, infectious diseases and chronic inflammatory diseases using versatile, proprietary approaches that alter immune system responses in highly specific ways. Our clinical development programs are based on immunostimulatory sequences, or ISS, which are short DNA sequences that we believe enhance the ability of the immune system to fight disease and control chronic inflammation. The most advanced clinical programs in Dynavax s ISS-based pipeline are a ragweed allergy immunotherapeutic and a hepatitis B vaccine.

We have developed a novel injectable product candidate to treat ragweed allergy that we call TOLAMBA™ (formerly, Amb a 1 ISS Conjugate or AIC). In early 2006, we announced results from a two-year Phase II/III clinical trial of TOLAMBA showing that patients treated with a single six-week course of TOLAMBA prior to the 2004 season experienced a statistically significant reduction in total nasal symptom scores compared to placebo-treated patients in the second year of the trial. The treatment effect was achieved on top of a background of antihistamine and decongestant use. The safety profile of TOLAMBA was favorable. Systemic side effects were indistinguishable from placebo and local injection site tenderness was minor and transient.

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The Company has recently discussed the TOLAMBA program with the U.S. Food & Drug Administration (FDA). The Company has decided to conduct an additional major safety and efficacy trial with the goal of determining whether a more intensive, single-course dosing regimen can elicit an even greater treatment effect than prior regimens. This trial is anticipated to start by the beginning of the second quarter 2006 to take advantage of the 2006 ragweed season. We plan to conduct the trial as a multi-center, well-controlled study and evaluate the results after both the 2006 and 2007 ragweed seasons. The trial broadens the TOLAMBA clinical program and is designed to complement data derived from the Company s recently completed Phase II/ III clinical trial and its ongoing trial in ragweed allergic children initiated in 2005. The Company s goal is to discuss the pathway to registration with the FDA following receipt of results from the first year of this trial.

We have developed a product candidate for hepatitis B prophylaxis called HEPLISAV™. A Phase II/ III trial in subjects who are more difficult to immunize with conventional vaccines conducted in Singapore has been completed. Results from the final analysis of this trial showed statistically significant superiority in protective antibody response and robustness of protective effect after three vaccinations when compared to GlaxoSmithKline s Engerix-B®. In June 2005, we initiated a pivotal Phase III trial in the older, more difficult to immunize population in Asia. We are in the process of planning additional trials designed to support registration activities. We believe that strategic opportunities for HEPLISAV exist in key global markets. Our initial commercialization strategies will likely target these markets and focus on high-value, underserved populations. These populations include pre-hemodialysis patients, HIV and Hepatitis C Virus (HCV) positive patients, other populations with compromised immune systems as well as professionals in healthcare and law enforcement for whom achieving seroprotection quickly is critical. In October 2005, we announced the initiation of a U.S.-based Phase I clinical trial of HEPLISAV in patients with end-stage renal failure (pre-hemodialysis).

We have an inhaled therapeutic product candidate for treatment of asthma, which has completed a Phase IIa trial in Canada. We are performing additional preclinical work to optimize the route of administration and regimen for the asthma clinical program and have postponed additional clinical trials in asthma.

We are evaluating the potential of ISS to enhance the effect of monoclonal antibodies in cancer therapies. We have conducted an open-label Phase I, dose-escalation trial of ISS in combination with Rituxan® (rituximab) in 20 patients with Non-Hodgkin s lymphoma (NHL). Results of this study showed dose dependent pharmacological activity without significant toxicity. A follow-up Phase II trial of ISS with Rituxan in NHL is currently underway in 30 patients with histologically confirmed CD20+, B-cell follicular NHL who have received at least one previous treatment regimen for lymphoma. The primary objective is to assess the proportion of patients who are alive and without disease progression one year after initiating Rituxan therapy. Mechanistic studies will be performed to characterize the enhancement of antitumor activity by ISS.

We have preclinical programs focused on other allergies, chronic inflammation, antiviral therapies and improved, next-generation vaccines using ISS and other technologies.

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The Immune System

The immune system is the body s natural defense mechanism against infectious pathogens, such as bacteria, viruses and parasites, and plays an important role in identifying and eliminating abnormal cells, such as cancer cells. The body s first line of defense against any foreign substance is a specialized function called innate immunity, which serves as a rapid response that protects the body during the days or weeks needed for a second longer-term immune response, termed adaptive immunity, to develop. Unique cells called dendritic cells have two key functions in the innate immune response. They produce molecules called cytokines that contribute to the killing of viruses and bacteria. In addition, they ensure that pathogens and other foreign substances are made highly visible to specialized helper T cells, called Th1 and Th2 cells, which coordinate the longer-term adaptive immune response. Dendritic cells recognize different types of pathogens or offending substances and are able to guide the immune system to make the most appropriate type of response. When viruses, bacteria and abnormal cells such as cancer cells are encountered, dendritic cells trigger a Th1 response, whereas detection of a parasite infection leads dendritic cells to initiate a Th2 response. Th1 and Th2 responses last for extended periods of time in the form of Th1 and Th2 memory cells, conferring long-term immunity.

The diagram above is a visual representation of how the immune system reacts when it encounters antigen. Upon encountering antigen, a cascade of events is initiated that leads to either a Th1 or a Th2 immune response, as described more fully in the paragraphs above.

The Th1 response involves the production of specific cytokines, including interferon-alpha, interferon-gamma and interleukin 12, or IL-12, as well as the generation of killer T cells, a specialized immune cell. These cytokines and killer T cells are believed to be the body s most potent anti-infective weapons. In addition, protective IgG antibodies are generated that also help rid the body of foreign antigens and allergens. Once a population of Th1 cells specific to a particular antigen or allergen is produced, it persists for a long period of time in the form of memory Th1 cells, even if the antigen or allergen target is eliminated. If another infection by the same pathogen occurs, the immune system is able to react more quickly and powerfully to the infection, because the memory Th1 cells can reproduce immediately. When the Th1 response to an infection is insufficient, chronic disease can result. When the Th1 response is inappropriate, diseases such as rheumatoid arthritis can result, in part from elevated levels of Th1 cytokines.

Activation of the Th2 response results in the production of other cytokines, IL-4, IL-5 and IL-13. These cytokines attract inflammatory cells such as eosinophils, basophils and mast cells capable of

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destroying the invading organism. In addition, the Th2 response leads to the production of a specialized antibody, IgE. IgE has the ability to recognize foreign antigens and allergens and further enhances the protective response. An inappropriate activation of the Th2 immune response to allergens, such as plant pollens, can lead to chronic inflammation and result in allergic rhinitis, asthma and other allergic diseases. This inflammation is sustained by memory Th2 cells that are reactivated upon subsequent exposures to the allergen, leading to a chronic disease.

ISS and the Immune System

Our principal product development efforts are based on a technology that uses short synthetic DNA molecules called ISS that stimulate a Th1 immune response while suppressing Th2 immune responses. ISS contain specialized sequences that activate the innate immune system. ISS are recognized by a specialized subset of dendritic cells containing a unique receptor called Toll-Like Receptor 9, or TLR-9. The interaction of TLR-9 with ISS triggers the biological events that lead to the suppression of the Th2 immune response and the enhancement of the Th1 immune response.

We believe ISS have the following benefits:

ISS work by changing or reprogramming the immune responses that cause disease rather than just treating the symptoms of disease.

ISS influence helper T cell responses in a targeted and highly specific way by redirecting the response of only those T cells involved in a given disease. As a result, ISS do not alter the ability of the immune system to mount an appropriate response to infecting pathogens. In addition, because TLR-9 is found only in a specialized subset of dendritic cells, ISS do not cause a generalized activation of the immune system, which might otherwise give rise to an autoimmune response.

ISS, in conjunction with an allergen or antigen, establish populations of memory Th1 cells, allowing the immune system to respond appropriately to each future encounter with a specific pathogen or allergen, leading to long-lasting therapeutic effects.

We have developed a number of proprietary ISS compositions and formulations that make use of the different ways in which the innate immune system responds to ISS. Depending on the indication for which ISS is being explored as a therapy, we use ISS in different ways.

ISS Linked to Allergens

We link ISS to allergens that are known to cause specific allergies. By chemically linking ISS to allergens, rather than simply mixing them, we generate a superior Th1 response due to the fact that the ISS and allergen are presented simultaneously to the same part of the immune system. The linked molecules generate an increased Th1 response by the immune system in the form of IgG antibodies and interferon-gamma. In addition, the ISS-linked allergens have a highly specific and potent inhibitory effect on the Th2 cells, thereby reprogramming the immune response away from the Th2 response that causes specific allergies. Upon subsequent natural exposure to the allergens, the Th1 memory response is triggered, providing long-term suppression of allergic responses.

ISS Linked to or Combined with Antigens

We also link ISS to antigens associated with cancer and pathogens such as viruses and bacteria to stimulate an immune response that will attack and destroy infected or abnormal cells. ISS, linked to or combined with appropriate antigens, increase the visibility of the antigen to the immune system and induce a highly specific and enhanced Th1 response, including increased IgG antibody production. As with ISS linked to allergens, this treatment also generates memory T cells, conferring long-term protection against specific pathogens. This treatment may also have the potential for synergy with other cancer or infectious disease therapies.

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ISS Alone

We use ISS alone in diseases like asthma, where a large variety of allergens may be associated with an inappropriate immune response. ISS administered alone may suppress the Th2 inflammatory response caused by any number of allergens, modifying the underlying cause of inflammation, as well as providing symptomatic relief. ISS may also be used in conjunction with a variety of anti-tumor monoclonal antibodies as a combination therapy, with the goal of stimulating the elimination of cancer cells.

Advanced ISS Technologies

We have developed proprietary technologies that modify the molecular structure of ISS to significantly increase its versatility and potency. We are using these technologies in most of our preclinical programs and believe that they will be essential to our future product development efforts. Our advanced ISS technologies include novel ISS-like compounds, which we call CICs, as well as advanced ISS formulations.

CICs are molecules that are a mixture of nucleotide and non-nucleotide components. We have identified optimal sequences that induce particular immune responses, including potent interferon-alpha induction. CICs can be tailored to have specific immunostimulatory properties and can be administered alone, or linked to allergens or antigens.

We have also developed novel formulations for ISS and CICs that can dramatically increase their potency. These advanced formulations can be used in situations where high potency is required to see a desired clinical outcome and can decrease the dosage of ISS or CICs required to achieve therapeutic effect.

Our Primary Development Programs

We are using a proprietary ISS, a 22-base synthetic DNA molecule called 1018 ISS, in our clinical development programs for ragweed allergy, hepatitis B prophylaxis and asthma. To date, we have administered 1018 ISS to more than 1,000 people without observing any serious, drug-related, adverse events. We have demonstrated the clinical benefit of TOLAMBA and our hepatitis B vaccine, which are both 1018 ISS-based product candidates, in Phase II/ III clinical trials. Our principal programs are Seasonal Allergy Immunotherapy, Hepatitis B Products and Chronic Inflammation, as described below.

Seasonal Allergy Immunotherapy

Ragweed Allergy

TOLAMBA for Ragweed Allergy and its Benefits

Our lead anti-allergy product, TOLAMBA, consists of 1018 ISS linked to the purified major allergen of ragweed, called Amb a 1. TOLAMBA may target the underlying cause of seasonal allergic rhinitis caused by ragweed and offers a convenient six-week treatment regimen potentially capable of providing long-lasting therapeutic results. The linking of ISS to Amb a 1 ensures that both ISS and ragweed allergen are presented simultaneously to the same immune cells, producing a highly specific and potent inhibitory effect. Preclinical data suggest that Th2 cells responsible for inflammation associated with ragweed allergy are suppressed, leading to reprogramming of the immune response away from the Th2 response and toward a Th1 memory response so that, upon subsequent natural exposure to the ragweed allergen, long-term immunity is achieved.

Clinical Status

Over the last several years, we have generated a substantial amount of clinical data on TOLAMBA. TOLAMBA has been tested in fourteen clinical trials in the U.S., France and Canada, and more than 4,700 TOLAMBA injections have been administered to more than 650 patients. In these trials, TOLAMBA was shown to be safe and well tolerated, to provide measurable improvements in allergy

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symptoms and to reduce medication use. We have completed a two-year multi-site Phase II/ III trial in the U.S. to evaluate the efficacy of TOLAMBA. The trial originally enrolled 462 eligible patients. Prior to the 2004 ragweed season, patients received a six-week regimen of either placebo or escalating doses of up to 30 micrograms of TOLAMBA. Some patients received two additional booster shots of TOLAMBA prior to the 2005 ragweed season. The primary endpoint of this trial is the change in nasal symptoms (i.e., congestion, runny nose, itchy nose, sneezing) relative to placebo following the 2005 ragweed season.

In early 2006, we announced results from a two-year Phase II/III clinical trial of TOLAMBA showing that patients treated with a single six-week course of TOLAMBA prior to the 2004 season experienced a statistically significant reduction in total nasal symptoms scores (TNSS) from baseline during the two-week peak season compared to placebo-treated patients in the first year of the trial (21.2% effect, p=0.04) and in the second year of the trial (28.5% effect, p=0.02). The treatment effect was achieved on top of a background of antihistamine and decongestant use. The group receiving a single course of TOLAMBA achieved a statistically significant reduction in major secondary endpoints such as hayfever composite score (p=0.04) as well as a reduction in antihistamine use and in decongestant use (p=0.04 and p=0.03, respectively). Results showed that a booster dose prior to the second season (2005) was not required to achieve clinical benefits. Unlike the TOLAMBA-treated group, the boosted group did not achieve statistical significance relative to the efficacy endpoints compared to placebo. The safety profile of TOLAMBA was favorable. Systemic side effects were indistinguishable from placebo and local injection site tenderness was minor and transient.

The Company has recently discussed the TOLAMBA program with the U.S. Food & Drug Administration (FDA). The Company has decided to conduct an additional major safety and efficacy trial with the goal of determining whether a more intensive, single-course dosing regimen can elicit an even greater treatment effect than prior regimens. This trial is anticipated to start by the beginning of the second quarter 2006 to take advantage of the 2006 ragweed season. We plan to conduct the trial as a multi-center, well-controlled study and evaluate the results after both the 2006 and 2007 ragweed seasons. The trial broadens the TOLAMBA clinical program and is designed to complement data derived from the Company s recently completed Phase II/ III clinical trial and its ongoing trial in ragweed allergic children initiated in 2005. The Company s goal is to discuss the pathway to registration with the FDA following receipt of results from the first year of this trial.

Commercial Opportunity

Medical management of seasonal allergic rhinitis is a multibillion-dollar global market. In the U.S. alone, approximately 40 million people suffer from allergic rhinitis. The direct costs of prescription interventions for allergic rhinitis in the U.S. were $8 billion in 2004. Ragweed is the single most common seasonal allergen, affecting up to 75% of those with allergic rhinitis, or 30 million Americans. In addition, 20-30% of those who suffer from allergic rhinitis progress to asthma, leading to increased morbidity and disease management costs. We believe that a significant market opportunity exists for TOLAMBA in the treatment of ragweed allergic individuals currently undergoing conventional immunotherapy or using multiple prescription or over-the-counter (OTC) medications. In addition, the product may also play a role in earlier stage disease, potentially preventing the allergic march from allergic rhinitis to asthma.

Current Allergy Treatments and their Limitations

Drug Treatments Many individuals turn to prescription and OTC pharmacotherapies such as antihistamines, corticosteroids, anti-leukotriene agents and decongestants to manage their seasonal allergy symptoms. Although currently available pharmacotherapies may provide temporary symptomatic relief, they can be inconvenient to use and can cause side effects. Most importantly, these pharmacotherapies need to be administered chronically and do not modify the underlying disease state.

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Allergy Shots (Immunotherapy) Allergy shots, or immunotherapy, are employed to alter the underlying immune mechanisms that cause allergic rhinitis. Patients are recommended for allergy immunotherapy only after attempts to reduce allergic symptoms by drugs or limiting exposure to the allergen have been deemed inadequate. Conventional immunotherapy is a gradual immunizing process in which increasing individualized concentrations of pollen extracts are mixed by the allergist and administered to induce increased tolerance to natural allergen exposure. The treatment regimen generally consists of weekly injections over the course of six months to a year, during which the dosing is gradually built up to a therapeutic level so as not to induce a severe allergic reaction. Once a therapeutic dosing level is reached, individuals then receive bi-weekly or monthly injections to build and maintain immunity over another two to four years. A patient typically receives between 60 and 90 injections over the course of treatment. Adverse reactions to conventional allergy immunotherapy are common and can range from minor swelling at the injection site to systemic reactions, and, in extremely rare instances, death. Other major drawbacks from the patients perspective include the inconvenience of repeated visits to doctors offices for each injection, the time lag between the initiation of the regimen and the reduction of symptoms, and the total number of injections required to achieve a therapeutic effect. Consequently, patient compliance is a significant issue.

Other Seasonal Allergy Immunotherapy Candidates

As TOLAMBA progresses through clinical development, we intend to produce similar ISS-allergen linked product candidates for the treatment of other major seasonal allergies. Each of grass, birch and cedar-induced seasonal allergic rhinitis is caused by an allergic immune system response to identified and characterized allergens. Consequently, product candidates for each can be produced in a manner similar to TOLAMBA. For example, the major grass allergens, Lol p 1 and Ph1 p 5, and the major cedar tree allergens, Cry j 1 and Cry j 2, can be linked to ISS. As with TOLAMBA, we believe our approach may provide distinct advantages over conventional immunotherapy for these allergies, including a potentially favorable safety profile, significantly shorter dosing regimen and long-term therapeutic benefits.

TOLAMBA and our other seasonal allergy products should be well positioned to compete against not only currently available immunotherapies, but also other interventions targeting the symptoms of seasonal allergic rhinitis. We believe that our additional seasonal allergy products will present the same advantages over symptomatic interventions as described for TOLAMBA. As a result of these advantages and by providing a broader set of seasonal allergy immunotherapies, we may ultimately achieve an expansion into the large group of patients that currently choose pharmacotherapies over existing immunotherapies.

Peanut Allergy

ISS for Peanut Allergy and its Benefits

We believe that ISS linked with a major peanut allergen, Ara h 2, may be able to suppress the Th2 response and reduce or eliminate the allergic reaction without inducing anaphylaxis during the course of immunotherapy. Our anticipated advantage in this area is the potentially increased safety that may be achieved by linking ISS to the allergen. By using ISS to block recognition of the allergen by IgE and therefore prevent subsequent histamine release, we may be able to administer enough of the ISS-linked allergen to safely reprogram the immune response without inducing a dangerous allergic reaction. We believe the resulting creation of memory Th1 cells may provide long-term protection against an allergic response due to accidental exposure to peanuts.

Preclinical Status

We have developed a peanut allergy product candidate that consists of ISS linked to a major peanut allergen, Ara h 2. We have demonstrated in mice that peanut allergen linked to ISS induces much higher levels of Th1-induced IgG antibodies and lower levels of IgE than natural peanut allergen. ISS-linked Ara h 2 also induces much higher levels of interferon-gamma and much lower levels of IL-5 than unmodified Ara h 2 in mice. Immunization with our product candidate has also been shown to protect

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peanut allergic animals from anaphylaxis and death following exposure to peanut allergen. In addition, we have demonstrated that ISS-linked Ara h 2 has significantly reduced allergic response as measured by in vitro histamine release assays using blood cells from peanut allergic patients.

Commercial Opportunity

Peanut allergy accounts for the majority of severe food-related allergic reactions. Approximately 1.5 million people in the U.S. have a potentially life-threatening allergy to peanuts and the incidence is growing rapidly. There are an estimated 100 to 200 deaths from severe peanut allergy in the U.S. each year.

Current Peanut Allergy Treatments and their Limitations

There are currently no products available that treat peanut allergy. People allergic to peanuts must take extreme avoidance measures, carefully monitoring their exposure to peanuts and peanut byproducts. Emergency response following peanut exposure and the onset of allergic symptoms primarily consists of the administration of epinephrine to treat anaphylaxis. Our peanut allergy immunotherapy is designed to allow patients to tolerate exposure to higher levels of peanut products without experiencing severe reactions.

License and Development Agreement with UCB

In March 2005, we agreed to end the collaboration with UCB Farchim, S.A., a subsidiary of UCB, S.A. (UCB), and regained full rights to our allergy program. We assume financial responsibility for all further clinical, regulatory, manufacturing and commercial activities related to TOLAMBA and for preclinical development programs in grass and in peanut allergy.

Hepatitis B Products

Hepatitis B Prevention

HEPLISAV: Our Hepatitis B Vaccine Product Candidate and its Benefits

Current hepatitis B vaccines consist of hepatitis B surface antigen combined with alum as an adjuvant. HEPLISAV is composed of hepatitis B surface antigen combined with 1018 ISS and, unlike conventional three-dose vaccines, appears to require only two immunizations over two months to achieve protective hepatitis B antibody responses in healthy young adults. In addition, clinical studies have demonstrated that HEPLISAV offers higher levels of immunity in the age 40-70 population, which traditionally responds poorly to current vaccines. Therefore, we believe HEPLISAV may offer an efficacy advantage versus currently available vaccines for patients that are traditionally difficult to immunize, including pre-dialysis, HIV or HCV infected individuals.

Clinical Status

Results from Phase I and from Phase II trials showed that HEPLISAV was well tolerated and induced more rapid immunity with fewer immunizations in both healthy young and older adults than Engerix-B®, a major currently available vaccine. Our Phase I trial investigated the effects of escalating doses of ISS, from 0.3 mg to 3.0 mg, in each case administered with the same amount of hepatitis B surface antigen as used in conventional vaccines. In this trial we enrolled 48 subjects and demonstrated that all subjects who received two injections of at least 0.65 mg ISS with hepatitis B surface antigen achieved protective hepatitis B antibody responses. We conducted a Phase II trial in Canada evaluating the efficacy of two injections of our vaccine candidate (hepatitis B surface antigen plus 3.0 mg of 1018 ISS) compared to Engerix-B. A total of 99 healthy young adults were enrolled in this study, randomized to our vaccine or Engerix-B. Results show that our vaccine induces a 79% rate of protective hepatitis B antibody response after one injection and protective hepatitis B antibody response in 100% of recipients after the second injection at two months. In contrast, subjects receiving Engerix-B had protective hepatitis B antibody responses after the first and second injections in 12% and 64% of recipients, respectively. We

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have completed a Phase II/ III trial in Singapore that evaluated the efficacy of our vaccine in older subjects (ages 40-70 years) who have a diminished ability to respond to current commercial vaccines. Results showed superiority of HEPLISAV compared to Engerix-B relative to the primary efficacy endpoint of seroprotection (100% seroprotection in the HEPLISAV-treated group compared to 90.5% in the Engerix-B treated group; p=0.034) and relative to geometric mean concentration or GMC (1698 compared to 569 mIU/mL; p=0.023). Results also showed that subjects treated with HEPLISAV experienced more durable seroprotection. At week 50, the HEPLISAV-treated group measured 100% seroprotection and GMC of 499 mIU/mL compared to 86% and 153 mIU/mL for the Engerix-B treated group (p=0.009 and p=0.005, respectively). The Phase II/ III trial was conducted in an older adult population, aged 40-70 years, in whom achieving seroprotection with conventional vaccine is more difficult than in younger adults. The primary endpoint of the trial was seroprotection following three doses, and a key secondary endpoint was GMC, a measure of the robustness of antibody response. The safety profile of the vaccine was highly favorable.

We initiated a pivotal Phase III clinical trial of HEPLISAV in June 2005. This trial involves 400 subjects, aged 40-70, and is being conducted in Asia. We are in the process of planning additional trials designed to support registration activities. We initiated a Phase I trial in pre-dialysis patients in the U.S. in October 2005. The Company also plans to conduct additional trials in selected high-risk populations.

Commercial Opportunity

Hepatitis B is a common chronic infectious disease with an estimated 350 million chronic carriers worldwide. Prevention of hepatitis caused by the hepatitis B virus is central to managing the spread of the disease, particularly in regions of the world with large numbers of chronically infected individuals. While many countries have instituted infant vaccination programs, compliance is not optimal. Moreover, there are large numbers of individuals, born prior to the implementation of these programs, who are unvaccinated and are at risk for the disease. In addition, not all individuals respond to currently approved vaccines. Annual sales of hepatitis B vaccines are approximately $1.0 billion globally.

Our commercial strategy for HEPLISAV is designed to target high-value, high-risk patient populations whose need for rapid and effective protection against HBV is urgent and who are underserved by conventional vaccines. We are initially focusing on patients with chronic renal failure who are either about to undergo hemodialysis or are already on hemodialysis, and who are at substantial risk for HBV infection. We also intend to focus on people with HIV and hepatitis C infections for whom co-infection with HBV is a serious concern. We believe that healthcare workers and emergency personnel, who face significant occupational risks of infection, as well as discretionary travelers, also represent important potential markets for HEPLISAV.

Current Hepatitis B Vaccines and their Limitations

Current hepatitis B vaccines consist of a three-dose immunization regimen administered over six months. If completed, current hepatitis B vaccination confers protective hepatitis B antibody responses to approximately 95% of healthy young adults. However, the protective hepatitis B antibody responses achieved by conventional vaccines is lower for persons who are immunocompromised. Additionally, there is an inversely proportional relationship between age and the degree to which current vaccines confer protective hepatitis B antibody responses: the older you are, the less effective current vaccines are. Compliance with the immunization regimen is also a significant issue, as many patients fail to receive all three doses. According to a survey of U.S. adolescents and adults published by the Centers for Disease Control, of those who received the first dose of vaccine, only 53% received the second dose of vaccine and only 30% received the third. We believe that compliance rates in other countries are similar or worse. For healthy young adults, protective hepatitis B antibody responses after the first dose are reported to be between 10% and 12% and improve to only 38% to 56% after the second dose. Consequently, an unacceptably large number of individuals who start the immunization series remain susceptible to infection. Poor field efficacy is of particular concern in regions with high hepatitis B prevalence and constitutes a major public health issue.

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Hepatitis B Therapy

Benefits of our Approach to Hepatitis B Therapy

Our hepatitis B therapeutic candidate, in which advanced ISS is both linked to and combined with hepatitis B surface antigen, may provide a more effective alternative for the elimination of infection in chronic carriers, in conjunction with existing antiviral therapies. Our immunotherapy is expected to induce a potent immune response against virus-infected cells in the liver and has the potential to eradicate the infection.

Preclinical Status

Preclinical experiments in mice have shown that our product candidate for hepatitis B therapy redirects the immune response toward Th1-based immunity, producing strong interferon-gamma and cytotoxic T cell responses. Interferon-gamma and cytotoxic T cell responses are thought to be important for the control and/or elimination of chronic hepatitis B infection.

Commercial Opportunity

Hepatitis B infection is a major cause of acute and chronic viral hepatitis, with morbidities ranging from asymptomatic infection to liver failure, cancer and death. There is a large population chronically infected with hepatitis B, including an estimated one million patients in the U.S., two million in Europe, nine million in Japan and three hundred fifty million in the rest of the world. In many countries in Southeast Asia and the Pacific Basin, HBV endemicity is as high as 20-25% of the population.

Currently Available Hepatitis B Therapies and their Limitations

Currently available therapies for chronic hepatitis B infection include interferon alpha and antiviral drugs. Interferon-alpha has been shown to normalize liver enzyme function in approximately 40% of individuals treated. The approved antiviral drugs, which work by inhibiting viral replication, reduce hepatitis B viral load approximately 3,000-fold and normalize liver enzymes in 50% to 75% of patients. However, both interferon-alpha and antiviral drugs are expensive and may induce significant side effects. In addition, patients typically become resistant to antiviral drugs within one year of initiating treatment, ultimately rendering them ineffective as long-term therapies.

License and Supply Agreement with Berna Biotech

In October 2003, we entered into an agreement with Berna Biotech, a publicly traded company based in Bern, Switzerland, in which Berna agreed to supply us with its proprietary hepatitis B surface antigen for use in our Phase III clinical trials for our hepatitis B vaccine and, if merited, its subsequent commercialization. According to terms of the agreement, we will receive adequate supplies of hepatitis B surface antigen for clinical development, and then will pay fixed amounts for use of the antigen in the potential commercial vaccine. In 2006, Berna was acquired by Crucell N.V. We do not expect the acquisition to have any impact on our ability to receive the agreed upon supply of hepatitis B surface antigen.

Chronic Inflammation

Asthma

Inhaled ISS for Asthma and its Benefits

In most people, asthma is an allergic inflammatory disease caused by multiple allergens. As a result, an approach relying on the linkage of ISS to a large number of allergens would be technically and commercially challenging. To address this issue, we have formulated ISS for pulmonary delivery with no linked allergen, relying on natural exposure to multiple allergens to produce specific long-term immunity. We anticipate that ISS would be administered initially on a weekly basis. Once the immune response to

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asthma-causing allergens has been reprogrammed to a Th1 response, it may be possible to reduce administrations of ISS to longer periodic intervals or only as needed. In addition, based on preclinical data, we believe that this therapy may lead to reversal of airway remodeling caused by asthma.

Clinical Status

We have an inhaled therapeutic product candidate for treatment of asthma, which has completed a Phase IIa trial in Canada. We are performing additional preclinical work to optimize the route of administration and regimen for the asthma clinical program and have postponed additional clinical trials in asthma.

Additional Programs

In addition to our primary product portfolio, we are pursuing earlier stage programs in Next-Generation Vaccines, Cancer, Antiviral Applications, Chronic Inflammation and Autoimmune Disorders, as described below.

Next-Generation Vaccines

Anthrax

We are using our advanced ISS technology to develop an improved anthrax vaccine that we expect will be well tolerated and provide protective immunity after one or two immunizations. The only available anthrax vaccine, Anthrax Vaccine Adsorbed, or AVA, was approved in the U.S. in 1970 and has been used extensively by the military. The vaccine has been reported to cause relatively high rates of local and systemic adverse reactions. In addition, the administration of AVA requires six subcutaneous injections over 18 months with subsequent annual boosters. Our vaccine candidate will be composed of recombinant anthrax protective antigen, or rPA, combined with advanced ISS enhanced by a proprietary formulation. The use of advanced ISS in this formulation should enhance both the speed and magnitude of the antibody response developed against rPA compared to AVA and other rPA-based products in development. Preclinical experiments have demonstrated that rPA combined with our advanced ISS formulations has generated significantly higher toxin neutralizing antibody responses compared to rPA alone or rPA combined with the standard vaccine adjuvant, alum in mouse and monkey models. In addition, the rPA combined with advanced ISS formulations has provided protection from respiratory anthrax spore challenge in mouse, guinea pig, and rabbit models. In the third quarter of 2003, the National Institute of Allergy and Infectious Diseases, or NIAID, awarded us a $3.6 million grant over three and a half years to fund research and development of an advanced anthrax vaccine as part of its biodefense program.

Human Viral Influenza

Human viral influenza is an acute respiratory disease of global dimension with high morbidity and mortality in annual epidemics. In the U.S., there are an estimated 20,000 viral influenza-associated deaths per year. Pandemics occur infrequently, on average every 33 years, with high rates of infection resulting in increased mortality. The last pandemic occurred in 1968, and virologists anticipate that a new pandemic strain could emerge any time.

Current flu vaccines are directed against specific surface antigen proteins. These proteins vary significantly each year, requiring the vaccine to be reconfigured and administered annually. Our approach links advanced ISS to nucleoprotein, one of the flu antigens that varies little from year to year, and then adds it to conventional vaccine to augment its activity. We believe that linked ISS-nucleoprotein added to conventional vaccine will not only increase antibody responses capable of blocking viral infections but also confer protective immunity against divergent influenza strains. We have demonstrated that a single ISS-linked nucleoprotein product can protect mice from challenge with widely divergent influenza virus strains. In the third quarter of 2003 we were awarded a $3.0 million grant over three and a half years to fund

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research and development of an advanced pandemic influenza vaccine under an NIAID program for biodefense administered by the National Institutes of Health.

Cancer

We are evaluating the potential of 1018 ISS to enhance the cytotoxic effects of monoclonal antibodies on cancer cells. This strategy has been shown to be effective in preclinical models utilizing various anticancer monoclonal antibodies. We have conducted an open-label Phase I, dose-escalation trial of 1018 ISS in combination with Rituxan in 20 patients with a cancer of the blood called non-Hodgkin s lymphoma (NHL) to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of 1018 ISS administered in combination with Rituxan. Results of this study showed interferon-alpha/beta inducible gene expression, without significant toxicity. These results provide a rationale for further testing of this combination immunotherapy approach to NHL.

Antiviral Applications

Increasing the resistance of individuals to a wide range of potential pathogens by stimulating their innate immune response would provide a complementary approach to vaccination against specific pathogens. As the most likely route of exposure to biological weapons is through the air, stimulation of innate immune mechanisms in the lungs would be particularly important.

We have shown in animal models that ISS enhances innate immunity and increases resistance to a variety of pathogens in both prophylactic and therapeutic settings. We are currently evaluating the effects of advanced ISS as prophylaxis against a broad spectrum of biological agents in both mouse and primate models. In the third quarter of 2003, we were awarded an NIAID biodefense grant of $1.7 million over two and one-half years. This grant will fund research and development of a product candidate using pulmonary delivery to elicit prophylactic innate immunity to airborne biological agents.

Chronic Inflammation

We are conducting preclinical studies on a novel class of chemical compounds called thiazolopyrimidines, or TZPs, for the potential treatment of inflammatory diseases. Tumor necrosis factor (TNF) alpha is a cytokine that plays a major role in the body s response to infectious diseases. TZPs are our proprietary small molecules that inhibit the production of TNF-alpha and IL-12. They appear to have a novel mechanism of action, including a high degree of specificity, increasing their potential to be used as drugs. Based on the outcome of these preclinical studies, we will determine a potential clinical application for this approach.

Autoimmune Disorders

We have pioneered a new approach to treating autoimmune disease based upon a novel class of oligonucleotides, named immunoregulatory sequences (IRS), that specifically inhibit the toll-like receptor (TLR)-induced inflammatory response implicated in disease progression. We are exploring development of an IRS-based treatment for autoimmune disease, including systemic lupus erythematosis (SLE or lupus). Based upon this initial research, in the fourth quarter of 2004, the Alliance for Lupus Research (ALR) awarded us a $0.5 million grant over two years to explore new treatment approaches for SLE based on the Company s novel IRS technology.

Intellectual Property

Our intellectual property portfolio can be divided into four main technology areas: ISS, TZP, vaccines using DNA and IRS. We have entered into exclusive, worldwide license agreements with the Regents of the University of California for technology and related patent rights in these three technology areas.

ISS technology: We have 29 issued U.S. and foreign patents, 31 pending U.S. patent applications, and 101 pending foreign applications that seek worldwide coverage of compositions and methods

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using ISS technology. Some of these patents and applications have been exclusively licensed worldwide from the Regents of the University of California. Among others, we hold issued U.S. patents covering 1018 ISS as a composition of matter; the use of ISS alone to treat asthma; and ISS linked to allergens and viral or tumor antigens.

TNF-alpha inhibitors: We have 22 issued U.S. and foreign patents and 4 pending U.S. and foreign patent applications providing worldwide rights to a group of small-molecule TNF-alpha synthesis inhibitors including TZPs. We hold exclusive, worldwide licenses to these patents and patent applications held by the Regents of the University of California.

Vaccines using DNA: We have 24 issued U.S. and foreign patents and 6 pending U.S. and foreign patent applications covering methods and compositions for vaccines using DNA and methods for their use. We hold an exclusive, worldwide license from the Regents of the University of California for patents and patent applications relating to vaccines using DNA, and we have the right to grant sublicenses to third parties. Effective January 1998, we entered into a cross-licensing agreement with Vical, Inc. that grants each company exclusive, worldwide rights to combine the other firm s patented technology for DNA immunization with its own for selected indications.

Immunoregulatory sequences (IRS) including immunoinhibitory sequences: We have 2 issued U.S. and foreign patents and 7 pending U.S. and foreign patent applications providing worldwide rights to certain compositions and methods using IRS (including immunoinhibitory sequences). We hold exclusive, worldwide licenses to these patents and patent applications held by the Regents of the University of California.

Under the terms of our license agreements with the Regents of the University of California, we are required to pay license fees, make milestone payments and pay royalties on net sales resulting from successful products originating from the licensed technologies. We may terminate these agreements in whole or in part on 60 days advance notice. The Regents of the University of California may terminate these agreements if we are in default for failure to make royalty payments, produce required reports or fund internal research and we do not cure a breach within 60 days after being notified of the breach. Otherwise, the agreements do not terminate until the last patent claiming a product licensed under the agreement or its manufacture or use expires, or in the absence of patents, until the date the last patent application is abandoned, except for the TZP agreement, which will expire on such date or in October 2013, whichever is later.

Although we believe our patents and patent applications, including those that we license, provide a competitive advantage, the patent positions of pharmaceutical and biopharmaceutical companies are highly uncertain and involve complex legal and factual questions. We and our collaborators or licensors may not be able to develop patentable products or be able to obtain patents from pending patent applications. Even if patent claims are allowed, the claims may not issue, or in the event of issuance, may not be sufficient to protect the technology owned by or licensed to us. These current patents, or patents that issue on pending applications, may be challenged, invalidated, infringed or circumvented, and the rights granted in those patents may not provide proprietary protection or competitive advantages to us. Patent applications filed before November 29, 2000 in the U.S. are maintained in secrecy until patents issue; later filed U.S. applications and patent applications in most foreign countries generally are not published until at least 18 months after they are filed. Scientific and patent publication often occurs long after the date of the scientific discoveries disclosed in those publications. Accordingly, we cannot be certain that we were the first to invent the subject matter covered by any patent application or that we were the first to file a patent application for any inventions.

Our commercial success depends significantly on our ability to operate without infringing patents and proprietary rights of third parties. A number of pharmaceutical companies, biotechnology companies, including Coley Pharmaceutical Group, or Coley, as well as universities and research institutions may have filed patent applications or may have been granted patents that cover technologies similar to the technologies owned or licensed to us. We cannot determine with certainty whether patents or patent applications of other parties may materially affect our ability to

make, use or sell any products. The

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existence of third-party patent applications and patents could significantly reduce the coverage of the patents owned by or licensed to us and limit our ability to obtain meaningful patent protection.

If patents containing competitive or conflicting claims are issued to third parties, we may be enjoined from pursuing research, development or commercialization of products or be required to obtain licenses to these patents or to develop or obtain alternative technology. In addition, other parties may duplicate, design around or independently develop similar or alternative technologies to ours or our licensors. If another party controls patents or patent applications covering our products, we may not be able to obtain the rights we need to those patents or patent applications in order to commercialize our products. We have developed second-generation technology that we believe reduces many of these risks.

Litigation may be necessary to enforce patents issued or licensed to us or to determine the scope or validity of another party s proprietary rights. U.S. Patent Office interference proceedings may be necessary if we and another party both claim to have invented the same subject matter. Coley has issued U.S. patent claims, as well as patent claims pending with the U.S. Patent and Trademark Office, that, if held to be valid, could require us to obtain a license in order to commercialize one or more of our formulations of ISS in the United States, including TOLAMBA and HEPLISAV. In December 2003 the U.S. Patent and Trademark Office declared an interference to resolve first-to-invent disputes between a patent application filed by the Regents of the University of California, which is exclusively licensed to us, and an issued U.S. patent owned by Coley relating to immunostimulatory DNA sequences. The declaration of interference named the Regents of the University of California as senior party, indicating that a patent application filed by the Regents of the University of California and licensed to us was filed prior to a patent application owned by Coley that led to an issued U.S. patent. The interference provides the first forum to challenge the validity and priority of certain of Coley s patents. On March 10, 2005, the U.S. Patent and Trademark Office issued a decision in the interference which did not address the merits of the case, but dismissed it on a legal technicality related to the timing of Dynavax s filing of its claims and request for interference. Dynavax has appealed this decision. If we prevail in the appeal, we will be able to continue the interference to address the merits of the case. If we prevail in the interference proceeding, it would establish our founders as the inventors of the inventions in dispute. However, even a favorable outcome in the interference would not prevent Coley from asserting its other patents or patent claims that were not the subject of the interference, against our ISS products, which could harm our ability to commercialize those products. If we do not prevail in the interference proceeding, we may not be able to obtain patent protection on the subject matter of the interference, which would have a material adverse impact on our business. In addition, if Coley prevails in the interference, it may seek to enforce its rights under issued claims, including, for example, by suing us for patent infringement. Consequently, we may need to obtain a license to issued and/or pending claims held by Coley by paying cash, granting royalties on sales of our products or offering rights to our own proprietary technologies. Such a license may not be available to us on acceptable terms, if at all.

We could incur substantial costs if:

- litigation is required to defend against patent suits brought by third parties;
- we participate in patent suits brought against or initiated by our licensors;
- we initiate similar suits; or
- we pursue an interference proceeding.

In addition, we may not prevail in any of these actions or proceedings. An adverse outcome in litigation or an interference or other proceeding in a court or patent office could:

- subject us to significant liabilities;
- require disputed rights to be licensed from other parties; or
- require us to cease using some of our technology.

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We also rely on trade secrets and proprietary know-how, especially when we do not believe that patent protection is appropriate or can be obtained. Our policy is to require each of our employees, consultants and advisors to execute a confidentiality and inventions agreement before beginning their employment, consulting or advisory relationship with us. These agreements generally provide that the individuals must keep confidential and not disclose to other parties any confidential information developed or learned by the individuals during the course of their relationship with us except in limited circumstances. These agreements also generally provide that we own all inventions conceived by the individuals in the course of rendering services to us.

In the future, we may collaborate with other entities on research, development and commercialization activities. Disputes may arise about inventorship and corresponding rights in know-how and inventions resulting from the joint creation or use of intellectual property by us and our collaborators, licensors, scientific collaborators and consultants. In addition, other parties may circumvent any proprietary protection we do have. As a result, we may not be able to maintain our proprietary position.

Manufacturing

The process for manufacturing oligonucleotides such as ISS is well established and uses commercially available equipment and raw materials. To date, we have manufactured small quantities of our oligonucleotide formulations for research purposes. We have relied on a single contract manufacturer to produce our ISS for clinical trials. We have identified several additional manufacturers with whom we could contract for the manufacture of ISS.

TOLAMBA consists of ISS linked to Amb a 1, the principal ragweed allergen, which is purified from ragweed pollen purchased on an as-needed basis from commercial suppliers of ragweed pollen. If we are unable to purchase ragweed pollen from commercial suppliers, we may be required to contract directly with collectors of ragweed pollen which may in turn subject us to unknown pricing and supply risks.

As we develop product candidates addressing other allergies, including grass, tree and plant allergies, we may face similar supply risks. In the past, TOLAMBA was produced for us by a single contract manufacturer. Our existing supplies of TOLAMBA are sufficient for us to conduct our currently planned Phase III clinical trial. We plan to qualify and enter into manufacturing agreements with one or more new commercial manufacturers to produce additional supplies of TOLAMBA as required for completion of clinical trials and commercialization.

HEPLISAV consists of ISS combined with GMP hepatitis B surface antigen using standard formulation processes. Hepatitis B surface antigen is manufactured worldwide by several companies. We have acquired hepatitis B surface antigen for our clinical trials to date from a single commercial manufacturer. We entered into a license and supply agreement with Berna Biotech (acquired by Crucell N.V.), under which Berna will provide a supply of antigen necessary to permit us to commence our planned Phase III trials and to commercialize HEPLISAV.

Marketing

We have no sales, marketing or distribution capability. We intend to seek global or regional partners to help us market certain product candidates. We are inclined to license commercial rights to larger pharmaceutical or biotechnology companies with appropriate marketing and distribution capabilities, except in instances where it may prove feasible to build a small direct sales organization targeting a narrow specialty or therapeutic area.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. Many of our competitors, including biotechnology and pharmaceutical companies, academic institutions and other research organizations, are

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actively engaged in the discovery, research and development of products that could compete directly or indirectly with our products under development.

If TOLAMBA is approved and commercialized, it will compete directly with conventional allergy immunotherapy. Conventional allergy immunotherapy products are mixed by allergists and customized for individual patients from commercially available plant material extracts. Because conventional immunotherapies are customized on an individual patient basis, they are not marketed or sold as FDA approved pharmaceutical products. Other companies such as ALK-Abello, Allergy Therapeutics and Cytos are developing enhanced allergy immunotherapeutic products formulated for both injection and sublingual delivery. We believe that our TOLAMBA program for ragweed allergy is the more advanced and, if developed, approved and commercialized, could reach the market ahead of these other products. A number of companies, including GlaxoSmithKline Plc, Merck & Co., Inc., and AstraZeneca Plc, produce pharmaceutical products, such as antihistamines, corticosteroids and anti-leukotriene agents, which manage seasonal allergy symptoms. We consider these pharmaceutical products to be indirect competition for TOLAMBA because although they are targeting the same disease, they do not attempt to treat the underlying cause of the disease.

Our hepatitis B vaccine, if it is approved and commercialized, will compete directly with existing, three-injection vaccine products produced by Merck & Co., Inc., GlaxoSmithKline Plc, and Berna Biotech AG (acquired by Crucell N.V.), among others. There are also two-injection hepatitis B vaccine products in clinical development, including a vaccine being developed by GlaxoSmithKline Plc. In addition, our hepatitis B vaccine will compete against a number of multivalent vaccines that simultaneously protect against hepatitis B in addition to other diseases. Our hepatitis B immunotherapy, if developed, approved and commercialized, may compete directly with existing hepatitis B therapeutic products (including antiviral drugs and interferon alpha) manufactured by Roche Group, Schering-Plough Corporation, Gilead Sciences, Inc., GlaxoSmithKline Plc and other companies.

Our inhaled 1018 ISS asthma product candidate would indirectly compete with existing asthma therapies, including corticosteroids, leukotriene inhibitors and IgE monoclonal antibodies, including those produced by Novartis Corporation, AstraZeneca Plc, Schering-Plough Corporation and GlaxoSmithKline Plc. We consider these existing therapies to be indirect competition because they only attempt to address the symptoms of the disease and, unlike our product candidate, do not attempt to address the underlying cause of the disease. We are also aware of a preclinical inhaled product, which may target the underlying cause of asthma, rather than just the symptoms, which is being developed by Aventis Group under a collaboration agreement with Coley Pharmaceutical Group. This product, if approved and commercialized, may compete directly with our asthma product candidate.

Many of the entities developing and marketing these competing products have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing than us. Smaller or early-stage companies may also prove to be significant competitors, particularly for collaborative agreements with large, established companies and access to capital. These entities may also compete with us in recruiting and retaining qualified scientific and management personnel, as well as in acquiring technologies complementary to, or necessary for, our programs.

We expect that competition among products approved for sale will primarily be based on the efficacy, ease of use, safety profile, and price. Our ability to compete effectively, develop products that can be manufactured cost-effectively and market them successfully based on differentiated label claims will depend on our ability to: