Altimmune (ALT)

Initiation Report

LifeSci Investment Abstract

Altimmune (NasdaqGM: ALT) is an infectious disease company developing a differentiated prophylactic vaccine for seasonal and pandemic influenza as well as immunotherapy treatments for chronic hepatitis B virus (HBV), anthrax infection, and cancer. The Company, which recently became public through a reverse merger with PharmaAthene, has important data readouts from each of their programs in the next 2-3 quarters and may continue to drive pipeline expansion down the road with two proprietary vaccine platform technologies, RespirVec and Densigen. Altimmune's immunotherapeutics pipeline may be underappreciated by investors given the key advantages that they offer over existing therapies.

Key Points of Discussion

■ Successful Reverse Merger Creates Company Focused on Immunotherapeutics. On May 4th, Altimmune announced the closing of a reverse merger agreement with PharmAthene and began trading on the Nasdaq Global Market the following day under the ticker ALT. Following the merger, Altimmune shareholders own 58.2% of the combined company. The Company is testing multiple, novel immunotherapeutics for a wide range of infectious diseases, including seasonal and pandemic influenza, chronic hepatitis B virus (HBV), and anthrax infection. Data readouts from four clinical studies are expected over the course of the next 2-3 quarters, which should provide further validation of the Company’s clinical pipeline and could represent important inflection points in the Company’s valuation.

■ Altimmune Recently Announced Launch of Phase II Trial for Intranasal Flu Vaccine NasoVAX. Altimmune is developing NasoVAX as a vaccine for the prophylactic treatment of seasonal and pandemic influenza and recently announced the launch of a Phase II study in approximately 60 patients. The trial is testing 3 doses of NasoVax and is expected to read out data in the first quarter of 2018. This trial will provide important information on the safety and immunogenicity of these NasoVax doses as well as help with dose optimization for subsequent studies.

Expected Upcoming Milestones

■ H2 2017 – Launch of preclinical bridging study for SparVax-L.
■ Q4 2017 – Initial data from ongoing Phase I study for HepTcell.
■ Q1 2018 – Preliminary data expected from Phase II study for NasoVAX.
■ Q1 2018 – Launch of Phase I study for NasoShield.
■ H1 2018 – Data expected from SparVax-L bridging study.
■ Q2 2018 – Data expected from NasoShield Phase I study.
■ Q3 2018 – Full data expected from HepTcell Phase I study.

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Market Data

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For analyst certification and disclosures please see page 42
The flu affects millions of individuals each year and is one of the leading causes of mortality worldwide. Traditional influenza vaccinations, which contain inactivated or live attenuated influenza virus particles or subunit proteins, are the most important and effective method of preventing infection and controlling the spread of influenza during seasonal epidemics and pandemics. NasoVAX is a fundamentally differentiated product, as it does not contain influenza virus particles, and it may confer robust and broad protection against a broad range of influenza strains by eliciting a rapid innate immune response and long-term adaptive immunity. Altimmune is developing NasoVAX as a more convenient and efficacious alternative to traditional influenza vaccines, which are typically administered via intramuscular injection, since it can be easily and painlessly administered directly to the upper respiratory tract by intranasal treatment.

- **NasoVAX Has a Differentiated Mechanism of Action.** Traditional influenza vaccines contain inactivated or live attenuated influenza virus particles or subunit proteins, often combined with an immune-boosting adjuvant. When administered by intramuscular injection, influenza vaccines stimulate the immune system to produce neutralizing antibodies against the virus, thus conferring protection against subsequent infections. Due to the high mutation rate of influenza, flu vaccines must be administered annually to maintain immunity against changing viral strains. Unlike traditional vaccines, NasoVAX does not contain actual influenza virus particles. Instead, NasoVAX consists of a genetically engineered replication-deficient adenovirus serotype 5 (Ad5) vector that drives the expression of influenza hemagglutinin (HA) within host cells. Since adenoviruses occur widely in nature and are strongly immunogenic, intranasal administration of NasoVAX rapidly stimulates an innate immune response within the upper respiratory tract, thus priming the immune system and broadly protecting against subsequent influenza infections. This effect is independent of influenza strain subtype, providing a significant advantage over traditional strain-specific vaccines.

- **Large Market Opportunity for an Intranasal Flu Vaccine.** According to the CDC, approximately 146 million doses of seasonal influenza vaccine were administered in the US during the 2016-2017 influenza season. The average cost of one dose of a classical inactivated influenza vaccine ranges from approximately $15-18 in the private sector, representing a total addressable market of approximately $2.4 billion. However, the CDC reports that only 40% of Americans received influenza vaccination in recent years, while recommending a goal of 70% vaccination coverage. AstraZeneca's (NYSE: AZN) FluMist Quadrivalent (live influenza vaccine) is an intranasal vaccine that contains live attenuated influenza viruses, and has demonstrated the potential for an intranasal agent to achieve market penetration in a space dominated by vaccines administered via intramuscular injection. FluMist achieved US sales of $206 million in 2015 and $290 million globally. These data speak to the potential adoption of influenza vaccines administered intranasally, although we note that NasoVAX is further differentiated from such a product due to its ability to confer rapid, broad protection against all known viral strains.

Importantly, in the last two years, the CDC has recommended against the use of LAIV vaccines (available only by means of intranasal delivery, and FluMist is the only product) due a body of data collected over several years that points to its limited efficacy in preventing influenza. For example, during the 2015-2016 season, it was observed that only 3% of LAIV vaccine recipients between the ages of 2 -17 were conferred protection from influenza, while IIV vaccines in comparison conferred 63% protection. While the reason for this discrepancy is unknown, it is thought to be specific to FluMist particularly, or LAIV vaccines in general, and unrelated to the mode of administration. However, we do not see potential for a similar issue to arise with NasoVAX due to its differentiated mechanism of action.

Overall, we have a favorable view of both the time FluMist spent on market due to its market penetration, which highlighted the demand for a therapy with a more convenient and less intimidating mode of administration, as well as the subsequent CDC recommendation against this therapy, as it has eliminated a competing intranasal vaccine in the US.

- **HepTcell Has Potential to Reawaken Immune System in Chronic HBV.** Altimmune is developing the therapeutic vaccine, *HepTcell*, for the treatment of individuals chronically infected with hepatitis B virus (HBV). HBV is the most common serious infection of the liver, and is generally characterized as chronic when it persists for longer than six months. Chronic HBV infections primarily develop in infants and young children, and can lead to life-threatening liver cirrhosis, liver failure, and liver cancer later in life. *HepTcell* is a synthetic peptide product that targets all known HBV genotypes, and utilizes the Company’s Densigen technology that Altimmune believes may help eliminate HBV infected cells to ultimately provide a functional cure for this disease. Some of the compounds differentiating features include: a stabilization feature that may induce sustained immunity against HBV, potential activation of T cells which has been shown in preclinical findings, and potential to target all of the existing HBV strains concurrently. These features result from *HepTcell*’s design, which includes a combination of nine viral peptide sequences each coupled to a fluorocarbon chain. While the peptide sequences may be effective against the full spectrum of HBV genotypes through generation of a human leukocyte antigen (HLA) type-independent immune response, the fluorocarbon chain produces a short-term depot of *HepTcell* that may lead to sustained activation of the immune system. The Company is currently conducting a Phase I study with *HepTcell* for patients chronically infected with HBV in the UK, and initial results are expected in the fourth quarter of 2018. Altimmune plans to file an IND in the US for *HepTcell* in 2018, and subsequently commence Phase II studies.

- **Altimmune is Pursuing Two Vaccines to Protect Against Anthrax.** Since spores from the bacterium *Bacillus anthracis*, the causative agent of anthrax, can potentially be disseminated as a biological weapon, it is critical to have a vaccine that induces rapid and sustained immunity. Furthermore, anthrax vaccines should be optimized for easy administration to mass populations by nonmedical personnel. To address this need, Altimmune is developing two anthrax vaccine candidates, *SparVax-L* and *NasoShield*. We note that the Company has received substantial funding for both programs—$15 million from the National Institute of Allergy and Infectious Diseases (NIAID) for *SparVax-L* and $127 million from Biomedical Advanced Research and Development Authority (BARDA) for *NasoShield*—providing important validation of these programs. Altimmune expects to initiate a Phase I study for *NasoShield* in the first quarter of 2018, and initial data are expected in the second quarter of 2018.

- **Market Opportunity for an Anthrax Vaccine with More Rapid Onset of Protection.** Although the number of adults with naturally occurring anthrax is virtually zero, there is a substantial need for an anthrax vaccine used for biodefense purposes. The CDC has classified *B. anthracis* as the highest priority in biodefense research and as one of the nine class A agents. Following the anthrax attacks in 2001, the US government allocated $50 billion to prevent biological warfare epidemics from occurring. Two government agencies that protect against biological warfare, the Joint Program Executive Office for Chemical Biological Defense (JPEO-CBD) and Biomedical Advanced Research and Development Authority (BARDA), currently provide substantial funds and stockpiles of vaccines against anthrax. In 2015, Emergent BioSolutions’ (NYSE: EBS) *BioThrax*—which is administered by three intramuscular injections at 0, 1 and 6 months—became the first anthrax vaccine to be approved by the FDA. In 2016, *BioThrax* had sales of $237 million, highlighting the existing market for an anthrax vaccine. We note the potential for Altimmune’s *NasoShield* to gain substantial market share if ultimately approved, given it is delivered through a single intranasal dose, and offers faster and more durable protection against anthrax.
Financial Discussion

Second Quarter 2017 Financial Results. On August 10th, Altimmune reported financial results for the second quarter of 2017. Revenue from grants and contracts amounted to $3.0 million for the second quarter. The Company reported research and development costs of $5.3 million and general and administrative expenses of $1.8 million. The net loss attributable to shareholders for the quarter was $3.2 million or $0.26 per share. As of June 30th, Altimmune had cash and cash equivalents of $8.4 million.

Reverse Merger. On May 4th, Altimmune announced the closing of their reverse merger with PharmAthene and began trading on the Nasdaq Global Market the following day under the ticker ALT. Following the merger, Altimmune shareholders own 58.2% of the combined company.

August Financing. On August 17th, Altimmune closed an offering to sell 15,656 shares of Series B preferred shares for gross proceeds of $14.7 million and roughly $13 million in net proceeds. The preferred shares have a $1,000 stated value and 6% original issue discount. The deal also included warrants to purchase a total of 2,345,427 shares of common stock at an exercise price of $2.67 per share. The warrants expire on August 15, 2022. The Company has agreed to redeem the preferred shares—with cash or stock—at the stated value in nine equal monthly installments beginning December 15, 2017.
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Company Description

Altimmune is a clinical-stage biotechnology company focused on the development of novel immunotherapeutics for a wide range of infectious diseases. The Company recently completed a reverse merger with PharmAthene to become a publicly traded company and is currently traded on the Nasdaq Global Market under the ticker ALT. The Company’s lead program is NasoVAX, a prophylactic vaccine for seasonal and pandemic influenza, which is dosed intranasally and provides for faster immunogenicity and protection against a broad range of influenza strains through the induction of innate and adaptive immune mechanisms. Altimmune submitted an Investigational New Drug (IND) application for NasoVAX and recently launched a Phase II study for the vaccine candidate in the third quarter of 2017. An initial data readout is expected in the first quarter of 2018. The Company’s full development pipeline is shown in Figure 1.

![Figure 1. Altimmune’s Development Pipeline](image)

Source: LifeSci Capital

Altimmune is developing HepTcell, a therapeutic vaccine, for the treatment of individuals chronically infected with hepatitis B virus (HBV). HBV is the most common serious infection of the liver, and is generally characterized as chronic when it persists for longer than six months. Chronic HBV infections can lead to life-threatening liver cirrhosis, liver failure, and liver cancer later in life. HepTcell is a synthetic peptide product that targets all known HBV genotypes, and utilizes the Company’s Densigen technology to promote the clearance of HBV-infected cells. The Company is currently conducting a Phase I study with HepTcell in chronic HBV patients in the UK and South Korea, and initial results are expected in the fourth quarter of 2018. Altimmune plans to file an IND in the US for HepTcell in 2018, and subsequently commence Phase II studies.

Altimmune also has two anthrax vaccines in development, one that was developed in-house and another that was acquired through the reverse merger with PharmAthene. Since B. anthracis, the causative agent of anthrax infection, has been developed by many countries as a biological warfare agent, and has been a top bioterrorism concern since the 2001 anthrax attacks in the US, there is significant interest in developing more effective prophylactic measures to
prevent anthrax infections. The Company has received substantial funding for both programs, including $15 million from the National Institute of Allergy and Infectious Diseases (NIAID) for SparVax-L, and $127 million from Biomedical Advanced Research and Development Authority (BARDA) for NasoShield. Altimmune plans to launch a Phase I clinical study for NasoShield in the first quarter of 2018, and initial data are expected in the second quarter of 2018. The Company is also planning to initiate a nonclinical bridging study for SparVax-L in the second half of 2017.

NasoVAX: An Intranasal Flu Vaccine to Rapidly Protect Against Seasonal and Pandemic Influenza

Altimmune is developing NasoVAX as a vaccine for the prophylactic treatment of seasonal and pandemic influenza. Seasonal influenza is an acute respiratory disease caused by circulating influenza viruses, and is commonly known as the flu. This virus affects millions of individuals each year and is one of the leading causes of mortality worldwide. Traditional influenza vaccinations, which contain inactivated or live attenuated influenza virus particles or subunit proteins, are the most important and effective method of preventing infection and controlling the spread of influenza during seasonal epidemics and pandemics. NasoVAX is a fundamentally differentiated product, as it does not contain influenza virus particles, and is built on a novel platform technology called RespirVec. This technology confers robust and broad protection against different influenza strains by eliciting a rapid innate immune response and long-term adaptive immunity. Altimmune is developing NasoVAX as a more convenient and efficacious alternative to traditional influenza vaccines, which are typically administered via intramuscular injection, since it can be easily and painlessly administered directly to the upper respiratory tract by intranasal treatment.

The Company conducted two Phase I studies with NasoVAX to assess safety and immunogenicity in healthy adults. Results from these studies indicate that NasoVAX was effective in inducing an immune response in up to 67% of patients following a single dose and 83% following two doses. We also note that up to 25 percent of the high dose group showed at least a fourfold increase. Additionally, HAI antibodies were also detected post-immunization with a prepandemic version of NasoVAX in up to 33 percent of the highest dose cohort tested. Following these findings, Altimmune has initiated a Phase II study evaluating higher doses of NasoVAX in healthy volunteers. Initial data are expected in the first quarter of 2018. Altimmune plans to use the results of this trial to select dosing for a larger dose confirmation trial.

Mechanism of Action. Traditional influenza vaccines contain inactivated or live attenuated influenza virus particles or subunit proteins, often combined with an immune-boosting adjuvant. When administered by intramuscular injection, influenza vaccines stimulate the immune system to produce neutralizing antibodies against the virus, thus conferring protection against subsequent infections. Due to the high mutation rate of influenza, flu vaccines must be administered annually to maintain immunity against changing viral strains. Unlike traditional vaccines, NasoVAX does not contain actual influenza virus particles. Instead, NasoVAX consists of a genetically engineered viral vector that drives the expression of influenza hemagglutinin (HA) within host cells. More specifically, NasoVAX is a replication-deficient adenovirus serotype 5 (Ad5) vector engineered to encode the influenza viral HA protein. Since adenoviruses occur widely in nature and are strongly immunogenic, intranasal administration of NasoVAX rapidly stimulates an innate immune response within the upper respiratory tract, thus priming the immune system and broadly

protecting against subsequent influenza infections. This effect is independent of influenza strain subtype, providing a significant advantage over traditional strain-specific vaccines.

In addition, adenovirus-mediated expression of influenza HA in host tissue elicits a long-term adaptive immune response in the body, driving the production of neutralizing antibodies against the head domain of HA. The red antibodies depicted in Figure 2 demonstrate how neutralizing HA head-specific antibodies bind HA on the surface of influenza particles, thus preventing attachment to host cell surface receptors and inhibiting budding and viral egress.6

Figure 2. Mechanism of Neutralizing Antibodies Against Influenza Virus

Since administration of adenovirus vectors elicits a strong immune response to a foreign antigen without the use of adjuvants, NasoVAX more closely mimics a natural pathogen infection, providing a safe approach to stimulate both antibody and cell-mediated immunity. Furthermore, the Ad5 vector used in NasoVAX lacks critical components necessary for viral replication, allowing NasoVAX to stimulate an immune response without a host adenovirus

infection. In addition, Ad5 transgenes do not become stably integrated into the host genome, allowing transient influenza hemagglutinin expression that can stimulate long-term adaptive immunity.\(^8\)

**Route of Administration.** Most individuals have pre-existing immunity to Ad5 due to the abundance of adenoviruses in nature. Therefore, neutralizing antibodies often prevent uptake of Ad5 vectors when they are administered by injection, causing loss of transgene expression.\(^9\) However, emerging evidence suggests that intranasal administration of Ad5 bypasses pre-existing immunity, allowing for a robust immunogenic response. This is due to efficient gene delivery in cells along the mucosal barrier and strong immunocompetence of the superficial epithelium layer.\(^10\) Therefore, *NasoVAX* is administered as an intranasal vaccine. This painless and convenient route of administration may facilitate broader use compared to injectable vaccines, and could represent a significant benefit to patients.

**Preclinical Data**

The immunoprophylactic activity of *NasoVAX* has been demonstrated in multiple preclinical studies.\(^11\) Using a mouse model of influenza infection, preclinical data show that intranasal administration of a non-replicative Ad5 vaccine encoding influenza virus hemagglutinin 1 (HA1) domain conferred protection as a prophylactic drug and elicited long-term protective immunity against subsequent influenza infections. These data provided rationale for Altimmune to move *NasoVAX* into clinical studies, which are currently progressing.

**Adenovirus Vectored Vaccination Study in Mice.** This study assessed the use of adenovirus vectors as a prophylactic treatment to protect against influenza. Mice were immunized with either an Ad5 vector encoding the HA1 domain of the A/New Caledonia/20/99 H1N1 influenza virus strain (AdNC.H1.1) or a transgene-free, non-replicative Ad5 empty (AdE) vector. Following this, mice were challenged with exposure to a live strain of influenza virus. Mice were treated intranasally with varying doses of AdE or AdNC.H1.1 particles, then challenged with intranasal instillation of a lethal dose of live A/Puerto Rico/8/34 H1N1 influenza virus (PR8). The proportion of surviving mice was assessed daily for 18 days following the influenza challenge, with a 30% body weight loss serving as the disease endpoint.

Survival data from this study are presented in **Figure 3**. As shown in panel A, intranasal (IN) administration of 1.76 x 10^8 infectious units (IFU) of AdE or AdNC.H1.1 protected 100% and 70% of mice against a lethal dose of PR8, respectively. Only 10% of untreated mice survived (graph H). Use of a lower dose (1.76 x 10^6 IFU) resulted in survival rates of 20% and 0% (B,F). Intramuscular vaccination (C, G) 2 days prior to challenge conferred no survival benefit. These results show that intranasal administration of an adenovirus-based vaccine can induce early protection against influenza infection. The protective effect of the transgene-free non-replicating AdE vector and the HA1 domain specific AdNC.H1.1 suggests that this class of vaccine can rapidly confer a prophylactic benefit even before adaptive immunity is established, which may be due to the immediate stimulation of innate immunity. It has previously been

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shown that Ad5 particles can induce a wide range of innate immune responses, including the production of inflammatory cytokines and chemokines, activation of natural killer cells, and the production of antiviral nitric oxide.\textsuperscript{12,13,14}

Figure 3. Prophylactic Vaccination Against Lethal Influenza Challenge

\begin{figure*}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Prophylactic Vaccination Against Lethal Influenza Challenge}
\end{figure*}

\textsuperscript{*} denotes a dose of $1.7 \times 10^6$ IFU; -2 corresponds with treatment administration 2 days prior to influenza challenge, whereas +1 corresponds with treatment administration 1 day after influenza challenge; im and in refer to intramuscular and intranasal administration, respectively.

Source: Zhang et al., 2011

Aside from rapid protection, which occurred over a course of several days, the preclinical data also demonstrate that protection against influenza could be sustained for several weeks. As shown in graph A of Figure 4, IN administration of AdNC.H1.1 47 days before the PR8 challenge protected 100% of mice, which correlates with HA1-induced adaptive immunity. As shown in graph B, AdE vaccination had a similar long-term benefit, protecting 70% of mice from the PR8 challenge.

The preclinical data also demonstrate that this adenovirus vector-based vaccination approach can protect against a range of influenza strains. For example, mice were treated with AdE or AdNC.H1.1 and given a lethal dose of the pandemic H1N1 swine flu A/California/04/2009 2 or 22 days later, and 90-100% of mice survived as compared to approximately 10% for placebo. Overall the results of the preclinical data demonstrate that the adenovirus vector vaccine approach can confer rapid and long-term protection against a broad range of influenza virus strains with IN administration. Figure 5 highlights the cross-strain protection afforded by NasoVax when challenge with a divergent strain, against which a conventional vaccine would be ineffective.

**Safety Profile.** Based on extensive characterization and use in many vaccination and gene therapy trials, adenovirus vectors are generally considered to be safe for use in humans. In the case of influenza specifically, results from clinical studies have shown that intranasal application of an Ad5-derived vector encoding influenza HA is safe and well tolerated in human subjects. In a Phase I trial testing that assessed the effects of Ad-vector influenza vaccination through IN or topical administration, no serious reactions were observed either systemically or locally at the site of inoculation. Furthermore, of the reported side effects, 85% were mild and only consisted of mild nasal irritation after

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intranasal immunization. A small number of patients experienced moderate nausea after primary immunization.\textsuperscript{16} An acceptable safety profile has also been observed in an additional Phase I clinical study for a pandemic \textit{NasoVAX} product, and there were no emergent concerns.

**Influenza**

Seasonal influenza is an acute respiratory disease caused by circulating influenza viruses. More commonly known as the flu, influenza affects millions of individuals each year and is one of the leading causes of mortality worldwide. With limited antiviral treatment options, this highly infectious disease is a significant global public health and economic burden. Annual vaccination is the most important and effective method of preventing infection and controlling the spread of influenza during seasonal epidemics and pandemics.

**Causes and Pathogenesis.** Seasonal influenza epidemics occur annually throughout the world. Influenza is highly infectious due to the rapid transmission of viral particles from one host to another. The virus is usually spread when an infected individual sneezes or coughs, which disperses infectious droplets containing viral particles into the air. Influenza can also be spread by contact with surfaces contaminated with viral particles.

There are three main influenza subtypes that are differentiated by the specific expression of viral surface glycoproteins and the composition of viral ribonucleoproteins. Influenza A and B circulate widely throughout the global population and are the subtypes responsible for seasonal epidemics, which affect 2-5 million individuals annually.\textsuperscript{17} Type A is typically the most severe and occasionally causes pandemics such as the Spanish Influenza of 1918. Influenza type C is less common and is usually associated with milder symptoms.\textsuperscript{18}

Influenza viruses are enveloped, negative-sense, single-stranded RNA viruses. As shown in Figure 6, influenza infection begins when the viral surface glycoprotein hemagglutinin (HA) binds to host cell surface receptors and enters the cell by endocytosis. In the low pH environment of the host cell cytoplasm, the viral particle fuses with endosomes and releases the viral genome into the cytoplasm. Viral RNA is then transported into the nucleus, where it is transcribed and replicated. Viral proteins synthesized in the cytoplasm combine with newly replicated viral RNA into viral ribonucleoprotein (vRNP) complexes. vRNPs are then exported to the cytoplasm and packaged and assembled into viral particles, which bud off from the host cell membrane and enter the extracellular space. This replicative process propagates the infection throughout the host.\textsuperscript{19}

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The body’s immune system typically recognizes viral surface antigens upon initial exposure and produces antibodies to prevent against future re-infection by the same viral strain. However, influenza viruses are evolutionarily dynamic due to a high mutation rate while replicating. In a process known as antigenic drift, an accumulation of mutations in antigenic regions, such as surface glycoproteins, allows viruses to continually mutate and evade detection by the host’s immune system. This rapid viral evolution leads to antiviral drug resistant influenza strains that circulate widely throughout the population and cannot be treated with existing antiviral therapeutics. Although vaccination is the most effective method to prevent against infection, continuous viral evolution necessitates annual revaccination against new strains. Many efforts are underway to increase the long-term efficacy of vaccination, and Altimmune’s NasoVAX may address these concerns due to its’ potentially broad immunogenicity.

**Symptoms and Diagnosis.** Common symptoms of influenza manifest locally at the sites of virus replication and systemically due to the release of inflammatory mediators and cytokines. Localized symptoms within the respiratory tract include nasal congestion, cough and a sore throat. Systemic symptoms include a sudden onset of fever, chills and body aches. Symptoms usually begin approximately two days after infection, due to the viral incubation period, and resolve within a week of onset without requiring medical attention. However, in some cases, influenza can result in severe illness or death, particularly in high risk populations like children and the elderly. In addition to the common symptoms, influenza can also lead to more serious health complications. The most common complication resulting from influenza is the spread of the viral infection into the lungs, causing pneumonia. Occasionally influenza can also lead to extra-respiratory complications, including influenza-associated acute encephalopathy and myocarditis.

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Accurate and early diagnosis of influenza is necessary for the rapid initiation of antiviral therapy and prophylactic measures to control the infection during seasonal outbreaks and pandemics. The current gold standard for influenza diagnosis is the viral culture approach, which involves acquiring a clinical sample from an infected patient and propagating the virus in permissive cell lines or embryonated eggs for 7-10 days while monitoring the cytopathic effect in vitro. The influenza infection is then confirmed by methods such as antibody staining or hemadsorption tests using red blood cells.

Faster and simpler diagnostic methods include antigen-based rapid influenza diagnostic tests (RIDTs), which use antibodies to detect viral proteins in patient samples. Available in dipstick and cassette format, RIDT results can be easily observed based on a color change or other optical detection methods. Although this approach is less accurate than other tests, RIDTs allow rapid influenza diagnosis in less than 30 minutes within point-of-care settings. Additional diagnostic techniques are outlined in Figure 7.

**Figure 7. Influenza Diagnostic Techniques**

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
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<tbody>
<tr>
<td>Nucleic Acid-based Test (NAT)</td>
<td>Detects viral genetic material by polymerase chain reaction.</td>
</tr>
<tr>
<td>Direct Fluorescent Antibody (DFA)</td>
<td>Detects viral antigens by direct staining of respiratory epithelial cells from nasopharyngeal swabs.</td>
</tr>
<tr>
<td>Serological Assays</td>
<td>Detects virus-specific antibody responses in patient serum. Examples include the hemagglutination assay and the virus neutralization assay.</td>
</tr>
<tr>
<td>Nucleic Acid Sequencing</td>
<td>Particularly useful for the detection of antiviral resistance and high virulence markers in circulating influenza strains.</td>
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*Source: LifeSci Capital and Vemula, S.V., et al., 2016*

**Treatment Landscape**

The treatment landscape for influenza infections includes antiviral therapeutics to treat existing illnesses and prophylactic measures to prevent infections. Vaccination is the most critical method of preventing and controlling the spread of influenza, and is particularly important for populations at high risk for complications.

**Vaccines.** Influenza vaccines primarily focus on stimulating the production of antibodies against the viral surface protein hemagglutinin (HA), which facilitates virus entry into host cells. Once the body has produced strain-specific antibodies, infection can be prevented if an individual is exposed to the virus. Each year, seasonal vaccines must be reformulated to match the antigenic drift of influenza strains in the northern and southern hemispheres. Given the lengthy vaccine development process, strains included in the upcoming seasonal vaccine must be selected 7-8 months in advance.

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in advance of flu season. Seasonal influenza vaccines fall into three classes, all of which contain components of influenza A and B that are expected to circulate in the following influenza season:

- **Inactivated influenza vaccine (IIV)** – IIVs contain purified and inactivated virions and induce a serum IgG antibody response specific to influenza strains. The trivalent inactivated vaccine contains influenza A subtypes H1N1 and H3N2 and the dominant predicted strain of influenza B. The quadrivalent inactivated vaccine contains influenza A subtypes H1N1 and H3N2 and two strains of influenza B. IIV is administered intramuscularly or intradermally.

- **Live attenuated influenza vaccine (LAIV)** – LAIVs contain live influenza strains with temperature-sensitive mutations, which restricts viral replication to the cooler environment of the nasal cavity. LAIV is administered intranasally and induces the production of serum IgG antibodies against influenza A H1N1 and H3N2 and two strains of influenza B, as well as T cell and mucosal IgA responses. AstraZeneca’s FluMist is currently the only LAIV approved, although it is not currently recommended for use.

- **Recombinant HA vaccine** – Flublok, for example, contains recombinant HA proteins derived from insect cells. Unlike other influenza vaccines, which contain elements of the influenza virus that have been harvested from chicken eggs, Flublok uses an egg-free manufacturing process, allowing for faster vaccine development in the case of a vaccine supply shortage or pandemic.

Although vaccines are generally considered safe and are currently the best approach to prevent and control influenza outbreaks, there are several challenges associated with prophylactic treatment. Continuous antigenic drift necessitates annual re-vaccination to maintain protection against infection. Furthermore, given the lengthy period of vaccine production, global surveillance to select optimal strains for inclusion must be conducted months prior to the flu season. To circumvent these challenges, many research efforts are underway to generate universal and broadly protective influenza vaccines that can prevent against influenza A and B regardless of viral subtype or antigenic drift season to season. This approach requires a mechanism of action that either targets conserved domains of viral proteins or induces universal protection through innate immunity mechanisms. For example, there are universal vaccine candidates in late stage clinical development that target the conserved stalk domain of the hemagglutinin molecule, as opposed to the highly plastic and continually mutating head region.

**Antiviral Therapeutics.** Aside from prophylactic vaccines, antiviral drugs are also important methods of treatment, particularly in severe cases and in the early stages of a pandemic when suitable vaccines are not available. There are two classes of drugs with anti-influenza activity:

1) **Adamantanes** – For example, Endo Pharmaceutical’s (NASDAQ: ENDP) Symmetrel (amantadine), and the generic drug rimantadine, block a critical component needed for viral replication. Adamantanes are effective against both influenza A and B, but studies have shown that both drugs can rapidly select for resistant viral strains. Furthermore, it has been shown that resistance to one drug can result in complete cross-resistance to the other drug, rendering the entire drug class ineffective against certain mutated strains. Currently, most circulating influenza strains are resistant to adamantanes. Therefore, the CDC is not recommending adamantanes for influenza treatment at present.

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2) Neuraminidase inhibitors (NAIs) – NAIs interfere with the release of newly formed virions from host cells. NAIs are effective against both influenza A and B. The CDC recommended three FDA-approved treatments for the 2016-2017 flu season, which included GlaxoSmithKline’s (NYSE: GSK) Relenza (zanamivir), BioCryst Pharmaceuticals’ (NASDAQ: BCRX) Rapivab (peramivir), and Roche’s (SIX: ROG) Tamiflu (oseltamivir).

Although antiviral drugs improve recovery and reduce the severity of infections, drug resistance remains a significant challenge. Mutations in antiviral targets occur rapidly during viral replication, leading to a loss of drug binding and viral resistance on both regional and global scales. Therefore, many ongoing clinical trials are testing influenza antivirals with novel mechanisms of action.

Influenza Market Information

Epidemiology. Influenza typically arises in populations in a pattern of seasonal epidemics, causing higher-than-expected rates of cases during regular annual periods within local populations. These periodic spikes in disease activity are due to the regular emergence of antigenic mutant forms of the virus that, unlike the subsequent strains of the virus, have not caused the development of population-wide immunity through prior infection. If minor changes in antigen structure allows for viable transmission and infectivity that can undermine pre-existing immunological defenses, the strain becomes the predominant agent of infection through natural selection. The precise timing of the appearance, spike, and drop in influenza incidence varies from season to season. However, in the US and EU the appearance of antigenically-novel influenza occurs during the fall and typically causes a period of increased influenza incidence between October/November and April followed by an abrupt drop in number of cases that remains consistent throughout the summer months.26,27

Of the three types of seasonal Influenza (A, B, and C) type A is the most virulent tends to be the agent of yearly increases in severe cases, hospitalizations, ICU visits, and deaths. Seasonal Influenza affects all age groups and genders. Groups that experience the greatest number of complications, hospitalizations, and deaths from influenza are adults over the age of 65, and children under the age of 5.28,29,30 Elderly persons over 65 years of age accounted for 54% to 70% of hospitalizations and 71% to 85% of deaths associated with influenza in the US between 2010-2013. Overall, it is estimated that influenza was associated with 100,000 to 600,000 hospitalizations in the US, based on data from the 2010-2011 through 2012-2013 seasons.31 Assuming a similar hospitalization rate in the EU, we assume that approximately 200,000 to 1,000,000 hospitalizations occur in the EU. Influenza is estimated to be associated with an

average of 3,300 to 49,000 deaths in the US.\(^{32}\) According to a study on direct medical costs resulting from seasonal influenza, costs averaged approximately $10.4 billion per year in the US. Furthermore, an annual economic burden of about $87.1 billion is attributed to the condition.\(^{33}\)

**Market Size.** According to the CDC, approximately 146 million doses of seasonal influenza vaccine were administered in the US during the 2016-2017 influenza season. The average cost of one dose of a classical inactivated influenza vaccine ranges from approximately $15-18 in the private sector, representing a total addressable market of approximately $2.4 billion. However, the CDC reports that only 40% of Americans received influenza vaccination in recent years, while recommending a goal of 70% vaccination coverage. To assess the market potential of a seasonal intranasal influenza vaccine such as *NasoVAX*, we performed a scenario analysis in Figure 8. We found that with a price of $25 per dose and 10% market penetration, *NasoVAX* could achieve annual sales of $365 million in the US. This scenario analysis assesses US sales only for seasonal influenza, with EU and pandemic uses as potential upside. Our analysis utilized the following assumptions:

- **Vaccines Administered Annually** – We assume that at least 146 million vaccines will be administered in subsequent influenza seasons in the US.
- **Pricing** – We assume that *NasoVAX* has potential to be priced at a premium to traditional influenza vaccines, in the $25 range per dose. This is due to its convenient mode of administration that may allow for faster immunogenicity and protection against a broad range of influenza strains.

### Figure 8. Scenario Analysis for *NasoVAX* in the US

<table>
<thead>
<tr>
<th>Penetration</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pricing - High</td>
<td>$146 M</td>
<td>$292 M</td>
<td>$438 M</td>
</tr>
<tr>
<td>Pricing - Mid</td>
<td>$183 M</td>
<td>$365 M</td>
<td>$548 M</td>
</tr>
<tr>
<td>Pricing - Low</td>
<td>$219 M</td>
<td>$438 M</td>
<td>$657 M</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

AstraZeneca’s (NYSE: AZN) *FluMist Quadrivalent* (live influenza vaccine) is an intranasal vaccine that contains live attenuated influenza viruses, and has demonstrated the potential for an intranasal agent to achieve market penetrance in a space dominated by vaccines administered via intramuscular injection. In particular, this therapy achieved US sales of $206 million in 2015 and $290 million globally. These data speak to the potential adoption of influenza vaccines administered intranasally, although we note that *NasoVAX* is further differentiated from such a product as it does not utilize actual influenza particles and has potential to confer broad protection against multiple viral strains. Importantly, in the last two years, the CDC has recommended against the use of LAIV vaccines (available only by means of intranasal delivery, and *FluMist* is the only product) due a body of data collected over several years that points to its limited effectiveness in preventing influenza. For example, during the 2015-2016 season, it was observed that only 3%...
of LAIV vaccine recipients between the ages of 2 -17 were conferred protection from influenza, while IIV vaccines in comparison conferred 63% protection. While the reason for this discrepancy is unknown, it is thought to be specific to FluMist particularly, or LAIV vaccines in general, and unrelated to the mode of administration.

However, we do not see potential for a similar issue to arise with NasoVAX due to its differentiated mechanism of action. Overall, we have a favorable view of both the time FluMist spent on market due to its market penetration, which highlighted the demand for a therapy with a more convenient and less intimidating mode of administration, as well as the subsequent CDC recommendation against this therapy, as it has eliminated a competing intranasal vaccine in the US.

Clinical Data Discussion

Altimmune has assessed NasoVAX in two Phase I studies that demonstrated an immune response in a meaningful proportion of patients. The Company is currently conducting a Phase II study for NasoVax, which is assessing the safety and immunogenicity of single intranasal doses, using a higher dose than tested in the prior trials. This study will assess cellular and mucosal immunity post-vaccination as well as antibody titers against both matched and divergent strains. Altimmune may also test NasoVAX in an influenza challenge model, to evaluate the vaccine candidate’s potential in providing early protection. Following this, Altimmune intends to conduct two additional trials—a dose-ranging study and a confirmatory study— for a quadrivalent NasoVAX formulation against an active comparator in healthy adults and elderly subjects, and a larger confirmatory study. Subjects will likely be assessed for antibody response and other measures of immunogenicity one-month post vaccination as well as followed long-term for safety and durability of antibody response. Data from the Phase II study are expected in the first quarter of 2018.

Phase I Trials

Seasonal Influenza. This was an ascending-dose Phase I study in 24 healthy young adult males were vaccinated with one of 3 transdermal doses or 5 x 10^8 viral particles given intranasally of a vaccine construct expressing the HA gene from the H1N1 seasonal influenza strain A/PR/8/34. In the study, intranasal administration was shown to be more effective than transdermal administration. Even at lower doses, intranasal delivery induced higher antibody titers. All dose groups were well tolerated. In the intranasal dose group, 67% (4/6) had a greater than four-fold increase in hemagglutination inhibition (HAI) titers after one dose and this increased to 83% (5/6) subjects following a booster dose. Figure 9 shows data from the intranasal arm of the study.

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Pre-Pandemic Influenza

**Trial Design.** This was a randomized, double-blind, placebo controlled Phase I study for an adenovirus-vectored pandemic influenza vaccine (AdhVN1203/04.H5 or NasoVAX) in healthy adults up to age 49. 48 patients were randomized 1:1:1:1 to receive $10^7$, $10^8$, or $10^9$ viral particles of NasoVAX or placebo, administered via intranasal spray on days 0 and 28. The primary endpoint was safety NasoVAX, and the secondary endpoint was immunogenicity.

**Trial Results.** Data from this study indicate that NasoVAX was safe and well-tolerated with no difference in incidence or severity of AEs compared to the placebo group. NasoVAX was effective in inducing an immune response. In the highest dose group, 5 of 12 had increases in microneutralization and 4 of 12 had increases in HAI titer.

Phase IIa Trial

This Phase IIa study is testing the safety and immunogenicity of NasoVAX at 3 dose higher than used in prior studies. The primary endpoint is safety and signs of the vaccine’s efficacy will be assessed as a secondary endpoint. The Company recently launched this trial and expects to report results in the first quarter of 2018.

**Trial Design.** This is a randomized, double-blind, placebo controlled Phase IIa single-ascending dose (SAD) study for NasoVAX in healthy adults. Approximately 60 participants will be enrolled to receive intranasal doses of NasoVAX of $10^9$, $10^{10}$, or $10^{11}$ viral particles. The study is evaluating the safety and immunogenicity of higher doses than previously evaluated and will assess antibody response to matched and divergent influenza strains, and cellular and mucosal immune responses. The primary endpoints are the incidence of treatment-emergent adverse events and reactogenicity events (i.e. nasal irritation, sneezing, headache, fatigue, muscle ache, and fever). Secondary outcomes include HAI and micro-neutralization immune responses. The Company launched this trial recently and expects to report initial results in the first quarter of 2018.

35 https://clinicaltrials.gov/show/NCT00755703
36 https://clinicaltrials.gov/ct2/show/NCT03232567
Other Drugs in Development

Altimmune is developing *NasoVAX* for the treatment of both seasonal and pandemic influenza. We note that there are a handful of competitors developing vaccines for influenza that have more advanced programs than Altimmune, but *NasoVAX* also holds key aspects of differentiation that may be beneficial in terms of market potential. Other therapies in development are listed in Figure 10, and include CSL Limited’s (ASX: CSL) aflunov, BiondVax’s (NasdaqCM: BVXV) M-001, and Sanofi’s (NYSE: SNY) Fluzone. *NasoVAX* is differentiated in terms of mechanism, route of administration, and by its potential broad applicability in prophylaxis against both seasonal and pandemic influenza.

Traditional influenza vaccines contain inactivated or live attenuated influenza virus particles that stimulate the immune system to produce neutralizing antibodies against the virus, thus conferring protection against subsequent infections. We note that these vaccines are broadly in-line with the mechanism of traditional influenza vaccines. Unlike these programs, *NasoVAX* does not contain actual influenza virus particles, and instead consists of a genetically engineered viral vector that drives the expression of influenza hemagglutinin (HA) within host cells. Since adenoviruses occur widely in nature and are strongly immunogenic, *NasoVAX* stimulates an innate immune response within the upper respiratory tract and offers broad protection against influenza infections. This mechanism is independent of influenza strain subtype as well, a significant advantage over traditional strain-specific vaccines. Furthermore, *NasoVAX* is administered intranasally (IN), which may offer patients immunogenicity faster and more conveniently than other vaccines in development, which all utilize intramuscular (IM) injections. Finally, due to the broad mechanism by which *NasoVAX* confers protection against a range of influenza strains, it is being pursued for both seasonal and pandemic prophylaxis, translates into expansive applicability and potentially greater patient and physician familiarity relative to pandemic only vaccines.

![Figure 10. Other Influenza Vaccines in Development](source: LifeSci Capital)

**Table: Other Influenza Vaccines in Development**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Phase</th>
<th>Route of Administration</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflunov</td>
<td>CSL Limited (ASX: CSL)</td>
<td>III</td>
<td>IM</td>
<td>Pandemic</td>
</tr>
<tr>
<td>M-001</td>
<td>BiondVax (NasdaqCM: BVXV)</td>
<td>IIb</td>
<td>IM</td>
<td>Pandemic</td>
</tr>
<tr>
<td>Fluzone</td>
<td>Sanofi (NYSE: SNY)</td>
<td>II</td>
<td>IM</td>
<td>Seasonal</td>
</tr>
<tr>
<td>H1N1 VLP Vaccine</td>
<td>Mitsubishi Tanabe Pharma (OTC: MTZPY)</td>
<td>I/II</td>
<td>IM</td>
<td>Seasonal</td>
</tr>
<tr>
<td>NasoVAX</td>
<td>Altimmune</td>
<td>I</td>
<td>IN</td>
<td>Pandemic and Seasonal</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

**HepTcell: A Novel Treatment for Patients with Chronic Hepatitis B Infection**

Altimmune is developing the therapeutic vaccine, *HepTcell*, for the treatment of individuals chronically infected with hepatitis B virus (HBV). HBV is the most common serious infection of the liver, and is generally characterized as
chronic when it persists for longer than six months. Chronic HBV infections primarily develop in infants and young children, and can lead to life-threatening liver cirrhosis, liver failure, and liver cancer later in life. HepTcell is a synthetic peptide product that targets all known HBV genotypes, and utilizes the Company’s Densigen technology that Altimmune believes may help eliminate HBV infected cells to ultimately provide a functional cure for this disease. Some of the compounds differentiating features include: a stabilization feature that may induce sustained immunity against HBV, potential activation of T cells which has been shown in preclinical findings, and potential to target all of the existing HBV strains concurrently. These features result from HepTcell’s design, which includes a combination of nine viral peptide sequences each coupled to a fluorocarbon chain. While the peptide sequences may be effective against the full spectrum of HBV genotypes through generation of a human leukocyte antigen (HLA) type-independent immune response, the fluorocarbon chain produces a short-term depot of HepTcell that may lead to sustained activation of the immune system. The Company is currently conducting a Phase I study with HepTcell for patients chronically infected with HBV in the UK, and initial results are expected in the fourth quarter of 2018. Altimmune plans to file an IND in the US for HepTcell in 2018, and subsequently commence Phase II studies.

Preclinical Studies

Altimmune has conducted multiple preclinical studies for HepTcell, which have validated the potential of this technology and provided a rationale to move forward into clinical trials. These studies include a mouse model for HBV-induced immunotolerance and an in vivo study utilizing HBV-infected cells, which demonstrated the association of HepTcell treatment with strong T cell response and cell destruction, respectively.

Mouse Model for HBV-Induced Immunotolerance. This was a preclinical study for HepTcell performed in a mouse model for HBV that intends to replicate HBV-induced immunotolerance. At week zero, animals were infected with AAV-HBV, which is a vector encoding the full HBV genome, or saline for control. Both treatment arms received HepTcell (FP-02.2) + IC-31 adjuvant, or excipient for control, at 12, 14, 16, and 21 weeks. One of the outcome measures was T cell response in the liver and spleen, which was assessed via measurement of interferon gamma (IFN-γ), as this cytokine is primary produced by T cells and indicates an innate immune response. These data are presented in Figure 11. Results indicate a strong immune response generated by T cells in animals receiving both HepTcell + IC-31 and control, which the Company has indicated is 3-fold greater than the immune-response elicited by the vaccine in the absence of the adjuvant. These findings are supportive of HepTcell’s mechanism of action and are supportive of the compounds continued development.

Figure 11. IFN-γ Production in Spleen and Liver

![Figure 11. IFN-γ Production in Spleen and Liver](source: Company 10-Q)
**In Vivo Mouse Cell Study.** Altimmune conducted a study for HepTcell in mice using cells pre-incubated either HBV proteins or proteins from an unrelated pathogen (influenza). Following incubation, mice treated with HepTcell or control were then injected with the pre-incubated cells. Results are presented in Figure 12, and indicate that 91.7% of HBV-loaded cells were eliminated in the animal that received HepTcell, relative to the control cell injection containing influenza-loaded cells. These data speak to the potential of HepTcell to destroy HBV-infected cells *in vivo*, as well as the specificity of the immune response propagated by HepTcell. This study also contributes to the body of evidence supporting further clinical investigation of HepTcell.

**Figure 12. In Vivo Cell Count for HepTcell and Control Animals Post-Treatment**

![Graph showing cell count for vaccinated and control animals](image)

*Source: Company 10-Q*

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**Chronic Hepatitis B**

Hepatitis B (HepB) is the most common serious infection of the liver. It is caused by the hepatitis B virus (HBV), which is a small, enveloped virus that is transmitted through blood and infected bodily fluids. Hepatitis is generally characterized as chronic when it persists longer than six months. Chronic HBV infections, which develop primarily in infants and young children, can lead to life-threatening liver cirrhosis, liver failure, and liver cancer later in life. According to the HepB Foundation, there are roughly 2 million patients in the US and an estimated 240 million patients worldwide with chronic HepB. Universal vaccination has been implemented in about 90% of countries, in accordance with World Health Organization (WHO) guidelines. This high rate of vaccination has had a substantial impact on the number of chronic HepB cases, but there is still demand for treatment options in patients that are already infected with the virus or without access to vaccination programs and who subsequently become infected.

**Causes and Pathogenesis.** HepB is caused by the HepB virus (HBV), a DNA virus that preferentially infects and damages hepatocytes in the liver. The virus evolved approximately 1,500 years ago from an avian ancestor strain. It’s circular genome contains four genes called C, P, S and X. They encode the following proteins:

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- C – viral core protein HBcAg.
- P – DNA polymerase.
- S – surface antigen HBsAg on the viral particle.
- X – a protein of unknown function.

HBV is one of the only DNA viruses that uses reverse transcription, which is a process that converts RNA into DNA. This feature of HBV is critical to its viral life cycle.

A detailed view of the life cycle of HBV is presented in Figure 13. HBV initially circulates in the bloodstream and subsequently infects the liver. It binds to a receptor on the surface of cells called NTCP or SLC10A1, and enters the cytoplasm via endocytosis. The viral DNA is released into the cytoplasm and is transported into the nucleus where the cell’s machinery transcribes it into mRNA. This mRNA is reverse-transcribed to make new copies of the viral genome or is translated to produce viral proteins. Virus particles are packaged in the cytoplasm and then are secreted by the cells, completing the viral life cycle.39

**Figure 13. Hepatitis B Virus Life Cycle**

Chronic HBV infection generally consists of two phases: an early replicative phase with active liver disease, and a late or low replicative phase with remission of liver disease. Chronic HBV is the most common risk factor for liver cancer. According to the Hepatitis B Foundation, approximately 90% of infected adults will clear infection and develop long-term immunity, while this is only true for 50% of adolescents.40 Chronic HBV infection has long-term effects on the liver including tissue damage, inflammation, viral propagation, and DNA damage, which can disrupt regulatory

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40 [http://www.hepb.org/patients/acute_vs_chronic.htm](http://www.hepb.org/patients/acute_vs_chronic.htm)
sequences that control cell growth. These consequences of infection lead to roughly 25-40% of HBV carriers developing serious liver complications at some point in their lifetime. As such, HBV causes about 50% of hepatocellular carcinoma and 30% of liver cirrhosis cases, respectively.

**Symptoms and Diagnosis.** Symptoms of an acute HBV infection include jaundice and liver inflammation. The diagnosis of hepatitis B virus (HBV) infection was revolutionized by the discovery of the hepatitis B surface antigen HBsAg. HepB is diagnosed by testing for signs of the virus in blood samples. Simple and inexpensive blood tests for HBsAg and other HBV antigens and antibodies are performed routinely in clinics around the world. Polymerase chain reaction (PCR) assays are used for direct determination of hepatitis B virus DNA (HBV DNA). The diagnosis of HBV infection can also be made by the detection of HBsAg or hepatitis B core antigen (HBcAg) in liver tissues by immunohistochemical staining.

By assessing which relevant antigen, antibody, and DNA are present, a diagnosis can be made. HBsAg serves as the first indication of infection, and Anti-HBc (hepatitis B core antibody) serves to differentiate between acute and chronic. HBeAg is used to differentiate between different phases of chronic infection. The blood tests used for diagnosis are in Figure 14 with their respective clinical indications and populations who should be tested.

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Figure 14. HBV Blood Tests

<table>
<thead>
<tr>
<th>Blood Test</th>
<th>Positive Indication</th>
<th>Relevant Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg (hepatitis B surface antigen)</td>
<td>Acute or chronic infection</td>
<td>• Adolescents in high risk areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnant women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Previous HBV patient contact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV drug users</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple sex partners</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Men who have sex with men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HCV and HIV infected</td>
</tr>
<tr>
<td>Anti-HBc (hepatitis B core antibody)</td>
<td>Acute infection</td>
<td>• HBsAg positive (+) patients</td>
</tr>
<tr>
<td>HBeAg (hepatitis B e antigen)</td>
<td>Phase I or II chronic infection</td>
<td>• Anti-HBc negative (-) patients</td>
</tr>
<tr>
<td></td>
<td>(phase III/IV if negative)</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs (hepatitis B surface</td>
<td>Viral clearance, future</td>
<td>• Previously Infected</td>
</tr>
<tr>
<td>antibody)</td>
<td>HBV resistance</td>
<td>• Chronic HBV</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Current acute or chronic infection</td>
<td>• Organ/Tissue/Blood donor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HBsAg (+) pregnant women</td>
</tr>
</tbody>
</table>

*Source: Aspinall, E.J. et al., 2011*

When the viral antigens HBsAg and HBeAg are no longer present in the blood serum and antibodies against them are present, a patient’s immune system has mounted a successful response and cleared the acute infection for the near-term. Thus, the screening of these antigens is thought to be sufficient for at risk populations.

Chronic HBV is diagnosed by the detection of HBsAg in a patient’s blood or serum for a period greater than 6 months. Adult patients will transition into chronic HepB about 5-10% of the time, compared with 50% in adolescents and 90% in neonates whose mothers are HBeAg positive. The presence of HBeAg can be used as a point of clinical differentiation, as it represents higher virulence and replication rate if present. The phases of chronic HBV are presented in Figure 15. Progression through these phases is followed closely with intermittent blood testing, which aids in assessing future risk for liver complications. For individuals with chronic HBV, cirrhosis develops in 8-20% of patients within 5 years, and out of the cirrhotic patients about 2-5% will develop hepatocellular carcinoma each year.

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46 [http://www.hepb.org/patients/acute_vs_chronic.htm](http://www.hepb.org/patients/acute_vs_chronic.htm)
### Figure 15. Chronic HBV Disease Phases

<table>
<thead>
<tr>
<th>Phase of Disease</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **1. Immune Tolerant** | HBeAg (+)  
HBsAg (+)  
High HBeAg  
Low aminotransferase  
Highly contagious  
▪ No/low inflammation & necrosis  
▪ Slow progression of fibrosis  
▪ Immediate, lasting up to several years |
| **2. Immune Clearance** | HBeAg (+)  
HBsAg (+)  
Low HBeAg  
Moderate/severe inflammation & necrosis  
▪ Moderate progression of fibrosis  
▪ Initiate HBsAb production  
▪ Lasts several weeks to years |
| **3. Inactive Carrier** | HBeAg (-), Anti-HBe (+)  
HBsAg (+)  
No/low HBV DNA  
Normal aminotransferase  
▪ Good long-term prognosis  
▪ Low risk of cirrhosis / cancer  
▪ Lasts years to decades, HBV DNA tests 2x/yr. |
| **4. HBeAg-Negative** | HBeAg (-), Anti-HBe (+)  
HBsAg (+)  
Periods of HBV reactivation  
Oscillating levels of HBV DNA  
▪ Liver inflammation (hepatitis)  
▪ High risk of advanced cirrhosis & hepatocellular carcinoma  
▪ Lasts years, w/ HBV DNA & alanine aminotransferase tests |
| **5. HBsAg-Negative** | HBeAg (-), Anti-HBe (+)  
HBsAg (-), Anti-HBs (+)  
No/low HBV DNA  
Immunosuppression may reactivate  
▪ Phase may result from treatment or spontaneously |

*Source: European Association for the Study of the Liver*  

**Treatment.** The primary goal of treating chronic HepB is to prevent the virus from causing liver cirrhosis and cancer. Current treatment options fall into two general categories: immune modulator drugs and antiviral drugs. The most common therapies are listed and discussed in detail below.

- **Nucleoside Analogs (NAs)** – Nucleoside analogs inhibit viral DNA polymerase activity. They are administered orally and are dosed once-daily. In chronic HBV patients treated with these agents, HBeAg is cleared in 20-30% and remission of virus is achieved in 65-70% of patients at 12 months. Five examples of nucleoside analogs are lamivudine, adefovir, entecavir, telbivudine, and tenofovir. These are oral therapy taken daily for at least one year. Pathogen resistance can occur with long-term use, and the mode of resistance is due to selection for HBV polymerase mutants.

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- **Interferon alpha (IFN-α)** – IFN-α therapy inhibits viral replication and enhances immune responses against the virus. The drug is administered multiple times per week over 6-12 months. Treatment is only effective in approximately 20% of patients, and can cause flu-like symptoms, mood changes, and depression.\(^{49}\)

- **Pegylated interferon alpha (PEG-IFN-α)** – PEG-IFN-α is a form of IFN-α conjugated to a polyethylene glycol (PEG) molecule. This modification stabilizes the drug and increases the period of exposure, allowing for once-weekly dosing. PEG-IFN-α is thought to have the same effects on HBV replication as IFN-α but with greater magnitude.\(^{50}\)

**Figure 16** highlights the clinical response to treatment with entecavir, tenofovir, or PEG-IFN-α in patients with chronic hepatitis B.\(^{51}\) These data were obtained in separate clinical trials. Both NAs resulted in high rates of patients who had no detectable levels of HBV DNA. However, in both HBeAg positive and negative patients, the rate of HBsAg loss, an indication of a functional cure, was very low. In HBeAg-positive patients, entecavir and tenofovir resulted in a 2% and 3.2% loss of HBsAg. PEG-IFN-α resulted in HBsAg loss in 2.9% of patients. The rate of HBsAg loss was near 0% with all three treatments in HBeAg-negative patients. These results highlight the positive effects on viral load achieved with nucleotide analogs or PEG-IFN-α treatment, but the limited effect on HBsAg and the need for improved treatments capable of higher cure rates.

**Figure 16. Clinical Response to Entecavir, Tenofovir, or PEG-IFN-α at 48 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>Entecavir</th>
<th>Tenofovir</th>
<th>PEG-IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg Positive</strong></td>
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<tr>
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<td>76%</td>
<td>25%</td>
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<tr>
<td>HBeAg seroconversion</td>
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<td>21%</td>
<td>27%</td>
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<tr>
<td>ALT normalization</td>
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<td>68%</td>
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<td>HBsAg loss</td>
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<td>0%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*Source: Zoulim, F. and Durantel, D., 2015*


\(^{50}\) Craxi, A. et al., 2003. Pegylated interferons for chronic hepatitis B. *Antiviral Research, 60*(2), pp87-89.

Clinical Data Discussion

Altimmune is currently conducting a Phase I study for HepTcell to assess the safety, tolerability, and immunogenicity of this compound as an add-on therapy to entecavir or tenofovir. This study will measure levels of HBV surface antigen (HBsAg) and anti-HBsAg antibodies as exploratory endpoints. The Company has guided that initial data from this trial will be available in the fourth quarter of 2017. Furthermore, the results from this study will guide dosing for a global Phase II study which is expected to begin enrolling 120-200 patients in the fourth quarter of 2018.

Phase I Trial

Trial Design. This is a randomized, double-blind, placebo controlled Phase I study to evaluate the safety, tolerability and immunogenicity of FP-02.2 (HepTcell) in patients with HepB as an add-on treatment to entecavir or tenofovir. Approximately 60 patients will be enrolled into one of the following treatment arms:

- Low dose FP-02.2
- High dose FP-02.2
- Low dose FP-02.2 with IC31 adjuvant
- High dose FP-02.2 with IC31 adjuvant
- Placebo
- Placebo with IC31 adjuvant

Patients will receive therapy on days 1, 29, and 57 of the study. The primary endpoint of this study is adverse events (AEs) and laboratory abnormalities. Secondary endpoints include immunological response, particularly T cell response, as well as a quantitative analysis of HBsAg levels. Initial data from this study are expected in the fourth quarter of 2017.

Prophylactic Vaccines to Protect Against Anthrax Infection

Since spores from the bacterium Bacillus anthracis, the causative agent of anthrax, can potentially be disseminated as a biological weapon, it is critical to develop next generation vaccines that induce rapid and sustained immunity. Furthermore, anthrax vaccines should be optimized for easy administration to mass populations by nonmedical personnel. To address this need, Altimmune is developing two anthrax vaccine candidates, SparVax-L and NasoShield. We note that the Company has received substantial funding for both programs, including $15 million from the National Institute of Allergy and Infectious Diseases (NIAID) for SparVax-L and $127 million from Biomedical Advanced Research and Development Authority (BARDA) for NasoShield. Altimmune expects to initiate a Phase I study for NasoShield in the first quarter of 2018, and initial data are expected in the second quarter of 2018.

SparVax-L: A Recombinant Protective Antigen (rPA) Anthrax Vaccine

Altimmune is developing SparVax-L, a liquid rPA anthrax vaccine, to protect patients from inhalational anthrax. This product is a lyophilized anthrax vaccine that utilizes highly purified rPA, requires two intramuscular doses for protection, and comes in a prefilled syringe with at least 6 years of shelf life. These characteristics make this product amenable to stockpiling requirements. Two Phase II studies for first generation compound SparVax were completed in 2007 by PharmAthene, who formerly owned this asset prior to merging with Altimmune in 2017. SparVax-L was
designed to improve time to protection, dosing regimen, and convenience of administration relative to the first-generation product. The Company is currently planning on conducting a preclinical bridging study that could be initiated as early as the second half of 2017, with data expected in the first quarter of 2018.

**NasoShield: A Recombinant Vector Anthrax Vaccine**

Altimmune is developing NasoShield for pre-exposure prophylaxis against anthrax following exposure to aerosolized B. anthracis spores. After an individual has been exposed to infectious anthrax spores, vegetative B. anthracis bacteria proliferate and release toxins within the host. Although antibiotic therapy is required to eliminate vegetative bacteria, vaccination is necessary to protect against the germination of dormant spores that can occur after termination of antibiotic therapy. This product is a virally vectored rPA vaccine, and is built on the Company’s RespirVec platform technology, which allows rapid and broad activation of innate and long-term adaptive immune responses. Since NasoShield can be administered as a single intranasal dose, it is a convenient and simple alternative relative to the only approved vaccine, Emergent BioSolutions’ (NYSE: EBS) injectable BioThrax, and has potential to offer faster and more durable protection against anthrax. Altimmune expects to initiate a Phase I clinical study for NasoShield in the first quarter of 2018 with initial data expected in the second quarter of 2018.

**Mechanism of Action.** Anthrax vaccines are not designed to inhibit B. anthracis growth, but are instead designed to interfere with Protective Antigen (PA) and disrupt its critical role in exotoxin-mediated pathogenesis. B. anthracis PA protein combines with lethal factor and edema factor to produce dangerous virulence factors called anthrax toxins. Neutralizing antibodies against B. anthracis PA have been shown to protect against anthrax infections in multiple studies. NasoShield is a replication-deficient adenovirus serotype 5 (Ad5)-vectored vaccine engineered to encode the B. anthracis PA gene. Similar to Altimmune’s influenza vaccine NasoVAX, intranasal administration of NasoShield mimics natural infection, thus inducing mucosal immunity that may improve the protection against anthrax pathogens entering the host through the upper respiratory tract. Once internalized through the nasal passage, adenovirus-mediated expression of B. anthracis PA elicits an adaptive immune response in the host, stimulating the production of neutralizing antibodies for long-term protection against B. anthracis PA. NasoShield’s painless and convenient route of administration offers a significant advantage over the only currently FDA-approved anthrax vaccine, Emergent BioSolutions (NYSE: EBS) BioThrax (Anthrax Vaccine Adsorbed,AVA), which requires five intramuscular injections over 18 months with additional annual booster shots to maintain immunity.

**Preclinical Data**

The immunoprophylactic activity of NasoShield has been demonstrated in preclinical studies. In 2015, a study found that a single intranasal dose of NasoShield conferred non-inferior protection compared to FDA approved BioThrax in rabbits challenged with inhaled anthrax. In 2012, a preclinical study showed that Ad5 vectors encoding B. anthracis PA could elicit rapid and robust long-term protection against inhalational anthrax in mice. These data provide rationale for the clinical assessment of NasoShield as a vaccine for anthrax.

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52 Little, S.F. et al., 2006. Duration of protection of rabbits after vaccination with Bacillus anthracis recombinant protective antigen vaccine. *Vaccine*, 24(14), pp.2530–2536.


Anthrax Vaccination Study in Rabbits. The goal of this preclinical study was to compare the efficacy of NasoShield to the approved BioThrax vaccine in rabbits exposed to anthrax spores. To produce the NasoShield vaccine, a replication-deficient Ad5 vector containing a gene encoding the B. anthracis PA protein was produced in the human PER.C6 cell line. To assess protective benefit, New Zealand white rabbits received intranasal administration of NasoShield at a low dose of $7.5 \times 10^7$ viral particles (VP), a medium dose of $1.5 \times 10^9$ VP, or a high dose of $3.5 \times 10^{10}$ VP. Animals were then challenged 70 days later with aerosolized B. anthracis spores at a dose 200 times the 50% lethal dose. To compare the efficacy of NasoShield to BioThrax, additional rabbits were treated with two doses of BioThrax at a 1:16 dilution by intramuscular injection on days 0 and 28, and then challenged with aerosolized anthrax spores on day 70. This BioThrax dosing regimen has previously been shown to result in near complete survival of inoculated rabbits exposed to aerosolized anthrax. The percent of surviving rabbits was assessed for three weeks following the anthrax challenge.

The results showed that all rabbits treated with a placebo died within 3-6 days after anthrax exposure, 100% of rabbits inoculated with a high dose of NasoShield and 97% of rabbits treated with a medium dose survived the anthrax challenge. As expected, 97% of rabbits treated with BioThrax also survived, indicating that single intranasal vaccination with NasoShield was non-inferior to two intramuscular injections of BioThrax. These results are depicted in Figure 17, which shows the percent of rabbits surviving the challenge on the Y-axis and the number of days to death post-challenge on the X-axis.

In addition, vaccination with NasoShield resulted in a rapid immune response, measured by a toxin neutralization assay, which reflects how well serum antibodies obtained from an immunized subject can neutralize lethal toxin in a cell culture system. In Figure 18, higher Geometric Mean Titer (GMT) values on the Y-axis correspond to stronger immunogenicity. The data show that vaccination with a high dose of NasoShield elicited strong immunogenicity in rabbits, while animals receiving placebo showed no production of toxin neutralizing antibodies. Furthermore, rabbits showed meaningfully more rapid responses when given NasoShield, relative to BioThrax. For example, toxin neutralizing antibody levels rose significantly between 7 and 14 days post-vaccination in rabbits vaccinated with NasoShield, whereas BioThrax did not stimulate toxin neutralizing antibody production until after the second

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vaccination on day 28. In addition, the immune response was more sustained in animals that received NasoShield. As shown in Figure 18, treatment with BioThrax resulted in high toxin neutralizing antibody levels, which began to decline after day 35. In contrast, rabbits treated with NasoShield maintained increases in antibody levels until the anthrax challenge on day 70.

Figure 18. Time Course of Immune Response After Prophylactic Anthrax Vaccination

Single Dose Intranasal Anthrax Vaccination Study in Mice. This was a preclinical study that assessed intranasal administration of Ad5 vectors encoding B. anthracis PA to protect against inhalational anthrax in mice.56 A/J mice were immunized by a single intranasal dose of one of several versions of the Ad5 vector anthrax vaccine, and then challenged one month later with B. anthracis spores at a concentration 50 times the 50% lethal dose. All mice treated with a control Ad5 vector died six days after exposure to spores, but 100% of mice treated with either of two different Ad5 vectors encoding PA survived the anthrax challenge. An examination of the kinetics and durability of the immune response following vaccination demonstrated that antibodies against PA were present in significant levels just two weeks after immunization, peaked at four weeks, and remained unchanged until week 56. These results indicate that immunization with Ad5 vector B. anthracis PA vaccines elicits rapid and robust immunity that lasts for over a year in mice.

Safety Profile. NasoShield utilizes Ad5 vectors, which have been proven to be safe for use in humans in multiple vaccine and gene therapy trials.57 Since Ad5 vectors are replication deficient, they can stimulate an immune response to B. anthracis PA without causing a host adenovirus infection.58 A Phase I clinical trial for NasoShield is expected to

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begin in the first quarter of 2018, and will provide greater details on the safety and immunogenicity of NasoShield use in humans.

**Anthrax Infection**

Anthrax is a rapidly progressing and often lethal disease caused by the gram-positive, aerobic *Bacillus anthracis* bacterium. *B. anthracis* exists in the environment as a hardy endospore that can remain dormant and viable for years. Anthrax typically affects grazing animals that feed from spore-infested soil. Infection in humans is relatively rare and most commonly occurs in agrarian communities where individuals are more frequently exposed to livestock. However, since *B. anthracis* spores have been developed by many countries as a biological warfare agent, and has been a top bioterrorism concern since the 2001 anthrax attacks in the United States, there is significant interest in developing more effective treatments and prophylactic measures to prevent anthrax infections.\(^{59}\)

**Causes and Pathogenesis**

Anthrax disease begins when *B. anthracis* spores are inhaled, ingested, or come into contact with the skin of a susceptible mammalian host. As shown in Figure 19, *B. anthracis* enters the host and begins to germinate, entering a vegetative state where the bacteria rapidly multiply. *B. anthracis* encodes for a poly-\(\gamma\)-D-glutamic acid capsule, a major virulence factor that renders the bacteria resistant to phagocytosis by host immune cells. In addition, the vegetative bacteria secrete pathogenic proteins, including Protective Antigen (PA), Lethal Factor (LF) and Edema Factor (EF). Each secreted protein is non-toxic on its own, but they pair to form dangerous virulence factors called anthrax toxins. PA and LF combine to form lethal toxin (LT) and PA and EF pair to form edema toxin (ET).\(^{60}\)

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During the early stages of infection, anthrax toxins bind host cell receptors and interfere with the innate immune system’s scavenger functions, allowing the bacteria to evade the antibacterial defense of myeloid cells, including macrophages and neutrophils. During later stages of the infection, as high levels of the bacteria have spread throughout the bloodstream and a systemic infection has been established, anthrax toxins can cause extensive damage to multiple organ systems, leading to sepsis and lethal vascular collapse. Lethal toxins primarily target vascular smooth muscle cells and cardiomyocytes in the heart, leading to dangerous effects on the cardiac system such as hypotension, tachycardia and vasodilation. Edema toxin causes tissue edema, including large accumulations of fluid within the intestine and tissue swelling near sites of localized infection. Edema toxin primarily targets hepatocytes in the liver and intestinal epithelial cells.

Symptoms and Diagnosis

There are four forms of anthrax infection depending on the route of spore entry into the host: cutaneous, gastrointestinal, inhalational and injectional.

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61 Liu, S. et al., 2010. Anthrax toxin targeting of myeloid cells through the CMG2 receptor is essential for establishment of Bacillus anthracis infections in mice. *Cell host & microbe*, 8(5), pp.455–462.
**Cutaneous.** Cutaneous anthrax infection is the least severe and most common form of anthrax, accounting for 95% of reported cases. It begins when infectious spores penetrate the skin and germinate locally at the site of infection. After an incubation period of 1-12 days, an itchy papule forms on the skin and eventually develops into a painless, black ulcer surrounded by significant swelling. Cutaneous anthrax may also present with systemic symptoms, including fever and lymphadenopathy. The mortality rate of cutaneous anthrax is <1%.67

**Gastrointestinal.** Gastrointestinal anthrax infections typically occur when an individual ingests meat contaminated with *B. anthracis*. Ulcers form in the mouth and esophagus after a three-day incubation period, accompanied by lymphadenopathy and fever. The lower gastrointestinal system also becomes compromised, resulting in abdominal pain and distention, nausea, and bloody diarrhea. The mortality rate of untreated gastrointestinal anthrax is as high as 60%.

**Inhalational.** By far the most lethal form of anthrax, inhalational infections occur when *B. anthracis* spores are inhaled and germinate in the lung. Flu-like symptoms manifest after a variable incubation period of one day to several weeks, followed by the onset of severe symptoms including fever, pleural effusions and hypotensive shock. Serious complications include acute respiratory distress syndrome and highly fatal hemorrhagic meningitis. The mortality rate of inhalational anthrax has historically been as high as 90%.

**Injectional.** The newly recognized injectional form of anthrax is associated with intravenous drug users. This form presents with skin lesions, but does not cause black ulcers characteristic of cutaneous anthrax. Systemic symptoms can include shock and meningitis. The mortality rate of injectional anthrax is 33%.68

**Diagnosis.** Early diagnosis of anthrax is critical to initiate antimicrobial treatment and improve survival outcomes. Aside from the identification of symptoms, clinical diagnostic tests are required to definitively differentiate anthrax from other bacterial infections. An anthrax diagnosis can be made by culturing *B. anthracis* isolated from clinical samples, such as blood, cerebrospinal fluid, sputum or fluid from a skin lesion. Anthrax can be identified by its characteristic morphology, motility and sporulation patterns, although recent antibiotic therapy can result in negative clinical findings. An anthrax diagnosis should be confirmed by additional supportive tests, such as a serologic test to look for antibodies against *B. anthracis* or a PCR test to detect virulent plasmids. If anthrax infection is ever suspected, state health departments should be notified immediately.

**Treatment**

**Antimicrobial drugs.** Regardless of whether an infection develops, individuals who have been exposed to *B. anthracis* should be treated immediately with antimicrobial drugs. FDA-approved antimicrobials including doxycycline and ciprofloxacin are recommended for post-exposure treatment, although other antimicrobial drugs can be used if first-line treatments are not well tolerated. Since ungerminated spores can remain in the lungs long after exposure, and

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incubation periods of up to 43 days have been observed, antimicrobial drugs should be administered for 60 days to ensure clearance of germinating *B. anthracis*.

In the case of anthrax infections, combination antimicrobial and antitoxin therapy should be administered as early as possible. For an uncomplicated case of cutaneous anthrax, treatment with ciprofloxacin or doxycycline for 7-10 days may be sufficient. However, if the infection was acquired through an intentional attack or another setting where inhalation of spores may have been possible, the treatment regimen should be extended to 60 days to cover the full potential incubation period.

Systemic anthrax infections should always be treated in a hospital setting, where supportive measures such as hemodynamic monitoring and mechanical ventilation are available. These infections are treated for a minimum of two weeks with intravenous combination antimicrobial therapy. Combination therapies should include a bactericidal component with an immediate bacterial killing effect, such as ciprofloxacin, as well as a protein synthesis inhibitor such as linezolid or clindamycin to neutralize the effects of anthrax exotoxins. If meningitis is suspected, a combination of three or more antimicrobials should be used, and drugs like doxycycline that do not adequately penetrate the blood brain barrier should be avoided.

**Antitoxin therapies.** Since the deleterious effects of anthrax are mediated by exotoxins, the CDC recommends the use of antitoxins in conjunction with antimicrobial therapy. Two antibody-based antitoxins exist for the treatment of anthrax, including Emergent BioSolutions (NYSE: EBS) *Antitoxin* (Anthrax Immune Globulin Intravenous, AIGIV) and GlaxoSmithKline (NYSE: GSK) *ABthrax* (raxibacumab). *ABthrax* is a human IgG1 monoclonal antibody and *Antitoxin* is a human IgG polyclonal antibody prepared from the plasma of human donors previously vaccinated against anthrax. Both antibody therapies primarily target *B. anthracis* PA.

**Vaccines.** Emergent BioSolutions (NYSE: EBS) *BioThrax* (Anthrax Vaccine Adsorbed, AVA) is approved by the FDA for both pre-exposure and post-exposure prophylaxis to prevent anthrax disease. It is used as a three-dose treatment regimen to achieve protective antibody levels. There are several limitations to *BioThrax* treatment. *BioThrax* consists of an undefined formulation of avirulent *B. anthracis* culture filtrates adsorbed to aluminum hydroxide as an adjuvant, which can cause both local and systemic reactions. In addition, *BioThrax* requires a long vaccination schedule over a series of 6 months, with additional booster doses administered at 12 months, 18 months and annually thereafter.

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Given these shortcomings, novel vaccines with defined components that elicit immunity within a rapid time frame are needed.\(^\text{75}\)

**Anthrax Market Information**

**Epidemiology.** Anthrax is a disease that primarily manifests in animals, commonly in agricultural regions, and areas without veterinary health programs. Humans contract anthrax through contact with infected animals or animal products. There are four types of the disease: inhalation, cutaneous, gastrointestinal, and injection, and they are named based on how they enter the body. In the US, anthrax is extremely rare, which is highlighted by Figure 20 that shows the total incidence for each type of anthrax. Cutaneous anthrax is the most common form of the disease, accounting for 95% of anthrax cases with only 224 new cases diagnosed between 1944 and 1994. Inhalation anthrax follows, with 18 known cases from 1900 to 1978. There has been a single recorded outbreak of gastrointestinal and no instances of injection anthrax in the United States.\(^\text{76}\)

![Figure 20. Historical Incidence of Naturally Occurring Anthrax in the US](image)

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<thead>
<tr>
<th>Type of Anthrax</th>
<th>Date Range</th>
<th>Incidence</th>
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<tbody>
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<td>Cutaneous</td>
<td>1944 - 1994</td>
<td>224</td>
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<tr>
<td>Inhalation</td>
<td>1900 - 1978</td>
<td>18</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2009</td>
<td>1</td>
</tr>
<tr>
<td>Injection</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

**Anthrax as a Biological Warfare Agent.** Although there are currently no cases of anthrax in the US, anthrax attacks in 2001 have led to rising concerns about *B. anthracis* spores being used as a biological warfare agent. During these attacks, terrorists sent envelopes containing *B. anthracis* to individuals through the mail. There were documented cases in Florida and New York, which killed 5 people and infected 17 others. *B. anthracis* has always been considered a high threat as an agent of bioterrorism, and there has been continued interest in creating more effective treatments and prophylactic measures to prevent anthrax infections.\(^\text{77}\) Exposure to the disease cannot be controlled. Bacterial spores can be produced in laboratories, and they are easily aerosolized and transformed into weapons that can be used against military and civilian populations. While there is no significant historical evidence pertaining to biological aerosol agents, the method is believed to be capable of large-scale infection due to ease of entry into the body. Inhalation anthrax can often be fatal, and antibiotic treatment becomes significantly less effective when treatment is delayed. The

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U.S. government has been taking measures to prevent and treat anthrax infections, developing stockpiles of the vaccine in case of bioterrorism attack and giving preemptive treatment to high-risk individuals, such as active military personnel.

**Market Size.** Although the number of adults with naturally occurring anthrax is virtually zero, there is a substantial need for an anthrax vaccine used for biodefense purposes. In 2015, the global biodefense market size was over $9.5 billion, and it is expected to nearly double by 2025, increasing to $18.0 billion. Anthrax made up 31.5% of the market in 2015 and is predicted to exceed $4.2 billion by 2023. The CDC has classified *B. anthracis* as the highest priority in biodefense research and as one of the nine class A agents. In 2015, North America generated the largest regional biodefense market share, which consisted of $8.9 billion. We note that an increasing number of government initiatives have largely contributed to this market. Following the anthrax attacks in 2001, the US government allocated $50 billion to prevent biological warfare epidemics from occurring. Two government agencies that protect against biological warfare, the Joint Program Executive Office for Chemical Biological Defense (JPEO-CBD) and Biomedical Advanced Research and Development Authority (BARDA), currently provide substantial funds and stockpiles of vaccines against anthrax. The 2004 BioShield legislation also contributes to the biodefense resources by allocating funds across federal agencies.

The landscape for biodefense drugs is relatively less competitive due to the specialized nature of the products, low commercial demand, and high barriers to entry. However, access to government contracts are highly sought after. Major biodefense competitors include Xoma Corporation (NasdaqCM: XOMA) and Emergent BioSolutions (NYSE: EBS), with Emergent being the only company with an approved drug for anthrax.

**Approved Anthrax Vaccine Generates Substantial Revenues.** In 2015, the FDA approved Emergent BioSolutions’ *BioThrax* (anthrax vaccine absorbed), for the treatment of anthrax infections. *BioThrax* is the only anthrax vaccine licensed by the FDA, and is indicated for both pre-exposure prevention and post-exposure treatment of anthrax. *BioThrax* is currently administered prophylactically to high risk individuals such as active military personnel. These individuals are given three intramuscular injection at zero, one, and six months, which is then followed by two injections to bolster the immune response one and two years later. In 2016, *BioThrax* had sales of $237 million. We note the potential for an agent to gain substantial market share given a simpler mode of administration, treatment regimen, and faster immune response. For example, Altimmune’s *NasoShield* is delivered through a single intranasal dose, and has potential to offer faster and more durable protection against anthrax.

**Clinical Data Discussion**

**Phase I Trial**

**Trial Design.** This is planned to be a randomized, placebo controlled Phase I study with *NasoShield* for protection against anthrax. Approximately 145 patients will be randomized to receive a single intranasal dose of *NasoShield* in 4 months.
different escalating dose cohorts, or placebo. The Company also intends to utilize Anthrax Vaccine Absorbed (AVA), or BioThrax, as an active comparator. Key endpoints will include safety and immunogenicity. Altimmune had guided potential initiation of this study in the first quarter of 2018.

Other Drugs in Development

In addition to Altimmune’s NasoShield and SparV’AX, there are two other anthrax vaccine candidates that are currently in clinical development. These candidates are Emergent BioSolutions’ (NYSE: EBS) NuThrax and Pfenex’s (NYSE: PFIN) Px563L. NuThrax (anthrax vaccine adsorbed) is a third-generation anthrax vaccine that consists of BioThrax, the Company’s approved anthrax vaccine, and an immunostimulatory compound called CPG 7909. Emergent indicated that initiation of a Phase III clinical study for this candidate is expected in 2018. Px563L is a rPA-based AVA product, and Pfenex has received a $143.5 million BARDA development contract to fund this candidate. While SparVax is also a rPA vaccine and requires 2 IM doses, similar to the other products in development, NasoShield is differentiated through its convenient and non-invasive, one-time IN administration. Furthermore, NasoShield is a virally vectored rPA vaccine, and is built on the Company’s RespirVec platform technology, which may allow for more rapid and broad activation of innate and long-term adaptive immune responses. These factors are major points of differentiation from the other anthrax vaccines in development, and may contribute to market share in the event of approval. Each compound and relevant details are presented in Figure 21.

![Figure 21. Anthrax Vaccine Candidates Currently in Clinical Development](image)

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<th>Stage</th>
<th>Next Steps</th>
<th>Delivery</th>
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<td>Altimmune</td>
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<td>Initiate Phase II in Q4 2018</td>
<td>2 dose IM</td>
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<tr>
<td>NuThrax</td>
<td>Emergent BioSolutions</td>
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<td>Phase III trial initiation in H1 2018</td>
<td>2-3 doses IM</td>
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<td>Phase II trial initiation in 2018</td>
<td>2 dose IM</td>
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<tr>
<td>NasoShield</td>
<td>Altimmune</td>
<td>I</td>
<td>Data in Q4 2017</td>
<td>1 dose IN</td>
</tr>
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</table>

Source: LifeSci Capital

OncoSyn for Active Cancer Immunotherapy

Altimmune is in preclinical development for OncoSyn, a cancer immunotherapeutic that targets biologically relevant tumor-specific antigens. Active cancer immunotherapy is an emerging field that uses the immune system to fight cancerous diseases. The technology has potential to be combined with a variety of products, such as checkpoint inhibitors, CAR-T cells, and small molecule modulators, and the technique continues to expand as new tumor specific antigens are discovered. Altimmune believes that its Densigen technology can promote T cell immunity against multiple solid cancers, including lung, colorectal, melanoma, breast, and ovarian, among others. Once T cells are activated, they kill diseased cells and prevent tumor escape, which is a key differentiating factor. OncoSyn can also stimulate dual CD4+ and CD8+ T cell response without HLA-restriction.
**Preclinical Study.** Altimmune conducted a preclinical study analyzing the efficacy of FP-OVA (OncoSyn) for the treatment of tumor cells in mice overexpressing ovalbumin. Animals were enrolled into one of three treatment arms, which can be described as follows:

- FP-OVA on Days 1 and 8
- FP-OVA on Days 3 and 10
- Placebo on Days 1 and 8

Findings indicate a survival benefit in animals that received either regimen of FP-OVA, relative to untreated mice. While none of the untreated mice survived, there was a 60 percent survival rate in mice treated with FP-OVA at 80 days. In ongoing and future cancer studies, Altimmune plans to investigate more complex tumor-specific antigens and explore the possibility of using immunomodulators and checkpoint inhibitors to further strengthen immunity against cancer. In the future, RespirVec technology may also be used to supplement OncoSyn and potentially increase antitumor efficacy.

**Intellectual Property & Licensing**

Altimmune owns or has licenses to several US and international patents covering NasoVAX, NasoShield, and its other developmental platforms. The Company also has patents pending for its product candidates, including NasoVAX, NasoShield, HepTCell, OncoSyn, and its technology platforms. Patents include composition, technologies, methods of use, and product families that relate to a set of indications. Altimmune is also the exclusive licensee of patents held by the University of Alabama at Birmingham Research Foundation (UABRF) for technology directed to topical application of genetic vectors. Altimmune's license agreement with UABRF allows them to develop, manufacture and commercialize a non-invasive vaccine technology within the field of use, which includes any diagnostic, vaccine or therapeutic use or methods, in any country in which the licensed patents are pending or have been granted. Altimmune is also the non-exclusive licensee of patent rights owned by Crucell Holland B.V. for a method of producing an adenoviral vector stock using the PER.C6 cell line, which may be used for the development and manufacture of vaccine products.

**Management Team**

**Bill Enright**  
*Chief Executive Officer*

Mr. Enright currently serves as our President and CEO and is a member of our board of directors. He was first elected to our board of directors in June 2008. Mr. Enright brings more than 25 years of experience in a variety of positions within the life science and biotech industries. Prior to joining Altimmune, Mr. Enright spent six years with GenVec, Inc. (NASDAQ: GNVC) with increasing responsibilities culminating in the Head of Business Development. Mr. Enright was responsible for helping to build GenVec’s vaccine business including generating approximately $140 million of funding for vaccine-related initiatives and moving four vaccines into clinical development. Prior to GenVec, Mr. Enright was a self-employed consultant providing business development and strategic marketing services to academic institutions and a number of small to mid-size life science companies. Prior to becoming a consultant, and after spending several years as a bench scientist at SUNY at Buffalo, Mr. Enright spent 12 years with Life Technologies,
Inc., working in various licensing, business management, manufacturing and research roles. Mr. Enright received a Master of Arts in Biology from SUNY at Buffalo and a Master of Science in Business Management from Johns Hopkins University.

**Scot Roberts, Ph.D.**  
*Chief Scientific Officer*

Dr. Roberts joined us in December 2012 and has nearly 20 years of senior technical leadership experience, most recently as Chief Scientific Officer at ImQuest BioSciences, Inc., where he was responsible for managing scientific operations as well as business development opportunities in cancer and antivirals. Dr. Roberts held key positions at Wellstat Biologies Corporation from August 1996 until October 2010, including Director of Research and Development where he was responsible for a portfolio of biologic candidates in oncology including a clinical stage asset. He also led bioassay development efforts for the company and assumed leadership roles in upstream process development and animal pharmacology while at Wellstat. Dr. Roberts has significant experience in both small molecule and biologics drug development with a focus on viral vectors and antiviral therapies. Dr. Roberts completed a post doctoral fellowship at the National Cancer Institute, Laboratory of Molecular Virology and has numerous patents and publications in peer-reviewed journals, and has been an invited speaker and Chair at numerous international conferences. Dr. Roberts received his Ph.D. from the Johns Hopkins School of Medicine, Department of Pharmacology and Molecular Sciences.

**Elizabeth A. Czerepak**  
*Chief Financial Officer and Executive Vice President of Corporate Development*

Ms. Czerepak joined us in April 2015 as our Chief Financial Officer, and serves as Secretary of our board of directors. An experienced finance executive, Ms. Czerepak has led a broad range of initiatives at public and privately held pharmaceutical and biotechnology companies. As a venture capital investor and board member of several portfolio companies at Bear Stearns Health Innvventures (BSHI), she played a key role in raising hundreds of millions of dollars in private financings and IPOs, and the successful sale of two portfolio companies. From April 2014 until April 2015, Ms. Czerepak served as CFO and Chief Business Officer at Isarna Therapeutics BV and, earlier, from January 2011 until March 2014, as CFO and Principal Accounting Officer at Cancer Genetics, Inc. (NASDAQ: CGIX). Prior to CGIX, from April 2000 until June 2009, she was a founding general partner at BSHI, and from April 2000 until December 2008, she was a managing director and an NASD Registered Representative at JP Morgan Inc. and Bear Stearns & Co. Earlier in her career, Ms. Czerepak was Vice President of Business Development and a member of the U.S. executive board at BASF Pharma, and held senior-level finance, licensing and corporate development positions at Hoffmann-La Roche and Merck & Co. Ms. Czerepak has an MBA from Rutgers University and a BA magna cum laude from Marshall University.

**Bertrand Georges, Ph.D.**  
*Chief Technology Officer*

Dr. Georges has 15 years expertise in the field of molecular & cellular immunology and T cell vaccine development. He was co-founder and Chief Technology Officer of Immune Targeting Systems (ITS) Limited from 2004 until its acquisition by us in March 2015. Prior to ITS, Dr. Georges held the position of head of immunology at SEDAC-Therapeutics from 1999 until 2003. Dr. Georges has significant experience in product formulation and manufacturing, preclinical and early clinical development with a focus on peptide-based vaccines. Dr. Georges has a special interest
in designing vaccines against infectious diseases and cancer and has developed T cell epitope identification methodologies combining in silico, in vitro and in vivo approaches. He received his Ph.D. in Molecular Immunology from the Pasteur Institute and is the co-author of 18 publications and co-inventor of 11 patent families.

**Sybil Tasker, M.D., FACP, FIDSA**  
*Senior Vice President of Clinical Research and Development*

Dr. Tasker joined the Company in April 2016, and is an experienced infectious disease clinician and fellow of the American College of Physicians and the Infectious Diseases Society of America. Prior to joining, she led development of a therapeutic herpes simplex vaccine at Genocea Biosciences and had positions of increasing responsibility in infectious disease product development strategy at two global CROs. A prior career military officer, she was the senior U.S. Navy infectious disease physician and technical advisor to Department of Defense leaders about a wide variety of infectious disease policy issues, including HIV, tropical disease, vaccination, infection control, bioterrorism and pandemic preparedness. She has extensive antimicrobial, vaccine and infectious disease related device and diagnostic development experience across all phases of the clinical development process. She holds a California medical license and is board certified in both internal medicine and infectious diseases. Dr. Tasker earned an A.B. degree in Biochemistry from Princeton University and an M.D. degree from Columbia University.

**Risk to an Investment**

We consider an investment in Minerva Neurosciences to be a high-risk investment. Minerva has generated limited clinical data to date, and early signs of safety and efficacy may not necessarily translate into late-stage success. There are clinical and commercialization risks associated with their program as well. As with any company, Minerva may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug, and Minerva may not receive FDA or EMA approval for its drug candidates despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.
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