

## Risk Factors Comparison 2024-04-11 to 2023-03-09 Form: 10-K

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Our business is subject to a number of risks, including risks that may prevent us from achieving our business objectives or may adversely affect our business, financial condition, results of operations, cash flows and prospects that you should consider before making a decision to invest in our common stock. These risks are discussed more fully in “Risk Factors” beginning on page 60 of this Report. These risks include, but are not limited to, the following:

- We are in the early stages of vaccine development and have a very limited operating history and no products approved for commercial sale, which may make it difficult for you to evaluate the success of our business to date and to assess our future viability.
- We have incurred significant net losses since inception, do not generate any revenue, and anticipate that we will continue to incur substantial net losses for the foreseeable future and may never achieve or maintain profitability. Our stock is a highly speculative investment.
- We will require significant additional capital to make the investments we need to execute our longer-term business plan. We estimate that, based on our existing cash as of December 31, 2022, which includes the net proceeds received from our initial public offering, the April Private Placement and the August Private Placement, we have cash on hand sufficient to fund our operations for at least the 12 months following the date of this Report. If we are unable to raise additional capital when needed, we could be forced to delay, reduce or terminate certain of our development programs or other operations, and we may be unable to continue as a going concern in the long term. If we cannot continue as a viable entity, our stockholders may lose some or all of their investment in us.
- Due to the significant resources required for the development of our vaccine candidates, and depending on our ability to access capital, we must prioritize development of certain vaccine candidates. Moreover, we may expend our limited resources on vaccine candidates that do not yield a successful vaccine and fail to capitalize on vaccine candidates that may be more profitable or for which there is a greater likelihood of success.
- We depend entirely on the success of a limited number of product candidates, which are in preclinical development and none of which have commenced a clinical trial. If we do not obtain regulatory approval for and successfully commercialize one or more of our product candidates or we experience significant delays in doing so, we may never become profitable.
- The marketing approval process of the U. S. Food and Drug Association, or FDA, is lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain marketing approval for our current product candidates and future product candidates we intend to develop, our business will be substantially harmed.
- The future results of our current or future clinical trials may not support our product candidates’ claims or may result in the discovery of unexpected adverse side effects.
- Even if we obtain regulatory approval of our vaccine candidates, the products may not gain market acceptance among regulators, advisory boards, physicians, patients, third-party payors and others in the medical community.
- We may be adversely affected by the ongoing coronavirus pandemic.
- We intend to rely on third parties to conduct our clinical trials and to conduct some aspects of our research and pre-clinical testing and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.
- Our Chief Executive Officer, Chief Financial Officer and other key personnel may allocate their time to other businesses thereby causing conflicts of interest in their determination as to how much time to devote to our affairs and potentially competitive fiduciary and pecuniary interests that conflict with our interests.
- We may in the future have conflicts with our current or future partners or third party providers that could delay or prevent the development or commercialization of our current and future product candidates.
- It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection. If our patent position does not adequately protect our product candidates, others could compete against us more directly, which would harm our business, possibly materially.
- We are dependent on licensed intellectual property. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing our product candidates, if approved. If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business.
- Some of the intellectual property covered by our licenses concerns patent applications and provisional applications. We cannot assure investors that any of the currently pending or future patent applications will result in granted patents, nor can we predict how long it will take for such patents to be granted.
- If we fail to comply with healthcare regulations, we could face substantial enforcement actions, including civil and criminal penalties and our business, operations and financial condition could be adversely affected.

Healthcare Reform in the United States has been implemented in the past, and we expect further changes to be proposed in the future, leading to potential uncertainty in the healthcare industry. Violations of healthcare laws can have an adverse impact on our ability to advance our product candidates and our operating results.

- Obtaining regulatory approval for clinical trials of our vaccine candidates in children and adolescents may require additional studies and / or longer duration of studies since the requirements for regulatory approval for the pediatric populations are more stringent.
- The market price of our common stock has been extremely volatile and may continue to be highly volatile due to numerous circumstances beyond our control, and stockholders could lose all or part of their investment.
- Our failure to meet the continued listing requirements of Nasdaq could result in a de-listing of our common stock.
- We are an “emerging growth company” and the reduced disclosure requirements applicable to emerging growth companies could make our common stock less attractive to investors.
- Our amended and restated certificate of incorporation (“Amended and Restated Certificate of Incorporation”) and our amended and restated bylaws (“Amended and Restated Bylaws”), and Delaware law may have anti-takeover effects that could discourage, delay or prevent a change in control, which may cause our stock price to decline.
- A possible “short squeeze” due to a sudden increase in demand of our common stock that largely exceeds supply may lead to price volatility in our common stock.

PART I Item 1.

**Business Overview** We are a biotechnology company focused on the research and development of transformational vaccines to prevent infectious diseases worldwide. We hold exclusive, global rights to novel technology licensed from renowned research institutions around the world, including St. Jude Children’s Research Hospital, the University of Oxford, Cincinnati Children’s Hospital Medical Center, and the University of Texas Health at San Antonio. We believe that our pipeline and vaccine platform are synergistic for developing next-generation preventive vaccines to improve both health outcomes and quality of life globally. We seek to develop vaccines that provide long-lasting immunity to harmful viral and bacterial pathogens that cause infections in patient populations with high unmet needs. Our most advanced vaccine candidate is a live-attenuated, intranasally delivered, serotype-independent *Streptococcus pneumoniae* vaccine to prevent middle-ear infections, also known as acute otitis media (AOM), and pneumococcal pneumonia. AOM is a significant burden globally, particularly in young children, and pneumococcal pneumonia primarily impacts the elderly population. Additionally, we believe that this attenuated bacterium can serve as a platform to protect against other infectious agents that cause acute otitis media, such as non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*, by anchoring antigens from these pathogens on the surface of BWV-201, our attenuated *Streptococcus pneumoniae* bacterial vaccine. We hold a global, exclusive license to this technology, which was generated from the laboratory of Jason Rosch, Ph.D., of St. Jude Children’s Research Hospital. Our influenza programs are based on technology developed by Sunetra Gupta, Ph.D. at the University of Oxford, for which we hold a global, exclusive license for use of epitopes of limited variability, ELVs, to develop novel influenza vaccine candidates. Identified through a proprietary computational research and discovery process, we believe a vaccine formulated with these epitopes from different influenza strains will produce a viable universal influenza vaccine candidate. We are exploring the development of these influenza-ELVs utilizing our norovirus shell and protrusion (S & P) nanoparticle vaccine platform, licensed from Cincinnati Children’s Hospital Medical Center, or CHMC. We are also utilizing this platform to develop a vaccine for the prevention of gastroenteritis caused by norovirus or rotavirus, as well as novel vaccines for malaria and monkeypox. The final candidate in our vaccine pipeline is a live-attenuated, orally delivered vaccine to prevent Chlamydia, for which we have a global, exclusive license to this technology originated from the University of Texas Health at San Antonio. We leverage the expertise of each of our collaborators to pursue the discovery and development of vaccines for these diseases, each of which represent high unmet needs globally. In addition, we have expertise in identifying business development opportunities for our platform vaccines technologies and portfolio. This allows for both internal pipeline expansion and the ability to generate non-dilutive revenue from potential licensing partners to utilize our discovery engine vaccine platform. There is potential for adjunctive or next-generation therapeutic exploration to enhance current standard of care options. Vaccination has been used as an effective method of protecting individuals against harmful diseases by utilizing the body’s natural defense system to develop resistance or immunity to infections (World Health Organization, <https://www.who.int/news-room/q-a-detail/herd-immunity-lockdowns-and-covid-19>). The body’s immune system naturally creates antibodies and cell-mediated immunity to defend against foreign pathogens. Vaccines introduce or present these foreign pathogens, prompting the body’s immune system produce a response protective against the pathogen without exposing the body to the relevant lethal or harmful infection (World Health Organization, <https://www.who.int/news-room/q-a-detail/herd-immunity-lockdowns-and-covid-19>). While vaccines are generally able to provide resistance against disease, many infectious diseases can evolve or mutate leading to shortcomings of traditional vaccines, such as yearly reformulations. We believe our vaccine candidates can provide an alternative to the current standards of care by harnessing durable and long-lived immune response to specific or multiple antigens. The global vaccine market has recently experienced significant growth caused by rising awareness of the importance of immunization and vaccination benefits in emerging markets as well as by projects to fuel further global market expansion. For instance, The World Health Organization (WHO) has undertaken initiatives to increase immunization awareness through its Global Vaccine Action Plan and Global Immunization Vision and Strategy. As such, market research professionals project the global vaccine market size to reach \$ 73.78 billion by 2028, representing a compounded annual growth rate (CAGR) of 7.3% over the forecast period, driven by rising prevalence of infectious diseases, increasing government funding for vaccine production and growing emphasis on becoming immunized. This market acceleration has been coupled with various strategic transactions in the sector, including consolidations and mergers and acquisitions in recent years. Major market participants have strategically acquired start-ups and mid-sized companies to broaden their products portfolios and service offerings. For instance, in February 2019, Bharat Biotech acquired Chiron Behring Vaccines, one of the leading manufacturers of rabies vaccines across the globe. Additionally, in October 2018, Emergent BioSolutions, a multinational specialty biopharmaceutical company, acquired PaxVax for \$ 270 million, and in July 2017 Sanofi acquired Protein Sciences for \$ 650 million. In the pneumococcal disease market specifically, for which we are targeting for our *Streptococcus pneumoniae* vaccine candidate, GlaxoSmithKline acquired Affinivax for up to \$ 3.3 billion in May 2022. The appetite of these companies to buttress their vaccine programs and pipelines reflects the increasing importance of vaccines in the healthcare sector, both nationally and worldwide. The U. S. Centers for Disease Control, or CDC, its Advisory Committee on Immunization Practices, or ACIP, and similar international advisory bodies develop vaccine recommendations for both children and adults. New pediatric vaccines that receive ACIP preferred recommendations are almost universally adopted, and adult vaccines that receive a preferred recommendation are widely adopted. We believe that our vaccine candidates will be well-positioned to obtain these preferred recommendations, by virtue of their longer and more durable immunity, which could drive rapid and significant market adoption. **PIPELINE** Our vaccine candidates are being developed in a manner that is scalable, designed to be cost-effective and provide long-term benefit to patients from infectious agents. The FDA regulatory approval process is lengthy and time-consuming, and we may experience significant delays in the clinical development and regulatory approval of our vaccine candidates. Our vaccine candidates are in early stages of development and may fail in development or suffer delays that materially and adversely affect their commercial viability. We may be unable to complete development of or commercialize our vaccine candidates or experience significant delays in doing so due to regulatory or other uncertainties. We aim to identify, discover and develop novel preventive vaccines for infectious

diseases. Key elements of our strategy include: ● Investment in advancing the development of our novel vaccine pipeline programs through IND-enabling activities and Phase I clinical studies. ● We plan to advance our main vaccine programs: S. pneumoniae induced AOM and pneumococcal pneumonia, influenza, norovirus-rotavirus, malaria, and Chlamydia. ● Our in-licensed vaccine candidates are carefully selected based on the following criteria: area of significant unmet medical need for preventive long-term vaccine; strong scientific rationale and established clinical and regulatory pathways; defined competitive landscape and potential future commercial opportunity; and license exclusivity. ● Prioritizing the research and development for our lead vaccine candidate, BWV-201, through Phase I. ● We plan to develop an intranasally delivered, serotype-independent Streptococcus pneumoniae vaccine, capable of protecting young children against acute otitis media, also known as middle ear infections, and the elderly against pneumococcal pneumonia. In collaboration with St. Jude Children's Research Hospital, we are exploring the potential to anchor antigens from additional otopathogens to the surface of this vaccine, including non-typeable Haemophilus influenzae and Moraxella catarrhalis. ● Maximize and utilize the value of our collaborators and third-party vendors. ● We will combine disciplined business strategies to further expand the potential synergies with current collaborators. ● Deploy and expand our proprietary norovirus S & P nanoparticle platform. ● Our immunogenic multi-purpose vaccine platform technologies can be utilized with an array of infectious disease agents to access multiple development pathways and allow for potential next-generation life cycle management to expand our pipeline and pursue business development opportunities. There is potential for the platform to pursue adjunctive therapies to currently available drugs, and for current therapies to be re-optimized and formulated to protect against multiple antigens. We plan to utilize this platform to explore the potential to formulate our influenza vaccine candidates by presenting patented epitopes of limited variability within the platform.

Management and History Blue Water Vaccines Inc. was founded in October 2018 by our Chief Executive Officer, or CEO, Joseph Hernandez, with the initial goal of developing a transformational universal flu vaccine to treat and prevent infections in patients globally. Our initial technology, licensed from the University of Oxford, provides a novel approach to developing a universal influenza vaccine. Subsequently, our team has identified other program candidates and technologies to broaden and diversify our vaccine pipeline. Mr. Hernandez, our Chairman and CEO, is a veteran entrepreneur, philanthropist, and operator with a broad skillset of founding, building, and selling companies, as well as executing business development transactions and securing private and public capital, including Digene, Noachis Terra and Blue Water Acquisition Corp. Mr. Hernandez was responsible for our initial \$7 million seed funding round from investors including CincyTech. In addition to his position as our Chairman and CEO, Mr. Hernandez also served on the board of directors for Clarus Therapeutics, Inc. (OTCpink: CRXTQ) until August 2022, and serves on the board of certain private companies. Subsequently, a team of veteran industry executives and advisors were assembled, bringing valuable expertise to our growing infectious disease company. Jon Garfield, our Chief Financial Officer, has over 20 years of financial leadership experience, including with healthcare companies. Mr. Garfield regularly provides consulting services to private equity funds and privately held companies and served as the CEO of Unity MSK from February 2021 to January 2023, and served as interim Chief Financial Officer of Blue Water Vaccines Inc. from September 2021 until the consummation of our initial public offering in February 2022, upon which he became our full-time Chief Financial Officer. Erin Henderson, who serves as our Chief Business Officer and Corporate Secretary, has over 20 years of leading strategic transactions, governmental and stakeholder relations and corporate expansion. Previously, since 2010, she was the Managing Principal at The Aetows Group, a management consulting firm serving both the public and private sectors. Andrew Skibo is our Head of Biologic Operations and was recently Head of Global Biologies Operations at MedImmune / AstraZeneca and previously worked for Amgen and Genentech (now Roche), where he was responsible for operations, engineering, construction, and validation for large-scale capital projects related to bio-pharmaceutical manufacturing. Ali Fattom, Ph. D. is our Head of Science and Discovery and was recently Chief Scientific Officer at BlueWillow Biologies, where he led their efforts to develop viral vaccines for various infectious diseases, including HSV, RSV, and influenza, and previously worked for Nabi Biopharmaceutical and The National Institutes of Health. Dr. Fattom is also an Adjunct Professor at the University of Michigan. Additionally, members of our Board of Directors have extensive expertise in the fields of life sciences, business, and finance. In addition to Mr. Hernandez, our directors include Vuk Jeremić, previous Chair of the Council of Europe's Committee of Ministers and previous President of the United Nations General Assembly; Simon Tarsh, a retired Deloitte Consulting Managing Director with experience in Life Sciences; Timothy Ramdeen, who has nearly a decade of experience in private equity and hedge fund investing, capital markets, and company formation; and James Sapirstein, R. Ph., M. B. A., President, CEO and Chairman of First Wave BioPharma, Inc. (Nasdaq: FWBI). Our Scientific Advisory Board includes Sunetra Gupta, Ph. D. Professor of Theoretical Epidemiology at The University of Oxford, a leading voice in infectious disease globally; and John Rice, Ph. D., Managing Director at CincyTech, with more than 30 years of biotechnology advising experience. Subject to certain non-compete restrictions, our chief executive officer, Joseph Hernandez, and other key personnel may pursue other business or investment ventures while employed with us. Accordingly, they may have conflicts of interest in allocating time among various business activities and potentially competitive fiduciary and pecuniary interests that conflict with our interests. See "Risk Factors — Our Chief Executive Officer, Joseph Hernandez and our Chief Financial Officer, Jon Garfield, hold certain management positions and directorships of other companies and may allocate their time to such other businesses, which may cause conflicts of interest in their determination as to how much time to devote to our affairs and potentially competitive fiduciary and pecuniary interests that conflict with our interests." For a complete discussion of the business affairs of our officers, directors and other personnel, please see "Management — Executive Officers and Directors." Any such additional business activities or ventures may present conflicts to our interests. We do not believe that any such potential conflicts would materially affect our ability to conduct our operations. Our Infectious Disease Vaccine Candidates Infectious diseases are one of the leading causes of death worldwide. Infectious disease is caused by microorganisms or pathogens, including viruses, bacteria, fungi, and parasites that infect an individual and cause disease. Diseases often cause high fever, inflammation, or other symptoms. While some diseases can be treated with drugs or therapeutics, some infectious agents

evolve to become resistant to commonly used drugs, such as antibiotics, and can become difficult to control. Infectious diseases can be passed from person to person or transmitted by insects or other animals. In many cases, vaccines are used to elicit a protective immune response in the absence of an infection to render an individual immune to a particular infectious disease.

**BWV-201: Streptococcus pneumoniae (S. pneumoniae) Vaccine** Our BWV-201 vaccine candidate is an intranasally delivered, live-attenuated, serotype-independent vaccine, for which early data supports further investigation to pursue a long-term preventive intranasal vaccine for S. pneumoniae induced acute otitis media, or AOM, and pneumococcal pneumonia. We licensed the novel live-attenuated S. pneumoniae strain from St. Jude Children's Research Hospital, or St. Jude, as a potential serotype-independent vaccine. Researchers from St. Jude developed a strain of S. pneumoniae that contains greatly reduced virulence, yet can transiently colonize the nasopharyngeal cavity, inducing immune responses to significantly decrease the incidence of AOM and sinusitis as demonstrated in animal models. Our vaccine production is a straightforward process, utilizing the entire attenuated bacterium with purification and concentration steps only in the downstream process, thereby reducing the time and cost of production significantly compared to commonly used polysaccharide or conjugate vaccines. There is potential for this vaccine to provide a long-term, leading alternative treatment for AOM and pneumococcal pneumonia and subsequent introduction of a novel preventative standard of care. The development of a novel vaccine could eradicate potential short-term pain and/or long-term harmful side effects from contracting the bacteria, as well as eliminate or decrease the need for antibiotic treatment. Complications from AOM include sensorineural hearing loss, or SNHL, in adults but are more relevant for the endangerment of children, while pneumococcal pneumonia primarily impacts elderly adults and can lead to hospitalization and other subsequent infections. Based on information from the American Academy of Pediatrics, over 5 million cases of AOM are reported annually in the U. S., resulting in approximately 30 million medical care visits and over 10 million antibiotic prescriptions, representing approximately \$ 4.3 billion spent on treatment in the U. S. alone. AOM is the most common condition treated with antibiotics in the United States and increasing antibiotic resistance among the organisms responsible for AOM is of concern to researchers and public health officials globally. Additional statistics supporting the need for a novel preventive vaccine:

- The global AOM rate is 10.85 %, or 709 million cases per year, with 51 % occurring in children under 5 years old (Tong et al. BMC Health Serv Res. 2018; 18: 318).
- By 3 years of age, 80 % of children globally are expected to have at least one episode of AOM. (Vergison A, Lancet Infect Dis. 2010 Mar; 10 (3): 195-203. Doi: 10.1016/S1473-3099(10)70012-8. PMID: 20185098).
- Current treatment for AOM is by antibiotic prescription, with more than 80 % of all consultations resulting in a prescription. (Haggard, M. Eur J Pediatr 170, 323-332 (2011). <https://doi.org/10.1007/s00431-010-1286-4>).
- Even with the introduction of the pneumococcal conjugate vaccine (PCV13) in 2010, 26-36 % of cases of AOM in U. S. were caused by S. pneumoniae. (Casey JR, Kaur R, Friedel VC, Pichiehero ME. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. Pediatr Infect Dis J. 2013; 32 (8): 805-809. Doi: 10.1097/INF.0b013e31828d9aee).
- Worldwide cases of AOM due to S. pneumoniae is estimated to be 30-50 %. (Bergenfelz C, Hakansson AP. Curr Otorhinolaryngol Rep. 2017; 5(2): 115-124. Doi: 10.1007/s40136-017-0152-6. Epub 2017 May 20. PMID: 28616365; PMCID: PMC5446555).
- An estimated \$ 4.3 billion USD is spent on AOM treatment each year in the U. S. alone. (Tong S, BMC Health Serv Res. 2018 May 2; 18 (1): 318. Doi: 10.1186/s12913-018-3139-1. PMID: 29720156; PMCID: PMC5932897).

The current standard of care treatment for AOM in children is reliant on antibiotics. The resolution rate of AOM in children is 81 % without antibiotic treatment vs. 93 % with antibiotic treatment. Antibiotic treatment of AOM in children has limitations, including recurrence within 30 days. Pneumococcal pneumonia, caused by colonization of S. pneumoniae in the lungs, primarily impacts elderly adults and, according to the CDC, results in approximately 150,000 hospitalizations in the United States alone each year. In addition to the disease burden, pneumococcal pneumonia accounts for approximately \$ 1.3 billion in direct medical costs annually plus costs associated with lost productivity (O'Brien K, Pneumococcus, Pneumococcal Disease and Prevention, The Vaccine Book (Second Edition), Academic Press, 2016, Pages 225-243, ISBN 9780128021743). While there are currently available pneumococcal vaccines, outlined below, these vaccines provide limited levels of protection against pneumonia, as they are administered intramuscularly and do not elicit strong mucosal immunity (Berild JD, 2020. Pathogens, 9 (4), 259. DOI: 10.3390/pathogens9040259). This technology from St. Jude is delivered intranasally, which is hypothesized to provide adequate levels of mucosal immunity to prevent non-invasive pneumococcal disease, including pneumonia and AOM. The CDC recommends broad pneumococcal vaccines for children younger than 2 and for adults over 65 years of age (CDC). The CDC also recommends vaccinations for children and adults aged 2 through 64 either previously unvaccinated or partially vaccinated. Three vaccines are currently approved in the U. S. and other countries: (i) Prevnar13 or PCV13 (under 18), (ii) Prevnar20 or PCV20 (Pfizer) and (iii) Pneumovax or PPSV23 (Merck). An additional vaccine, Synflorix, is approved for use outside of the U. S. for the prevention of pneumococcal disease and S. pneumoniae induced AOM for the 10 serotypes included in the vaccine. Therefore, an effective serotype-independent S. pneumoniae AOM vaccine could significantly impact pediatric healthcare demand and may reduce hospitalizations for pneumococcal pneumonia in older adults. As a preventative treatment, the vaccine's advantages include reduction of near-term pain; reduction of recurrent AOM that may result in the need for tympanostomy tube placement; lessening of antibiotic usage, which would decrease the number of antibiotic resistant organisms in the environment; avoiding potential long-term hearing loss; and prevention of hospitalizations and deaths caused by pneumococcal pneumonia. Previous live, attenuated strains of S. pneumoniae were generated by deleting several highly immunogenic virulent genes and therefore may not be optimal vaccine candidates. Some of these deletions include antigens that induce antibody responses following pneumococcal carriage and otitis media in young children and therefore may not be optimal vaccine candidates. Our technology licensed from St. Jude focuses on candidate genes essential for microbial adaptation to the host environment while maintaining virulence determinants. The St. Jude researchers developed a S. pneumoniae strain with a deletion in *ftsY*, a central component of the signal recognition pathway (SRP). SRP mutants have greatly reduced virulence, although virulence factors are still produced. The S. pneumoniae *ftsY* deletion strain may potentially make an ideal live-attenuated vaccine, as it can transiently colonize the nasopharyngeal

cavity without inducing immune responses to virulence protein antigens but does not cause invasive disease. Our candidate vaccine is a live-attenuated serotype-independent vaccine, that early data supports further development to pursue a potential long-term preventive intranasal treatment. BWV-201 will likely require two doses to provide life-long protection. BWV-201 has the ability to transiently colonize the nasopharyngeal cavity and significantly decrease the incidence of AOM and sinusitis in animal models. The vaccine candidate is derived from the noninvasive serotype 19F strain BHN97, which normally causes sinusitis/purulent rhinitis and AOM. As previously noted, the *ftsY* gene was deleted by St. Jude researchers, and is designated BHN97  $\Delta$  *ftsY* (Rosch, Jason W et al. EMBO molecular medicine vol. 6, 1 (2014): 141–54. Doi: 10.1002/emmm.201202150). We are also exploring the potential for BWV-201 to present antigens from additional AOM-causing pathogens, such as non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*. Based on preliminary data from St. Jude, we are able to present additional antigens and following intranasal vaccination with the new construct, vaccinated mice generate antibodies to both non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*, in addition to generating antibodies from various strains of *S. pneumoniae*. Our vaccine production is a straightforward approach, utilizing the entire bacterium with purification and concentration steps only in the downstream process thereby significantly reducing the time and cost of production compared to polysaccharide or conjugate vaccines. Preclinical data on colonization and invasiveness and Otitis Media/Sinusitis Efficacy Our pre-clinical data has shown encouraging results from the research and development of BWV-201 as a potential intranasally delivered vaccine candidate. Multiple animal models have demonstrated protection from AOM. To demonstrate vaccine efficacy against AOM and sinusitis, mice were immunized (prime and two boosts) with Plevnar 7 (PCV7), Plevnar 13 (PCV13), Pneumovax (PCV23), D39x and BHN197 *caxP* and *ftsY* deletion mutants. Deletion of *ftsY*, a central component of the signal recognition particle (SRP) pathway show heightened sensitivity to environmental stress and have greatly diminished virulence. Deletion of *caxP*, a calcium/magnesium transporter, renders host physiological conditions in blood and mucosa toxic to the bacterium. BHN97 *ftsY* serotype 19F is also characterized in PCV7, PCV13, and PCV23 (Rosch, Jason W et al. EMBO molecular medicine vol. 6, 1 (2014): 141–54. Doi: 10.1002/emmm.201202150). In this head-to-head preclinical study, mice (n = 25–31) were either mock-vaccinated (PBS) or live-attenuated vaccinated (with deletions of either type 2 or 19F backgrounds). PPV23 was used as a negative control. Two weeks following the second boost, the bioluminescent strain BHN97x (type 19F), a serotype included in Plevnar 7, Pneumovax and BHN97 *ftsY* (referred to as homologous challenge) were introduced to the mice and imaged twice daily for development of AOM and sinusitis. Only BHN97  $\Delta$  *ftsY* (BWV-201), and to a lesser extent Plevnar 7, showed significant reduction in AOM and only BHN97  $\Delta$  *ftsY* demonstrated significantly reduced sinusitis compared to mock infected animals. The incidence of AOM was significantly ( $p < 0.05$  compared to mock) lower in BHN97  $\Delta$  *ftsY* — vaccinated mice (Figure A—below). Only BHN97  $\Delta$  *ftsY* vaccine significantly decreased the incidence of sinusitis ( $p < 0.05$ ). Measurement of luminescence at 24 and 72 h confirmed protection engendered by BHN97  $\Delta$  *ftsY*. Figure 7. Vaccine protection against otitis media and sinusitis. Mice (n = 25–31 per group, performed at least twice for each group) were mock-vaccinated with PBS (Mock) or vaccinated with live-attenuated vaccines deleted for *caxP* or *ftsY* on either a type2 (D39  $\Delta$  *caxP*, D39  $\Delta$  *ftsY*) or type19F (BHN97  $\Delta$  *caxP*, BHN97  $\Delta$  *ftsY*) background. Mice were challenged with a bioluminescent *S. pneumoniae* strain BHN97X (type19F) and imaged twice daily for development of AOM or sinusitis. A. The proportion of mice developing an infection of the ear or sinus by Xenogen imaging. \* =  $p < 0.05$  by Chi-squared test compared to the mock vaccinated group. PPV23 was used as a negative control (60% otitis and 80% sinusitis). Error bars represent standard error of the mean. PCV7 is Plevnar 7, PPV23 is Pneumovax and BHN97  $\Delta$  *ftsY* is BWV-201. To determine if BHN97  $\Delta$  *ftsY*, or BWV-201, (serotype 19F) can induce heterotypic AOM protection (AOM caused by a *S. pneumoniae* serotype not contained in the vaccine), mice (n = 20) were immunized as detailed above and challenged with BHN54 (serotype 7), which causes otitis media in about 50% of challenged animals. The control vaccine Plevnar 13 contains serotype 7; therefore, this study compares heterotypic (BHN97  $\Delta$  *ftsY*) versus homotypic (Plevnar 13) vaccine protection. BHN97  $\Delta$  *ftsY* had a 10-fold lower incidence of AOM, (\*  $p < 0.05$ ) when compared to mock immunized animals, demonstrating that the attenuated vaccine does induce heterotypic protection. Bioluminescent signaling as well as, reduction in weight loss also demonstrated secondary analysis supporting vaccine protection. BHN97  $\Delta$  *ftsY* induced protection from AOM was additionally confirmed in a chinchilla (n = 20) animal model. The animals were immunized (prime and two boosts) and then challenged with BHN97 two weeks after the final boost. Vaccinated animals had a decreased incidence of culture-positive ears and had a significantly decreased number of recoverable bacteria from the middle ear (A). Following vaccination, a reduction in the number of culture positive ears in vaccinated group compared to the mock animals was observed (B) as well as significant reduction in recoverable CFUs from middle ear 7 days post challenge (C) \* =  $p < 0.05$  by Mann-Whitney. Figure 8. Vaccine protection in a chinchilla model of otitis media. The BHN97 strain is capable of causing otitis media in chinchillas via intranasal administration as observed by recoverable bacterial colony forming units (CFUs) from the middle ear (A) following challenge. B, C Following vaccination with BHN97  $\Delta$  *ftsY* (BWV-201), a reduction in the number of culture positive ears in the vaccinated group compared to the mock animals was observed (B) as well as a significant reduction in recoverable CFUs from the middle ear at 7 days post challenge (C). \* =  $p < 0.05$  by Mann-Whitney. Vaccine is BHN97  $\Delta$  *ftsY* (BWV-201). A potential advantage of an attenuated *S. pneumoniae* vaccine such as BHN97  $\Delta$  *ftsY* is that immune responses are directed to bacterial proteins rather than just polysaccharides and should not be limited to serotype specific protection. Purified polysaccharide (PPV) vaccines such as Pneumovax (produced by Merck & Co.) and pneumococcal conjugate vaccines such as Plevnar 7/13/20 (produced by Wyeth/Pfizer) or Synflorix (produced by GlaxoSmithKline plc) are generally considered serotype specific, inducing protection to disease caused only by pneumococcal strains contained in the vaccines. Utilizing BWV-201 as a platform to protect against other pathogens Although *S. pneumoniae* remains the leading cause of acute otitis media, other otopathogens are known to cause the disease, including non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*. To holistically address acute otitis media, we plan to evaluate the possibility of adding antigens from non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis* to the surface of the *S. pneumoniae* bacteria that make up BWV-201. To date, Dr. Jason Rosch at St. Jude Children's

s-Research Hospital has successfully anchored proteins from both additional pathogens to BWV-201 and has performed ELISAs to ensure antibodies were generated against each pathogen. Newly generated data, not yet published. Dr. Rosch engineered the live vaccine to express protective epitopes of non-typeable Haemophilus influenzae and Moraxella catarrhalis on the cell surface of BWV-201. Shown in the figure above, the novel vaccine construct raised antibodies against all three pathogens following intranasal vaccination by ELISA. Future development of this vaccine construct will include challenge studies in mice to determine efficacy of this vaccine construct in preventing disease caused by each pathogen. Mice will be vaccinated with the new construct, and will subsequently be exposed to S. pneumoniae, both heterologous and homologous strains, as well as non-typeable Haemophilus influenzae and Moraxella catarrhalis. Upon completion of this study and results showing decreased incidence of AOM in mice, we plan to pursue development of this vaccine construct and transfer to a partner CMO for manufacturing optimization.

**BWV-101: UNIVERSAL INFLUENZA & BWV-102: H1 INFLUENZA**

The company's influenza vaccine programs are focused on developing transformational and novel influenza vaccines: BWV-101 for an influenza vaccine to provide protection against H1, H3 and Flu-B infections; and BWV-102 for a H1 only vaccine. This program is licensed from the University of Oxford in which all relevant studies were performed to support our hypothesis. Our goal is to develop a vaccine that protects against all influenza strains that commonly infect humans by targeting specific parts of the influenza viruses, which are of limited variability across flu strains and induce a strong protective immune response. This proof of concept will be leveraged to develop BWV-101 by studying the cross-reactivity of different flu strains, H1, H3 and influenza B. The BWV-101 vaccine candidate may potentially provide a therapeutic benefit that negates the need for annual vaccination, vaccine reformulation, and provide long-lasting broad protection against the flu to millions globally (Thompson et al. Nature Communications. 2018. 9: 385).

**Influenza**

Influenza is a viral infection of the respiratory system, causing an infected person to suffer from certain symptoms, including fever, muscle aches, runny nose, cough, congestion, headaches, and fatigue. The four types of influenza viruses include type A, B, C, and D. The type A and B influenza viruses are referred to as human influenza viruses that are primarily responsible for seasonal flu epidemics each year. Type A flu viruses are further divided into two subtypes, named based on differences in two viral surface proteins called hemagglutinin (H) and neuraminidase (N). Influenza types C and D present a lower priority for vaccination, as Type C viruses cause a mild respiratory illness in humans and has not been associated with human epidemics, and Type D viruses primarily affect cattle and are not known to cause illness in humans (<https://www.cdc.gov/flu/about/viruses/types.htm>).

**Figure 3.** This graphic shows influenza virus types including the two types of influenza viruses (A, B) that cause most human illness and that are responsible for the flu season each year. Influenza A viruses are further classified into subtypes, while influenza B viruses are further classified into two lineages: B/Yamagata and B/Victoria. There is a major unmet need for the development of a novel universal flu vaccine as a prophylactic therapy. Influenza is a major respiratory pathogen. The WHO estimates there are an estimated 1 billion cases of influenza infection with 3-5 million severe cases and 290,000-650,000 related respiratory human deaths worldwide every year. The estimate does not take into account deaths from other diseases such as cardiovascular disease, which can be influenza related. The next influenza pandemic is believed by many experts to be a potentially devastating global health threat. Influenza mortality rates are highest for the very young and elderly. The global influenza vaccine market was valued at \$ 3.96 billion in 2018, and is projected to reach \$ 6.20 billion by 2026, representing a CAGR of 5.9% from 2019 to 2026. Currently, the standard of care and most effective protection against flu is through annual vaccination. The WHO estimates that worldwide, approximately \$ 4 billion is spent on influenza vaccines annually. However, the flu also a major cause of work absenteeism, leading to an estimated annual productivity loss in the U. S. of \$ 87 billion. Flu vaccination consists of a yearly injection of attenuated or inactivated (dead) influenza viruses to induce humoral immunity in the form of the antibodies against the current circulating or anticipated seasonal influenza strains. The induction of antibody-producing B-cells through vaccination allows the immune system to defend the body against the influenza virus circulating during the winter months. An annual seasonal flu vaccine is the best way to help protect against flu. Vaccination has been shown to have many benefits including reducing the risk of flu illnesses, hospitalizations and even the risk of flu-related death in children. The CDC recommends use of any licensed, age-appropriate influenza vaccine during the 2020-2021 influenza season, including inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live-attenuated influenza vaccine (LAIV). No preference is expressed for any influenza vaccine over another. Both trivalent and quadrivalent influenza vaccines will be available. The trivalent vaccines formulation will include A (H1N1) pdm09, A (H3N2) and B/Victoria. The quadrivalent vaccine formulations will include A (H1N1) pdm09, A (H3N2) and B/Victoria, plus B/Yamagata (<https://www.cdc.gov/flu/about/viruses/types.htm>). The current influenza vaccines induce antibodies that target regions of the virus that are highly variable and have serious shortcomings, as they: (i) must be administered annually, (ii) typically provide protection to only 50% of the individuals who receive it; and (iii) need to be updated annually and reformulated 6 months prior to influenza season, such that strains that are subsequently prevalent during the applicable "flu season" are not protected against by the vaccine. Our Proprietary Epitope Discovery Using the technology that we have exclusively licensed from the University of Oxford, we are developing a universal influenza vaccine. Our exclusive license agreements include patented influenza epitopes of limited variability, or ELV, identified through a proprietary computational research and discovery process, discovered by Dr. Sunetra Gupta and her team at the University of Oxford. We have acquired intellectual property for cross-protective epitopes to be used for our vaccine candidates that were developed and identified through a unique computational discovery process at Oxford University. The data produced through computational analysis at Oxford has shown that antigen evolution in influenza is limited to certain regions of the virus that facilitate binding and entry to host cells and these regions of limited antigenic variability are naturally immunogenic and therefore may be used to develop universal immunity to influenza viruses. We have identified epitopes of limited variability in H1 influenza that have circulated throughout history (since 1918) and make ideal vaccine targets and have completed similar analysis of H3 and Flu B strains for similar epitopes which will be used to produce our lead vaccine candidate BWV-101 as a universal vaccine for influenza infection. Due to the cross-reactive nature of the H1 epitopes in pre-pandemic H1 influenza A,

we are also pursuing the development of a stand-alone H1 vaccine (BWV-102). These epitopes are able to be formulated into a vaccine candidate using our virus-like particle (VLP) platform technologies and may be evaluated using other vaccine technologies through partnerships in order to accelerate development of potential vaccines or to explore adjuvant therapies (Thompson et al. *Nature Communications*. 2018. 9: 385). Figure 4. Current influenza vaccine targets. Antigenic Drift (Thompson et al. *Nature Communications*. 2018. 9: 385) A single conformational epitope is typically 8 to 15 amino acids in length and in an extreme circumstance (where every change creates an escape mutant), a single epitope could theoretically vary from 208 to 2015 different ways. Therefore, a highly variable virus like influenza should be able to mutate in countless ways during each subsequent season. This would inevitably lead to an explosion of genetic diversity and numerous circulating strains. However, it seems that there is a constraint limiting how influenza evolves, leading to a single or limited number of strains dominating each season. In 2007, Sunetra Gupta led a group of researchers at the University of Oxford who published a proprietary mathematical model proposing that the single strain dominance, typically seen worldwide annually, could be explained by hypothesizing that epitopes of 'limited variability' exist (Antigenic Drift Hypothesis). The model hypothesizes that while there is a significant amount of mutation of influenza strains, this variability occurs in a specific portion of the virus, while certain epitopes are required to remain relatively constant and are more limited in their variability in order for the virus to infect individuals, thus clarifying how influenza is not as variable as commonly thought. Antigenic Drift Hypothesis Illustration Figure 5. Identification of a site of limited variability in the head domain of the H1 HA. b, c Location of ABS of lowest variability containing position 147 with position 147 shown in yellow and the rest of the site colored in red. d Phylogenetic trees of pre-pandemic and post-pandemic highlighted rectangle H1N1 with tips colored according to the conformation of the epitope of limited variability (hereafter called OREGO). Please note the re-introduction of H1N1 influenza in 1977 involved a strain which previously circulated in 1949/50. The Antigenic Drift Hypothesis suggests the existence of epitopes of limited variability mediate a population's immunity to influenza strains. As a particular influenza strain circulates in the population, immunity to a specific pattern of epitopes is induced. This leads the virus to change its antigenic configuration and cycle through its limited repertoire of antigenic conformations. However, population immunity also changes due to birth and death within the population (i.e. individuals in the population who had experienced and developed immunity to certain conformations die). This allows prior epitope conformations to reappear. The loss of herd immunity to these epitopes of limited variability causes the emergence of epidemics (Thompson et al. *Nature Communications*. 2018. 9: 385). Oxford scientists have identified the naturally antigenic regions that drive immunity to influenza by evaluating serum from these from various age groups of humans using assays and ELISAs reveal periodic cross-reactivity to ELV. Pseudotype microneutralisation data reveals a cyclical pattern of epitope recognition. The studies of children's sera were used to detect antibodies and demonstrated that young children ages 6 to 12 had immunity to historical influenza strains that circulated many years prior to when they were born and they could never have possibly been exposed to, one of which that last circulated in 1934. Mutagenesis of the identified regions of limited variability in various historical viruses removed the protective immunity. Furthermore, vaccination of mice, as shown below, with these regions of the influenza virus produced an identical immune response that was observed in the children. For example, the mice vaccinated with either the region from the influenza virus circulating in 2006 or 1977 were protected against infection with an influenza with a virus that last circulated in 1934, replicating the immunity seen in children ages 6 to 12. (Thompson et al. *Nature Communications*. 2018. 9: 385) Figure 6. Sequential vaccination using chimeric HA constructs. Five groups of mice were sequentially vaccinated with 2009-like (blue), 2006-like (red), 1995-like (orange), 1977-like (green) and 1940-like (pink) epitope sequences substituted into H6, H5 and H11 HAs. Two further control groups were sequentially vaccinated with H6, H5 and H11 constructs without any sequence substituted into the Has (vaccinated controls). Further two groups were mock vaccinated (unvaccinated controls). e, d, f, g Pseudotype microneutralisation assays using 0.5µl of sera from the bleed at 21 weeks. Error bars are mean ± s.e. m. n = 6 for experimental groups and control groups. The values provided are an average of two replicates. This work demonstrated that vaccination with just four variants of one region of limited variability in H1 influenza was able to elicit immunity to all historical H1 influenza strains. As these regions periodically reappear and disappear over time, vaccination with all of the possible variants would be expected to provide protection against future influenza strains as well. The identified epitopes are restricted in their variability due to presence of a receptor-binding site and small alpha-helix structure between disulphide bonds. The following research findings form the basis for our influenza vaccine candidates: 1. Epitopes of limited variability which are under strong immune selection exist within influenza. 2. These epitopes drive the antigenic evolution of influenza. 3. These epitopes cycle between a limited number of different conformations. 4. Epitopes of limited variability would make ideal vaccine targets. BWV-101: Universal Influenza Vaccine Our approach to developing a novel, universal flu vaccine for the prevention and protection against human influenza strains and potential pandemic strains by targeting specific limited variability epitopes includes the following steps and processes. We are exploring development of an influenza vaccine utilizing both the S & P nanoparticles to determine the most effective and efficient presentation of our ELVs and the versatile S & P nanoparticle vaccine platform from CHMC with the H1 influenza antigens. Data in preclinical mice (Rotavirus-specific antibody-free BALB/c mice, n = 5-7) challenge studies inserted M2e, a spike protein of influenza, into a P-particle loop, showed mice that were vaccinated had 100% protection when injected with lethal doses of influenza (Tan et al. *JOURNAL OF VIROLOGY*, Jan. 2011, p. 753-764). This dual approach will allow us to gain valuable information as we further the development and manufacturing of the BWV-102 program and utilize it for the development of BWV-101. We are currently assessing the ELVs to determine the most effective and efficient route of antigen presentation. Additionally, we are currently optimizing antigens for H3 and Flu B to be included with the identified H1 antigens to finalize our universal influenza vaccine formulation. We are using established manufacturing methods, including E. coli fermentation to produce our chimeric proteins, to reduce the cost and increase the efficiency and scalability of our manufacturing process for the vaccine. The antigens will be displayed by a proprietary VLP that can be produced in E. coli (Pharmaceutics 2019, 11, 472; doi: 10.3390/pharmaceutics11090472). Our research and discovery model uses bioinformatics and phylogenetic analysis to identify possible



sites of epitopes of limited variability before confirming their existence experimentally. To date, we have identified naturally immunogenic epitopes for H1, H3 and influenza B. Bioinformatics studies and wet lab studies suggest that these epitopes, especially H1N1, and the chimeric scaffold configuration of our vaccine induce immunity due to induction of broad cross-reactive antibodies in other strains such as H10N3 (bird flu), and pandemic strains including H5NX, H7NX, and H9NX. H9NX (Thompson et al. *Nature Communications*. 2018. 9: 385). Therefore, we foresee the development of H1N1 vaccine as a priority due to its high cross-reactive priorities.

#### BWV-102 Stand-Alone H1 Vaccine

We are developing our H1 stand-alone influenza prophylactic product, BWV-102, to address potential pandemic zoonotic H1 strains, specifically the G4 EA H1N1 identified by scientists and reported in June 2020, as a potential next pandemic strain. BWV-102 is being developed using the H1 ELVs identified by the team at the University of Oxford. While the product is designed to protect against infection from any H1 strain, there is potential for cross-protection from H5 and H10 strain infections as well. Preclinical studies were conducted in Balb C mice (n=6) using a prime-boost-boost protocol (Thompson et al. *Nature Communications*. 2018. 9: 385). The proposed Phase I clinical study will employ this prime-boost protocol; however, it is possible that a single dose of the vaccine candidate will confer protection against current and historical H1 strains with a prime-boost dose or a single dose. As reported in 2020, the G4 EA H1N1 strain is the most prevalent influenza strain circulating among swine populations in China. The strain was first identified in 2016 and has been monitored by scientists in China through their swine surveillance program. The strain has genes from a mix of pig, avian and human viruses, including genes from the 2009 H1N1 flu pandemic virus. Currently, the G4 EA H1N1 strain is not transmissible human to human, however, scientists hypothesize that there is a high likelihood of strain reassortment occurring that could make human to human transmissibility possible. The current H1N1 influenza strain circulating may provide some protection against disease induced by G4 EA H1N1 infection. The ability of the BWV-102 ELVs to induce an immune response and protection against heterologous challenge with historical strains was assessed in Balb C mice (n=6) (Thompson et al. *Nature Communications*. 2018. 9: 385). We are currently assessing the ELVs in combination with the S60 particle, P24 particle and a proprietary VLP, currently in development, to determine the most effective and efficient route of antigen presentation. Manufacturing of the product is expected to occur in *E. coli* (Pharmaceutics 2019, 11, 472; doi: 10.3390/pharmaceutics11090472). We anticipate results of the VLP presentation assessments in the first half of 2022.

#### BWV Norovirus (NoV) S & P Nanoparticle Versatile Vaccine Platform

Bioengineering the shell (S) and protruding (P) domains of the norovirus capsid protein, polyvalent nanoparticles and polymers / oligomers provide a versatile vaccine platform with wide applications.

#### Our Approach to Stimulating the Immune System for Infectious Disease Protection

Our S & P platform was co-invented by two researchers, Xi Jason Jiang, Ph. D., and Ming Tan, Ph. D., of the Division of Infectious Disease at the Cincinnati Children's Hospital Medical Center. The pre-clinical research conducted at CHMC provided encouraging data that supports further investigation and development of the platform for our vaccine candidates. The S & P platform combines two or more immunogenic components, a norovirus antigen plus at least one additional antigen, together creating novel constructs. The norovirus nanoparticle enhances immunogenicity of the inserted antigen. The S & P particles themselves also act as antigens, and are large enough to trigger an immune response to a foreign substance. By combining the norovirus nanoparticle with one or more antigens from other infectious disease(s), the immune system is stimulated to create antibodies to both the norovirus and the additional antigen(s).

#### Key Elements of our Platform

We are leveraging our disruptive norovirus nanoparticle platform to develop novel, broad-spectrum vaccines for adult and child infectious disease prevention by taking advantage of:

- **Flexible and Scalable discovery platform engine.** We believe we are able to design and create novel vaccines that are stable and scalable for broad spectrum prophylactics. Through this platform's adaptability, we may opportunistically expand our pipeline and potentially collaborate with third parties for additional vaccines, as well as therapeutics.
- **Cost-effective and Rapid Production of Novel Vaccines.** We are potentially able to reduce the cost and time to manufacture a vaccine candidate by utilizing an *E. coli* expression platform, compared to traditional vaccine production which uses other, longer production-time platforms, such as Chinese Hamster Ovary (CHO) cells. We have bioengineered these nanoparticles to be stable and effective, as determined through animal immunogenicity studies, using *E. coli* expression which may provide cost savings and efficiency compared to other VLPs needing a eukaryotic expression system. (Pharmaceutics 2019, 11, 472; doi: 10.3390/pharmaceutics11090472).
- **Multi-antigen and Pathogen Capabilities.** One of the key features of our platform is its ability to carry multiple antigens at a time, thereby creating a multi-targeted vaccine. It also provides the opportunity to develop vaccines for protection against not only viral pathogens, but also bacterial and potentially parasitic and fungal pathogens.
- **Therapeutic potential.** We believe our platform may offer opportunities to develop non-infectious disease therapeutic products, for example being used as a carrier or vehicle to transport drugs to specific target locations. Viral capsid proteins are responsible for many basic functions necessary for viral life cycles, such as viral attachment and entry, and thus can elicit neutralizing antibodies against viral infection after immunization to humans and animals. Consequently, viral capsid proteins are promising vaccine targets against viral infection. Indeed, various capsid protein nanoparticles and complexes have been developed and used as nonreplicating subunit vaccines to combat various infectious diseases. Unlike traditional live-attenuated and inactivated virus vaccines that need cultivation of infectious virions and are associated with certain safety concerns, the nonreplicating VLP vaccines derived from bioengineered viral capsid proteins do not involve an infectious agent and, therefore, may be safer and have lower manufacturing costs than traditional vaccines. Thus, VLP vaccines represent a next generation of innovative vaccine strategy.

#### Structure

- **The NoV (VP1) capsid structure consists of two major domains: (i) a N-terminal shell (S) domain and (ii) a C-terminal protruding (P) domain.** The S domain builds the interior shell of the capsid and the P domain forms the dimeric protrusions of the capsid.
- **The protrusions (P) of norovirus capsid interact with viral glycan receptors for attachment to host cells to initiate an infection.**
- **The S domain interacts homotypically and drives self-formation of an approximately 60 nm VLP.**
- **The P domain exhibits homotypic interactions, forming a 24 nm VLP with dimeric protrusions for stabilization of the viral capsid.** Additionally, it can also form oligomers or polymers.

Figure 1. Lineage structures of norovirus capsid protein or viral protein 1 (VP1) and various nanoparticles derived from full-length or truncated VP1. The N-terminal shell (S) (green) and the C-terminal protruding (P)



(dark blue) domains with a short flexible hinge (light blue) in between (with amino acid numbers based on GI. 1 Norwalk virus VP1) are shown. (A) Production of full-length norovirus VP1s via a eukaryotic expression system self-assembles into virus-like particles (VLPs). (B) Production of the S or P domain via the Escherichia coli expression system self-assembles into S or P nanoparticles. Due to the homotypic interaction attributed to the norovirus capsid domains, researchers at CHMC, through bioengineering, designed and generated two subviral nanoparticles, the 24-valent P24 and the 60-valent S60 nanoparticles, and P-derived polymers to serve as a multifunctional vaccine platform against different pathogens and illnesses. • These nanoparticles and polymers are easily produced, highly stable, and extremely immunogenic which we believe makes them compelling platforms to serve to display foreign antigens, self-assembling into chimeric nanoparticles or polymers as vaccine candidates. • There are several preclinical studies that showed P24/S60 chimeric vaccine candidates that can display different foreign antigens and epitopes, as set forth below in Tables 1 and 2. Therefore, there may be additional candidates to further explore as human vaccines. (Xia et al. ACS Nano 2018, 12, 10665–10682). • Such VLPs and capsid-like nanoparticles may be excellent vaccine candidates against corresponding viral pathogens because they can retain arrays of antigenic epitopes that faithfully mimic those of the native virions, and these repeated viral antigens and epitopes stimulate strong immune responses in their animal and human hosts. In addition, such highly immunogenic subviral nanoparticles may also serve as versatile platforms that are able to display foreign antigens for improved immune responses to facilitate development of novel vaccines against various pathogens and diseases. • The fact that the P24 VLP nanoparticles and polymers are composed of authentic norovirus antigens and retain norovirus-specific molecular patterns make it an excellent vaccine candidate against the norovirus. • In addition, the natures of self-formation, high stability, polyvalence, and high immunogenicity, as evidenced by animal studies conducted in gnotobiotic pig models and mouse models, results included herein, of the nanoparticles and polymers make them strong vaccine candidate platforms to display foreign antigens, resulting in chimeric nanoparticles as vaccine candidates against further pathogens and diseases. Our multifunctional vaccine platform is a robust discovery engine and has broad application using both S60 and P24 nanoparticles to target multiple pathogens and illnesses. The P24 nanoparticle has also been used to display multiple viral epitopes for enhanced immunogenicity for novel subunit vaccine development, see Table 1 below. These include the M2e epitope of the matrix 2 (M2) protein and the HA2 protein B cell epitope of influenza viruses, the B cell epitope of VP3 of enterovirus 71 (EV71), the 4E10 and 10E8 epitopes of human immunodeficiency virus type 1 (HIV-1), among others. Table 1. Summary of norovirus nanoparticles and polymers as vaccine candidates and platforms to display foreign antigens and epitopes. Nanoparticle / Polymer Antigen / Epitope to be Displayed (Pathogen) Chimeric Products as Vaccine Candidate Immunity against Pathogens or Diseases S60 VP8\* (rotavirus) S60-VP8\* Rotavirus P24 P domain (norovirus) P24 Norovirus P24 VP8\* (rotavirus) P24-VP8\* Rotavirus and norovirus P24 M2e (influenza virus) P24-M2e Influenza virus P24 HA2 B cell epitope (influenza virus) Trivalent HA2-PP (P24-HA2: 90-105) Influenza A virus and influenza B virus P24 VP3 B cell epitope (EV71) PP-71-6 (P24-71-6) EV71 P24 4E10 / 10E8 epitopes (HIV-1) 4E10-PP / 10E8-PP HIV-1 P24 Amyloid-beta, Aβ PP-3copy-Aβ1-6 Alzheimer's disease P polymer P domains (norovirus) NoV PGI-NoV PGH GST NoV P Different noroviruses P polymer P domain (HEV) NoV P-HEV P Norovirus and HEV P polymer P domain (astrovirus) P domain (HEV) Ast P-HEV P-NoV P Norovirus, astrovirus, and HEV P polymer P domain (astrovirus) P domain (HEV) VP8\* (rotavirus) Ast P-HEV P-VP8\* Rotavirus, astrovirus, and HEV Note: EV71, enterovirus 71; HIV-1, human immunodeficiency virus type 1; HEV, hepatitis E virus; Ast, astrovirus, NoV, norovirus, P, protruding domain; PP, P particle; GI, norovirus genogroup I; GI, norovirus genogroup II. Please see the main text for details. The S60 Nanoparticle as a Multifunctional vaccine platform Recent technology has generated S nanoparticles using an E. coli system with stabilized expression and self-assembly. The S nanoparticles feature exposed C-terminal flexible hinge sites that offer ideal fusion sites for displaying foreign antigens. Researchers at CHMC have developed a technology to produce uniform 60-valent NoV S60 nanoparticles with high efficiency using a simple bacterial expression system. This was achieved by taking advantage of the homotypic interactions of the NoV VP1 S domain that naturally builds the interior shells of NoV capsids, as well as several modifications to stabilize the S domain proteins and enhance the inter-S domain interactions, respectively. Specifically, we introduced an R69A mutation to destruct the exposed protease cleavage sites on the surface of the native shell that otherwise leads to easy degradation of the S proteins. In addition, we introduced triple (V57C/Q58C/S136C) cysteine mutations to establish inter-S domain disulfide bonds between two pairs of sterically close residues that belong to two neighboring S domains. This led to significantly enhanced stability and yields of the self-assembled S60 nanoparticles produced by the simple E. coli system. The below bullets are supported by published data by Ming Tan, the co-inventor of the S & P platform, and his research team at CHMC. • An important feature of our technology was to rationally introduce intermolecular disulfide bonds to stabilize the S60 nanoparticles. This approach could also be used to stabilize other viral protein particles or complexes. • The 60 freely exposed C-termini are a key feature facilitating the S60 nanoparticle to be a useful vaccine platform. Foreign antigens or epitopes can simply be fused to the end of the S domain via flexible linker through recombinant DNA technology. • Uniform 60-valent NoV VLPs or S particles produced in a bacterial expression system have not been produced before. • Importantly, our S60 nanoparticles maintained the native conformation with authentic antigenicity; thus, our NoV S60 nanoparticle technology represents a significant bioengineering advancement as uniform 60-valent NoV VLP or S particle via an expression system have never been produced before (Xia et al. ACS Nano 2018, 12, 10665–10682). • Uniform complexity and size of vaccine particles are important factors in quality control of vaccine products, as variations in complexity and size will result in variations in immunization outcomes of the vaccines. Broad application to fuse several antigens to the S60 nanoparticle based on multiple studies shown below conducted by CHMC (Xia et al. ACS Nano 2018, 12, 10665–10682) CHMC has been able to fuse several antigens to the S60 nanoparticle to the same exposed S domain C-terminus via the same linker. These included (1) the rotavirus (RV) surface spike protein VP8\*; (2) the HA1 antigen or receptor-binding domain (RBD) (223 amino acids) of the hemagglutinin (HA) of an H7N9 influenza A virus; (2) the TSR antigen (67 amino acids) of the circumsporozoite surface protein

(CSP) of the malaria parasite *Plasmodium falciparum*; (3) the protruding domain antigen (187 amino acids) of a hepatitis E virus; (4) a longer version of the RV VP8\* antigen (231 amino acids); and (5) the VP8\* antigen (159 amino acids) of the murine RV (mRV) EDIM strain (Table 1). Particle formations of these fusion proteins have been shown by gel-filtration and/or EM (Table 1). In addition, they have shown that the S60 nanoparticle-displayed HA1 and mRV VP8\* antigens elicited significantly higher HA1- and mRV VP8\*-specific antibody titers, respectively, than those elicited by the free HA1 or mRV VP8\* antigens (Table 2).

**Table 2. List of Antigens That Have Been Displayed by the S60 Nanoparticles epitope / antigen size (residue) yield (mg / L bacteria culture) S60 — antigen particle formation significant immune enhancement in mice**

RV VP8* antigen 159	40	yes	yes	HA1 antigen	223	10	yes	yes
TSR / CSP antigen	67	10	yes	ND	full RV VP8* antigen	231	20	yes
ND murine RV VP8* antigen	159	5	yes	yes	HEV protruding domain antigen	187	10	yes
ND aHA1 antigen containing the receptor-binding site is the head portion of the hemagglutinin (HA) of H7N9 influenza A virus.								

TSR / CSP antigen is the C-terminal portion of the major surface protein of *Acireumsporozoite* (CSP) that plays a key role in host cell invasion of the malaria parasite *Plasmodium falciparum*. eFull RV VP8\* antigen is the full-length VP8\* domain of the spike protein of a human P[8] rotavirus. dMurine RV VP8\* antigen is the core portion of the VP8\* protein constituting the head of the spike protein of a murine rotavirus EDIM strain. eHEV protruding domain antigen is part of the protruding domain of a hepatitis E virus capsid. fImmune enhancements of the S60 nanoparticle-displayed antigens were measured in mice using free monomeric antigens as control for comparisons. “ND” = not determined. S60 nanoparticles may serve as a polyvalent vaccine platform (Xia et al. ACS Nano 2018, 12, 10665–10682).

- We believe the self-assembled, polyvalent S60 nanoparticle with 60 flexibly exposed S domain C-termini is an ideal vaccine platform for antigen presentation and immunogenicity enhancement.
- This has been supported by studies showing that when Hisx6 tag was fused to the hinge of the S domain via a linker, fusion proteins self-formed into the S60 nanoparticles.
- This has also been demonstrated by constructing a chimeric, and reconfirmed by cryoEM density map, S60 nanoparticle displaying 60 RV (rotavirus) VP8\* proteins, the major rotavirus neutralizing antigen. The S60-VP8\* particles can be easily produced with high stability. The chimeric nanoparticle induced higher immunoglobulin, or IgG, response in mice (n = 6) toward the displayed VP8\* antigen than soluble VP8\* antigen. Mouse sera experiments were completed analyzing vaccinated versus the control group to show neutralizing activity against RV infection. The statistical differences between the groups are (\* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001) as shown below (Figure 2) (Xia et al. ACS Nano 2018, 12, 10665–10682).
- The RV surface spike protein, VP8\* was tested for feasibility of the S60 nanoparticle by the analysis using EM micrograph examination and ESI-MS analysis. S60-VP8\* particles exhibited stronger blockade in mice (n = 6) sera after vaccination (P = 0.0003) (Xia et al. ACS Nano 2018, 12, 10665–10682).
- The polyvalent B- and T-cell epitopes of the antigens on the polyvalent VLP platform led to induction of stronger humoral and cellular immune responses, respectively, in animals and humans compared with those elicited by the monovalent epitopes of the free antigen. Thus, the polyvalent VLP platform is likely to increase the immunogenicity of the displayed antigens. Mouse sera experiments were completed analyzing vaccinated versus the control group to show neutralizing activity against RV infection. The statistical differences between the groups are (\* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001) as shown below. (Xia et al. ACS Nano 2018, 12, 10665–10682).

**Figure 2. S60-VP8\* particles enhanced immunogenicity toward the displayed RV VP8\* antigens.** The same dose / dosage of the S60-VP8\* particles, free VP8\* antigens, and S60 nanoparticles without VP8\* was given to mice (N = 6), respectively, followed by measurements of the VP8\*-specific IgG responses (A), 50% blocking titers (BT50) against RV-VP8\*-glycan ligand interaction (B), and neutralization activity against RV infection / replication in culture cells (C) of the resulting mouse antisera. (A) VP8\*-specific IgG responses / titers elicited by the S60-VP8\* particles, free VP8\* antigens, and the S60 nanoparticles, respectively. (B) BT50 against RV-VP8\*—ligand interactions by the mouse sera after vaccination with the same three immunogens, respectively. (C) Neutralizing activity against RV infection / replication in culture cells by mouse sera after immunization with the same three immunogens, respectively. In all these experiments mouse sera after immunization with diluent (PBS) are used as negative controls. The P24 Nanoparticle as a versatile platform (Tan et al. Nanomedicine, 2012, 7, 6, 1–9) The crystal structure of norovirus VLPs indicates that P domain is involved in strong dimeric interactions forming dimeric protrusions on the viral surface. The oligomeric interactions of the P domains are also observed at the five-fold axes to further stabilize the capsid structure. When the P domain protein was expressed using the E. coli system, it self-assembled into P dimers, as well as 24-valent P nanoparticles. P24. P dimers and P24 nanoparticles can exchange dynamically, depending on concentration of the P domain protein, indication that the assembled P24 particles at this stage were unstable and easy to disassemble back into P dimers. To facilitate P24 nanoparticle formation, inter-P domain disulfide bonds were introduced through fusion of a cysteine-containing peptide to the end of the P domain. During the P24 nanoparticle assembly, the cysteine patches were brought to the center of the P24 nanoparticles, resulting in sterically close contact and thus forming inter-P domain disulfide bonds that significantly stabilized the P24 nanoparticles, which could no longer disassemble back into the P dimers. • P24 nanoparticles can be produced using an E. coli expression system faster and a lower cost than VLPs. • Both VLP and P24 nanoparticles without adjuvant produce innate, humoral, and cellular immunity. • The platform can be used to display foreign antigens, epitopes and viral pathogens and non-infectious disease. • Studies have demonstrated immune response against flu, rotavirus, and norovirus using bi- or trivalent vaccine candidates developed using this approach, noting the potential for the development of a universal flu vaccine. Pre-clinical studies in influenza and rotavirus are provided below supporting our vaccine candidate programs. See — Our Infectious Disease Vaccine Candidates. BWV-301 Norovirus-Rotavirus Vaccine Program We are developing BWV-301 to prevent acute gastroenteritis, or AGE, caused by norovirus and rotavirus, utilizing the P24 nanoparticle of our vaccine platform. The vaccine is based on one or two doses of the norovirus P24 nanoparticle presenting 24 rotavirus VP8\* antigens. Most cases of gastroenteritis are caused by viruses. The CDC reports that viral gastroenteritis infections cause 200,000 deaths in children worldwide each year. Common symptoms of viral gastroenteritis causes nausea, vomiting, diarrhea, anorexia, weight loss, and dehydration. Gastroenteritis Gastroenteritis, often called stomach flu, is inflammation of the gastrointestinal tract—the stomach and intestine. Symptoms may include diarrhea, vomiting and

abdominal pain. Fever, lack of energy and dehydration may also occur. While gastroenteritis is usually caused by viruses, bacteria, parasites, and fungus can also cause gastroenteritis. Eating improperly prepared food, drinking contaminated water or close contact with a person who is infected can spread the disease. Norovirus and rotavirus are two viruses that cause gastroenteritis in adults and children. In 2015, there were two billion cases of gastroenteritis, resulting in 1.3 million deaths globally. Children and those in the developing world are affected the most. In 2011, there were about 1.7 billion cases, resulting in about 700,000 deaths of children under the age of five. In the developing world, children less than two years of age frequently get six or more infections a year. It is less common in adults, partly due to the development of immunity. In adults, norovirus is the most common cause of severe disease. Rotavirus, however, is the common cause of AGE in children. Norovirus causes significant debilitating AGE, with a reported 700 million infections and 20% of all diarrheal cases reported annually worldwide, according to the CDC. About 200 million cases are seen among children under 5 years old, leading to an estimated 50,000 child deaths every year. Norovirus is the cause of approximately 20% of all AGE cases worldwide each year. It is estimated that 68.9 cases of norovirus infection occur in every 1000 people. In North America, norovirus induced AGE tends to be seasonal, occurring in cooler, rainy months and particularly impacts groups in close proximity, such as in schools, dormitories, medical facilities, and cruise ships. Norovirus costs \$ 60.3 billion worldwide each year (CDC). Globally, norovirus resulted in a total of approximately \$ 4.2 billion in direct health system costs and approximately \$ 60.3 billion in societal costs per year. Disease among children younger than 5 years cost society \$ 39.8 billion, compared to \$ 20.4 billion for all other age groups combined. Costs per norovirus illness varied by both region and age and was highest among adults ages 55 years and older. Productivity losses represented 84-99% of total costs varying by region. While low and middle income countries and high income countries had similar disease incidence (10,148 vs. 9,935 illness per 100,000 persons), high income countries generated 62% of global health system costs (Bartsch et al. *PLoS One* 2016; 11: e0151219). In North America, the median yearly cost of outbreaks was \$ 7.6 million in direct medical costs, and \$ 165.3 million in productivity losses. An average of approximately 113,000 hospitalizations, 8.2-122.9 million missed school / work days, \$ 0.2-\$ 2.3 billion in direct medical costs, and \$ 1.4-\$ 20.7 billion in productivity losses was due to sporadic illness. The total economic impact of norovirus infection was \$ 10.6 billion based on the current incidence estimate 68.9 cases per 1000 population, or approximately \$ 0.15 million per person infected. The total economic burden is greatest in young children but the highest cost per illness is among older age groups in some regions. These large costs overwhelmingly are from productivity losses resulting from acute illness. Low, middle, and high income countries all have a considerable economic burden, suggesting that norovirus gastroenteritis is a truly global economic problem. There is not a norovirus vaccine on the market presently. There are, however, a number of rotavirus vaccines currently marketed around the world. RotaTeq, owned by Merck, a live, oral pentavalent vaccine and Rotarix, owned by GSK, a monovalent, human, live-attenuated vaccine are recommended by the WHO for global use in children and approved for use in the U. S., Canada and Europe. Other monovalent vaccines are available but only approved for use in one country, either China, Vietnam or India. Development P24 VLPs produced in *E. coli* and norovirus VP1 VLPs produced in a baculovirus expression system were both demonstrated to elicit innate, humoral and cellular immunity in a mouse model, indicating that both constructs have potential as norovirus virus candidates. In addition, when delivered intranasally both constructs were able to induce partial cross-variant protection against diarrhea in a gnotobiotic pig model. Ramesh et al. *Vaccines* 2019, 7, 777. Rotavirus is the most common cause of diarrheal disease among infants and young children, causing an estimated 111 million episodes of diarrhea annually, 2 million hospitalizations and 352,000-592,000 deaths annually, according to the CDC. After the introduction of live-attenuated oral vaccines the incidence of rotaviral hospitalizations and deaths have significantly declined. However, there is still a need for efficacious, cost-effective rotavirus vaccines. The rotavirus vaccine is recommended by the CDC and ACIP as a prevention for children. However, managing the symptoms is the only way to help adults and children infected with either of the viruses. Due to the potential of death, most treatments are focused on dehydration prevention and management. Treatment involves getting enough fluids. For mild or moderate cases, this can typically be achieved by drinking oral rehydration solution (a combination of water, salts and sugar). In those who are breastfed, continued breastfeeding is recommended. For more severe cases, intravenous fluids may be needed and care provided in the hospital. Fluids may also be given by a nasogastric tube. Zinc supplementation is recommended in children. Antibiotics are generally not needed. However, antibiotics are recommended for young children with a fever and bloody diarrhea. To determine the potential of the P24 VLP to serve as a rotavirus vaccine candidate, the 159 amino acid VP8\* protein was inserted into a P24 domain surface loop. The fusion proteins self-assembled into P24 VLPs, and the 24 rotavirus VP8\* antigens were demonstrated by cryo-EM to be displayed on the outermost surface of the chimeric P24 VLP. Mice (n=5-7) immunized intranasally with the P24-VP8\* or intramuscularly with Freund's adjuvant elicited significantly higher rotavirus neutralizing antibodies than the free VP8\* immunized under the same conditions (IN or IM). (P>0.05), (Tan et al. *J. Virol.* 85 (2): 753-764. 2011). P24-VP8\* VLPs were further characterized as a potential rotavirus vaccine in mouse and gnotobiotic pig challenge studies. A construct consisting of P24 and the VP8\* antigen from the murine rotavirus EDIM strain was constructed and tested using a murine rotavirus challenge model. Mice (n=5-7) were immunized with P24-mouseVP8\*, mouseVP8\* alone or P24-human VP8\* 3 times intranasally without adjuvant. Rotavirus shedding was significantly lower in animals immunized with P24-mouseVP8\* than mock vaccinated or animals that received mouseVP8\* only or P24-humanVP8\* (P>0.05) (Tan et al. *J. Virol.* 85 (2): 753-764. 2011). Additionally, an immunogenicity study was conducted in gnotobiotic pigs (n=25). A construct of P24 and the VP8\* antigen corresponding to human rotavirus Wa strain was tested in a gnotobiotic pig challenge model. Animals were immunized intramuscularly (IM) three times with either P24-WuVP8\* with aluminium hydroxide adjuvant or aluminium hydroxide alone and were challenged with human Wa rotavirus 7 days post dose three. Animals immunized with P24-WuVP8\* showed a significant reduction in the mean duration of diarrhea, virus shedding and significantly lower fecal cumulative consistency scores compared to adjuvant only control group (\*, p<0.05; \*\*, p<0.01). (Ramesh et al. *Vaccines* 7: 177 2019; doi: 10.3390/vaccines7040177). Figure 9.. P24-VP8\* vaccine protected against

VirHRV diarrhea and reduced overall virus shed among vaccinated pigs. Fecal consistency (A) and virus shedding (B) were monitored daily from post challenge day (PCD) 1 to PCD 7 after the challenge with VirHRV. Fecal consistency scores  $\geq 2$  were considered to be diarrheic (dashed line indicates the threshold of diarrhea). Statistical significance between vaccinated and control groups, determined by multiple t tests, are indicated by asterisks (\*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ). Additionally, serum samples were collected from the pigs at the times of P24-VP8\* vaccine administration (PID 0, PID 10, PID 21 and PID 21) and VirHRV challenge (PID 27) and upon euthanasia (PCD 7). The P24-VP8\* vaccine was highly immunogenic in Gn pigs. It induced strong VP8\*-specific serum IgG and Wa-specific virus-neutralizing antibody responses from post-inoculation day 21 to PCD 7. Comparisons between groups at the same time points were carried out using Student's t-test and significant differences are identified by \*\*\* ( $n = 10-15$ ;  $p < 0.001$ ). Tukey-Kramer HSD was used for the comparison of different time points within the same group, where different capital letters (A, B, C, D) indicate a significant difference,  $p < 0.01$ , and shared letters indicate no significant difference. These findings support further investigation of the noro-rotavirus dual nanoparticle vaccine. (Ramesh et al. *Vaccines* 7: 177-2019; doi: 10.3390/vaccines7040177) Figure 10. Geometric mean VP8\*-specific IgG (A) and IgA (B) and Wa-HRV neutralizing (C) antibody titers in serum collected from Gn pigs at PID 0, 10, 21, 28, and PCD 7. Pigs were vaccinated with P24-VP8\* vaccine or Al(OH)<sub>3</sub> adjuvant only. Each serum specimen was tested at an initial dilution of 1:4. Negative samples were assigned an arbitrary value of 2 for calculation and graphical illustration purposes. Comparisons between groups at the same time points were carried out using Student's t-test and significant differences are identified by \*\*\* ( $n = 10-15$ ;  $p < 0.001$ ). Tukey-Kramer HSD was used for the comparison of different time points within the same group, where different capital letters (A, B, C, D) indicate a significant difference,  $p < 0.01$ , and shared letters indicate no significant difference. An effective norovirus culture-based neutralization assay is not available, due to the lack of an efficient cell culture system to produce human norovirus. Therefore, a surrogate neutralization assay has been developed in the field, measuring the ability of antisera to block norovirus VLP binding to host receptors. In addition to generating rotavirus neutralizing antibody, Tan et al (*J. Virol.* 86: 753-764, 2011) demonstrated that anti-P24-VP8\* mouse sera blocked norovirus VLP binding, indicating that the insertion of the VP8\* fragment did not inhibit induction of norovirus VLP binding antibodies and suggesting the P24-VP8 construct could potentially serve as a single vaccine against both rotavirus and norovirus disease ( $p > 0.05$ ). Our Vaccine We hold the exclusive global license for the novel norovirus-rotavirus combination vaccine (except in China and Hong Kong) from Cincinnati Children's Hospital Medical Center, or CHMC, CHMC researchers engineered the norovirus major structural protein VP1 such that the N-terminal shell (S) and C-terminal protruding (P) domains of VP1 could be expressed as separate S60 and P24 VLPs. Unlike norovirus VLPs composed of the intact VP1 protein or the unmodified S60 fragment, our S60 and P24VLPs can be expressed in *E. coli*. The researchers demonstrated that S60 VLPs could be used to present foreign antigens on the surface of the S60 VLP. Further, it has also demonstrated that foreign antigens could also be expressed on the surface of the P24 VLP. The proposed norovirus-rotavirus vaccine is based on the P24 VLP technology. Our vaccine production is based on an *E. coli* expression platform. Following IND submission, if accepted, we intend to initiate our Phase I clinical trial in healthy adults ages 18 to 54. If approved, we believe our vaccine is well positioned to receive a recommendation from the CDC, ACIP, and similar international advisory groups for inclusion in vaccine programs. BWV-302: Norovirus-malaria vaccine program Additionally, we are currently investigating a malaria vaccine, BWV-302, utilizing our norovirus platform. The vaccine is designed to offer protection from both norovirus and malaria, infectious diseases that occur frequently together in geographic regions. The vaccine utilizes a protein identified on the surface of the plasmodium parasite being presented on the surface of the norovirus nanoparticle. Malaria Malaria can be a deadly disease caused by protozoan parasites from the Plasmodium family, primarily spread by mosquitos (CDC, <https://wwwnc.cdc.gov/travel/diseases/malaria>). Malaria may also, at times, be transmitted through blood transfusion, organ transplantation and from mother to fetus. (CDC, <https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria>). While transmission through blood transfusion is rare in the U.S., there are no approved blood tests currently available to screen blood donation for malaria. There were approximately 219 million cases of malaria reported in 2019 globally, resulting in approximately 409,000 deaths, of which approximately 67% were children. (WHO, <https://www.who.int/news-room/fact-sheets/detail/malaria>). Symptoms of malaria normally manifest themselves within 7 to 10 days of exposure, and can at times, be mistaken for other illnesses, including influenza. Severe malaria is life-threatening and can cause multi-organ failure in adults and severe anemia, metabolic acidosis and cerebral malaria in children. The World Health Organization estimates that almost half of the global population is at risk of contracting malaria. Infants, children under 5 years of age, pregnant women and immune compromised individuals are highest risk of developing the disease. Additionally, non-immune migrants, mobile populations and travelers are at risk of developing severe disease. Neurological issues in children may continue to persist after cerebral malaria, including ataxia, palsy, speech impairment, deafness and blindness. More than 100 species of Plasmodium have been identified. Four of the species have been recognized as naturally infecting humans, while one that infects macaques and has been identified as a cause of zoonotic malaria. In rare cases, additional species may infect humans. The primary four parasites that cause human infection are *P. falciparum*, *P. vivax*, *P. ovale* and (<https://www.cdc.gov/malaria/about/biology/index.html>). *P. knowlesi* is naturally occurring in macaques in Southeast Asia and has recently been reported as the cause zoonotic malaria, especially in Malaysia. *P. falciparum* is found world-wide, can cause severe malaria and is the predominate human malaria causing species around the world. There is currently one vaccine for malaria, RTS, S/AS01 (MVI-GSK) targeting the falciparum CS protein, which received a positive opinion from the European Medicines Agency (EMA) for use outside of the European Union in infants 6 weeks of age and older. (<https://www.ema.europa.eu/en/news/first-malaria-vaccine-receives-positive-scientific-opinion-ema>) According to the EMA, the World Health Organization and the relevant regulatory agencies for countries outside of the European Union can authorize its use. The vaccine is currently being administered to infants and children in parts of Africa within high transmission regions. The vaccine's efficacy appears to wane after five years (Laurens MB. RTS, S/AS01 vaccine (Mosquirix™): an overview. *Hum Vaccin Immunother.* 2020; 16 (3):

480–489. Doi: 10.1080/21645515.2019.1669415). The recommended course of action for preventing malaria is prevention of mosquito bites, and for those most vulnerable, a preventative treatment with sulfadoxine–pyrimethamine, especially in high transmission areas (WHO). In certain regions, the WHO has recommended the addition of amodiaquine to children under 5 years of age monthly during the high transmission season, along with sulfadoxine–pyrimethamine. Many regions employ mosquito control measures to reduce mosquito populations, however, 73 countries have reported mosquito resistance to at least 1 of the 4 most commonly used insecticides, while 23 countries have reported mosquito resistance to all of the commonly used insecticides. Once malaria is diagnosed, the two most common treatments are Chloroquine phosphate and Artemisinin–based combination (ACT) therapies. Chloroquine is the preferred treatment, however, some malaria parasites have become resistant to chloroquine and it may not be an effective treatment. ACT is a combination of two or more drugs that work against the malaria parasite in different ways. This is usually the preferred treatment for chloroquine–resistant malaria. However, as recently reported in Nature Medicine, there is growing concern about Artemisinin—derivative resistant *P. falciparum* in the Greater Mekong subregion (Cambodia, Thailand, Vietnam, Myanmar and Laos) (<https://www.nature.com/articles/s41591-020-1005-2.pdf>). Previous occurrences of resistant strains also first appeared in the Greater Mekong subregion and then spread to other parts of the world. (<https://www.nature.com/articles/s41591-020-1005-2.pdf>). We hold the exclusive global license for the novel norovirus–malaria combination vaccine from Cincinnati Children’s Hospital Medical Center, or CHMC. CHMC researchers engineered the norovirus major structural protein VP1 such that the N–terminal shell (S) and C–terminal protruding (P) domains of VP1 could be expressed as separate S60 and P24 VLPs. Unlike norovirus VLPs composed of the intact VP1 protein or the unmodified S60 fragment, our S60 and P24VLPs can be expressed in *E. coli*. The researchers, Xi Jason Jiang, Ph. D., and Ming Tan, Ph. D., demonstrated that S60 VLPs could be used to present foreign antigens on the surface of the S60 VLP. Further, it has also demonstrated that foreign antigens could also be expressed on the surface of the P24 VLP. (see BWV Norovirus (NoV) S & P Nanoparticle Versatile Vaccine Platform). The proposed norovirus–malaria vaccine, P–CS) TSR is based on the P24 VLP technology. Our vaccine production is based on an *E. coli* expression platform. The circumsporozoite (CS) protein is the major surface component of *P. falciparum* sporozoites and is essential for host cell invasion. Our vaccine, developed by Jiang and Ming from CHMC, combines a small domain of the CS protein with the norovirus P24 particle creating a chimeric nanoparticle capable of eliciting an immune response. A mouse immunization study was conducted using the P24 particle presenting the small domain of the CS protein. Mice (n = 16) were immunized three times with the chimeric nanoparticle using aluminum hydroxide as an adjuvant, 3D7–His, 3D7–GST and PBS. Sera was collected and evaluated. High antibody titers, as determined by ELISA, were observed after the second immunization and higher titers were observed after the third immunization. The antibodies were also shown to recognize the plasmodium falciparum 3D7 strain using immunofluorescence assays. These data demonstrate the potential of our vaccine candidate against malaria. We expect to conduct an animal challenge study to further analyze the protective nature of BWV–302 and support an IND application. Table 3. Mouse malaria antibody titer post–immunization Antibody titer after 2nd immunization Antibody titer after 3rd immunization Figure 11. IFA of plasmodium sporozoites (3D7) stained with anti–P24 particle presenting the small domain of the CS protein mouse sera We anticipate conducting an animal challenge study for BWV–302 in the second half of 2023. Upon completion, the technology will be transferred to a partner contract manufacturing organization (CMO) for process optimization, GMP production and toxicology studies, as well as other studies required by the FDA for IND submission, currently anticipated for the second half of 2022. Following IND submission immediately upon completion of the toxicology study, if successful, we intend to initiate our Phase I clinical trial in healthy adults ages 18 to 54 upon acceptance by the FDA. Exploration of a Novel Monkeypox Vaccine Using BWV VLP Platform In addition to norovirus, rotavirus, and malaria, we are exploring the potential to utilize the norovirus S & P platform to create a novel monkeypox vaccine. Research into the viability of this vaccine candidate is ongoing and includes insertion of selected monkeypox antigens into the S & P particles and sequence optimization; establishing the optimal expression system to enhance future manufacturing of the vaccine product, as well as immunogenicity and efficacy studies at various stages of development. To date, antigens of interest have been identified and the vaccine construct has been generated in small amounts using our VLP platform licensed from CHMC. Immunogenicity studies in mice are ongoing and results will inform our decision to move forward with a challenge study, which will evaluate the in vivo efficacy of this vaccine in the mouse model. Given this vaccine is in early stages of development and optimization, study designs and development paths are flexible. Upon completion of immunogenicity and efficacy studies with promising results, this technology may be transferred to a partner CMO for process optimization, GMP production and toxicology studies, as well as other studies required by the FDA for IND submission. Monkeypox is a viral zoonosis, or a virus transmitted from humans to animals, and is a member of the same genus as the smallpox virus, Orthopoxvirus. While clinical symptoms of monkeypox are less severe than those of smallpox, several recent outbreaks and the eradication of smallpox in 1980 have brought global attention to the prevention of monkeypox spread. Monkeypox primarily occurs in central and west Africa, often in proximity to tropical rainforests, but has been increasing in urban areas, particularly with a recent outbreak in 2022 that spread to 110 countries and caused approximately 85,000 cases as of January 2023. There are currently two approved vaccines for the prevention of monkeypox infection in the United States: JYNNEOS and ACAM2000. Both vaccines were originally approved to prevent smallpox infection but have been approved for use in monkeypox. JYNNEOS is a 2–dose vaccine, with doses given 4 weeks apart and is a live–attenuated, non–replicating vaccine while ACAM2000 is a live, replication–competent vaccinia virus given via bifurcated needle in a single dose. Both are designed to elicit an immune response to prevent monkeypox and smallpox infection without causing disease. While vaccines have shown efficacious in preventing disease, there remains a need for additional vaccination options, particularly those that are not comprised of live virus. BWV–401: Chlamydia Vaccine Chlamydia Background Chlamydia is a sexually transmitted infection caused by the bacterium Chlamydia trachomatis and can impact both men and women. According to the Centers for Disease Control and Prevention, there were about 1.6 million new cases of chlamydia reported in 2020 in the United States and globally, the World Health Organization estimates about 129

million new cases each year. Additionally, given high estimations of asymptomatic cases and low availability of diagnostic testing in low- and middle- income countries, these annual estimates may be an underrepresentation. Currently, there is no vaccine available to prevent chlamydia infection, and the main treatment is through antibiotic regimens with the possibility of reinfection after antibiotics have treated the disease. If left undetected or untreated, Chlamydia represents a major cause of pelvic inflammatory disease and infertility in women. It is estimated that about 10–15% of women that experience untreated chlamydia develop pelvic inflammatory disease and face chronic pain or fertility problems later in life. Additionally, should women contract chlamydia during pregnancy or give birth with an active infection, newborns may develop eye infections or pneumonia resulting from the disease. BWV-401 Approach BWV-401 is an orally delivered, live-attenuated chlamydia vaccine derived from a murine strain, *Chlamydia muridarum*, developed in the laboratory of Guangming Zhong, M.D., Ph.D. at the University of Texas Health at San Antonio. By administering this vaccine orally, BWV-401 may elicit transmucosal immunity and provide protection against chlamydia in the genital tract post-vaccination without altering the gut microbiota or the development of gut mucosal resident memory T cell responses to non-chlamydial infection. In the initial publication establishing this approach as a viable vaccine development pathway, mice were intragastrically inoculated with *C. muridarum* to mimic oral immunization. Following each inoculation, both vaginal and rectal swabs were periodically taken to monitor viable *C. muridarum* colonization or organs/tissues were harvested to titrate viable organisms. Through this study, researchers identified the following key findings supporting further development of this vaccine candidate. • GI tract *C. muridarum* induces transmucosal protection against genital tract infection. *C. muridarum* colonization in the gastrointestinal tract correlated with reduced *C. muridarum* infection in the genital tract of the same mice. First, the extent to which *C. muridarum* organisms spread from the genital tract into the GI tract inversely correlated with their course of shedding in the genital tract. Second, the coinoculation of *C. muridarum* organisms into the GI tracts of mice infected vaginally with plasmid-deficient *C. muridarum* significantly shortened the course of vaginal infection. Finally, the reduced spreading of plasmid-free *C. muridarum* into the GI tract also minimized immunity against reinfection in the genital tract (Fig. 1). Figure 1. Effect of intragastric inoculation as an oral vaccination on genital tract susceptibility to *C. muridarum* challenge infection. C57BL/6J mice intragastrically inoculated with buffer only (control group, n 8) (a and a1) or  $2 \times 10^5$  IFU of wild-type *C. muridarum* (clone CM-mCherry, immunization group, n 8) (b and b1) were challenged intravaginally on day 56 with  $2 \times 10^5$  IFU of wild-type *C. muridarum* clone G13-32-1. (A) Mice were monitored for live organism shedding by the collection of both vaginal (a and b) and rectal (a1 and b1) swab specimens over the time course displayed along the x axis. The results are expressed as the log<sub>10</sub> number of IFU per swab specimen along the y axis. Black bars, titers of G13-32-1; red bars, titers of CM-mCherry; dark red bars, titers of both G13-32-1 and CM-mCherry. Note that on days 3, 7, and 14 after intravaginal challenge (designated in parentheses as 3 =, 7 =, and 14 =, respectively) after intragastric immunization, immunized mice displayed a >1,000-fold decrease in the number of IFU by evaluation of vaginal swab specimens at each time point (\*,  $P < 0.05$ , Wilcoxon rank-sum test). The overall shedding course was also significantly reduced (\*,  $P < 0.05$ , Wilcoxon rank-sum test, AUC, for panel b versus panel a). (B) All mice were sacrificed on day 128 after intragastric immunization (or day 63 = after challenge) for evaluation of the upper genital tract pathology both macroscopically (a and b) and microscopically (d and e). (a and b) Representative macroscopic images of one entire genital tract from the control (a) and immunization (b) groups are shown. White arrows, oviducts positive for hydrosalpinx. Magnified images of oviduct/ovary regions are shown on the right of the overall genital tract images, with the white numbers indicating the hydrosalpinx scores. (c) Both the incidence and the severity of hydrosalpinx were quantitated. The group immunized in the GI tract developed a significantly lower incidence (\$,  $P < 0.05$ , Fisher's exact test) and a reduced score (\*,  $P < 0.05$ , Wilcoxon rank-sum test) compared with those for the control mice. (d and e) Microscopically, severely dilated oviducts (marked with a white line with arrows at both ends) were easily identified from control mice, as shown in the representative image (d), while the immunized mice mostly displayed normal oviduct cross sections ©. (d1 and e1) The inflammatory cells were identified using a 100x objective lens, as shown in the representative images from the control (d1) and immunized (e1) mice. The areas observed with a 100x objective lens are marked with white squares in the 10x images. (f) The severity of the inflammatory infiltration was semiquantitated using the criteria described in the Materials and Methods section. Note that the immunized mice developed scores significantly decreased (\*,  $P < 0.05$ , Wilcoxon rank-sum test) compared with those for the control mice. • Transmucosal protection is rapidly induced, durable, and independent of sustained *C. muridarum* colonization in the gastrointestinal tract. Both the time required for GI tract *C. muridarum* induction of transmucosal protection and the duration of protection were determined (Fig. 2). One week after intragastric inoculation with CM-mCherry, mice gained significant resistance to intravaginal challenge infection with G13-32-1, with G13-32-1 shedding being reduced by >100-fold on day 3 and the course of infection being shortened by ~1 week, leading to a significant reduction in both the overall infection course and the upper genital tract pathology. The protection was enhanced over time (Fig. 1) and lasted 20 weeks. Whether the transmucosal protection was dependent on ongoing CM-mCherry colonization in the GI tract was further determined (Fig. 3). Mice with or without CM-mCherry in the GI tract for 28 days were either left untreated or treated with doxycycline daily for 2 weeks. After resting for another 2 weeks, the mice were vaginally challenged with G13-32-1. Mice colonized with CM-mCherry in the GI tract for 56 days became highly resistant to intravaginal challenge infection and hydrosalpinx induction, as described above. Importantly, after the immunized mice received daily doxycycline treatment between days 28 and 42, which completely cured the GI tract CM-mCherry infection, the mice still maintained a robust resistance to intravaginal challenge infection and hydrosalpinx development. Thus, within 4 weeks, intragastrically inoculated *C. muridarum* induced a robust memory response that was protective. Mock-immunized mice similarly treated with doxycycline developed severe hydrosalpinx after the same intravaginal challenge, suggesting that the doxycycline treatment protocol did not affect chlamydial pathogenicity in the upper genital tract. It is worth noting that although the immunized mice were resistant to challenge infection with *C. muridarum* in the genital tract, the GI tract remained susceptible to colonization by the *C. muridarum* organisms. Figure 2. Intragastric immunization elicits rapid and durable protective immunity to genital tract challenge. C57BL/6J mice with (n 5)

or without (n 5) prior intragastric immunization with  $2 \times 10^5$  IFU of CM- mCherry for 1 week (1W) (a) or 20 weeks (20W) (b) were challenged vaginally with clone G13. 32. 1. The mice were monitored for *C. muridarum* shedding by evaluation of both vaginal and rectal (not shown) swab specimens on days 3 and 7 postinfection (3 = and 7 =, respectively) and weekly thereafter. The results are expressed as the log<sub>10</sub> number of IFU per swab specimen. Mice were significantly resistant to a genital tract challenge only 1 week after immunization in the GI tract (\*,  $P < 0.05$ , Wilcoxon rank-sum test, AUC), and the resistance increased and lasted for up to 20 weeks (\*,  $P < 0.01$ , Wilcoxon rank-sum test, AUC). All mice were sacrificed on day 56 after the challenge infection, and the upper genital tract was evaluated for the incidence (in percent) of hydrosalpinx and the severity score (mean standard deviation). Immunization via the GI tract resulted in significant protection against hydrosalpinx induced by the vaginal infection (#,  $P < 0.05$ , Fisher's exact test; \*,  $P < 0.05$ , Wilcoxon rank-sum test; \*,  $P < 0.01$ , Wilcoxon rank-sum test). Figure 3. The durable transmucosal protection induced by intragastric immunization is not dependent on long-term gastrointestinal infection. Groups of C57BL/6J mice immunized intragastrically with  $2 \times 10^5$  IFU of CM- mCherry (n 5 for panel a and n 7 for panel b) or not immunized (n 6) (c) were treated on day 28 with doxycycline (20 ug/kg of body weight intragastrically once daily) for 2 weeks (days 28 to 42) (b and c) or were not treated with doxycycline (a). The doxycycline-treated mice were then rested for 2 weeks (days 43 to 56). On day 56 after immunization in the GI tract, all mice were intravaginally challenged with  $2 \times 10^5$  IFU of clone G13. 32. 1. (A) Mice were monitored for the shedding of chlamydiae by evaluation of both vaginal (a to c) and rectal (a1 to c1) swab specimens over the course of infection (the days after challenge infection are designated 3 = to 56 = in parentheses). Results are expressed as the log<sub>10</sub> number of IFU per swab specimen. Mice in the immunization plus doxycycline treatment group displayed no IFU in the rectal swab specimens prior to the intravaginal challenge (days 31 to 56) (b) but maintained transmucosal protection against chlamydial infection in the genital tract (\*,  $P < 0.05$ , Wilcoxon rank-sum test, for panel b1 versus panel c1), equivalent to the findings for immunized mice not treated with doxycycline (\*,  $P < 0.05$ , Wilcoxon rank-sum test, for panel a1 versus panel c1). These two groups maintained similar levels of protection (\*,  $P < 0.05$ , Wilcoxon rank-sum test, for panel b1 versus panel a1). (b and c) The genital tract G13. 32. 1 organisms spread to the GI tracts. (a and a1) Black bars, G13. 32. 1 alone; dark red bars, both CM- mCherry and G13. 32. 1. (B) On day 114 after intragastric immunization, all mice were sacrificed to evaluate the upper genital tract pathology macroscopically. Representative images of the entire genital tracts from the groups receiving immunization without doxycycline treatment (a2), immunization plus doxycycline treatment (b2), or doxycycline treatment without immunization (c2) are shown. White arrows, oviducts positive for hydrosalpinges. Magnified images of oviduct/ovary regions are shown on the right of the overall genital tract images, with the white numbers indicating the hydrosalpinx scores. Both the incidence of hydrosalpinx and the hydrosalpinx severity score (mean standard deviation) are listed above the corresponding images. Regardless of doxycycline treatment, immunized mice were significantly protected from the development of hydrosalpinx (\*,  $P < 0.05$ , Wilcoxon rank-sum test, for the immunization alone group in panel a2 versus panel c2 and for the immunization plus doxycycline treatment group in panel b2 versus panel c2). • Gastrointestinal tract *Chlamydia muridarum* is nonpathogenic. Having demonstrated the strong transmucosal protective immunity induced by GI tract *C. muridarum*, researchers next evaluated whether *C. muridarum* colonization in the GI tract is pathogenic. Since long-lasting *C. muridarum* colonization is restricted to the cecum, colon, and rectum, researchers carefully examined the mouse colons. There was no significant difference in the gross appearance or length of the cecum, colon, and rectum between mice with *C. muridarum* colonization and mice without *C. muridarum* colonization for 7, 28, or 56 days, suggesting that *C. muridarum* did not cause colitis. *C. muridarum* inclusions were microscopically localized in the colon mucosal epithelial cells. Despite the presence of clusters of *C. muridarum*-infected epithelial cells, the epithelial tissue architecture remained intact when the adjacent sections were examined following hematoxylin-eosin (H&E) staining. Furthermore, there was a general lack of significant inflammatory infiltration, although scattered inflammatory cells were always detectable. Compared to control colonic tissue, no significant difference was found between infected and noninfected mice (data not shown). We believe that this data, presented by Zhong et al., is sufficient to pursue development of this vaccine candidate. Given the high numbers of Chlamydia cases both in the United States and around the globe each year, as well as the lack of an available Chlamydia vaccine, we believe this vaccine will serve a high unmet need. We hold a global, exclusive right to develop a novel Chlamydia vaccine from this technology at the University of Texas Health at San Antonio. BWV- 401 Development As the approach to utilize an attenuated murine strain of Chlamydia is novel, we plan to establish the infectivity of *C. muridarum* in a non-human primate model. This will provide robust data supporting potential efficacy of this vaccine candidate in humans, once we reach clinical trials. In collaboration with Dr. Zhong and the University of Texas Health at San Antonio, we will develop a protocol to test both wild-type *C. muridarum* and our attenuated strain in non-human primates and complete necessary endpoints for this study. Proper endpoints will allow us to determine the ability of murine strain *C. muridarum* to infect non-human primates and the efficacy of the attenuated strain, which will represent our vaccine candidate, following challenge of the non-human primates with human Chlamydia strain, *Chlamydia trachomatis*. Following completion of the non-human primate study, we plan to transfer this technology to a partner CMO for process optimization, GMP production and toxicology studies, as well as other studies required by the FDA for IND submission. Government Regulation and Product Approval The FDA and other regulatory authorities at federal, state and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring and post-approval reporting of drugs and biologics such as those we are developing. Small molecule drugs are subject to regulation under the Food, Drug, and Cosmetic Act, or FDCA, and biological products are additionally subject to regulation under the Public Health Service Act, or PHSA, and both are subject to additional federal, state, local and foreign statutes and regulations. We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates. U. S. Biopharmaceuticals Regulation The process



required by the FDA before drug and biologic product candidates may be marketed in the United States generally involves the following:

- completion of extensive preclinical laboratory tests and animal studies performed in accordance with applicable regulations, including the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an investigational new drug application, IND, which must become effective before clinical trials may begin;
- approval by an independent institutional review board or ethics committee at each clinical site before the trial is commenced;
- performance of adequate and well-controlled human clinical trials in accordance with FDA's Good Clinical Practice, or GCP, regulations to establish the safety and efficacy of a drug candidate and safety, purity and potency of a proposed biologic product candidate for its intended purpose;
- preparation of and submission to the FDA of a new drug application, or NDA, or biologics license application, or BLA, as applicable, after completion of all pivotal clinical trials;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- a determination by the FDA within 60 days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with current Good Manufacturing Practice requirements, or cGMPs, and of selected clinical investigation sites to assess compliance with GCPs; and
- FDA review and approval of an NDA, or licensure of a BLA, to permit commercial marketing of the product for particular indications for use in the United States.

Preclinical and Clinical Development Prior to beginning the first clinical trial with a product candidate, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol or protocols for preclinical studies and clinical trials. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology and pharmacodynamics characteristics of the product, chemistry, manufacturing and controls information, and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day period, raises safety concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial. Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Furthermore, an independent institutional review board for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed. Regulatory authorities, the institutional review board or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. For purposes of biopharmaceutical development, human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- Phase 1. The investigational product is initially introduced into patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.
- Phase 2. The investigational product is administered to a limited patient population to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks.
- Phase 3. The investigational product is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval. In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies may be made a condition to approval of the application. Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the characteristics of the product candidate and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life. During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. The FDA or the sponsor or its data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research patients or patients are being exposed to an unacceptable health risk. Similarly, an institutional review board can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the institutional review board's requirements or if the biological product candidate has been associated with unexpected serious harm to patients. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Sponsors of clinical trials of FDA-regulated products are required to register and disclose certain clinical trial information, which is

publicly available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). NDA/BLA Submission and Review Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as applicable, requesting approval to market the product for one or more indications. The application must include all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. The submission of an application requires payment of a substantial application user fee to the FDA, unless a waiver or exemption applies. The FDA has sixty days from the applicant's submission to either issue a refusal to file letter or accept the application for filing, indicating that it is sufficiently complete to permit substantive review. Once an NDA or BLA has been accepted for filing, the FDA's goal is to review standard applications within 10 months after it accepts the application for filing, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process is often significantly extended by FDA requests for additional information or clarification. The FDA reviews an NDA to determine whether a drug is safe and effective for its intended use and a BLA to determine whether a biologic is safe, pure and potent. FDA also reviews whether the facility in which the product is manufactured, processed, packed or held meets standards designed to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may convene an advisory committee to provide clinical insight on application review questions. Before approving an NDA or BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an application, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. After the FDA evaluates an application and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be manufactured, the FDA may issue an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response letter will describe all of the deficiencies that the FDA has identified in the application, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter without first conducting required inspections, testing submitted product lots and/or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may recommend actions that the applicant might take to place the application in condition for approval, including requests for additional information or clarification, which may include the potential requirement for additional clinical studies. The FDA may delay or refuse approval of an application if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product. If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the application with a risk evaluation and mitigation strategy, or REMS, to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a product and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies. Expedited Development and Review Programs The FDA offers a number of expedited development and review programs for qualifying product candidates. The fast track program is intended to expedite or facilitate the process for reviewing new products that meet certain criteria. Specifically, new products are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a fast track product has opportunities for frequent interactions with the review team during product development and, once an NDA or BLA is submitted, the product may be eligible for priority review. A fast track product may also be eligible for rolling review, where the FDA may consider for review sections of the NDA or BLA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application. A product intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase I and an organizational commitment to expedite the development and review of the product, including involvement of senior managers. Any marketing application for a drug or biologic submitted to the FDA for approval, including a product with a fast track designation and/or

breakthrough therapy designation, may be eligible for other types of FDA programs intended to expedite the FDA review and approval process, such as priority review and accelerated approval. A product is eligible for priority review if it has the potential to provide a significant improvement in the treatment, diagnosis or prevention of a serious disease or condition. Priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date. Additionally, products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-marketing clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast track designation, breakthrough therapy designation and priority review do not change the standards for approval but may expedite the development or approval process. Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

**Orphan Drug Designation** Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States for which there is no reasonable expectation that the cost of developing and making available in the United States a drug or biologic for this type of disease or condition will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. The orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review or approval process. If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusive approval (or exclusivity), which means that the FDA may not approve any other applications, including a full NDA or BLA, to market the same drug or biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA or BLA application fee. A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective.

**Post-Approval Requirements** Any products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing user fee requirements, under which the FDA assesses an annual program fee for each product identified in an approved NDA or BLA. Biopharmaceutical manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMPs and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMPs and other aspects of regulatory compliance. The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of a product, complete withdrawal of the product from the market or product recalls;
- fines, warning or untitled letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal of the FDA to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;
- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labelling, advertising and promotion of biopharmaceutical products. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. However, companies may

share truthful and not misleading information that is otherwise consistent with a product's FDA approved labelling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labelling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

U. S. Market Exclusivity A biological product can obtain pediatric market exclusivity in the U. S., which, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study. The Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHSA attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be interchanged after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA. The FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and the FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until 12 years after the date of first licensure of the reference product. "First licensure" typically means the initial date the particular product at issue was licensed in the U. S. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. The BPCIA is complex and continues to be interpreted and implemented by the FDA. In addition, government proposals have sought to reduce the 12-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate implementation and impact of the BPCIA is subject to significant uncertainty.

Pediatric Study Plan and Pediatric Exclusivity Under the Pediatric Research Equity Act, as amended, or the PREA, certain NDAs and certain NDA supplements must contain data that can be used to assess the safety and efficacy of the product candidate for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers. The PREA requires that a sponsor who is planning to submit a marketing application for a product candidate that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or the PSP, within 60 days of an end-of-phase 2 meeting or, if there is no such meeting, as early as practicable before the initiation of the phase 3 or phase 2/3 study. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach an agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from preclinical studies, early phase clinical trials and/or other clinical development programs. Unless otherwise required by regulation, the PREA does not apply to a drug for an indication for which orphan designation has been granted, except that the PREA will apply to an original NDA for a new active ingredient that is orphan-designated if the drug is a molecularly targeted cancer product intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. A drug can also obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

Patent Term Restoration and Extension Depending upon the timing, duration and specifics of the FDA approval of our product candidates, some of our U. S. patents may be eligible for limited patent term extension. The provisions of the Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act, permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved product is eligible for the extension and

the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA. Many other countries also provide for patent term extensions or similar extensions of patent protection for biologic products. For example, in Japan, it may be possible to extend the patent term for up to five years and in Europe, it may be possible to obtain a supplementary patent certificate that would effectively extend patent protection for up to five years. Federal and State Fraud and Abuse, Data Privacy and Security, and Transparency Laws and Regulations In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws may impact, among other things, our current and future business operations, including our clinical research activities, and proposed sales, marketing and education programs and constrain the business or financial arrangements and relationships with healthcare providers and other parties through which we market, sell and distribute our products for which we obtain marketing approval. These laws include anti-kickback and false claims laws and regulations, data privacy and security, and transparency laws and regulations, including, without limitation, those laws described below. The U. S. federal Anti-Kickback Statute prohibits any person or entity from, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term “remuneration” has been broadly interpreted to include anything of value. The U. S. federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Several courts have interpreted the statute’s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the U. S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or the civil monetary penalties laws. Federal civil and criminal false claims laws and civil monetary penalties laws, including the federal civil False Claims Act, which can be enforced by individuals through civil whistleblower and qui tam actions, prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes “any request or demand” for money or property presented to the U. S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies’ marketing of products for unapproved, and thus non-reimbursable, uses. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, impose specified requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA’s security standards directly applicable to “business associates,” defined as independent contractors or agents of covered entities, which include certain healthcare providers, healthcare clearinghouses and health plans, that create, receive, maintain or transmit individually identifiable health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney’s fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which are not pre-empted by HIPAA, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members. We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing, and state and local laws that require the registration of pharmaceutical sales

representatives. Because of the breadth of these laws and the narrowness of available statutory exceptions and regulatory safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to significant criminal, civil and administrative penalties including damages, fines, imprisonment, disgorgement, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, implementation of corporate compliance programs, reporting of payments or transfers of value to healthcare professionals, and additional data privacy and security requirements. Healthcare Reform Coverage and Reimbursement The future commercial success of our product candidates, if approved, will depend in part on the extent to which third-party payors, such as governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors, provide coverage of and establish adequate reimbursement levels for our product candidates. Third-party payors generally decide which products they will pay for and establish reimbursement levels for those products. In particular, in the United States, no uniform policy for coverage and reimbursement exists. Private health insurers and other third-party payors often provide coverage and reimbursement for products based on the level at which the government, through the Medicare program, provides coverage and reimbursement for such products, but also on their own methods and approval process apart from Medicare determinations. Therefore, coverage and reimbursement can differ significantly from payor to payor. In the United States, the European Union, or EU, and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of products, particularly for new and innovative products, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and usage. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general. Third-party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for products. For example, federal and state governments reimburse products at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of products. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Similarly, because certain of our product candidates are physician-administered, separate reimbursement for the product itself may or may not be available. Instead, the administering physician may only be reimbursed for providing the treatment or procedure in which our product is used. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of products, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party payor reimbursement may not be available to enable us to realize an appropriate return on our investment in product development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our product candidates, if approved, or exclusion of our product candidates from coverage and reimbursement. The cost containment measures that third-party payors and providers are instituting and any healthcare reform could significantly reduce our revenue from the sale of any approved product candidates. The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our product candidates profitably, if approved. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts, which include major legislative initiatives to reduce the cost of care through changes in the healthcare system, including limits on the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded healthcare programs, and increased governmental control of drug pricing. There have been several U. S. government initiatives over the past few years to fund and incentivize certain comparative effectiveness research, including creation of the Patient-Centered Outcomes Research Institute under the ACA. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. The ACA became law in March 2010 and substantially changed the way healthcare is financed by third-party payors, and significantly impacts the U. S. pharmaceutical industry. Among other measures that may have an impact on our business, the ACA established an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increased the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. Additionally, the ACA extended manufacturers' Medicaid rebate liability, expands eligibility criteria for Medicaid programs, and expanded entities eligible for discounts under the Public Health Service Act. At this time, we are unsure of the full impact that the ACA will have on our business. Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the ACA, and we expect such challenges and amendments to continue. Since January 2017, President

Trump has signed two Executive Orders and other directives designed to delay the implementation of certain ACA provisions or otherwise circumvent requirements for health insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on nonexempt medical devices. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the ACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In July 2018, CMS published a final rule permitting further collections and payments to and from certain ACA-qualified health plans and health insurance issuers under the ACA adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. In December 2018, a U. S. District Court Judge in the Northern District of Texas, or Texas District Court Judge, ruled that the individual mandate is a critical and inseparable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. While the Texas District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the President signed into law the Budget Control Act of 2011, as amended, which, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which began in 2013 and, following passage of subsequent legislation, including the BBA, will continue through 2027 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 was enacted which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Further, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there have been several recent U. S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation. Additionally, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. In August 2022, Congress passed the Inflation Reduction Act of 2022, which included a provision allowing Medicare to negotiate drug prices directly with pharmaceutical manufacturers. This provision may impact pricing strategies and determinations in the future. The U. S. Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and is implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2019. On January 31, 2019, the HHS Office of Inspector General proposed modifications to U. S. federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. In addition, CMS issued a final rule, effective on July 9, 2019, that requires direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product if it is equal to or greater than \$35 for a monthly supply or usual course of treatment. Prescription drugs and biological products that are in violation of these requirements will be included on a public list. Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine which drugs and suppliers will be included in their healthcare programs. Furthermore, there has been increased interest by third party payors and governmental authorities in reference pricing systems and publication of discounts and list prices. These measures could reduce future demand for our products or put pressure on our pricing. Additionally, in May 2018, the Trickett-Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act. Foreign Regulation In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing



authorization, commercial sales and distribution of our product candidates. For example, in the EU, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a drug, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the drug in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. Further, some countries outside of the United States, including the EU member states, Switzerland and the United Kingdom, have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EU, the collection and use of personal health data is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR became effective on May 25, 2018, repealing its predecessor directive and increasing responsibility and liability of pharmaceutical companies in relation to the processing of personal data of EU subjects. The GDPR, together with the national legislation of the EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to process personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern potentially burdensome documentation requirements, granting certain rights to individuals to control how we collect, use, disclose, retain and process information about them, the information provided to the individuals, the transfer of personal data out of the EU, security breach notifications, and security and confidentiality of the personal data. The processing of sensitive personal data, such as physical health condition, may impose heightened compliance burdens under the GDPR and is a topic of active interest among foreign regulators. In addition, the GDPR provides for more robust regulatory enforcement and fines of up to € 20 million or 4 % of the annual global revenue of the noncompliant company, whichever is greater. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU. Guidance on implementation and compliance practices are often updated or otherwise revised. European Union Coverage Reimbursement and Pricing In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies, or so called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or may instead adopt a system of direct or indirect controls on the profitability of the company. EU Drug regulation In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable foreign regulatory authorities before we can commence clinical trials or marketing of the product in foreign countries and jurisdictions such as in China and Japan. Although many of the issues discussed above with respect to the United States apply similarly in the context of the EU, the approval process varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others. Failure to comply with applicable foreign regulatory requirements, may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution. Non-clinical studies and clinical trials Similarly to the United States, the various phases of non-clinical and clinical research in the EU are subject to significant regulatory controls. Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical or biological substances. Non-clinical studies must be conducted in compliance with the principles of good laboratory practice (GLP) as set forth in EU Directive 2004/10/EC. In particular, non-clinical studies, both in vitro and in vivo, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements. Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization (ICH) guidelines on good clinical practices (GCP) as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. Additional GCP guidelines from the European Commission, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products. If the sponsor of the clinical trial is not established within the EU, it must appoint an entity within the EU to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU member states, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial. Certain countries outside of the United States, including the EU, have a similar process that requires the submission of a clinical study application (CTA) much like the IND prior to the commencement of human clinical studies. A CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved by the national health authority and the ethics committee has granted a positive opinion in relation to the conduct of the trial in the relevant member state (s), in accordance with a country's requirements, clinical study development may proceed. The CTA must include, among other things, a copy of the trial protocol

and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, CTAs must be submitted to the competent authority in each EU member state in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is currently expected to become applicable by early 2022, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the CTA must be notified to or approved by the relevant competent authorities and ethics committees. Medicines used in clinical trials must be manufactured in accordance with good manufacturing practice (GMP). Other national and EU-wide regulatory requirements also apply. Marketing Authorizations To market a medicinal product in the EU and in many other foreign jurisdictions, we must obtain separate regulatory approvals. More concretely, in the EU, medicinal product candidates can only be commercialized after obtaining a Marketing Authorization (MA). To obtain regulatory approval of an investigational medicinal product under EU regulatory systems, we must submit a marketing authorization application (MAA.) The process for doing this depends, among other things, on the nature of the medicinal product. There are two types of MAs: • the “ Union MA ”, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and which is valid throughout the entire territory of the EU. The Centralized Procedure is mandatory for certain types of products, such as (i) medicinal products derived from biotechnology medicinal products, (ii) designated orphan medicinal products, (iii) advanced therapy products (such as gene therapy, somatic cell therapy or tissue-engineered medicines), and (iv) medicinal products containing a new active substance indicated for the treatment certain diseases, such as HIV / AIDS, cancer, neurodegenerative diseases, diabetes, other auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EU, or for products that constitute a significant therapeutic, scientific or technical innovation or that the granting of authorization would be in the interest of public health in the EU; and • “ National Mas ”, which are issued by the competent authorities of the EU member states and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in an EU member state, this National MA can be recognized in another member state through the Mutual Recognition Procedure. If the product has not received a National MA in any member state at the time of application, it can be approved simultaneously in various member states through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the member states in which the MA is sought, one of which is selected by the applicant as the Reference member state. Under the above-described procedures, in order to grant the MA, the EMA or the competent authorities of the EU member states make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. Under the Centralized Procedure, the maximum timeframe for the evaluation of a MAA by the EMA is 210 days. Where there is a major public health interest and an unmet medical need for a product, the CHMP may perform an accelerated review of a MA in no more than 150 days (not including clock stops). Innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the breakthrough therapy designation in the US PRIME is a voluntary scheme aimed at enhancing the EMA’s support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. Product developers that benefit from PRIME designation can expect to be eligible for accelerated assessment but this is not guaranteed. The benefits of a PRIME designation include the appointment of a CHMP rapporteur before submission of a MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process. MAs have an initial duration of five years. After these five years, the authorization may be renewed for an unlimited period on the basis of a reevaluation of the risk-benefit balance, unless the EMA decides, on justified grounds relating to pharmacovigilance, to mandate one additional five-year renewal period. Data and marketing exclusivity The EU also provides opportunities for market exclusivity. Upon receiving MA, new chemical entity, or reference product candidates, generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, the data exclusivity period prevents generic or biosimilar applicants from relying on the pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial authorization of the reference product in the EU. The overall 10-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those 10 years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. However, there is no guarantee that a product will be considered by the EU’s regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity. Pediatric Development In the EU, MAAs for new medicinal products candidates have to include the results of trials conducted in the pediatric population, in compliance with a pediatric investigation plan (PIP) agreed with the EMA’s Pediatric Committee (PDCO). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the MA is obtained in all EU Member States and study results are included in the product information, even

when negative, the product is eligible for six months' supplementary protection certificate extension (if any is in effect at the time of authorization). Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the European Commission and / or the competent regulatory authorities of the member states. The holder of a MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports (PSURs). All new MAA must include a risk management plan (RMP) describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. The advertising and promotion of medicinal products is also subject to laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each member state and can differ from one country to another. The aforementioned EU rules are generally applicable in the European Economic Area (EEA) which consists of the 27 EU member states plus Norway, Liechtenstein and Iceland. For other countries outside of the EU, such as countries in Latin America or Asia (e.g. China and Japan), the requirements governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution. Privacy and data protection laws We are also subject to laws and regulations in non-US countries covering data privacy and the protection of health-related and other personal information. For instance, EU member states and other jurisdictions have adopted data protection laws and regulations, which impose significant compliance obligations. Laws and regulations in these jurisdictions apply broadly to the collection, use, storage, disclosure, processing and security of personal information that identifies or may be used to identify an individual, such as names, contact information, and sensitive personal data such as health data. These laws and regulations are subject to frequent revisions and differing interpretations. As of May 2018, the General Data Protection Regulation (GDPR) replaced the Data Protection Directive with respect to the processing of personal data in the European Union. The GDPR imposes many requirements for controllers and processors of personal data, including, for example, higher standards for obtaining consent from individuals to process their personal data, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention and secondary use of information, increased requirements pertaining to health data and pseudonymised (i.e., key-coded) data and additional obligations when we contract third-party processors in connection with the processing of the personal data. The GDPR allows EU member states to make additional laws and regulations further limiting the processing of genetic, biometric or health data. Failure to comply with the requirements of GDPR and the applicable national data protection laws of the EU member states may result in fines of up to € 20,000,000 or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, and other administrative penalties. Japanese drug regulation Being a member of the International Conference on Harmonization (ICH), Japan has pharmaceutical regulations fundamentally similar to those of the United States or EU. Non-clinical studies are performed to demonstrate the health safety of new chemical or biological substances. Non-clinical studies must be conducted in compliance with the principles of Japanese good laboratory practice (GLP) which reflect the Organization for Economic Co-operation and Development requirements. Currently, Japan and EU have a mutual recognition agreement for GLP, and data generated compliant with EU requirements will be accepted by the Japanese authorities. There is no similar agreement with the United States. Clinical trials of medicinal products in Japan must be conducted in accordance with Japanese regulations based on ICH guidelines governing good clinical practices (GCP). They focus on ethics of the clinical trial and protection of the privacy of the trial subjects. If the sponsor of the clinical trial is not established within Japan, it must appoint an entity within the country to act as its caretaker who should be authorized to act on the sponsor's behalf. The sponsor must take out a clinical trial insurance policy, and, according to the industry agreement, should put in place a common compensation policy for the injuries from the trial. Prior to the commencement of human clinical studies, the sponsor must complete evaluation of the safety of the investigational product, and submit a clinical trial notification and the protocol to the authorities in advance, upon agreement of the IRB of the participating institutions. When the authorities do not comment on the notification, the sponsor may proceed with the clinical trial. Any substantial changes to the trial protocol or other information submitted must be cleared by the IRB and notified to the authorities. Medicines used in clinical trials must be manufactured in accordance with good manufacturing practice (GMP). Product approval To market a medicinal product in Japan, we must obtain regulatory approval. To obtain regulatory approval of an investigational medicinal product, we must submit a new drug application. The process for doing this depends, among other things, on the nature of the medicinal product and there are currently a few different pathways for approval. If the product is designed for treating certain "difficult diseases" or those whose patient size is limited, we may be able to obtain designation as an orphan drug product if it demonstrates unique therapeutic value. Approval application for such designated orphan products will be processed on an expedited basis and the authorities' requirement for clinical data will be much limited. Separately, the latest amendment to the law introduced separate pathways for (i) truly innovative products with a unique mode of action and (ii) those which will satisfy unmet medical needs. These products will also be processed on an expedited basis. The evaluation of applications will be based on an assessment of

the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. Once the review organization complete its review task, the matter will be considered by the advisory committee of experts, and the government will grant approval upon positive recommendation from the committee. The volume and quality of the clinical data will be the key determinant of the approval decision. Clinical trial data generated overseas will be accepted as part of the data package consistent with the ICH recommendation. Typically, a limited dose response clinical trial for Japanese subjects is required to ensure that data are extrapolatable for the Japanese population. In a more recent development, the authorities encourage manufacturers to organize an international joint clinical trial with some Japanese participation under a joint protocol to expedite the clinical trial process. Regulatory approval does not expire. Licensing requirement Separate from the approval requirement, it is also mandatory to possess a distribution license of an appropriate class for the manufacturer to commercially distribute the product in Japan. Non-Japanese companies who possess only the product approval may designate an appropriate license holder in Japan to commercially distribute the product, rather than distributing it on its own. The license is valid for 5 years. Intellectual Property Exclusive License Agreement with Children's Hospital Medical Center, d/b/a Cincinnati Children's Hospital Medical Center On June 1, 2021 (the "Effective Date"), the Company entered into a license agreement with Children's Hospital Medical Center, d/b/a Cincinnati Children's Hospital Medical Center ("CHMC") to develop and commercialize certain CHMC patents and related technology directed at a VLP vaccine platform that utilizes nanoparticle delivery technology, which may have potential broad application to develop vaccines for multiple infectious diseases ("the CHMC Agreement"). The license is exclusive, worldwide, and is for all uses (other than the "Excluded Field" of immunization against, and prevention, control, or reduction in severity of gastroenteritis caused by Rotavirus and Norovirus in China and Hong Kong). The license is sublicensable with prior CHMC written approval consistent with the terms of the CHMC Agreement. The CHMC Agreement includes the below patents, which we refer to as the "Licensed Patents", and any divisionals, continuations and continuations-in-part thereto (solely to the extent that the claims in the continuations-in-part are directed to the subject matter specifically claimed in the Licensed Patents, and they have the same priority date as the Licensed Patents, but do not include any different or additional claims), and any patents resulting therefrom: U. S. Patent Application No. U. S. Patent No. Granted Claim Type U. S. Expiration Foreign Counterparts 12 / 797, 396 8, 486, 421 Compositions of the vaccine / vaccine platform 1 / 13 / 2031 CN107043408B EP2440582B1 JP5894528B2 13 / 924, 906 9, 096, 644 Method of treatment 9 / 20 / 2030 CN107043408B EP2440582B1 JP5894528B2 13 / 803, 057 9, 562, 077 Compositions of the vaccine platform 11 / 8 / 2033 none 16 / 489, 095 pending pending \* \* [ 3 / 15 / 2038 ] \* Pending applications in Canada, China, EU, Hong Kong and Japan 63 / 149, 742 (filed 2 / 16 / 2021) pending pending \* \* [ February 2042 ] # TBD 63 / 162, 369 (filed 3 / 17 / 2021) pending pending [ March 2042 ] # TBD \* Projected expiration if patent issues: 20 years from earliest non-provisional application filing date. # Non-provisional application not yet filed. Expiration projected 21 years from provisional application filing date. Dependent on timely conversion to non-provisional application and issuance of patent. \* \* This is a pending application. Claim type will be determined after U. S. prosecution is complete. The claim type sought includes compositions of the vaccine and vaccine platform. The CHMC Agreement also grants the Company a non-exclusive limited license to use and copy internally any technical information in existence and known before the Effective Date by CHMC solely as necessary for the use and practice of the Licensed Patents (the "CHMC Technology"). The term of the CHMC Agreement begins on the Effective Date and extends on a jurisdiction-by-jurisdiction and product-by-product basis until the later of: (i) the last to expire Licensed Patent; (ii) ten (10) years after the first commercial sale; or, (iii) entrance onto the market of a biosimilar or interchangeable product. CHMC has reserved the right to practice, have practiced, and transfer the Licensed Patents and CHMC Technology for research and development purposes, including education, research, teaching, publication and public service, but not to use or practice the Licensed Patents or CHMC Technology in Field of Use for any commercial or profit purpose. The Licensed Patents granted to the Company under the CHMC Agreement are also subject to any rights of the United States federal, state and / or local Government (s), as well as nonprofit entities, if certain patents or technologies were created in the course of Government-funded or non-profit entity-funded research. The CHMC Agreement also contains compulsory licensing provisions under which CHMC must notify the Company in writing whenever CHMC may become aware of third parties that are interested in obtaining rights to the Licensed Patents or CHMC Technology for purposes that are beyond the scope of the Company's development and commercialization plan. The Company may elect to pursue the new purposes itself (and negotiate commercially reasonable development targets), or enter into sublicense negotiations with the interested third party. However, if the Company fails to meet its development targets for the new purposes or fails to enter into a sublicense agreement with the interested third party within nine (9) months of the notice from CHMC, then the new purpose will be excluded from the license grant and CHMC will be free to pursue licensing of the Licensed Patents or CHMC Technology within the Excluded Field to an interested third party. Any patented modification, alteration or improvement of any invention claimed in a Licensed Patent or CHMC Technology which is conceived or reduced to practice solely by the Company ("Company Improvement") is owned by the Company; however, for any such Company Improvement, the Company will automatically grant to CHMC a worldwide, perpetual, sublicensable, nonexclusive, paid-up, royalty-free license to use any Company Improvements solely for clinical or non-clinical, non-commercial research, testing, educational and patient care purposes. The CHMC Agreement also provides the Company with an option to license any CHMC or jointly patented modification, alteration or improvement of any invention claimed in a Licensed Patent ("CHMC Improvement" and "Joint Improvement, respectively"), with option fee for each Improvement that the Company elects to include in the license grant of the CHMC Agreement. The Company is required to pay CHMC an aggregate of up to \$ 59.75 million upon the achievement of specified development milestones, of approximately \$ 0.5 million, regulatory milestones, of approximately \$ 1.25 million and commercial milestones, of approximately \$ 58 million (excluding any royalty arrangements). In the event the Company enters into a sublicense agreement with a third party who is not an affiliate, then the Company is obligated to pay CHMC a percentage of all non-royalty sublicensing revenue. Specifically, the Company must pay twenty-five percent (25 %) for revenue received

from the sublicensee prior to first net sale of a licensed product, fifteen percent (15%) for revenue received after first net sale of a licensed product or five percent after the first sale of a second licensed product. No annual maintenance fee is required. Pursuant to the CHMC Agreement, the Company paid to CHMC a one-time \$ 25,000 initial license fee; thereafter, in fiscal year ended December 31, 2022, the Company paid \$ 200,000 in deferred license fees. Under the CHMC Agreement, the Company is obligated to use commercially reasonable efforts to bring licensed products to market through diligent research and development, testing, manufacturing and commercialization and to use best efforts to make all necessary regulatory filings and obtain all necessary regulatory approvals, and achieve milestones relating to development and sales, and report to CHMC on progress. The Company will also be obligated to pay the agreed upon development milestone payments to CHMC. Development milestones include: (i) IND filings of each Licensed Product; (ii) BLA or equivalent allowed for Licensed Product in U. S. or E. U.; (iii) first commercial sale of licensed product in the U. S.; (iv) first commercial sale of licensed product in the E. U.; (v) first commercial sale of licensed product in Japan; (vi) first commercial sale in Rest of World (ROW); (vii) conclusion of the first calendar year. Pursuant to the terms of the CHMC Agreement, if the Company fails to achieve milestones or make milestone payments on certain milestones, and cannot mutually agree with CHMC on an amendment to the milestones, then CHMC will have the option of converting any and all of such exclusive licenses to nonexclusive licenses. In addition to the fees discussed above, beginning on the first Net Sale, the Company will pay CHMC running royalties on a quarterly basis as a percentage of Net Sales (as defined in the CHMC Agreement) of the Company, its affiliates and any subsidiaries. Similarly, in the event the Company enters into a sublicense agreement, the Company shall pay CHMC a percentage of all non-royalty sublicensing revenues received from the sublicensee. There is a 5% royalty rate for products and processes for P-Particle VLP Divalent vaccine for norovirus and rotavirus; a 4% royalty rate for products and processes for Universal Flu Vaccine (s); and a 2% royalty rate for all other products or processes for other indications. To date, no payments have been made related to the milestones or royalties. Before any Valid Claims (as defined in the CHMC Agreement) exist, the running royalty rates are reduced by fifty percent (50%). The CHMC Agreement also contains an anti-stacking provision pursuant to which in the event the Company is legally required to pay royalties to one or more third parties whose patent rights dominate the Licensed Patents, and would therefore be infringed by exercise of the license rights granted in the CHMC Agreement, the Company may reduce running royalty payments by fifty percent (50%). In the event the Company grants sublicenses, the Company is obligated to pay CHMC as follows: (i) specified percentage of revenue received prior to first Net Sale of first Licensed Product; (ii) specified percentage for revenue received after first Net Sales of first Licensed Product but before first Net Sales of second Licensed Product; or (iii) specified percentage for revenues received after first Net Sales of second Licensed Product. CHMC reserved the first and sole right, using in-house or outside legal counsel selected by CHMC, to prepare, file, prosecute, maintain and extend patents and patent applications, and the Company agreed to reimburse CHMC for its legal and administrative costs incurred in the course of doing such. The Company also agreed to reimburse CHMC for incurred legal fees of approximately \$ 177,100 as of the Effective Date. CHMC will provide the Company a reasonable opportunity to comment during prosecution and will consider the Company's comments, but CHMC retained control over all final decisions. If CHMC elects to not be responsible for the prosecution or maintenance of any such patents, the Company will receive a sixty (60) days' written notice upon which the Company may elect, at the Company's expense, to assume the responsibilities and obligations to prosecute and maintain the patents (among other things); thereafter, the Company will use reasonable efforts to give CHMC an opportunity to comment, but the final decision with respect to such matter will remain with the Company. The CHMC Agreement contains no CHMC representations or warranties. The CHMC Agreement also requires the Company to indemnify CHMC and other related parties against all claims, suit, actions, demands, judgments, or investigations arising out of any product the Company produces under the CHMC Agreement, as set forth in the CHMC Agreement, and requires the Company, beginning with the earlier of the first clinical trial or commercial sale or other commercialization to obtain liability insurance. CHMC will have the first and sole right but not the obligation, at its own expense, to initiate an infringement suit or other appropriate actions against third party infringers and receives all therefrom. For joint suits initiated against third party infringers and receives damages or profits recovered therefrom. In the event CHMC does not, within six (6) months after becoming aware of infringement, secure cessation of the infringement, the Company will have the right to initiate suit at its own expense. Any damages or profits that the Company recovers will be treated as Net Sales subject to royalties after the Company has been compensated for its costs in handling such action. In the event of a joint infringement suit, the Company and CHMC will agree in writing who will control the action and how cost and recoveries will be shared. The Company may terminate the CHMC Agreement for convenience, at any time prior to first commercial sale of a product or process by providing one hundred and eighty (180) days' written notice to CHMC. It may also terminate for a CHMC uncured material breach. CHMC may terminate the CHMC Agreement for an uncured Company material breach or insolvency or bankruptcy. In the event the Company's material breach is for failure to meet any of the milestone payments, the Company is entitled to a nonexclusive license to continue developing indications that have already entered development at any stage or in which the Company has invested in developing. CHMC may also terminate the CHMC Agreement to the fullest extent permitted by law in the countries of the worldwide territory, in the event the Company or its affiliates challenge or induce others set up challenges to the validity or enforceability of any of the Licensed Patents and the Company will be obligated reimburse CHMC for its costs, including reasonable attorneys' fees. In addition to the CHMC Agreement, the Company also entered into a sponsored research agreement dated June 30, 2022 with CHMC for research related to the CHMC Agreement (the "CHMC SRA"). Pursuant to this research agreement, the Company is obligated to pay CHMC an aggregate amount not to exceed \$ 247,705. Option Agreement between Oxford University Innovation Limited and Blue Water Vaccines Inc. On December 18, 2018, the Company entered into an option agreement with Oxford University Innovation Limited ("OUI"), pursuant to which the Company paid an option fee of between \$ 25,000, to OUI in exchange for a period of exclusivity, in advance of a fundraising of fifteen million dollars (\$ 15,000,000). Under the option agreement, the Company has the right to exercise the option for the grant of the right to the Company to an exclusive,

worldwide license to PCT Patent Application number PCT/GB/2017/052510, any patents granted in response to that application, any corresponding foreign patents and applications deriving priority from that application, and any addition, continuation, continuation-in-part, division, reissue, renewal or extension based thereon, and related know-how and confidential information (the "OUI Technology"). Exercise of the option by the Company was conditional upon the Company submitting a business plan for the subsequent two years, including a development plan for the OUI Technology and a financial projection, demonstrating the Company's ability to develop the OUI Technology and evidence of the Company's solvency and receipt of fifteen million dollars (\$ 15, 000, 000) in funds for the development of the OUI Technology. The Company has agreed that, as a condition precedent to the license becoming effective, it must provide funding for three years of salary for Dr. Craig Thompson in Oxford's Department of Zoology of four hundred and twenty thousand pounds (£ 420, 000). No additional funds are required to fulfill the three-year salary commitment, at this time, and none are anticipated prior to the completion of the three-year term. License Agreement between Oxford University Innovation Limited and Blue Water Vaccines Inc. On July 16, 2019, the Company entered into an exclusive, worldwide agreement ("OUI Agreement") with Oxford University Innovation Limited ("OUI"), pursuant to which the Company obtained an exclusive worldwide license for all fields to PCT Patent Application number PCT/GB/2017/052510, entitled "Immunogenic Composition," any patents granted in response to that application, any corresponding foreign patents and applications deriving priority from that application, and any addition, continuation, continuation-in-part, division, reissue, renewal or extension based thereon, and a nonexclusive license to related know-how and confidential information, as set forth in the below chart (the "Licensed Technology"): U. S. Patent Application No. U. S. Patent No. Granted Claim Type U. S. Expiration Foreign Counterparts 16/326, 749-11, 123, 422 Compositions and method of treatment 8/25/2037 Pending applications in Australia, Canada, China, EU and Japan 17/458, 712 pending pending \*\* [ 8 / 25 / 2037 ] \* \* \* This is a pending application. Claim type will be determined after U. S. prosecution is complete. The claim type sought includes compositions of the compositions and method of treatment. The OUI Agreement has a term concluding ten years following the last to expire of all licensed patents and patent applications as defined under the terms of the OUI Agreement. The license was conditional upon the Company entering into a separate agreement with Oxford University to provide funding for three years' salary for Dr. Craig Thompson in the University's Department of Zoology, which amounted to four hundred and twenty thousand pounds (£ 420, 000), which was paid by the Company in January 2020. No additional funds are required to fulfill the three-year salary commitment, at this time, and none are anticipated prior to the completion of the three-year term. Improvements to the Licensed Technology as defined in the OUI Agreement belong to OUI and are included in the Licensed Technology. All Company Improvements of belong to the Company. The Company granted to OUI, and OUI subsequently granted to Oxford University, a non-transferable, irrevocable, perpetual, royalty-free license to use and publish the Licensed Technology and the Company's Improvements upon the Licensed Technology for non-commercial use. If a Licensed Product is covered by the Medicines Access Policy of Oxford University to promote, the Company shall adhere to the requirements of the Medicines Access Policy. The Company is required to pay OUI milestone payments of up to an aggregate of \$ 51. 25 million upon the achievement of specified development milestones, of approximately \$ 2. 25 million; regulatory milestones, of approximately \$ 9. 5 million and commercial milestones, of approximately \$ 39. 5 million (excluding any royalty arrangements). An annual maintenance fee, or minimum sum, \$ 10, 000 to \$ 20, 000 will be required beginning in 2023 through launch, increasing to \$ 250, 000, which would be the highest "minimum sum" of royalties in any year prior until expiration or revocation of the last valid claim covering a licensed product, in which case the annual maintenance fee will no longer be required and the "step down" royalty rate will apply. The Company did not pay a signing fee to OUI and is obligated to pay a 6 % royalty on all net sales of licensed products, as defined in the OUI Agreement, as well as royalties of 25 % on any sums received by the Company from any sublicensee (including all up-front, milestone and other one-off payments received by the Company from any sub-licenses or other contracts granted by the Company with respect to the licensed technology). After the expiration or revocation of the last Valid Claim (as defined in the OUI Agreement) covering a Licensed Product, a "step down" royalty rate shall apply to such Licensed Technology and no minimum sum will be payable by the Company. If the Company has to pay royalties to a third party to use a proprietary manufacturing process proprietary adjuvants in order to make or have made a Licensed Product, the Company will be able to deduct from all royalty payments, up to a maximum amount of twenty-five percent (25 %) of the royalties due to OUI. The OUI Agreement entitles the Company to supply a commercially reasonable quantity (not exceeding 5 % of units sold in any quarter) of licensed products for promotional sampling. In the event that royalties paid to OUI do not amount to the "minimum sum", as discussed above, under the OUI Agreement for a particular year, the Company is obligated to make up the difference between the royalties actually paid and such minimum sum. The minimum sums vary over time, and reduces to \$ 0 once the "step down" applies. The minimum sums and milestone fees are indexed to the RPI (Retail Prices index for all items which is published in the United Kingdom by the Office for National Statistics, or any replacement of it) and will be increased or decreased as appropriate as set forth in the OUI Agreement. The Company is obligated to use its best efforts to develop and market Licensed Products in accordance with its development plan report to OUI on progress and achieve the following milestones and must pay OUI nonrefundable milestone fees as follows when it achieves them: initiation of first Phase I study; initiation of first Phase II study; initiation of first Phase III / pivotal registration studies; first submission of application for regulatory approval (BLA / NDA); marketing authorization in the United States; marketing authorization in any EU country; marketing authorization in Japan; first marketing authorization in any other country; first commercial sale in Japan; first commercial sale in any ROW country; first year that annual sales equal or exceed certain thresholds. Upon consultation with the Company and at the Company's expense, OUI shall prosecute, use all reasonable endeavors to maintain and renew the patents throughout the duration of the OUI Agreement. The Company and OUI agreed to inform each other in writing of any misappropriation or infringement of any rights to the licensed technology; however, the Company has the first right to take legal action at its own cost in relation to any such misappropriation or infringement, but must discuss any proposed legal action with OUI and take into account any legitimate interest of OUI in the legal action that it takes.

If the Company notifies OUI that it does not intend to take legal action in such matters, OUI may take any legal action at its own cost. All profits or damages recovered after unrecovered costs and expenses are deducted are treated as net sales for which royalties would be due. OUI makes no warranties at all with regard to the Licensed Technology or whether use of it will infringe third party rights. The Company is required to indemnify OUI and Oxford University from all third party claims, damages, and liabilities asserted by third parties arising directly or indirectly from use of the Licensed Technology; marketing of Licensed Products; or breach of the OUI Agreement. The OUI Agreement is governed by English law and the parties agreed to submit to the exclusive jurisdiction of English Courts for resolution of any disputes arising out of or in connection with the OUI Agreement, with the exception of actions relating to intellectual property disputes or confidential information which may be brought in any court of competent jurisdiction. Either party may terminate the OUI Agreement for an uncured material breach. The Company may terminate the OUI Agreement for any reason at any time upon six months' written notice expiring after the third anniversary of the OUI Agreement. OUI may terminate immediately if the Company has a petition presented for its winding up or passes a resolution for winding up other than for a bona fide amalgamation or reconstruction or compounds with its creditors or has a receiver or administrator appointed. OUI may also terminate if the Company opposes or challenges the validity of any of the patents or applications in the Licensed Technology; raises the claim that the know-how of the Licensed Technology is not necessary to develop and market Licensed Products; or in OUI's reasonable opinion, is taking inadequate or insufficient steps develop or market Licensed Products and does not take any further steps that OUI requests by written notice within a reasonable time. Pursuant to the terms of the OUI Agreement, the Company entered into a sponsored research agreement (the "OUI SRA"), dated December 18, 2019 with Oxford University for research related to the OUI Agreement for a period of three years for a total of £ 420, 000. The Company prepaid the full amount to Oxford of \$ 554, 802 for the services in January 2020. Pursuant to an amendment to the SRA (the "OUI SRA Amendment"), dated May 16, 2022, the term of the research under the SRA was extended for an additional 18 months, culminating on June 18, 2024. The OUI SRA Amendment also requires that the Company provide additional funding in connection with the research in the amount of £ 53, 500. Exclusive License Agreement between St. Jude Children's Research Hospital, Inc. & Blue Water Vaccines Inc. On January 27, 2020 (the "Effective Date"), the Company entered into an exclusive, worldwide license agreement with St. Jude Children's Research Hospital, Inc. ("St. Jude"), pursuant to which St. Jude granted the Company an exclusive license to develop licensed products and produce vaccines for use in humans ("St. Jude Agreement") under U. S. Provisional Patent Application No. 61 / 537, 290 (U. S. Patent No. 9, 265, 819 issued on February 23, 2016), and U. S. Provisional Patent Application No. 62 / 817, 748 (filed March 13, 2019), and any issued patents, divisions, continuations, continuations-in-part, to the extent that the claims are directed to subject matter described in the above-referenced patent applications and are entitled to the priority date of the existing patent rights, re-examinations, substitutions, renewals, restorations, additions, or registrations thereof, as well as non-United States counterparts thereof, and extensions and supplementary protection certificates thereon ("Patent Rights"), all as set forth in the below chart: U. S. Patent Application No. U. S. Patent No. Granted Claim Type U. S. Expiration Foreign Counterparts 14 / 345, 988 9, 265, 819 Compositions and method of treatment 9 / 19 / 2032 none 17 / 602, 414 # pending pending \*\* [ 3 / 12 / 2040 ] \* Pending Applications in: Australia, Brazil, Canada, China, Europe, Hong Kong, Japan and Korea # U. S. National stage entry of WO 2020 / 183420 (PCT / IB2020 / 052250). \*\* This is a pending application. Claim type will be determined after U. S. prosecution is complete. The claim type sought includes compositions and method of treatment. The license is sublicenseable consistent with the terms and conditions of the St. Jude Agreement, provided that the Company remains responsible for the performance by each of its sublicensees. The license is subject to any government rights the United States has reserved, and St. Jude retained the right to make, have made, provide and use for St. Jude's non-commercial research and clinical purposes, including the right to distribute St. Jude's biological material disclosed and claimed in the Patent Rights for non-profit academic research use to non-commercial entities as is customary in the scientific community and to sell the biological materials as research reagents for research use only by the scientific community. In the event the Company enters into a sublicense agreement with a third party who is not an affiliate, then the Company is obligated to pay St. Jude fifteen percent of any sublicense consideration, subject to specified exclusions, but including any upfront or milestone fees and including any premium paid by sublicensee over Fair Market Value (as defined in the agreement) for the Company's stock. In exchange for the licenses, the Company paid St. Jude an initial license fee of \$ 15, 000 and is required to pay an annual maintenance fee of \$ 10, 000 beginning on the first anniversary of the Effective Date (which is waived if all of the developmental milestones scheduled for completion before such annual fee is due have been achieved), milestone payments, patent reimbursement, and running royalties based on net sales of licensed products under the St. Jude Agreement. Under the St. Jude Agreement, the Company is obligated to use commercially reasonable efforts to develop and commercialize the licensed product(s). If the Company fails to achieve the development milestones contained in the St. Jude Agreement, and if the Company and St. Jude fail to agree upon a mutually satisfactory revised time line, St. Jude will have the right to terminate the St. Jude Agreement. On May 11, 2022, the Company and St. Jude entered into a first amendment to the St. Jude Agreement (the "St. Jude Amendment"). The St. Jude Amendment provides for a revised development milestone timeline and a one-time license fee of \$ 5, 000. The St. Jude Amendment also provides for an increase in the aggregate milestone payments that are due upon the achievement of specified developmental milestones, from \$ 1. 0 million to \$ 1. 9 million; specifically, development milestones of \$ 0. 3 million, regulatory milestones of \$ 0. 6 million, and commercial milestones of \$ 1. 0 million. The milestones include the following events: (i) complete IND-enabling study by 2022; (ii) Initiate animal toxicology study by last half of 2022; (iii) file IND by last half of 2023; (iv) complete Phase I Clinical Trial by last half of 2024; (v) commence Phase II Clinical Trial by 2025; (vi) commence Phase III Clinical Trial by 2027; and, (vii) regulatory approval, U. S. or foreign equivalent by 2032. Upon achievement of certain development and commercialization milestones, the Company is required to make milestone payments to St. Jude between the achievement of certain milestones (commencement of a Phase III clinical trial through first commercial sale). As of the date of this Report, none of these milestones have been achieved. Additionally, the Company is obligated to



make running 5 % royalty payments payable, for each licensed product (s) sold by the Company, its affiliates or sublicensees, based on the net sales for the duration of the St. Jude Agreement. Furthermore, the Company is obligated to pay a percentage between 15 % of other consideration received for any sublicensees. The Company is responsible for and shall bear all expenses relating to the filing, prosecution, and maintenance of all patent rights licensed under the St. Jude Agreement. The Company has the first right to enforce any patent against infringement, and shall keep St. Jude informed of the status of such; however, before the Company may commence any action with respect to any such alleged infringement, the Company shall take into consideration the views of St. Jude and the potential effect on the public interest. Prior to initial human testing or first commercial sale of a licensed product, and thereafter so long as the licensed products are being sold in any particular country, the Company (and its sublicensees) is required to obtain and maintain insurance to cover its indemnity obligations, and to obtain and maintain product liability insurance coverage. St. Jude represented and warranted that it has good and marketable title to the Patent Rights, but made no other representations and warranties. The term of the agreement commenced on the Effective Date, and shall continue, in each country, until the date of expiration of the last to expire valid claim included within the Patent Rights in that country. Either party may terminate the St. Jude Agreement in the event the other party (a) files or has filed against it a petition under the Bankruptcy Act (among other things) or (b) fails to perform or otherwise breaches its obligations under the St. Jude Agreement, and has not cured such failure or breach within sixty (60) days. The Company may terminate for any reason on thirty (30) days written notice. In addition to the St. Jude Agreement, the Company also entered into a sponsored research agreement (the "St. Jude SRA") dated May 3, 2021 with St. Jude for research related to the St. Jude Agreement. Pursuant to the St. Jude SRA, the Company is obligated to pay St. Jude an aggregate amount of \$ 73, 073 in two parts, Phase I for \$ 57, 624 and Phase II for \$ 15, 449. This sponsored research project began during the year ended December 31, 2021. The Company entered into a second sponsored research agreement with St. Jude, dated August 29, 2022, pursuant to which the Company is obligated to pay St. Jude an amount of \$ 75, 603 which is due within 30 days of the effective date of the agreement. Exclusive License Agreement between the University of Texas Health Science Center at San Antonio & Blue Water Vaccines Inc. On November 18, 2022, the Company entered into a patent and technology license agreement (the "UT Health Agreement"), with the University of Texas Health Science Center at San Antonio ("UT Health"). Under the terms of the UT Health Agreement, the Company holds an exclusive, worldwide license (other than the excluded field of vectors) to certain specified patent rights relating to the development of a live attenuated, oral Chlamydia vaccine candidate, as set forth in the chart below:

U. S. Patent Application No.	U. S. Patent No.	Granted	Claim Type	U. S. Expiration	Foreign Counterparts
15 / 551, 829	10, 596, 247				
Compositions and method of treatment	3 / 24 / 2040	none	63 / 424, 281	pending	pending * * [ 11 / 2 / 2042 ] * none

An initial non-refundable license fee of \$ 100, 000 was due upon execution of the UT Health Agreement and subsequent annual license fees of \$ 20, 000 per year for each of the four years ending on December 31, 2026; \$ 40, 000 per year for each of the two years ending on December 31, 2028, and \$ 60, 000 for the year ending December 31, 2029 and each year thereafter. See Note 7 to our financial statements included elsewhere in this Report for information on milestone payments as well as royalty obligations required under the UT Health Agreement. The UT Health Agreement will expire upon the expiration of the last date of expiration or termination of the patent rights, unless terminated earlier. The Company may terminate the UT Health Agreement for convenience, by providing 90 days' written notice to UT Health. UT Health may terminate the UT Health Agreement in the event the Company (a) becomes arrears in payment due and does not make payment within 30 days after notification from UT Health or (b) is in breach of any non-payment provision and does not cure such breach within 60 days after notification from UT Health or (c) UT Health delivers notice to the Company of three or more actual material breaches of the UT Health Agreement in any 12-month period or (d) in the event the Company or its affiliates initiates any proceeding or action to challenge the validity, enforceability, or scope of any of the licensed patents. Pursuant to the UT Health Agreement, as disclosed in Note 7 to our financial statements included elsewhere in this Report, the Company is obligated to pay certain milestone and royalty payments in the future, as the related contingent events occur. Specifically, the Company is obligated to pay UT Health a royalty on net sales, being 5 % or 3 % depending on whether the product is covered by a valid claim or not, as defined in the agreement. The Company is also obligated to pay a 20 % royalty on any sums received by the Company from any sublicensee. In addition, the Company is required to pay UT Health milestone payments of up to an aggregate of approximately \$ 2. 2 million; specifically, upon the achievement of specified development milestones of approximately \$ 0. 7 million and regulatory milestones of approximately \$ 1. 5 million. Manufacturing and Supply We currently do not own or operate any manufacturing facilities, but our strategic partnership with Ology Bioservices, Inc. (which was later acquired by National Resilienc, Inc.) ("Ology") provides us with access to substantial resources to facilitate an independent supply path to the market. Ology is a leading global contract manufacturer with deep domain expertise and experience in large and small-scale production of clinical, as well as commercial-stage products. We have entered into agreements with Ology to secure capacity, technical expertise and resources to support the production of our products and processes that are intended to scale to commercial scale at Ology or other commercial manufacturing sites. In July 2019, we entered into a development and manufacturing master services agreement with Ology, which we refer to, as amended, as the Ology Agreement, pursuant to which Ology is obligated to perform manufacturing process development and clinical manufacture and supply of components. Under the Ology Agreement, we will pay Ology agreed-upon fees for Ology's performance of manufacturing services, and we will reimburse Ology for its out-of-pocket costs associated with purchasing raw materials, plus a customary handling fee. The Company entered into an initial Project Addendum on October 18, 2019 and the Company was required to pay Ology an aggregate of approximately \$ 4 million. Due to unforeseen delays associated with COVID-19, the Company and Ology entered into a letter agreement dated January 9, 2020 to stop work on the project, at which point, the Company had paid Ology \$ 100, 000 for services. The second Project Addendum was executed May 21, 2021 and the Company is obligated to pay Ology an aggregate amount of approximately \$ 2. 8 million, plus reimbursement for materials and outsourced testing, which will be billed at cost plus 15 %. During 2022, the Company entered into three amendments to the Ology Agreement, to adjust the scope of work defined in the

second Project Addendum. The amendments resulted in a net increase to the Company's obligations under the second Project Addendum of \$ 154,000. During the years ended December 31, 2022 and 2021, the Company incurred research and development expenses related to the Ology Agreement of approximately \$ 1,329,000 and \$ 328,000, respectively, and had approximately \$ 476,000 and \$ 669,000 recorded as related accounts payable and accrued expenses, respectively, at December 31, 2022, and approximately \$ 164,000 and \$ 115,000 recorded as related accounts payable and accrued expenses, respectively, at December 31, 2021. Either party may terminate a Project Addendum and/or the Ology Agreement upon the material breach of any provision of this Agreement by the other Party if such breach is not cured by the breaching party within thirty (30) calendar days after receipt by the breaching Party of written notice of such default. The Company may terminate the Ology Agreement or the associated Project Addendum for any or no reason upon sixty (60) days' prior written notice to Ology.

Employees As of March 6, 2023, we had 12 employees. None of our employees are represented by a collective bargaining agreement, and we have never experienced any work stoppage. We believe we have good relations with our employees.

Properties and Facilities We are currently leasing an office located at 201 E Fifth Street, Suite 1900, Cincinnati, OH 45202, which is renewed on a monthly basis. We also lease office space located at 150 Worth Avenue, Palm Beach, FL 33480, which lease expires on April 30, 2023. All of our research and development is performed on the premises of our third-party providers.

Buyback Program On November 10, 2022, the Company's Board of Directors approved a share repurchase program to allow for the Company to repurchase up to 5 million shares of common stock, with discretion to management to make purchases subject to market conditions. The maximum purchase price is \$ 2.00 per share and there is no expiration date for this program.

Fundraising Activities April Private Placement On April 19, 2022, we consummated the closing of a Private Placement (the "April Private Placement"), in which we received approximately \$ 6.9 million in net cash proceeds, pursuant to the terms and conditions of the Securities Purchase Agreement, dated as of April 13, 2022 (the "April Purchase Agreement"), by and among the Company and certain purchasers named on the signature pages thereto. At the closing of the April Private Placement, the Company issued 590,406 shares of common stock, pre-funded warrants to purchase an aggregate of 590,406 shares of common stock and preferred investment options to purchase up to an aggregate of 1,180,812 shares of common stock. The purchase price of each share and associated preferred investment option was \$ 6.775 and the purchase price of each prefunded warrant and associated preferred investment option was \$ 6.774. The aggregate gross proceeds to the Company from the April Private Placement were approximately \$ 8.0 million, before deducting placement agent fees and other offering expenses. H. C. Wainwright & Co., LLC ("Wainwright") acted as the exclusive placement agent for the April Private Placement. In connection with the April Private Placement, we entered into a registration rights agreement with the purchasers, dated as of April 13, 2022 (the "April Registration Rights Agreement"), pursuant to which we filed a registration statement covering the resale of registrable securities under the April Registration Rights Agreement, which was declared effective on May 20, 2022. Upon the occurrence of any Event (as defined in the April Registration Rights Agreement), which, among others, includes the purchasers being prohibited from reselling the securities acquired in the April Private Placement for more than ten (10) consecutive calendar days or more than an aggregate of fifteen (15) calendar days during any 12-month period, we are obligated to pay to each purchaser, on each monthly anniversary of each such Event, an amount in cash, as partial liquidated damages and not as a penalty, equal to the product of 2.0% multiplied by the aggregate subscription amount paid by such purchaser pursuant to the April Purchase Agreement. Wainwright served as the exclusive placement agent for the April Private Placement and received a cash fee of 7.5% of the aggregate gross proceeds of the offering and received warrants (the "April Wainwright Warrants") to purchase up to 70,849 shares of our common stock, which was equivalent to 6.0% of the shares and prefunded warrants sold in the April Private Placement. We also agreed to pay Wainwright a management fee equal to 1.0% of the aggregate gross proceeds from the offering and reimburse certain out-of-pocket expenses up to an aggregate of \$ 85,000. We also agreed, upon any exercise for each of any preferred investment options, to issue to Wainwright warrants to purchase the number of shares equal to 6.0% of the aggregate number of placement shares underlying the preferred investment options that have been exercised (the "April Contingent Warrants"). The maximum number of April Contingent Warrants issuable under this provision is 70,849. On August 11, 2022, the Company consummated the closing of a private placement (the "August Private Placement"), pursuant to the terms and conditions of a securities purchase agreement, dated as of August 9, 2022. At the closing of the August Private Placement, the Company issued 1,350,000 shares of common stock, pre-funded warrants to purchase an aggregate of 2,333,280 shares of common stock and preferred investment options to purchase up to an aggregate of 4,972,428 shares of common stock. The purchase price of each share of common stock together with the associated preferred investment option was \$ 2.715, and the purchase price of each pre-funded warrant together with the associated preferred investment option was \$ 2.714. The aggregate net cash proceeds to the Company from the August Private Placement were approximately \$ 8.7 million, after deducting placement agent fees and other offering expenses. In addition, the investors in the August Private Placement, who are the same investors from the April Private Placement, agreed to cancel preferred investment options to purchase up to an aggregate of 1,180,812 shares of the Company's common stock issued in April 2022. The pre-funded warrants have an exercise price of \$ 0.001 per share, are exercisable on or after August 11, 2022, and are exercisable until the pre-funded warrants are exercised in full. On September 20, 2022, 945,000 of the pre-funded warrants were exercised, and as such the Company issued 945,000 shares of common stock on that date. The preferred investment options are exercisable at any time on or after August 11, 2022 through August 12, 2027, at an exercise price of \$ 2.546 per share, subject to certain adjustments as defined in the agreement. Wainwright acted as the exclusive placement agent for the August Private Placement. The Company agreed to pay Wainwright a placement agent fee and management fee equal to 7.5% and 1.0%, respectively, of the aggregate gross proceeds from the August Private Placement and reimburse certain out-of-pocket expenses up to an aggregate of \$ 85,000. In addition, the Company issued warrants to Wainwright (the "August Wainwright Warrants") to purchase up to 220,997 shares of common stock. The August Wainwright Warrants are in substantially the same form as the preferred investment options, except that the exercise price is \$ 3.3938. The form of the preferred investment options is a

warrant, and as such the preferred investment options, the pre-funded warrants, and the August Wainwright Warrants are collectively referred to as the “August Private Placement Warrants”. Further, upon any exercise for cash of any preferred investment options, the Company agreed to issue to Wainwright additional warrants to purchase the number of shares of common stock equal to 6.0% of the aggregate number of shares of common stock underlying the preferred investment options that have been exercised, also with an exercise price of \$ 3.3938 (the “August Contingent Warrants”). The maximum number of August Contingent Warrants issuable under this provision is 298,346, which includes 70,849 of April Contingent Warrants that were modified in connection with the August Private Placement. In connection with the August Private Placement, the Company entered into a Registration Rights Agreement with the purchasers, dated as of August 9, 2022 (the “August Registration Rights Agreement”). The August Registration Rights Agreement provides that the Company shall file a registration statement covering the resale of all of the registrable securities (as defined in the August Registration Rights Agreement) with the SEC no later than the 30th calendar day following the date of the August Registration Rights Agreement and have the registration statement declared effective by the SEC as promptly as possible after the filing thereof, but in any event no later than the 45th calendar day following August 9, 2022 or, in the event of a full review by the SEC, the 80th day following August 9, 2022. The registration statement on Form S-1 required under the Registration Rights Agreement was filed with the SEC on August 29, 2022, and became effective on September 19, 2022. Upon the occurrence of any Event (as defined in the August Registration Rights Agreement), which, among others, prohibits the purchasers from reselling the securities for more than ten consecutive calendar days or more than an aggregate of fifteen calendar days during any 12-month period, and should the registration statement cease to remain continuously effective, the Company is obligated to pay to each purchaser, on each monthly anniversary of each such Event, an amount in cash, as partial liquidated damages and not as a penalty, equal to the product of 2.0% multiplied by the aggregate subscription amount paid by such purchaser in the August Private Placement.

**Legal Proceedings** From time to time we may be involved in various disputes and litigation matters that arise in the ordinary course of business. We are currently not a party to any material legal proceedings. **Boustead Settlement** On April 15, 2022, the Company received a demand letter (the “Demand Letter”) from Boustead Securities, LLC (“Boustead”). The Demand Letter alleged that the Company breached its underwriting agreement with Boustead, in connection with the Company’s February 2022 initial public offering. The Demand Letter alleged that, by engaging H. C. Wainwright & Co., LLC as placement agent for the April Private Placement, the Company breached Boustead’s right of first refusal (“ROFR”) to act as placement agent granted to Boustead under the underwriting agreement and, as a result of selling securities in the April Private Placement, breached the Company’s obligation under the underwriting agreement not to offer, sell, issue, agree or contract to sell or issue or grant or modify the terms of any option for the sale of, any securities prior to February 17, 2023 (the “Standstill”). On October 9, 2022, the Company and Boustead entered into a Settlement Agreement and Release effective as of September 28, 2022, pursuant to which Boustead agreed to waive the ROFR and the Standstill and to release the Company from certain claims with respect to the April Private Placement, the August Private Placement, and all future private, public equity or debt offerings of the Company. As consideration for such waiver, the Company agreed to pay Boustead a cash fee of \$ 1,000,000 plus \$ 50,000 in legal expenses and release Boustead from all claims, subject to certain exceptions. In addition, the Company agreed to issue to Boustead 93,466 shares of restricted common stock in exchange for the cancellation of 111,111 warrants that were issued to Boustead in connection with the initial public offering. Concurrent with the execution of the Settlement Agreement, the Company and Boustead Capital Markets, LLP (“Boustead Capital”) entered into a three-month Advisory Agreement (the “Advisory Agreement”) for which consideration equal to 200,000 shares of restricted common stock, with no vesting provisions, was issued to Boustead Capital upon execution of the Advisory Agreement.

**Changes in and Disagreements with Accountants** None. **Corporation Information** We were incorporated in Delaware on October 26, 2018. Our principal executive offices are located at 201 E Fifth Street, Suite 1900, Cincinnati, OH 45202, and our telephone number is (513) 620-4101. Our corporate website address is [www.bluewatervaccines.com](http://www.bluewatervaccines.com). The information contained on or accessible through our website is not part of this Annual Report on Form 10-K. Available Information We maintain a website at [www.bluewatervaccines.com](http://www.bluewatervaccines.com). You may access our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act with the SEC free of charge at our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC. The reference to our website address does not constitute incorporation by reference of the information contained on our website, and you should not consider the contents of our website in making an investment decision with respect to our common stock.

**Item 1A. Risk Factors.** Investing in our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Report, including our financial statements, the notes thereto and the section entitled “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, reputation, financial condition, results of operations and future growth prospects, as well as our ability to accomplish our strategic objectives. As a result, the trading price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations and the market price of our common stock.

**Risks Related to our Financial Position and Need for Capital** We are in the early stages of vaccine development and have a very limited operating history and no products approved for commercial sale, which may make it difficult for you to evaluate the success of our business to date and to assess our future viability. To date, we have devoted substantially all of our resources to performing research and development, undertaking preclinical studies and enabling manufacturing activities in support of our product development efforts, hiring personnel, licensing and developing our technology and vaccine candidates, organizing and staffing our company, performing business planning, establishing our intellectual property portfolio, potential asset and business acquisitions, expenditures associated with the commercial launch of ENTADFI, and raising capital to support and expand

such activities. As an organization, we have not yet demonstrated an ability to successfully complete clinical development, obtain regulatory approvals, manufacture a commercial-scale product or conduct sales and marketing activities necessary for successful commercialization or arrange for a third party to conduct these activities on our behalf. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history. Our current vaccine candidate pipeline includes multiple preclinical programs. We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives, including with respect to our products vaccine candidates. We will need to **are in the process of transition transitioning** in the future from a company with a research and development focus to a company capable of supporting commercial activities and may not be successful in such a transition. We have incurred significant net losses since inception, **do not have only generate generated any minimal** revenue, and anticipate that we will continue to incur substantial net losses for the foreseeable future and may never achieve profitability. Our stock is a highly speculative investment. We are a **preclinical commercial-stage** biotechnology vaccine company that was incorporated in October 2018. Investment in preclinical stage companies and vaccine development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential vaccine candidate will not gain regulatory approval or become commercially viable. We do not have any products approved for sale and have not generated any revenue from product sales. As a result, we are not profitable and have incurred losses in each year since inception. Our net loss was \$ **13-37**. 4 million and \$ **3-13**. 4 million for the years ended December 31, **2023 and** 2022 and 2021, respectively. As of December 31, **2022-2023**, we had an accumulated deficit of \$ **19-56**. 48 million. We also generated negative operating cash flows of \$ **8-13**. 76 million for the year ended December 31, **2022-2023**. We expect to continue to spend significant resources to **commercialize** fund research and development of, and seek regulatory approvals for, our **products** vaccine candidates. We expect to incur substantial and increasing operating losses over the next several years as our research, development, manufacturing, preclinical testing and clinical trial activities increase. As a result, our accumulated deficit will also increase significantly. Additionally, there can be no assurance that the **our current product products** candidates currently under development or **those** that may be under development by us in the future will be approved for sale in the U. S. or elsewhere. Furthermore, there can be no assurance that if such products are approved they will be successfully commercialized **commercially viable**, and the extent of our future losses and the timing of our profitability are highly uncertain. If we are unable to achieve profitability, we may be unable to continue our operations. **We There is substantial doubt about our ability to continue as a "going concern," and we** will require substantial additional funding to finance our long-term operations. If we are unable to raise additional capital when needed, we could be forced to delay, reduce or terminate certain of our **products** development programs or other operations. **The Company has incurred substantial operating losses since inception and expects to continue to incur significant operating losses for the foreseeable future.** As of December 31, **2022-2023**, we **the** Company had cash of **approximately \$ 25-4**. 6 million, a working capital deficit of **approximately \$ 11**. 4 million and an accumulated deficit of **approximately \$ 56**. 8 million. **On January 23** As of December 31, **2021-2024**, we had **the** Company issued the Debenture in exchange for \$ **4**. 6 million in net cash of \$ **1**. 9 million. On April 19, 2022, we closed the April Private Placement from which we received aggregate net proceeds of approximately \$ **6**. **The Debenture is repayable in full upon** 9 million, after deducting placement agent fees and other **the earlier of (i)** offering expenses. On August 11, 2022, we closed the August Private Placement from which we received approximately \$ **8**. 7 million in net proceeds, after deducting placement agent fees and other **the offering expenses** closing under the Subscription Agreement and **(ii) June 30, 2024**. We estimate that, based on our existing cash as of the date of this Report, we will **not** have cash on hand sufficient to fund our operations for at least the 12 months following the date of this Report. We believe that we will need to raise substantial additional capital to fund our continuing operations, **satisfy existing** and the development **future obligations** and **liabilities, and otherwise support the Company's working capital needs and business activities, including making the remaining payments to Veru, and the commercialization of our Proclarix and ENTADFI (should we decide to resume its commercialization).** In addition, if Stockholder Approval is not obtained by January 1, 2025, the Company may be obligated to cash settle the Series B Preferred Stock. The Company does not **current currently** have sufficient cash to redeem the shares of Series B Preferred Stock. Based on the closing price of \$ **0**. 166 for the Company's stock as of April 5, 2024, the Series B Preferred Stock would be redeemable for approximately \$ **44**. 8 million. Management's plans include generating product candidates and future revenue from sales of Proclarix, which may still be subject to further successful commercialization activities within certain jurisdictions. In addition, should we decide to resume the commercialization of ENTADFI, we plan to also generate product sales from ENTADFI candidates in the long-term. Our business or operating plan may change as a result of many factors currently unknown to us, **which is subject** and we may need to **further successful commercialization activities** seek additional funds sooner than planned. **Certain of the commercialization activities are outside of the Company's control** We expect to finance our subsequent cash needs through public or private equity or debt financings, **including but not limited to, securing contracts with wholesalers and third-party (including government) funding and marketing and distribution arrangements payers, securing contracts with third-party logistics providers, obtaining required licensure in various jurisdictions**, as well as **attempting to secure additional required funding through equity or debt financings if available.** However, **other-- there are currently no commitments in place** collaborations, strategic alliances and licensing arrangements or **for further financing nor is there any assurance** combination of these approaches. In addition, we may need to accelerate the growth of our sales capabilities and distribution beyond what **that such financing will** is currently envisioned, and this would require additional capital. However, we may not be able **available to the Company** secure funding when we need it or on favorable terms and we may not be, **if at all. If the Company is able-unable to secure** raise sufficient funds to commercialize our current and future product candidates we intend to develop. Our ability to raise additional capital, **it may be adversely impacted by potential worsening global economic required to delay or curtail any future commercialization of products, and it may take additional measures to reduce**



expenses in order to conserve its cash in amounts sufficient to sustain operations and meet its obligations. These conditions and raise substantial doubt about the recent disruptions Company's ability to continue as a and volatility in the credit and financial markets in the United States and worldwide, including the trading price of common stock, resulting from the ongoing going COVID-19 pandemic concern for a period of time within one year following the date of this Report. Our future capital requirements will depend on many factors, including: • the timing, scope, progress, results and costs of research and development, testing, screening, manufacturing, preclinical development and clinical trials; • the outcome, timing and cost of seeking and obtaining regulatory approvals from the FDA and comparable foreign regulatory authorities, including the potential for such authorities to require that we perform field efficacy studies for our vaccine candidates, require more studies than those that we currently expect or change their requirements regarding the data required to support a marketing application; • the cost of building a sales force in anticipation of any product commercialization; • the costs of future commercialization activities, including product manufacturing, marketing, sales, royalties and distribution, for any of our vaccine candidates Proclarix, and ENTADFI (if we decide to resume its commercialization), and other products for which we have received or will receive marketing approval; • our ability to maintain existing, and establish new, strategic collaborations, licensing or other arrangements and the financial terms of any such agreements, including the timing and amount of any future milestone, royalty, or other payments due under any such agreement; • any product liability or other lawsuits related to our products; • the expenses needed to attract, hire, and retain skilled personnel; • the revenue, if any, received from commercial sales, or sales to foreign governments, of Proclarix and ENTADFI (if we decide to resume its commercialization), our or vaccine candidates other products for which we may receive marketing approval; • the costs to establish, maintain, expand, enforce, and defend the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make, or that we may receive, in connection with licensing, preparing, filing, prosecuting, defending, and enforcing our of any patents or other intellectual property rights; and • the costs of operating as a public company; and • the impact of the COVID-19 pandemic, which may exacerbate the magnitude of the factors discussed above. Our ability to raise additional funds will depend on financial, economic, and other factors, many of which are beyond our control. We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may be forced to delay, reduce the scope of our business activities. We owe a significant amount of money to Veru, which funds we do not have. Veru may take action against us to significantly delay enforce its rights to payment in the future, which could have a material adverse effect on us and our operations. Due to recent financial constraints, the Company may be unable to timely pay amounts due to Veru, from whom we purchased ENTADFI in April 2023. The Company is currently in ongoing discussions with Veru to negotiate our payment obligations in connection with our acquisition of ENTADFI. However, no definitive terms or extensions have been agreed to, to date. While we are hopeful that we can come to mutually agreeable terms regarding a settlement, payment plan, and / or extension with Veru, we may not have sufficient funds to pay amounts due to Veru in the near term, if at all, including but not limited to \$ 10 million, \$ 5 million of which is due on each of April 19, 2024 and September 30, 2024, and Veru may take action against us, including filing legal proceedings against us seeking amounts due and interest or attempting to terminate its relationship with us. If Veru were to take legal action against us, we may be forced to scale back or our business plan and / or discontinue the development or commercialization of our or vaccine candidates seek bankruptcy protection. We may be subject to litigation and damages for our failure to pay due to Veru, and may be forced to pay interest and penalties, which funds we do not currently have. We are currently considering strategic options for ENTADFI and plan to seek to raise funding in the future to support our operations, and to pay amounts due to Veru, through a combination of equity offerings, debt financing or other research capital sources, including potential collaborations, licenses, sales, and development initiatives other similar arrangements, which may not be available on favorable terms, if at all. The sale of additional equity or debt securities, if accomplished, may result in dilution to our stockholders. Our license agreements may also be terminated current liabilities are significant, and if those to whom we we owe are unable to meet accounts payable, such as Veru, IQVIA or the other vendors, were to demand payment, we obligations or milestones under the agreements. We could be required to seek collaborators for our vaccine candidates at an earlier stage than otherwise would be desirable or on terms that unable to pay. As of December 31, 2023, we had total current liabilities of approximately \$ 17. 2 million, including accounts payable of approximately \$ 5. 3 million, accrued expenses of approximately \$ 2. 2 million, and approximately \$ 9. 6 million (net of discount) related to the notes payable due to Veru. As of the same date, we had cash of only \$ 4. 6 million. We are less favorable than might otherwise currently considering strategic options for ENTADFI and plan to seek to raise funding in the future to support our operations. If those to whom these payments are due were to demand immediate payment, as they are entitled to do, and we are not able to make the required payments, we would be available, subject to liability if or our creditors chose to enforce their relinquish or license on unfavorable terms our rights to our vaccine candidates, which could result in markets where we otherwise our bankruptcy and insolvency, at worst. Under such a scenario, our assets would seek be distributed to pursue development or our commercialization ourselves creditors leaving nothing to be distributed to our stockholders. We may consider strategic alternatives in order to maximize stockholder value, including financings- financing, strategic alliances, licensing arrangements, acquisitions or the possible sale of our business. We may not be able to identify or consummate any suitable strategic alternatives and any consummated strategic alternatives may not be successful have an adverse impact on our vaccine candidates. We may consider all strategic alternatives that may be available to us to maximize stockholder value, including financings- financing, strategic alliances, licensing arrangements, acquisitions, or the possible sale of our business. Our exploration of various strategic alternatives may not result in any specific action or transaction. To the extent that this engagement results in a transaction, our business objectives may change depending upon the nature of the transaction. There can be no assurance that we will enter into any transaction as a

result of the engagement. Furthermore, if we determine to engage in a strategic transaction, we cannot predict the impact that such strategic transaction might have on our operations or stock price. We also cannot predict the impact on our stock price if we fail to enter into a transaction. In addition, we face significant competition in seeking appropriate strategic partners, and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for our ~~vaccine candidates~~ **business activities** because they may be deemed to be at too early of a stage of development for collaborative effort, ~~and third parties may not view our vaccine candidates as having the requisite potential to demonstrate safety and efficacy.~~ Any delays in entering into new strategic partnership agreements related to our vaccine candidates could delay the development and commercialization of our vaccine candidates in certain geographies for certain indications, which would harm our business prospects, financial condition and results of operations. If we license ~~or acquire~~ products or businesses, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture. We cannot be certain that, following a strategic transaction ~~or~~, license, ~~or acquisition~~, we will achieve the results, revenue or specific net income that justifies such transaction. Raising additional capital may cause dilution to our existing stockholders and investors, restrict our operations or require us to relinquish rights to our ~~product~~ **products** candidates on unfavorable terms to us. We may seek additional capital through a variety of means, including through private and public equity offerings and debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, or through the issuance of shares under other types of contracts, or upon the exercise or conversion of outstanding options, warrants, convertible debt or other similar securities, the ownership interests of our stockholders will be diluted, and the terms of such financings may include liquidation or other preferences, anti-dilution rights, conversion and exercise price adjustments and other provisions that adversely affect the rights of our stockholders, including rights, preferences and privileges that are senior to those of our holders of common stock in terms of the payment of dividends or in the event of a liquidation. In addition, debt financing, if available, could include covenants limiting or restricting our ability to take certain actions, such as incurring additional debt, making capital expenditures, entering into licensing arrangements, or declaring dividends and may require us to grant security interests in our assets. If we raise additional funds through collaborations, strategic alliances, or marketing, distribution, ~~or licensing arrangements with third parties~~, we may have to relinquish valuable rights to our technologies, future revenue streams, ~~or product~~ **products** or ~~product~~ **products** candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt ~~financings~~ **financing** when needed, we may need to curtail or cease our operations. Due to the significant resources required for the development ~~commercialization~~ of our ~~products~~ **products** vaccine candidates, and depending on our ability to access capital, we must prioritize development ~~commercialization~~ of certain ~~products~~ **products** vaccine candidates. Moreover, we may expend our limited resources on ~~products~~ **products** vaccine candidates that do not yield a successful vaccine ~~product~~ **product** and fail to capitalize on ~~products~~ **products** vaccine candidates that may be more profitable or for which there is a greater likelihood of success. Due to the significant resources required for the development of our ~~products~~ **products** vaccine candidates, we must decide which ~~products~~ **products** vaccine candidates to pursue and advance and the ~~amount~~ **number** of resources to allocate to each. Our decisions concerning the allocation of research, development, management and financial resources toward particular ~~products~~ **products** vaccine candidates may not lead to the development of any viable commercial ~~vaccines~~ **products** and may divert resources away from better opportunities. Similarly, our potential decisions to delay, terminate, license, ~~or collaborate with third parties in respect of certain~~ ~~products~~ **products** vaccine candidates may subsequently also prove to be less than optimal and could cause us to miss valuable opportunities. If we make incorrect determinations regarding the viability or market potential of any of our ~~products~~ **products** vaccine candidates or misread trends in the ~~biopharmaceutical~~ ~~pharmaceutical or diagnostic~~ industry, ~~in particular for vaccines~~, our business could be seriously harmed. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other ~~vaccine~~ ~~products and / or product~~ **products and / or product** candidates that may later prove to have greater commercial potential than those we choose to pursue or relinquish valuable rights to such ~~vaccine~~ ~~products and / or product~~ **products and / or product** candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain sole development and commercialization rights. ~~We have identified weaknesses in our internal controls, and we cannot provide assurances that these weaknesses will be effectively remediated or that additional material weaknesses will not occur in the future.~~ As a public company, we are subject to the reporting requirements of the Exchange Act, and the Sarbanes-Oxley Act. We expect that the requirements of these rules and regulations will continue to increase our legal, accounting and financial compliance costs, make some activities more difficult, time-consuming and costly, and place significant strain on our personnel, systems and resources. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures, and internal control over financial reporting. We do not yet have effective disclosure controls and procedures, or internal controls over all aspects of our financial reporting. We are continuing to develop and refine our disclosure controls and other procedures that are designed to ensure that information required to be disclosed by us in the reports that we will file with the SEC is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms. Our management has deemed certain conditions to be material weaknesses in our internal controls. For example, we failed to employ a sufficient number of staff to maintain optimal segregation of duties and to provide optimal levels of oversight in order to process financial information in a timely manner, analyze and account for complex, non-routine transactions, and prepare financial statements. In addition, we do not yet have adequate internal controls in place for the timely identification, approval or reporting of related party transactions. Our management is responsible for establishing and maintaining adequate internal control over our financial reporting, as defined in Rule 13a-15 (f) under the Exchange Act. We will be required to expend time and resources to further improve our internal controls over financial reporting, including by expanding our staff to include financial consultants and other qualified resources, which we commenced during the fourth quarter of 2021. However, we cannot assure you that our internal control over financial

reporting, as modified, will enable us to identify or avoid material weaknesses in the future. Our current controls and any new controls that we develop may become inadequate because of changes in conditions in our business, including increased complexity resulting from our international expansion. Further, weaknesses in our disclosure controls or our internal control over financial reporting may be discovered in the future. Any failure to develop or maintain effective controls, or any difficulties encountered in their implementation or improvement, could harm our operating results or cause us to fail to meet our reporting obligations and may result in a restatement of our financial statements for prior periods. Any failure to implement and maintain effective internal control over financial reporting could also adversely affect the results of management reports and independent registered public accounting firm audits of our internal control over financial reporting that we will eventually be required to include in our periodic reports that will be filed with the SEC. Ineffective disclosure controls and procedures, and internal control over financial reporting could also cause investors to lose confidence in our reported financial and other information, which would likely have a negative effect on the market price of our common stock. We are required to comply with the SEC rules that implement Section 404 of the Sarbanes-Oxley Act, and are therefore required to make a formal assessment of the effectiveness of our internal control over financial reporting for that purpose. We are required to provide an annual management report on the effectiveness of our internal control over financial reporting in our annual report on Form 10-K. Our independent registered public accounting firm is not required to audit the effectiveness of our internal control over financial reporting until after we are no longer an “emerging growth company” as defined in the JOBS Act. At such time, our independent registered public accounting firm may issue a report that is adverse in the event it is not satisfied with the level at which our internal control over financial reporting is documented, designed or operating. Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited, each of which could harm our business. As of December 31, 2022-2023, we had U. S. federal, foreign, and state net operating loss carryforwards of approximately \$ 12-27.5-9 million and, \$ 12-18.1-0 million, and \$ 23.8 million, respectively. Under Sections 382 and 383 of the Internal Revenue Code, or the Code, if a corporation undergoes an “ownership change,” the corporation’s ability to use its pre-ownership change net operating loss carryforwards and other pre-ownership change tax attributes, such as research tax credits, to offset its post-ownership change income and taxes may be limited. In general, an ownership change will occur when the percentage of the Corporation’s ownership (by value) of one or more “5-percent stockholders” (as defined in the Code) has increased by more than 50 percent over the lowest percentage owned by such stockholders at any time during the prior three years (calculated on a rolling basis). Similar rules may apply under state tax laws. An entity that experiences an ownership change generally will be subject to an annual limitation on its pre-ownership change tax loss and credit carryforwards equal to the equity value of the corporation immediately before the ownership change, multiplied by the long-term, tax-exempt rate posted monthly by the U. S. Internal Revenue Service (subject to certain adjustments). The annual limitation would be increased each year to the extent that there is an unused limitation in a prior year. In the event that it is determined that we have in the past experienced an ownership change as a result of transactions in our stock, or if we experience one or more ownership changes as a result of future transactions in our stock, then we may be limited in our ability to use our net operating loss carryforwards and other tax assets to reduce taxes owed on the net taxable income that we earn. Any limitations on the ability to use our net operating loss carryforwards and other tax assets could harm our business. Our insurance coverage may be inadequate or expensive. We are subject to claims in the ordinary course of business. These claims may involve substantial amounts of money and involve significant defense costs. It is not possible to prevent or detect all activities giving rise to claims and the precautions we take may not be effective in all cases. We maintain voluntary and required insurance coverage, including, among others, general liability, property, director and officer, business interruption, cyber and data breach. Our insurance coverage is expensive and maintaining or expanding our insurance coverage may have an adverse effect on our results of operations and financial condition. Our insurance coverage may be insufficient to protect us against all losses and costs stemming from operational and technological failures and we cannot be certain that such insurance will continue to be available to us on economically reasonable terms, or at all, or that any insurer will not deny coverage as to any future claim. The successful assertion of one or more large claims against us that exceed available insurance coverage, or the occurrence of changes in our insurance policies, including premium increases or the imposition of large retention, or deductible, or co-insurance requirements, could have an adverse effect on our business, financial condition, and results of operations. We entered into an asset purchase agreement and management services agreement with WraSer, which have been terminated because we believe that a material adverse event has occurred with respect to the WraSer Assets. However, the termination is subject to WraSer’s right to challenge the termination and assert claims against us. On June 13, 2023, we entered into the WraSer APA and the WraSer MSA with WraSer in connection with the purchase of the WraSer Assets. Under the WraSer APA, we paid \$ 3.5 million in cash to WraSer at signing. In October 2023, WraSer alerted us that its sole manufacturer for the API for Zontivity, the key driver for the WraSer acquisition, would no longer manufacture the API for Zontivity. We believed that this development constituted a Material Adverse Effect under the WraSer APA enabling us to terminate the WraSer APA and the WraSer MSA. On October 20, 2023, we filed a motion for relief from the automatic stay in the Bankruptcy Court to exercise our termination rights under the WraSer APA, as amended. On December 18, 2023, the Bankruptcy Court entered an Agreed Order lifting the automatic stay to enable us to exercise our rights to terminate the WraSer APA and the WraSer MSA without prejudice to the parties’ respective rights, remedies, claims, and defenses they had against one another under the WraSer APA and the WraSer MSA. On December 21, 2023, we filed a Notice with the Bankruptcy Court terminating the WraSer APA and the WraSer MSA. WraSer has advised us that it does not believe that a Material Adverse Event occurred. Due to the WraSer bankruptcy filing and our status as an unsecured creditor of WraSer, it is also unlikely that we will recover the \$ 3.5 million Signing Cash or any costs and resources in connection with services provided by the Company under the WraSer MSA. As a result of our failure to timely file our Quarterly Report on Form 10-Q for the quarter ended June 30, 2023, we are currently ineligible to file new short form registration



statements on Form S-3, which may impair our ability to raise capital on terms favorable to us, in a timely manner or at all. Form S-3 permits eligible issuers to conduct registered offerings using a short form registration statement that allows the issuer to incorporate by reference its past and future filings and reports made under the Securities Exchange Act of 1934, as amended, or the Exchange Act. In addition, Form S-3 enables eligible issuers to conduct primary offerings “off the shelf” under Rule 415 of the Securities Act of 1933, as amended, or the Securities Act. The shelf registration process, combined with the ability to forward incorporate information, allows issuers to avoid delays and interruptions in the offering process and to access the capital markets in a more expeditious and efficient manner than raising capital in a standard registered offering pursuant to a Registration Statement on Form S-1. As a result of our failure to timely file our Quarterly Report on Form 10-Q for quarter ended June 30, 2023, we are currently ineligible to file new short form registration statements on Form S-3 and we will be unable to conduct “off the shelf” offerings under Rule 415 of the Securities Act using our currently effective Registration Statement on Form S-3 (File No. 333-270383) after we file this Report. As a result, we may be unable to conduct an “at the market” offering pursuant to our At The Market Offering Agreement with Wainwright after such date. In addition, if we seek to access the capital markets through a registered offering during the period of time that we are unable to use Form S-3, we may be required to publicly disclose the proposed offering and the material terms thereof before the offering commences, we may experience delays in the offering process due to SEC review of a Form S-1 registration statement and we may incur increased offering and transaction costs and other considerations. Disclosing a public offering prior to the formal commencement of an offering may result in downward pressure on our stock price. In addition, our inability to conduct an offering “off the shelf” may require us to offer terms that may not be advantageous (or may be less advantageous) to us or may generally reduce our ability to raise capital in a registered offering. If we are unable to raise capital through a registered offering, we would be required to conduct our financing transactions on a private placement basis, which may be subject to pricing, size and other limitations imposed under Nasdaq rules. Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or any guidance we may provide. Our quarterly and annual revenue and operating results may fluctuate significantly, which makes it difficult for us to predict our future operating results. Our quarterly and annual operating results may fluctuate as a result of a variety of factors, many of which are outside our control and, as a result, may not fully reflect the underlying performance of our business. These fluctuations may occur due to a variety of factors, including, but not limited to: • the level of demand for our diagnostic tests, which may vary significantly; • the timing and cost of manufacturing our diagnostic tests, which may vary depending on the quantity of production and the terms of our agreements with third-party suppliers and manufacturers; • expenditures that we may incur to acquire, develop, or commercialize additional tests and technologies; • unanticipated pricing pressures; • the rate at which we grow our sales force and the speed at which newly hired salespeople become effective, and the cost and level of investment therein; • currency fluctuations due to our expectation of generating future revenue from international sales, subjecting us to risks such as currency exchange rate volatility; • geopolitical instability, economics problems, and other uncertainties in certain foreign countries in which we operate; • the degree of competition in our industry and any change in the competitive landscape of our industry, including consolidation among our competitors or future partners; and • coverage and reimbursement policies with respect to cancer treatment equipment, and potential future diagnostic tests that compete with our diagnostic tests. The cumulative effects of these factors could result in large fluctuations and unpredictability in our future financial results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Further, our historical results are not necessarily indicative of results expected for any future period, and quarterly results are not necessarily indicative of the results to be expected for the full year or any other period, and accordingly should not be relied upon as indicative of future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any guidance we may provide, or if the guidance we provide is below the expectations of analysts or investors, the price of our common stock and warrants could decline substantially. Such a stock price decline could occur even when we have met any publicly stated guidance we may provide, and could in turn negatively impact our business, financial condition and results of operations.

**Risks Related to the Development and Commercialization of our Product Candidates**—We depend entirely on the success of a limited number of product candidates, which are in preclinical development and none of which have commenced a clinical trial. If we do not obtain regulatory approval for and successfully commercialize one or more of our product candidates or we experience significant delays in doing so, we **not be** profitable. **Our** We do not have any products that have received regulatory approval and may never be able to develop marketable product candidates. We expect that a substantial portion of our efforts and expenses over the next few years will be devoted to the development of our product candidates; specifically, the commencement of Phase I clinical trials for our vaccine candidates. As a result, our business currently depends heavily on the successful development, regulatory approval and, if approved, commercialization of these **our product candidates**. We cannot be certain that our product candidates will receive regulatory approval or will be successfully commercialized even if they receive regulatory approval. The research, testing, manufacturing, safety, efficacy, labeling, approval, sale, marketing, and distribution of our product candidates are, and will remain, subject to comprehensive regulation by the FDA and similar foreign regulatory authorities. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through pre-clinical studies and clinical trials that the product candidate is safe and effective for use in each target indication. Vaccine development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our clinical trials. Failure to obtain regulatory approval for our product candidates in the United States will prevent us from

commercializing and marketing our product candidates. The success of our product candidates will depend on several additional factors, including: • completing clinical trials that demonstrate their efficacy and safety; • receiving marketing approvals from applicable regulatory authorities; • completing any post-marketing studies required by applicable regulatory authorities; • establishing commercial manufacturing capabilities; • launching commercial sales, marketing and distribution operations; • establishing relationships with partners having established distribution, marketing and sales capabilities; • the prevalence and severity of adverse events experienced with our product candidates; • acceptance of our product candidates by patients, the medical community, and third-party payors; • a continued acceptable safety profile following approval; • obtaining and maintaining healthcare coverage and adequate reimbursement for our product candidates; • competing effectively with other therapies and diagnostics, including with respect to the sales and marketing of our product candidates, if approved; and • qualifying for, maintaining, enforcing and defending our intellectual property rights and claims. Many of these factors are beyond our control, including the time needed to adequately complete clinical testing, the regulatory submission process, potential threats to our intellectual property rights and changes in the competitive landscape. It is possible that none of our product candidates will ever obtain regulatory approval, even if we expend substantial time and resources seeking such approval. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully complete clinical trials, obtain regulatory approval or, if approved, commercialize our product candidates, which would materially harm our business, financial condition, and results of operations. The marketing approval process of the FDA is lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain marketing approval for our current product candidates and future product candidates we intend to develop, our business will be substantially harmed. We are at a very early stage of development for all of our product candidates. The product candidates we intend to develop have not gained marketing approval in the U. S., and we cannot guarantee that we will ever have marketable products. Our business is substantially dependent on our ability to complete the development of, obtain marketing approval for, and successfully commercialize our current and future product candidates in a timely manner. We cannot commercialize our product candidates in the United States without first obtaining approval from the FDA to market each product candidate. Our product candidates could fail to receive marketing approval for many reasons, including among others: • the FDA may disagree with the design or implementation of our clinical trials; • Our clinical trials for our product candidate (s) must be successful if we are to seek and obtain regulatory marketing application through the submission of a new Biological License Application (BLA) and marketing authorization application (MAA) with the U. S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively. Advanced clinical trials are often not successful even if prior trials were successful, and even if we are able to conduct advanced clinical trials and those trials are successful, we may not obtain necessary regulatory approvals for our product candidate (s) or we may be unable to successfully commercialize our products even if we receive the necessary regulatory approvals. In addition, the process of seeking regulatory approval to market the product candidates we intend to develop is expensive and time consuming and, notwithstanding the effort and expense incurred, approval is never guaranteed. If we are not successful in obtaining timely approval of our product candidates from the FDA, we may never be able to generate significant revenue and may be forced to cease operations. The new Biological License Application, or BLA, process is costly, lengthy and uncertain. Any BLA application filed by us will have to be supported by extensive data, including, but not limited to, technical, pre-clinical, clinical, manufacturing and labelling data, to demonstrate to the FDA's satisfaction the safety and efficacy of the product for its intended use. In order to commence a clinical trial in the United States, we will be required to seek FDA acceptance of an IND for each of our product candidates. We cannot be sure any IND we submit to the FDA, or any similar clinical trial application we submit in other countries, will be accepted. If we will be required by regulatory authorities to conduct additional preclinical testing prior to filing an IND or similar application to clinically evaluate any of our product candidates, this may result in delay in our product candidate development. The results of any such preclinical testing may not be positive and may not support an application to study any of our product candidates in additional clinical trials. It is possible that the FDA or EMA will not view our ongoing or planned trials as providing adequate support for future clinical trials or for an application for marketing approval, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. If we are unable to confirm or replicate the results of our trials in larger patient group or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development any of our product candidates. Additionally, the FDA or EMA may disagree with the sufficiency of our proposed reliance upon the preclinical, manufacturing or clinical data generated by third-party academic-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from our ongoing trials. If so, the FDA or EMA may require us to obtain and submit additional preclinical, manufacturing or clinical data. Obtaining approvals from the FDA and from the regulatory agencies in other countries is an expensive and time-consuming process and is uncertain as to outcome. The FDA and other agencies could ask us to supplement our submissions, collect non-clinical data, conduct additional clinical trials or engage in other time-consuming actions, or it could simply deny our applications. In addition, even if we obtain a BLA approval or pre-market approvals in other countries, the approval could be revoked or other restrictions imposed if post-market data demonstrate safety issues or lack of effectiveness. We cannot predict with certainty how, or when, the FDA will act. If we are unable to obtain the necessary regulatory approvals, our financial condition and cash flow may be adversely affected, and our ability to grow domestically and internationally may be limited. Additionally, even if cleared or approved, our products may not be approved for the specific indications that are most necessary or desirable for successful commercialization or profitability. We may encounter substantial delays in completing our clinical studies which in turn will require additional costs, or we may fail to demonstrate adequate safety and efficacy to the satisfaction of applicable regulatory authorities. It is impossible to predict if or when our current or future product candidates, will prove safe or effective in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the

product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include: ● delays in reaching, or failing to reach, a consensus with regulatory agencies on study design; ● delays in reaching, or failing to reach, agreement on acceptable terms with a sufficient number of prospective contract research organizations, or CROs, and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites; ● delays in recruiting a sufficient number of suitable patients to participate in our clinical studies; ● imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites; ● failure by our CROs, other third parties or us to adhere to clinical study, regulatory or legal requirements; ● failure to perform in accordance with the FDA's good clinical practices, or GCPs, or applicable regulatory guidelines in other countries; ● delays in the testing, validation, manufacturing and delivery of sufficient quantities of our product candidates to the clinical sites; ● delays in having patients complete participation in a study or return for post-treatment follow-up; ● clinical study sites or patients dropping out of a study; ● delay or failure to address any patient safety concerns that arise during the course of a trial; ● unanticipated costs or increases in costs of clinical trials of our product candidates; ● occurrence of serious adverse events associated with the product candidates that are viewed to outweigh its potential benefits; or ● changes in regulatory requirements and guidance that require amending or submitting new clinical protocols. We could also encounter delays if a clinical trial is suspended or terminated by us, by the Institutional Review Board, or IRB, or the Ethics Commission of the institutions in which such trials are being conducted, by an independent Safety Review Board, or SRB, for such trial or by the FDA or other regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Any inability to successfully complete pre-clinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical study delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates. In addition, any delays in completing our clinical trials will increase our costs, slow down our product candidates' development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may significantly harm our business, financial condition and prospects. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. The outcome of pre-clinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Further, pre-clinical and clinical data are often susceptible to various interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain marketing approval. If the results of our clinical studies are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may: ● be delayed in obtaining marketing approval for our product candidates, if approved at all; ● obtain approval for indications or patient populations that are not as broad as intended or desired; ● obtain approval with labeling that includes significant use or distribution restrictions or safety warnings; ● be required to change the way the product is administered; ● be required to perform additional clinical studies to support approval or be subject to additional post-marketing testing requirements; ● have regulatory authorities withdraw their approval of a product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy; ● be sued; or ● experience damage to our reputation. Additionally, our product candidates could potentially cause other adverse events that have not yet been predicted. The inclusion of ill patients in our clinical studies may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using. As described above, any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products. Obtaining and maintaining regulatory approval of our **products vaccine candidates** in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our **vaccine candidates** in other jurisdictions. Obtaining and maintaining regulatory approval of our **products vaccine candidates** in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, while a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a **vaccine candidate pharmaceutical product**, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the **product vaccine candidate** in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a **product vaccine candidate** must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval. We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the United States have requirements for approval of **vaccine candidates pharmaceutical or diagnostic products** with which we must comply prior to marketing in those jurisdictions. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties, and costs for us and could delay or prevent the

introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and / or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our vaccine candidates will be harmed. Modifications to our products- **product, ENTADFL**, may require new **BLA FDA** approvals. Once a particular product receives FDA approval, expanded uses or uses in new indications **of our products** may require additional human clinical trials and new regulatory approvals, including additional IND and **BLA submissions / or NDA**, and premarket approvals before we can begin clinical development, and / or prior to marketing and sales. If the FDA requires new approvals for a particular use or indication, we may be required to conduct additional clinical studies, which would require additional expenditures and harm our operating results. If the products are already being used for these new indications, we may also be subject to significant enforcement actions. Conducting clinical trials and obtaining approvals can be a time-consuming process, and delays in obtaining required future approvals could adversely affect our ability to introduce new or enhanced products in a timely manner, which in turn would harm our future growth. **Additional delays to the completion of clinical studies may result from modifications being made to the protocol during the clinical trial, if such modifications are warranted and / or required by the occurrences in the given trial. Each modification to the protocol during a clinical trial has to be submitted to the FDA. This could result in the delay or halt of a clinical trial while the modification is evaluated. In addition, depending on the quantity and nature of the changes made, the FDA could take the position that the data generated by the clinical trial are not poolable because the same protocol was not used throughout the trial. This might require the enrollment of additional subjects, which could result in the extension of the clinical trial and the FDA delaying approval of a product. Any such delay could have a material adverse effect on our business and results of operations. There can be no assurance that the data generated from our clinical trials using modified protocols will be acceptable to the FDA or other regulatory authorities. There can be no assurance that the data generated using modified protocols will be acceptable to the FDA or other regulatory authorities or that if future modifications during the trial are necessary, that any such modifications will be acceptable to the FDA or other regulatory authorities. If the FDA or other regulatory authorities believe that prior approval is required for a particular modification, they can delay or halt a clinical trial while they evaluate additional information regarding the change. Serious injury or death resulting from a failure of our product candidates during current or future clinical trials could also result in the FDA or other regulatory authority delaying our clinical trials or denying or delaying approval of a product. Even though an adverse event may not be the result of the failure of our product candidate, the FDA or other regulatory authority could delay or halt a clinical trial for an indefinite period of time while an adverse event is reviewed, and likely would do so in the event of multiple such events. Any delay or termination of our current or future clinical trials as a result of the risks summarized above, including delays in obtaining or maintaining required approvals from the FDA or other regulatory authorities, delays in patient enrollment, the failure of patients to continue to participate in a clinical trial, and delays or termination of clinical trials as a result of protocol modifications or adverse events during the trials, may cause an increase in costs and delays in the filing of any product submissions with the FDA or other regulatory authorities, delay the approval and commercialization of our products or result in the failure of the clinical trial, which could adversely affect our business, operating results and prospects. We will depend on enrollment and retention of patients in our clinical trials for our product candidates. If we experience delays or difficulties enrolling or retaining patients in our clinical trials, our research and development efforts and business, financial condition, and results of operations could be materially adversely affected. Successful and timely completion of clinical trials will require that we enroll and retain a sufficient number of patient candidates. Any clinical trials we conduct may be subject to delays for a variety of reasons, including as a result of patient enrollment taking longer than anticipated, patient withdrawal, or adverse events. These types of developments could cause us to delay the trial or halt further development. Our clinical trials will compete with other clinical trials that are in the same therapeutic areas as our product candidates, and this competition reduces the number and types of patients available to us, as some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Moreover, enrolling patients in clinical trials for diseases in which there is an approved standard of care is challenging, as patients will first receive the applicable standard of care. Many patients who respond positively to the standard of care do not enroll in clinical trials. This may limit the number of eligible patients able to enroll in our clinical trials who have the potential to benefit from our product candidates and could extend development timelines or increase costs for these programs. Patients who fail to respond positively to the standard of care treatment will be eligible for clinical trials of unapproved drug candidates. However, these prior treatment regimens may render our therapies less effective in clinical trials. Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. Patient enrollment depends on many factors, including: ● the size and nature of the patient population; ● the severity of the disease, condition or infection under investigation; ● eligibility criteria for the trial; ● the proximity of patients to clinical sites; ● the design of the clinical protocol; ● the ability to obtain and maintain patient consents; ● perceived risks and benefits of the product candidate under evaluation; ● the ability to recruit clinical trial investigators with the appropriate competencies and experience; ● the risk that patients enrolled in clinical trials will drop out of the trials before the administration of our product candidates or trial completion; ● the availability of competing clinical trials; ● the availability of such patients during the COVID-19 pandemic; ● the availability of new drugs approved for the indication the clinical trial is investigating; and ● clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies. These factors may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process, and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, some of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Conducting successful clinical studies may require the enrollment of**



large numbers of patients, and suitable patients may be difficult to identify and recruit. Patient enrollment in clinical trials and completion of patient participation and follow-up depends on many factors, including the size of the patient population; the nature of the trial protocol; the attractiveness of, or the discomforts and risks associated with, the treatments received by enrolled subjects; the availability of appropriate clinical trial investigators; support staff; and the proximity of patients to clinical sites and ability to comply with the eligibility and exclusion criteria for participation in the clinical trial and patient compliance. For example, patients may be discouraged from enrolling in our clinical trials if the trial protocol requires them to undergo extensive post-treatment procedures or follow-up to assess the safety and effectiveness of our products or if they determine that the treatments received under the trial protocols are not attractive or involve unacceptable risks or discomforts. Patients may also not participate in our clinical trials if they choose to participate in contemporaneous clinical trials of competitive products. The results of our future clinical trials may not support our product candidates' claims or may result in the discovery of unexpected adverse side effects. Even if our clinical trials are completed as planned, we cannot be certain that their results will support our product candidates claims or that the FDA or foreign authorities will agree with our conclusions regarding them. Success in pre-clinical studies and early clinical trials does not ensure that later clinical trials will be successful, and we cannot be sure that the later trials will replicate the results of prior trials and pre-clinical studies. The clinical trial process may fail to demonstrate that our product candidates are safe and effective for the proposed indicated uses. If the FDA concludes that the clinical trials for any product for which we might seek approval, has failed to demonstrate safety and effectiveness, we would not receive FDA approval to market that product in the United States for the indications sought. In addition, such an outcome could cause us to abandon a product candidate and might delay development of others. Any delay or termination of our clinical trials will delay the filing of any product submissions with the FDA and, ultimately, our ability to commercialize our product candidates and generate revenues. It is also possible that patients enrolled in clinical trials will experience adverse side effects that are not currently part of our product candidates' profiles. Adverse events involving ENTADFI our products may lead the FDA or other regulatory authorities to delay or deny approval for our products or result in product recalls that could harm our reputation, business and financial results. If Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, and other non-U.S. regulatory authorities could impose other specific obligations as a condition of approval to ensure that the benefits outweigh its risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, and restrictions on how or where the product can be distributed, dispensed or used. Furthermore, if we or others later identify undesirable side effects caused by ENTADFI any of our product candidates, several potentially significant negative consequences could result, including: • regulatory authorities may suspend or withdraw approvals of such a product candidate; • regulatory authorities may require additional warnings or limitations of use in product labeling; • we may be required to change the way a product candidate is distributed, dispensed, or administered or conduct additional clinical trials; • we could be sued and held liable for harm caused to patients; and • our reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of ENTADFI our product candidates and could significantly harm our business, prospects, financial condition and results of operations. Once a product receives FDA approval, the agency has the authority to require the recall of commercialized products in the event of adverse side effects, material deficiencies or defects in design or manufacture. The authority to require a recall must be based on an FDA finding that there is a reasonable probability that the product would cause serious injury or death. Manufacturers may, under their own initiative, recall a product if any material deficiency in a product is found. A government-mandated or voluntary recall by us or one of our distributors could occur as a result of adverse side effects, impurities or other product contamination, manufacturing errors, design or labeling defects or other deficiencies and issues. Recalls of ENTADFI any of our products would divert managerial and financial resources and have an adverse effect on our financial condition and results of operations. The FDA requires that certain classifications of recalls be reported to FDA within ten working days after the recall is initiated. Companies are required to maintain certain records of recalls, even if they are not reportable to the FDA. We may initiate voluntary recalls involving ENTADFI our products in the future. A future recall announcement could harm our reputation with customers and negatively affect our sales. In addition, the FDA and / or other regulatory agencies could take enforcement action for failing to report the recalls when they were conducted. If Even if we decide to resume obtain regulatory approval of our vaccine candidates, the products commercialization of ENTADFI, it may not gain market acceptance among regulators, advisory boards, physicians, patients, third-party payors, and others in the medical community. If we decide to resume Even if any of our vaccine candidates receive marketing approval, they the commercialization of ENTADFI, it may fail to receive recommendations for use by regulators or advisory boards that recommend vaccines, or gain market acceptance by physicians, patients, third-party payors, and others in the medical community. If ENTADFI does such vaccine candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of any product vaccine candidate, if approved for commercial sale, will depend on a number of factors, including but not limited to: • receiving CDC and ACIP governing or advisory recommendations for use, as well as recommendations of comparable foreign regulatory and advisory bodies; • prevalence and severity of the disease targets for which our product is vaccine candidates are approved; • physicians, hospitals, third-party payors, and patients considering our product vaccine candidates as safe and effective; • the potential and perceived advantages of our product vaccine candidates over existing vaccines therapies, including with respect to treatment of disease spectrum coverage or immunogenicity; • the prevalence and severity of any side effects; • product labeling or product insert requirements of the FDA or comparable foreign regulatory and advisory bodies; • limitations or warnings contained in the labeling approved by the FDA or comparable foreign regulatory and advisory bodies; • the timing of market introduction of our products vaccine candidates as well as competitive products; • the cost of treatment in relation to alternative treatments; • the availability of coverage and adequate reimbursement and pricing by third-party payors, including government authorities; • the willingness of

patients to pay out-of-pocket in the absence of coverage and adequate reimbursement by third-party payors, including government authorities; • relative convenience and ease of administration, including as compared to competitive vaccines products and alternative treatments; and • the effectiveness of our sales and marketing efforts. **In If our product fails to receive recommendations by governing or advisory bodies in either** the United States, the CDC and ACIP develop vaccine recommendations for **or** both children and adults, as do similar agencies around the world. To develop its recommendations, ACIP forms working groups that gather, analyze and prepare scientific information. The ACIP also considers many of the factors above, as well as myriad additional factors such as the value of vaccination for the target population regarding the outcomes, health economic data and implementation issues. ACIP recommendations are also made within categories, such as in an age group or a specified risk group. For example, the ACIP may determine that a preferred recommendation in a smaller child population may be more economical than recommending vaccinations for a larger adult population, which could adversely impact our market opportunity. New pediatric vaccines that receive an ACIP preferred recommendation are almost universally adopted, and adult vaccines that receive a preferred recommendation are widely adopted. For example, in 2014, the ACIP voted to recommend Prevnar 13 for routine use to help protect adults ages 65 years and older against pneumococcal disease, which caused Prevnar 13 to become the standard of care along with continued use of Pneumovax 23. ACIP can also modify its preferred recommendation. For instance, in June 2019, the ACIP voted to revise the pneumococcal vaccination guidelines and recommend Prevnar 13 for adults 65 and older based on the shared clinical decision making of the provider and patient, rather than a preferred use recommendation, which means the decision to vaccinate should be made at the individual level between health care providers and their patients. Pfizer recently noted that this revised recommendation is expected to have a negative effect on Prevnar 13 revenue for future periods. **If our vaccine candidates are approved but fail to receive CDC and ACIP recommendations, or recommendations of other countries comparable foreign regulatory and advisory bodies, or achieve market acceptance among physicians, healthcare providers, patients, third-party payors or others in the medical community, we will not be able to generate significant revenue. Even if our products-product achieve achieves** market acceptance, we may not be able to maintain that market acceptance over time if new products or technologies are introduced that are more favorably received than our products-product, are more cost effective or render our products-product obsolete. **Obtaining regulatory approval for clinical trials of our vaccine candidates in children and adolescents may require additional studies and/or longer duration of studies since the requirements for regulatory approval for the pediatric populations are more stringent. Pediatric vaccine candidates' development may require additional studies to determine safe dosing and long-term monitoring. These additional studies may require investment of significant additional resources beyond those required for regulatory approval of the vaccines in adults. Approval of our vaccine candidates may be delayed due to these additional requirements and this may have an adverse effect on the commercial prospects of our vaccine candidates, especially our pediatric vaccine candidate, BWV-201, as well as delay our ability to generate product revenue, possibly materially. In addition, as a result of COVID-19 (or other potential pandemics), there may be a smaller pool of children from which we can enroll for our clinical trials. We cannot guarantee that we will receive regulatory approval to commercialize our product candidates in the pediatric populations or the adult population. Even if we are able to commercialize our product candidates, such products, they** may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business. The regulations that govern marketing approvals, pricing, coverage, and reimbursement for new drugs and diagnostics vary widely from country to country. In the United States, new and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product-licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial marketing approval is granted. **As a result, we might obtain marketing approval for a vaccine in a particular country but then be subject to price regulations that delay its commercial launch, possibly for lengthy time periods, and negatively impact the revenue we are able to generate from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to commercialize and generate revenue from our product candidates, even if our product candidates obtain marketing approval. Our ability to commercialize our current and any future product products candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these this products-product and related treatments will be available from government health programs, private health insurers, integrated delivery networks and other third-party payors. Third-party payors decide which vaccines-drugs they will pay for and establish reimbursement levels. A significant trend in the U. S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of payment for particular vaccines-drugs. Increasingly, third-party payors are requiring that drug companies provide predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any product that we commercialize and, if reimbursement is available, the level of reimbursement may not be sufficient for commercial success. Coverage and reimbursement may impact the demand for, or the price of, any-our product candidate for which we obtain marketing approval. If coverage and reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any-our product candidate for which we obtain marketing approval. There may be significant delays in obtaining coverage and adequate reimbursement for newly approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for coverage and reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Coverage and reimbursement rates may vary according to the use of the drug and the medical circumstances under which it is used may be based on reimbursement levels already set for lower cost products or procedures or may be incorporated**

into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Commercial third- party payors often rely upon Medicare coverage policies and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government- funded programs and private payors for **our any approved products- product that we develop** could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize our **approved products- product** and our overall financial condition. **Any-Our product products candidate for which we obtain marketing approval** could be subject to marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products. **Any-Our product products candidate for which we obtain marketing approval**, along with the manufacturing processes and facilities, post- approval clinical data, labeling, advertising, and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of promotional materials and safety and other post- marketing information and reports, registration and listing requirements, current Good Manufacturing Practice (“ cGMP ”) requirements for product facilities, quality assurance and corresponding maintenance of records and documents and requirements regarding the distribution of samples to physicians and related recordkeeping. **Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval or contain requirements for costly post- marketing testing and surveillance to monitor the safety or efficacy of the medicine.** The FDA closely regulates the post- approval marketing and promotion of drugs to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. However, companies may share truthful and not misleading information that is otherwise consistent with the product’ s FDA approved labeling. The FDA imposes stringent restrictions on manufacturers’ communications regarding off- label use and if we do not comply with these restrictions, we may be subject to enforcement actions. In addition, later discovery of previously unknown problems with our products, manufacturers or manufacturing processes and facilities or failure to comply with regulatory requirements, may result in, among other things: • restrictions on **such our** products, manufacturers or manufacturing processes or facilities; • restrictions on the labeling, marketing, distribution, or use of a product; • requirements to conduct post- approval clinical trials, other studies, or other post- approval commitments; • warning or untitled letters; • withdrawal or recall of **the our** products from the market; • refusal to approve pending applications or supplements to approved applications that we submit; • fines, restitution or disgorgement of profits or revenue; • suspension or withdrawal of marketing **approvals- approval**; • refusal to permit the import or export of our products; • product seizure; and • **injunctions or the imposition of civil or criminal penalties.** Failure to obtain regulatory approvals in foreign jurisdictions will prevent us from marketing our products internationally. We intend to market future products in international markets. In order to market our future products in regions such as the **European Economic Area, or EEA, Asia Pacific, or APAC,** and many other foreign jurisdictions, we must obtain separate regulatory approvals. For example, in the EEA, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. Before granting the MA, the European Medicines Agency, or the competent authorities of the member states of the EEA make an assessment of the risk- benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. In Japan, the Pharmaceuticals and Medical Devices Agency, or the PMDA, of the Ministry of Health Labour and Welfare, or MHLW, must approve an application under the Pharmaceutical Affairs Act before a new drug product may be marketed in Japan. We have had limited interactions with foreign regulatory authorities. The approval procedures vary among countries and can involve additional clinical testing, and the time required to obtain approval may differ from that required to obtain FDA approval. Moreover, clinical studies conducted in one country may not be accepted by regulatory authorities in other countries. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one or more foreign regulatory authorities does not ensure approval by regulatory authorities in other foreign countries or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. We may not be able to file for regulatory approvals and even if we file, we may not receive necessary approvals to commercialize our products in any market. **Legislation, such as the Inflation Reduction Act, may impact our ability to market and commercialize ENTADFI and reduce our profitability from such asset. Legislation, either in the United States or in a foreign country, may impact our ability to market and commercialize ENTADFI and may reduce our profitability from such asset. For example, the Inflation Reduction Act (“ IRA ”) was signed into law in the United States in 2022 and intended to lower out- of- pocket costs associated with pharmaceutical drugs. Key impacts of the IRA include the following: • Medicare can now directly negotiate lower prescription drug prices with pharmaceutical manufacturers; • the cost of insulin for Medicare beneficiaries is now capped at \$ 35; • all recommended adult vaccines are free; and • drug companies are required to pay rebates if they raise prices of their products faster than the rate of inflation. Should we decide to raise the price of ENTADFI, and raise it higher than the rate of inflation, we may be exposed to rebates owed to Medicare. This may affect the profitability of our product and reduce revenues associated with it. Company shareholders may not realize a benefit from the ENTADFI or Proteomedix acquisitions commensurate with the ownership dilution they have experienced in connection with the transactions. If the Company is unable to realize the full strategic and financial benefits currently anticipated from the recent ENTADFI and Proteomedix acquisitions, our shareholders may experience a dilution of their ownership interests in our Company without receiving any commensurate benefit, or only receiving part of the commensurate benefit to the extent the Company is able to realize only part of the strategic and financial benefits currently anticipated from the transactions. We expect to rely on third- party manufacturers for ENTADFI and**



Proclarix. For the foreseeable future, we expect to and do rely on third- party manufacturers and other third parties to produce, package and store sufficient quantities of Proclarix and ENTADFI (if we decide to resume its commercialization) to meet demand. ENTADFI and Proclarix are complicated and expensive to manufacture. If our third- party manufacturers fail to deliver ENTADFI or Proclarix for commercial sale on a timely basis, with sufficient quality, and at commercially reasonable prices, we may be required to delay or suspend commercial sales and / or production of ENTADFI and Proclarix. While we may be able to identify replacement third- party manufacturers or develop our own manufacturing capabilities for ENTADFI and Proclarix, this process would likely cause a delay in the availability of ENTADFI and / or Proclarix and an increase in costs. In addition, third- party manufacturers may have a limited number of facilities in which ENTADFI and Proclarix can be produced, and any interruption of the operation of those facilities due to events such as equipment malfunction or failure or damage to the facility by natural disasters could result in the cancellation of shipments, loss of product in the manufacturing process or a shortfall in ENTADFI and Proclarix. In addition, regulatory requirements could pose barriers to the manufacture of ENTADFI and Proclarix. Third- party manufacturers are required to comply with the FDA' s cGMPs for ENTADFI and to register their activities and manufactured devices in databases and for Proclarix, manufacturers and developers (software) are required to comply with ISO 13485 and the host of the software with ISO 27001; these parties can be then subject to audits or inspections. As a result, the facilities used by any manufacturers of ENTADFI, must maintain a compliance status acceptable to the FDA. Holders of NDAs, or other forms of FDA approvals or clearances, or those distributing a regulated product under their own name, are responsible for manufacturing even though that manufacturing is conducted by a third- party CMO. Our third- party manufacturers will be required to produce ENTADFI under FDA cGMPs in order to meet acceptable standards. Our third- party manufacturers may not perform their obligations under their agreements with us or may discontinue their business before the time required by us to commercialize our products. In addition, our manufacturers will be subject to ongoing periodic unannounced inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements. For medical devices in United States, the contract manufacturer will be subject to FDA inspections (while in the EU, these would be subject to Notified Body audits (on demand)). Failure by any of our manufacturers to comply with applicable cGMPs, ISO 13485, ISO 27001 or applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, interruptions in supply, recalls, withdrawals, issuance of safety alerts and criminal prosecutions, any of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Finally, we also could experience manufacturing delays if our CMOs give greater priority to the supply of other products over ENTADFI or Proclarix or otherwise do not satisfactorily perform according to the terms of their agreements with us. If any supplier for ENTADFI or Proclarix experiences any significant difficulties in its manufacturing processes, does not comply with the terms of the agreement between us or does not devote sufficient time, energy and care to providing our manufacturing needs, we could experience significant interruptions in the supply of ENTADFI and / or Proclarix, which could impair our ability to supply ENTADFI and / or Proclarix at the levels required for commercialization and prevent or delay its successful development and commercialization. Disruptions to or significantly increased costs associated with transportation and other distribution channels for ENTADFI and / or Proclarix may adversely affect our margins and profitability. We expect to rely on the uninterrupted and efficient operation of third- party logistics companies to transport and deliver ENTADFI and Proclarix. These third- party logistics companies may experience disruptions to the transportation channels used to distribute our products, increased airport and shipping port congestion, a lack of transportation capacity, increased fuel expenses, and a shortage of manpower or capital or due to other business interruptions. Disruptions to the transportation channels experienced by our third- party logistics companies may result in increased costs, including the additional use of airfreight to meet demand. Disruptions to this business model or our relationship with the third party if, for example, performance fails to meet our expectations, could harm our business. We may fail or elect not to commercialize our products. We may not successfully commercialize our products. We or our collaboration partners in any potential commercial marketing efforts of our products may not be successful in achieving widespread patient or physician awareness or acceptance of this product. Also, we may be subject to pricing pressures from competitive products or from governmental or commercial payors or regulatory bodies that could make it difficult or impossible for us to commercialize our products. Any failure to commercialize our products could have a material adverse effect on our future revenue and our business. In light of (i) the time and resources needed to continue pursuing commercialization of ENTADFI, and (ii) the Company' s cash runway and indebtedness, the Company has determined to temporarily pause its commercialization of ENTADFI, as it considers strategic alternatives. The Company expects to appoint a new Chief Executive Officer in early April 2024, after which the new CEO and the Board will reassess its ENTADFI program in light of the foregoing and other relevant factors. If we fail to commercialize our products, our business, financial condition, results of operations and prospects may be materially adversely affected and our reputation in the industry and in the investment community would likely be damaged. We may not be able to gain and retain market acceptance for our products. Physicians and other authorized health care practitioners may not prescribe our products, which would prevent our products from generating revenue. Market acceptance of our products by healthcare providers, patients and payors, will depend on a number of factors, many of which are beyond our control, including the following: • the clinical indications for which our products are approved; • acceptance by healthcare providers and payors of our products as safe and effective treatment or test; • the cost in relation to alternative treatments or tests; • the relative convenience and ease of administration of our products for the conditions for which they are intended; • the availability and efficacy of competitive drugs or tests; • the effectiveness of our sales and

marketing efforts; • the extent to which our products are approved for inclusion on formularies of hospitals and managed care organizations; • the availability of coverage and adequate reimbursement by third parties, such as insurance companies and other health care payors, or by government health care programs, including Medicare and Medicaid; • limitations or warnings contained in a product's FDA or other applicable regulatory agency's approved labeling; and • prevalence and severity of adverse side effects. Even if the medical community accepts that our products are safe and efficacious for its approved indications, healthcare providers may not immediately be receptive to the use or may be slow to adopt such products as an accepted treatment or test for the conditions for which it is intended. Without head-to-head comparative data, we will also not be able to promote our products as being superior to competing products. If our products do not receive favorable achieve an adequate level of acceptance by healthcare providers and payors, we may not generate sufficient or any revenue from this product. In addition, our efforts to educate the medical community and third-party reimbursement, payors on the benefits of our product may require significant resources and may never be successful. In addition, even if our products achieve new restrictive legislation is adopted, market acceptance of our, we may not be able to maintain that market acceptance over time if: • new products may be limited and we may or technologies are introduced that are more favorably received than our products, are more cost effective or render our products obsolete; • unforeseen complications arise with respect to use of our products or • sufficient third-party insurance coverage or reimbursement does not remain available generate significant revenues. Our ability Proclarix is subject to commercialize our competition from other prostate cancer diagnostics and larger, well-established companies with substantially greater resources than us. The molecular diagnostics field is intensely competitive and characterized by rapid technological changes, frequent new products- product will depend introductions, changing customer preferences, emerging competition, evolving industry standards, reimbursement uncertainty and price competition. Moreover, recent consolidation in part on the extent industry permits larger clinical laboratory service providers to increase cost efficiencies and service levels, resulting in more intense competition. The market for assessing men at risk for prostate cancer is large, with many competitors some of which possess substantially greater financial appropriate reimbursement levels for the cost of our proposed formulations and products and related treatments are obtained by governmental authorities, selling private health insurers and other organizations, logistical and laboratory resources such as Health Maintenance Organizations, or HMOs. Reimbursement from more experience in dealing with third-party payors, parties depends greatly on our ability to present data which demonstrate positive outcomes and reduced utilization of other products or services greater market penetration, purchasing power and marketing budgets, as well as cost data more experience in providing diagnostic services. Some companies and institutions are developing liquid biopsy (blood and urine)- based tests and diagnostic tests based on the detection of proteins, mRNA, nucleic acids, or the presence of fragments of mutated genes that are associated with prostate cancer. These competitors could have technological, financial, reputational, and market access advantages over us. ENTADFI is subject to competition from other BPH drugs and larger, well-established companies with substantially greater resources than us. We are engaged in the marketing of a product in industries, including the pharmaceutical industry, that are highly competitive. The pharmaceutical industry is also characterized by extensive research and rapid technological progress. Potential competitors with respect to ENTADFI in North America, Europe and elsewhere include major pharmaceutical companies, specialty pharmaceutical companies and biotechnology firms, universities and other research institutions and government agencies. Many of our competitors have substantially greater research and development and regulatory capabilities and experience, and substantially greater management, manufacturing, distribution, marketing, and financial resources, than we have. We may be unable to compete successfully against current and future competitors, and competitive pressures could have a negative effect on our net revenues and profit margins. Zydus Life Sciences recently received FDA approval for a combined finasteride- tadalafil (5 mg / 5 mg) capsule, pursuant to the FDA's Competitive Generic Therapy Program, which show was designed to enhance patient access to affordable medications by encouraging the development and commercialization of generic drugs in clinical areas with limited generic options for patients. Pursuant to the program, Zydus has a 180 day period to be the sole supplier of the generic version of the drug in the market and during this period, other generic manufacturers cannot enter the market with their versions of the same drug, provided that treatment costs using Zydus commences marketing the drug by 75 days from approval. As a result, the there new product are equal to or less than what is currently covered a risk that the Company will face additional challenges in resuming commercializing ENTADFI, if it chooses to do so. Other parties have developed and marketed drugs for BPH that have been accepted by the healthcare provider, patient, and payor communities. Many of these other products have also reached the point where they are now generic drugs, which means that they are sold at a very low price, a price which ENTADFI may not be able to meet which could limit the reach of ENTADFI into the healthcare provider, patient and payor communities, including government payors. We may not be able to successfully implement our strategy to grow sales of ENTADFI in the U. S. market and Proclarix in the European markets or, if authorized, grow sales of either in any other market. We may not be able to expand sales of ENTADFI or Proclarix through partnering with telemedicine or other partners or with commercial diagnostic providers or through our own commercialization efforts. We may not be able to command a price with private and government payors for ENTADFI or Proclarix that would justify our devotion of significant resources to attempting to grow sales of ENTADFI or Proclarix. We may not be able to compete efficiently or effectively in a mature market, which is heavily generic, or the prostate cancer diagnostics market, which is highly competitive. Failure to grow sales of ENTADFI or Proclarix would have a negative effect on our revenue and future plans. The commercial success of our in- development and future diagnostic tests and services and our revenue growth depend upon attaining significant market acceptance among payers, providers, clinics, patients, and biopharmaceutical companies. Our commercial success depends, in part, on the acceptance of our diagnostic tests and

services as being safe and relatively simple for medical personnel to learn and use, clinically flexible, operationally versatile and, with respect to providers and payers, cost effective. We cannot predict how quickly, if at all, payers, providers, clinics, and patients will accept future diagnostic tests and services or, if accepted, how frequently they will be used. These constituents must believe that our diagnostic tests offer benefits over other available alternatives. The degree of market acceptance of our current and future diagnostic tests and services depends on a number of factors, including:

- whether there is adequate utilization of our tests by clinicians, laboratories and other target groups based on the potential and perceived advantages of our diagnostic tests over those of our competitors;
- the convenience and ease of use of our diagnostic tests relative to those currently on the market;
- the effectiveness of our sales and marketing efforts;
- the ability of our distribution partners to meet sales forecasts;
- our ability to provide incremental data that show the clinical benefits and cost effectiveness, and operational benefits, of our diagnostic tests;
- the coverage and reimbursement acceptance of our products and services;
- pricing pressure, including from group purchasing organizations (“GPOs”), seeking to obtain discounts on our diagnostic tests based on the collective bargaining power of the GPO members;
- negative publicity regarding our or our competitors’ diagnostic tests resulting from defects or errors; and
- the diagnostic sensitivity and diagnostic specificity of our tests relative to those of our competitors.

Additionally, even if our diagnostic tests achieve widespread market acceptance, they may not maintain that market acceptance over time if competing diagnostic tests or technologies, which are more cost effective or are received more favorably, are introduced. Failure to achieve or maintain market acceptance and / or market share would limit our ability to generate revenue and would have a material adverse effect on our business, financial condition, and results of operations. If we fail to increase our sales and marketing capabilities ~~our- or products~~ develop broad awareness of our diagnostic tests in a cost- effective manner, we may not be able to generate revenue growth. We plan to dedicate significant resources to the expansion of our distribution network and to supporting their marketing efforts. It will negatively affect our business, financial condition, and results of operations if our marketing efforts and expenditures do not receive favorable generate a corresponding increase in revenue. In addition, we believe that developing and maintaining broad awareness of our diagnostic tests in a cost- effective manner is critical to achieving broad acceptance of our diagnostic tests. Promotional activities may not generate patient or physician awareness or increase revenue, and even if they do, any increase in revenue may not offset the costs and expenses we incur in building our brand. If we fail to successfully promote, maintain and protect our brand, we may fail to attract or retain the physician acceptance necessary to realize a sufficient return on our brand building efforts, or to achieve the level of brand awareness that is critical for broad use of our diagnostic tests, which in turn could have a material adverse effect on our business, financial condition and results of operations. If we cannot maintain our current relationships, or enter into new relationships, with CROs, universities, clinics, laboratories or tissue sample banks, our revenue prospects could be reduced. We engage contract research organizations, universities, clinics, and tissue banks to enroll or access patients primarily to support clinical studies. The ability of our contractors to enroll patients in clinical studies may also fluctuate in the future, which could have a material adverse effect on our product development timelines, financial condition and results of operations. In addition, the termination of these relationships could result in a temporary or prolonged delay in commercial launches resulting in a loss of revenue. We engage in conversations with diagnostic laboratories regarding potential commercial opportunities on an ongoing basis. There is no assurance that any of these conversations will result in a commercial agreement, or if an agreement is reached, that the resulting relationship will be successful or that clinical or research studies conducted as part of the engagement will produce successful outcomes. Speculation in the industry about our existing or potential relationships with diagnostic laboratories and biopharmaceutical companies can also be a catalyst for adverse speculation about us, our tests and our technology, which can adversely affect our reputation and our business. We need to ensure strong product performance and quality to maintain and grow our business. We will need to maintain and continuously improve the performance of our diagnostic tests to maintain CE marking or other applicable market approvals and compliance with QMS (ISO 13485). Poor product performance and quality could lead to customer dissatisfaction, adversely affect our reputation and revenues, and increase our service and distribution costs and working capital requirements. Our diagnostic tests may contain errors or defects, and while we have made efforts to control them extensively, we cannot assure that our current diagnostic tests, or those developed in the future, will not have performance problems. Any performance issues with our diagnostic tests now or in the future will increase our costs and accordingly adversely affect our business, financial condition, and results of operations. The sizes of the markets for our diagnostic tests and services and any future diagnostic tests and services may be smaller than we estimate and may decline. Our estimates of the annual total addressable market for our diagnostic tests and services are based on a number of internal and ~~third- party reimbursement~~ estimates and assumptions, including, without limitation, the assumed prices at which we can sell our diagnostic tests and services in the market. While we believe our assumptions and the data underlying our estimates are reasonable, these assumptions and estimates may not be correct and the conditions supporting our assumptions or estimates may change at any time, thereby reducing the predictive accuracy of these underlying factors. As a result, our estimates of the annual total addressable market for our diagnostic tests and services in different market segments may prove to be incorrect. If the actual number of patients who would benefit from our diagnostic tests, the price at which we can sell them or the annual total addressable market for them is smaller than we have estimated, it may impair our sales growth and negatively affect our business, financial condition and results of operations. We have a significant customer concentration, with a limited number of customers accounting for a large portion or all of our revenues. We derive a large portion or all of our revenues from a few major customers. For the year ended December 31, 2023, we generated 100 % of our revenue from one customer, in the context of a partnership with Immunovia AB (Sweden). In 2022, Immunovia AB partnered with Proteomedix to leverage

Proteomedix's research and development capabilities and to advance their research and development efforts. There are unwilling or unable to pay inherent risks whenever a large percentage of the total revenue is concentrated with a few customers. It is not possible for us to predict the future level of demand for our products that, out-of-pocket, it could limit our revenues and harm our business. The continuing efforts of government and insurance companies, health maintenance organizations and other payers of healthcare costs to contain or reduce costs of health care may affect our future revenues and profitability, and the future revenues and profitability of our potential customers, suppliers and collaborative partners and the availability of capital. For example, in certain foreign markets, pricing or profitability of prescription pharmaceuticals is subject to government control. In the United States, recent federal and state government initiatives have been directed at lowering the total cost of health care. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Federal and state legislatures will likely continue to focus on health care reform, controlling the cost of prescription pharmaceuticals and on the reform of the Medicare and Medicaid systems. While we cannot predict whether any such legislative or regulatory proposals will be adopted, generated by these announcement customers or the future demand or for adoption our products by these customers. If any of these customers' demands decline or delayed demands due to market, economic or competitive conditions, we could be pressured to reduce our prices, which could have an adverse effect on our financial position and could negatively affect our revenues and results of operations. If any of our largest customers terminate the purchase of our products, such proposals termination could would materially harm negatively affect our business revenues, results of operations and financial condition and. Our results of operations -Risks Related will be materially harmed if we are unable to our Business accurately forecast customer demand for, and Industry We-utilization of, our diagnostic tests and manage our inventory. To ensure adequate inventory supply, we must forecast inventory needs and manufacture our diagnostic tests based on our estimates of future demand for our diagnostic tests. Our ability to accurately forecast demand for them could be negatively affected by may many factors, including our failure to accurately manage our expansion strategy, product introductions by competitors, an increase or decrease in customer demand for our diagnostic tests or for those of our competitors, our failure to accurately forecast customer acceptance of new diagnostic tests, unanticipated changes in general market conditions or regulatory matters and weakening of economic conditions or consumer confidence in future economic conditions. Inventory levels in excess of customer demand may result in inventory write-downs or write-offs, which would cause our gross margin to be adversely affected by the ongoing coronavirus pandemic. The outbreak of the novel coronavirus COVID-19 ("COVID-19") has evolved into a global pandemic. The coronavirus has spread to many regions of the world. The extent to which the coronavirus impacts our business and operating results will depend on future developments that are highly uncertain and cannot be accurately predicted, including new information that may emerge concerning the coronavirus and the actions to contain the coronavirus or treat its impact, among others. As a result of the continuing spread of COVID-19, our business operations could be delayed impair the strength of or our interrupted. Currently, we operate virtually, i. e., our program activities are and brand. Conversely will continue to be carried out, on if we underestimate customer demand for our behalf diagnostic tests, our supply chain by competent contract research organizations (CROs) with expertise in pre-clinical, clinical manufacturing partners and / or internal chemistry and manufacturing team areas. Due to COVID-19, our planned project timelines may be delayed due to reduced availability of human resources or critical supplies needed to carry out such plans. Due to shelter-in-place / stay-at-home orders and other government restrictions, our employees conducting research and development or manufacturing activities at external vendor locations across the globe may not be able to access their laboratory deliver components and diagnostic tests to meet or our requirements, and this could result in damage to our reputation, sales growth and customer relationships. In addition, if we experience a significant increase in demand, additional supplies of raw materials or additional manufacturing space capacity may not be available when required on terms that are acceptable to us, or at all, or suppliers may not be able to allocate sufficient capacity in order to meet our increased requirements, which may will adversely affect our business, financial condition and results of operations. The timing of our new product offerings is uncertain. We have multiple products in various phases of development, and we intend to devote considerable future resources to research and product development, our core business strategy. There can be no assurance that our development activities will always produce tests with the sensitivity and specificity necessary to be clinically and commercially competitive, or that any test will result in a commercially successful product. In addition, before we can develop diagnostic tests for new cancers our- or core activities being other diseases and commercialize any new products, we will need to: • conduct substantial research and development; • conduct analytical and clinical performance testing (verification and validation); and • expend significantly-- significant funds. Our product development process involves a high degree of risk and may take several years in some instances. Our product development efforts may fail for many reasons, including, but not limited or curtailed, possibly to: • failure of the product at the research for- or an extended period of time. Moreover development phase; • difficulty in accessing samples, especially samples with known clinical results; our- or • lack of clinical performance data to support the safety and effectiveness of the product. Few research and development projects result in commercial products, and success in early clinical trials often is not replicated in later studies. At any point, we may abandon development of a product candidate, or we may be required to expend considerable resources repeating clinical trials, which would adversely impact the timing for generating potential revenues from those product candidates. In addition, as we develop products, we will have to make significant investments in product development. If a clinical validation study fails to demonstrate the prospectively defined endpoints of the study, we might choose to abandon the development of the product or product feature that was the subject of the clinical trial, which could harm its business. In



addition, our competitors may develop and commercialize competing products faster than we are able to do so. Our access to samples may hinder our ability to research, develop, and commercialize future products. Our planned and future products are focused primarily on exploitation of blood plasma or serum as a medium for both biomarker identification and validation and ultimately for our commercial testing applications. Our clinical development relies on our ability to secure access to high quality, well-characterized samples, as well as information pertaining to the samples associated clinical outcomes. Our competitors have demonstrated their ability to obtain these samples and often compete with us for access to such samples. Additionally, the process of negotiating access to samples is lengthy since it typically involves numerous parties and approval levels to resolve complex issues such as usage rights, institutional review board (ethical) approval, privacy rights, publication rights, intellectual property ownership and research parameters. If we are not able to negotiate access to samples with hospitals, clinical partners, or other companies on a timely basis, or at all, or if competitors secure access to these samples before us, then our ability to research, develop, and commercialize future products will be limited or delayed. Adherence to complex test protocols is required. We validate our tests in our lab in Switzerland using blood samples obtained from a variety of sources. Tests results can be affected by a number of variables including how the blood is extracted, how the blood is handled, the type of test tube used, the number and speed of centrifuge spins, the temperature the blood is exposed to during processing, the concentration of the reagents, and the timing of reagent use. All of these COVID-19 pandemic. Site initiation, participant recruitment and other variables in the process are set forth in and an enrollment, participant dosing, availability and assay protocol that we provide to our distributor of clinical trial lab partners along with training in proper compliance. If, due to human or equipment failure, there is material deviation from the protocols, study monitoring and data analysis may the accuracy of our tests can be negatively impacted paused or delayed due to changes in hospital or university policies, federal, state or local regulations, prioritization of hospital resources toward pandemic efforts, or other reasons related to the COVID-19 pandemic. If the coronavirus continues to spread, some participants and clinical investigators may not be able to execute clinical trial protocols per the expected timelines. The new mutations of the virus may also make it harder for us to predict the exact impact (if any) on the progression of COVID-19 on our development programs. For example, quarantines or other travel limitations (whether voluntary or required) may impede participant movement, affect sponsor access to study sites, or interrupt healthcare services, and we may be unable to conduct our clinical trials. Further, if the spread of the COVID-19 pandemic continues and our operations are adversely impacted, we risk a delay, default and / or nonperformance under existing agreements which may increase our costs. These cost increases may not be fully recoverable or adequately covered by insurance. Infections and deaths related to the pandemic may disrupt the United States' healthcare and healthcare regulatory systems. Such disruptions could divert healthcare resources away from, or materially delay FDA review or review by other regulatory agencies and / or approval with respect to, our clinical trials. It is unknown how long these disruptions could continue, were they to occur. Any elongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development and study of our product candidates. The spread of the coronavirus, which has caused a broad impact globally, including restrictions on travel and quarantine policies put into place by businesses and governments, may have a material economic effect on our business. While the potential economic impact brought by and the duration of the pandemic may be difficult to assess or predict, it has already caused, and is likely to result in further, significant disruption of global financial markets, which may reduce our ability to access capital either at all or on favorable terms. In addition, a recession, depression or other sustained adverse market event resulting from the spread of the coronavirus could materially and adversely affect our business and the value of our common stock. The ultimate impact of the current pandemic, or any other health epidemic, is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, our research programs, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the situation closely. We may be adversely affected by the ongoing monkeypox outbreak. The monkeypox outbreak of 2022 has spread to many regions of the world, including the United States. The extent to which the monkeypox outbreak impacts our business and operating results will depend on future developments that occurs are highly uncertain and cannot be accurately predicted, including new information that may emerge, if the reputation of outbreak is ultimately upgraded to a pandemic, and the actions to contain monkeypox or our products treat its impact, among others. As of August 2022, it is still classified as an and outbreak by the World Health Organization, but this may be upgraded to a pandemic in the event of future spread of the disease. As a result of the continuing spread of monkeypox infections, our revenue business operations could be negatively delayed or interrupted. Currently, we operate virtually, i. e., our program activities are and will continue to be carried out on our behalf, by competent contract research organizations (CROs) with expertise in pre-clinical, clinical and / or chemistry and manufacturing areas. Due to monkeypox, our planned project timelines may be delayed due to reduced availability of human resources or critical supplies needed to carry out such plans. In the event of any future shelter-in-place / stay-at-home orders and other government restrictions, our employees conducting research and development or manufacturing activities at external vendor locations across the globe may not be able to access their laboratory or manufacturing space which may result in our core activities being significantly limited or curtailed, possibly for an extended period of time. Moreover, our clinical trials may be affected by the monkeypox outbreak. Site initiation, participant recruitment and enrollment, participant dosing, availability and distribution of clinical trial materials, study monitoring and data analysis may be paused or delayed due to changes in hospital or university policies, federal, state or local regulations, prioritization of hospital resources toward pandemic efforts, or other reasons related to the outbreak. If monkeypox continues to spread and regulations are developed and enacted, some participants and clinical investigators may not be able to execute clinical trial protocols per the expected timelines. Further, if the spread of the monkeypox outbreak continues and our operations are adversely impacted, we risk a delay, default and / or nonperformance under existing agreements which may increase our costs. Risks These cost increases may not be fully recoverable or adequately

covered by insurance. Infections and deaths related **Related** to this outbreak may disrupt the United States' healthcare and healthcare regulatory systems. Such disruptions could divert healthcare resources away from, or **our** materially delay FDA review or review by other regulatory agencies and / or approval with respect to, our clinical trials. It is unknown how long these disruptions could continue, were they to occur. Any elongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development and study of our product candidates. The spread of monkeypox, which may cause a broad impact globally, including restrictions on travel and quarantine policies put into place by businesses and governments, may have a material economic effect on our business **Business** in the event of continued spread of the virus. While the potential economic impact brought by and **Industry** the duration may be difficult to assess or predict, it may result in disruption of global financial markets, which may reduce our ability to access capital either at all or on favorable terms. In addition, a recession, depression or other sustained adverse market event resulting from the spread of monkeypox could materially and adversely affect our business and the value of our common stock. The ultimate impact of the current outbreak, or any other health epidemic, is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, our research programs, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the situation **closely**. Our reliance on third parties heightens the risks faced by our business. We rely on suppliers, vendors, **subcontractors**, and partners for certain key aspects of our business, including support for information technology systems and certain human resource functions. We do not control these partners, but we depend on them in ways that may be significant to us. **If However, if** these parties fail to meet **our expectations or fulfill** their **defined** obligations to us, we may fail to receive the expected benefits. In addition, if any of these third parties fails to comply with applicable laws and regulations in the course of its performance of services for us, there is a risk that we may be held responsible for such violations as well. This risk is particularly serious in emerging markets, where corruption is often prevalent and where many of the third parties on which we rely do not have internal compliance resources comparable to our own. Any such failures by third parties, in emerging markets or elsewhere, could adversely affect our business, reputation, financial condition or results of operations. We **rely on, and intend to continue to rely on third parties to conduct our pre-clinical testing, research and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.** We have been relying on third parties for our preclinical studies, and we expect to continue to rely on third parties, such as CROs, contract manufacturers of clinical supplies, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials and to conduct some aspects of our research and pre-clinical testing. These third parties may terminate their engagements with us at any time. If these third parties do not successfully carry out their duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If we are required to enter into alternative arrangements, it could delay our product development activities. Our reliance on third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA and other international regulatory authorities require us to comply with GCP standards for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov), within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. Upon commercialization of our products, we may be dependent on third parties to market, distribute and sell our products. Our ability to receive revenues **is** may be dependent upon the sales and marketing efforts of any future co-marketing partners and third-party distributors. **At this time, we have not entered into an agreement with any commercialization partner and only plan to do so prior to commercialization.** If we fail to reach an agreement with any commercialization partner, or upon reaching such an agreement that partner fails to sell a large volume of our products, it may have a negative impact on our business, financial condition, and results of operations. We have no experience manufacturing **our product products candidates** on a clinical or commercial scale and **are will be** dependent on third parties for the manufacture of our **product products candidates**. If we experience problems with any of these third parties, they could delay **clinical development or marketing approval of our product candidates or our ability to sell our any approved products.** We do not have any manufacturing facilities. We **will expect to rely on third-party manufacturers for the manufacture of our product candidates for clinical trials and for commercial supply of any product candidate for which Proclarix and ENTADFI (if we obtain marketing approval resume the commercialization of ENTADFI).** We may be unable to establish agreements with third-party manufacturers for clinical or commercial supply on terms favorable to us, or at all. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including: ● reliance on the third party for regulatory compliance and **through quality assurance-management system;** ● the possible breach of the manufacturing agreement by the third party, including the inability to supply sufficient quantities or to meet quality standards or timelines; and ● the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us. Third-party manufacturers may not be able to comply with U. S. cGMPs, **QSR** or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with cGMPs or other applicable regulations, even if such failures do not relate specifically to our **product candidates or approved products**, could result in sanctions being imposed on us or the manufacturers, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or **product** recalls of **product candidates**, operating restrictions and

criminal prosecutions, any of which could adversely affect supplies of our ~~product~~ **products candidates** and harm our business and results of operations. ~~Any~~ **Our product products** that we develop may compete with other **products and / or** product candidates and products for access to these manufacturing facilities. There are a limited number of manufacturers that operate under cGMPs and that might be capable of manufacturing for us. Any performance failure on the part of our manufacturers, including a failure that may not relate specifically to our ~~product candidates or approved~~ products, could ~~delay clinical development or marketing approval or~~ adversely impact our ability to generate commercial sales. If our contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Our anticipated future dependence upon others for the manufacture of our ~~current and future product candidates or~~ products may adversely affect our future profit margins and our ability to commercialize ~~any~~ **our product products** candidates that receive marketing approval on a timely and competitive basis. ~~Furthermore, we expect to rely on third parties to release, label, store and distribute drug supplies for our clinical trials. Any performance failure on the part of these third parties, including a failure that may not relate specifically to our product candidates, could delay or otherwise adversely impact clinical development or marketing approval of our product candidates or commercialization of our drug, producing losses and depriving us of potential revenue.~~ Moreover, our manufacturers and suppliers may experience difficulties related to their overall businesses and financial stability, which could result in delays or interruptions of supply of our ~~product~~ **products candidates**. Manufacturing risks may adversely affect our ability to manufacture our product and could reduce our gross margin and profitability. Our business strategy depends on our ability to manufacture our ~~product~~ **products candidates** in sufficient quantities and on a timely basis so as ~~to meet our obligations with respect to our clinical trials and upon marketing approval,~~ to meet consumer demand, while adhering to product quality standards, complying with regulatory requirements and managing manufacturing costs. We are subject to numerous risks relating to our manufacturing capabilities, including: ● quality or reliability defects in product components that we source from third- party suppliers, including manufacturing compliance with federal and state regulations; ● our inability to secure product components in a timely manner, in sufficient quantities or on commercially reasonable terms; ● our failure to increase production of products to meet demand; ● our inability to modify production lines to enable us to efficiently ~~produce future products or~~ implement changes ~~in current products~~ in response to regulatory requirements; and ● Potential damage to or destruction of our manufacturing equipment or manufacturing facility. If demand for our ~~product~~ **products candidates** increases in the future, we will have to invest additional resources to purchase components, hire and train employees, and enhance our manufacturing processes. If we fail to increase our production capacity efficiently, our sales may not increase in line with our forecasts and our operating margins could fluctuate or decline. **Manufacturing** In addition, although we expect some of our ~~product~~ **products candidates** in development to share product features and components, manufacturing of some of our product candidates may require the modification of our production lines, the hiring of specialized employees, the identification of new suppliers for specific components, or the development of new manufacturing technologies. It may not be possible for us to manufacture these ~~product~~ **products candidates** at a cost or in quantities sufficient to make these ~~product~~ **products candidates** commercially viable. Any of these factors may affect our ability to manufacture our product and could reduce our gross margin and profitability. We maintain single supply relationships for certain key components, and our business and operating results could be harmed if supply is restricted or ends or the price of raw materials used in its manufacturing process increases. We are dependent on sole suppliers or a limited number of suppliers for certain components that are integral to its finished products. If these or other suppliers encounter financial, operating or other difficulties or if our relationship with them changes, we may be unable to quickly establish or qualify replacement sources of supply and could face production interruptions, delays and inefficiencies. In addition, technology changes by our vendors could disrupt access to **the** required manufacturing capacity or require expensive, time ~~consuming~~ development efforts to adapt and integrate new equipment or processes. Our growth may exceed the capacity of one or more of these suppliers to produce the needed equipment and materials in sufficient quantities to support our growth. Any one of these factors could harm our business and growth prospects. We may not be able to manage our manufacturing and supply chain effectively, which would harm our results of operations. We must accurately forecast ~~our clinical trial obligations, and, in the future,~~ market demand ~~for~~ our ~~product~~ **products candidates** in order to have adequate product inventory available to fulfil our timeline and customer orders timely. Our forecasts will be based on multiple assumptions that may cause our estimates to be inaccurate, and thus affect our ability to ensure adequate manufacturing capability to satisfy ~~product candidate needs or~~ market demand. Any material delay in our ability to obtain timely product inventories from our manufacturing facility and our ingredient suppliers could prevent us from satisfying increased consumer demand for our products, resulting in material harm to our ~~clinical trials,~~ brand and business. In addition, we will need to continuously monitor our inventory and product mix against forecasted demand to avoid having inadequate product inventory or having too much product inventory on hand. If we are unable to manage our supply chain effectively, our operating costs may increase materially. We may in the future have conflicts with our current or future partners or third ~~party~~ providers that could delay or prevent the ~~development or~~ commercialization of our current ~~and future product~~ **products candidates**. We may in the future have conflicts with our current or future partners or third ~~party~~ providers, such as conflicts concerning ~~the interpretation of pre-clinical or clinical data,~~ the achievement of milestones, the interpretation of contractual obligations, payments for services, development obligations or the ownership of intellectual property developed during our collaboration. If any conflicts arise with any of our partners, such partner may act in a manner that is adverse to our best interests. Any such disagreement could result in one or more of the following, each of which could delay or prevent the ~~development or~~ commercialization of our current ~~and future product~~ **products candidates**, and in turn prevent us from generating revenues: ● unwillingness on the part of a partner to pay us milestone payments or royalties we believe are due to us under a collaboration; ● uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations; ● unwillingness by the partner to cooperate in the ~~development or~~ manufacture of the product, including providing us with product data or materials; ● unwillingness on the part of a partner to keep us informed regarding the progress of its ~~development and~~ commercialization



activities or to permit public disclosure of the results of those activities; • initiating of litigation or alternative dispute resolution options by either party to resolve the dispute; or • attempts by either party to terminate the agreement. Our product candidates may face competition sooner than anticipated from biosimilar products. Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, our product candidates may face competition from biosimilar products. In the United States, our product candidates are regulated by the FDA as biologic products and we intend to seek approval for these product candidates pursuant to the BLA pathway. The Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated pathway for the approval of biosimilar and interchangeable biologic products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as “interchangeable” based on its similarity to an existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. There is a risk that any exclusivity we may be afforded if any of our product candidates are approved as a biologic product under a BLA could be shortened due to congressional action, the results of recent litigation, or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic or biosimilar competition sooner than anticipated. Moreover, the extent to which a biosimilar product, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biologic products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. In addition, a competitor could decide to forego the biosimilar approval path and submit a full BLA after completing its own preclinical studies and clinical trials. In such cases, any exclusivity to which we may be eligible under the BPCIA would not prevent the competitor from marketing its product as soon as it is approved. In addition, critics of the 12-year exclusivity period in the biosimilar pathway law will likely continue to seek to shorten the data exclusivity period and/or to encourage the FDA to interpret narrowly the law’s provisions regarding which new products receive data exclusivity. In December 2019, the US agreed to remove from the United States-Mexico-Canada Agreement a requirement for at least 10 years of data exclusivity for biologic products. Also, the FDA is considering whether subsequent changes to a licensed biologic would be protected by the remainder of the reference product’s original 12-year exclusivity period (a concept known in the generic drug context as “umbrella exclusivity”). If the FDA were to decide that umbrella exclusivity does not apply to biological reference products or were to make other changes to the exclusivity period, this could expose us to biosimilar competition at an earlier time. There also have been, and may continue to be, legislative and regulatory efforts to promote competition through policies enabling easier generic and biosimilar approval and commercialization, including efforts to lower standards for demonstrating biosimilarity or interchangeability, limit patents that may be litigated and/or patent settlements and implement preferential reimbursement policies for biosimilars. If competitors are able to obtain marketing approval for biosimilars referencing our product candidates, if approved, such products may become subject to competition from such biosimilars, with the attendant competitive pressure and potential adverse consequences. Such competitive products may be able to immediately compete with us in each indication for which our product candidates may have received approval. Our primary competitors have significantly greater resources and experience than we do, which may make it difficult for us to successfully develop our vaccine candidates, or may result in others discovering, developing or commercializing products before or more successfully than us. The vaccine market is intensely competitive and is dominated by a small number of multinational, globally established pharmaceutical corporations with significant resources; Pfizer, Merck, GlaxoSmithKline and Sanofi together control approximately 75% of the global vaccine market. We may also face competition from many different sources, including pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions. For example, Sanofi and SK Chemicals have partnered to develop a PCV, and Affinivax and Astellas have partnered to develop an affinity-bound pneumococcal vaccine. Vaccine candidates that we successfully develop and commercialize may compete with existing vaccines and new vaccines that may become available in the future. Many of our competitors have substantially greater financial, lobbying, technical, human and other resources than we do and may be better equipped to develop, manufacture and market technologically superior vaccines, including the potential that our competitors may develop chemical processes or utilize novel technologies for developing vaccines that may be superior to those we employ. In addition, many of these competitors have significantly greater experience than we have in undertaking preclinical testing and clinical trials of new products and in obtaining regulatory approvals, including for many vaccine franchises. Accordingly, our competitors may succeed in obtaining FDA approval or a preferred recommendation for their products. For example, Prevnar 13 obtained FDA approval for the prevention of invasive pneumococcal disease, or IPD, in infants based on non-inferior IgG antibody responses relative to Prevnar, using the surrogate immune endpoints established by the prior Prevnar field efficacy study. Pfizer is currently implementing a similar approach to development of its 20-valent PCV vaccine candidate, and may have a more efficient path to regulatory approval given Pfizer’s and the FDA’s previous experience with Prevnar 13. Many of our competitors have established distribution channels for the commercialization of their vaccine products, whereas we have no such established channels or capabilities. In addition, many competitors have greater name recognition, more extensive collaborative relationships or the ability to leverage a broader vaccine portfolio. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize vaccines that are safer, more effective, more convenient, less expensive or with a more favorable label than any vaccine candidates that we may develop. As a result of these factors, our competitors may obtain regulatory approval of their products before we are able to, which may limit our ability to develop or commercialize our vaccine candidates. Our competitors may also develop vaccines that are safer, more effective, more widely accepted or less expensive than ours, and may also be more successful than we are in manufacturing and marketing their products. These advantages could render our vaccine candidates obsolete or non-competitive before we can recover the costs of such vaccine candidates’ development and commercialization.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and subject enrollment for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any our products that we may develop. We face an inherent risk of product liability exposure related to the testing-commercialization of our current product candidates or our future product candidates in human clinical trials and will face an even greater risk if we commercially sell any products that we may develop. Product liability claims may be brought against us by subjects enrolled in our clinical trials, patients, healthcare providers or others using, administering, or selling our product. **In addition, we face an inherent risk of product liability as a result of the marketing and sale of Proteomedix's diagnostic tests and services. For example, we may be sued if the diagnostic tests or services cause or are perceived to cause injury or are found to be otherwise unsuitable during manufacturing, marketing or sale. Any such product liability claim may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, or a breach of warranties. In addition, we may be subject to claims against us even if the apparent injury is due to the actions of others or the pre-existing health of the patient. For example, medical personnel, care partners and patients collect samples for our diagnostic tests. If these medical personnel, care partners or patients are not properly trained, are negligent or use our diagnostic tests incorrectly, the capabilities of such tests may be diminished, or the patient may suffer critical injury. We may also be subject to claims that are caused by the activities of our suppliers, such as those who provide us with components and sub-assemblies for our diagnostic tests.** If we cannot successfully defend ourselves against product liability claims that our product candidates or product caused injuries, we could may incur substantial liabilities or be required to limit or halt the marketing and sale of our diagnostic tests and services. **Even a successful defense would require significant financial and management resources.** Regardless of the merit merits or eventual outcome, liability claims may result in: • decreased demand for any product candidates or our products that we may develop; • termination of clinical trial sites or entire clinical trial programs; • injury to our reputation and significant negative media attention; • withdrawal of clinical trial participants; • significant costs to defend the related litigation; • substantial monetary awards to trial subjects or patients; • loss of revenue; • diversion of management and scientific resources from our business operations; and • the inability to commercialize any our products that we may develop. **Prior to engaging in future clinical trials; • the initiation of investigations by regulators; and • product recalls, we intend to obtain withdrawals or labeling, marketing, or promotional restrictions. We have** product liability insurance coverage at a level that we believe is customary for similarly situated companies and adequate to provide us with insurance coverage for foreseeable risks; **however**, we may be unable to obtain such coverage at a reasonable cost, if at all. If we are able to obtain product liability insurance, we may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise, and such insurance may not be adequate to cover all liabilities that we may incur. Furthermore, we intend to expand our insurance coverage for products to include the sale of commercial products if we obtain regulatory approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products that receive regulatory approval. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim, or series of claims brought against us, particularly if judgments exceed our insurance coverage, could decrease our cash, and adversely affect our business. We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources. In the future, we may enter into transactions to acquire other businesses, products or technologies. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may fail to strengthen our competitive position and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies, and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results. Security threats to our information technology infrastructure and / or our physical buildings could expose us to liability and damage our reputation and business. It is essential to our business strategy that our technology and network infrastructure and our physical buildings remain secure and are perceived by our customers and corporate partners to be secure. Despite security measures, however, any network infrastructure may be vulnerable to cyber-attacks by hackers and other security threats. We may face cyber-attacks that attempt to penetrate our network security, sabotage, or otherwise disable our research, products and services, misappropriate our or our customers' and partners' proprietary information, which may include personally identifiable information, or cause interruptions of our internal systems and services. Despite security measures, we also cannot guarantee the security of our physical buildings. Physical building penetration or any cyber-attacks could negatively affect our reputation, damage our network infrastructure and our ability to deploy our products and services, harm our relationship with customers and partners that are affected, and expose us to financial liability. Additionally, there are a number of state, federal and international laws governing the collection, use, processing and protecting-protection the privacy and security of health information and personal data. **For example, the Most states have data security breach laws requiring data protection measures and potentially requiring notification to regulators and impacted consumers. The** Health Insurance Portability and

Accountability Act of 1996, **as amended by the Health Information Technology or for Economic and Clinical Health Act of 2009 (collectively, "HIPAA")**, imposes limitations on the use and disclosure of an individual's healthcare information **"covered entities," which include** by healthcare providers **who submit certain standard transactions electronically (mostly related to claims for payment from health insurers)**, healthcare clearinghouses, and health insurance plans ~~or, collectively, covered entities~~, and also grants individuals rights with respect to their health information. **Although we do not currently submit standard transactions electronically and therefore are not a HIPAA covered entity, HIPAA has been in effect for over 20 years and accordingly individuals expect that providers of health care items or services will safeguard their health information in accordance with HIPAA. Moreover, many states' laws impose similar or more stringent limitations on uses and disclosures of healthcare information than does HIPAA, and such laws also provide individuals rights to access, amend, and withhold sharing of their health information.** HIPAA also **requires reporting** imposes compliance obligations and corresponding penalties for non-compliance on individuals and entities that provide services to healthcare providers and other covered entities. As part of **certain impermissible** the American Recovery and Reinvestment Act of 2009, or ARRA, the privacy and security provisions of HIPAA were amended. ARRA also made significant increases in the penalties for improper use **uses or and disclosure disclosures** of an individual's health information under HIPAA and extended enforcement authority to state attorneys general. As amended by ARRA and subsequently by the final omnibus rule adopted in 2013, **including security breaches** HIPAA also imposes notification requirements on covered entities in the event that certain health information has been inappropriately accessed or disclosed, notification requirements to **affected** individuals, federal regulators **the Office for Civil Rights of the U. S. Department of Health and Human Services**, and in some cases **the** ~~notification to local and national~~ media. Notification is not required under HIPAA if the health information that is improperly used or disclosed is deemed secured in accordance with encryption or other standards developed by the U. S. Department of Health and Human Services. Most states **also** have laws requiring notification of affected individuals and / or state regulators in the event of a breach of personal information, which is a broader class of information than the health information protected by HIPAA. Many state laws impose significant data security requirements, such as encryption or mandatory contractual terms, to ensure ongoing protection of personal information. Activities outside of the U. S. implicate local and national data protection standards, impose additional compliance requirements and generate additional risks of enforcement for non-compliance. We may be required to expend significant capital and other resources to ensure ongoing compliance with applicable privacy and data security laws, to protect against security breaches and hackers or to alleviate problems caused by such breaches. We will need to grow the size of our organization in the future, and we may experience difficulties in managing this growth. As of **March 6 April 5, 2023-2024**, we had 12 **full-time and 11 subcontracted** employees. We will need to **grow-increase** the size of our organization in order to support our continued ~~development and potential~~ commercialization of our **product-products** candidates. As our ~~development and~~ commercialization plans and strategies continue to develop, our need for additional managerial, operational, manufacturing, sales, marketing, financial and other resources may increase. Our management, personnel and systems currently in place may not be adequate to support this future growth. Future growth would impose significant added responsibilities on members of management, including: 

- ~~managing our clinical trials effectively;~~
- identifying, recruiting, maintaining, motivating, and integrating additional employees;
- managing our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors and other third parties;
- improving our managerial, development, operational, information technology, and finance systems; and
- expanding our facilities.

If our operations expand, we will also need to manage additional relationships with various strategic partners, suppliers and other third parties. Our future financial performance and our ability to commercialize our **product-products** candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively, as well as our ability to develop a sales and marketing force when appropriate. To that end, we must be able to ~~manage our development efforts and pre-clinical studies and clinical trials effectively and~~ hire, train and integrate additional management, ~~research and development,~~ manufacturing, administrative and sales and marketing personnel. The failure to accomplish any of these tasks could prevent us from successfully growing our company. Our future success depends on our ability to retain our executive officers and to attract, retain and motivate qualified personnel. We are highly dependent upon our personnel **and**, including Joseph Hernandez, our ~~Chief Executive-officer~~ **executive Officer-officers** and members of our board of directors. The loss of Mr. Hernandez's services could ~~impede the achievement of our research, development and commercialization objectives~~. We have not obtained, do not own, nor are we the beneficiary of, key-person life insurance. Our future growth and success depend on our ability to recruit, retain, manage and motivate our employees. The loss of any member of our senior management team or the inability to hire or retain experienced management personnel could compromise our ability to execute our business plan and harm our operating results. Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. The competition for qualified personnel in the biotechnology field is intense and as a result, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business. Our Chief Executive Officer, Joseph Hernandez, and our Chief Financial Officer, Jon Garfield, also hold certain ~~management positions and directorships of other companies and may allocate their time to such other businesses, thereby causing conflicts of interest in their determination as to how much time to devote to our affairs. This could have a negative impact on our ability to implement our plan of operation. Our Chief Executive Officer, Joseph Hernandez is engaged in other business endeavors for which he may be entitled to substantial compensation, which may result in a conflict of interest in allocating his time between our operations and his other businesses. Pursuant to Mr. Hernandez's employment agreement, Mr. Hernandez shall be employed with the Company on a full-time basis, but shall be permitted to participate in certain limited business activities. Subject to our Board's prior approval, Mr. Hernandez may serve as an officer, stakeholder, or member of the board of directors or advisory board (or the equivalent in the case of a non-corporate entity) of non-competing for-profit businesses and charitable organizations, provided, however, that such activities do not materially interfere, individually or in the~~

aggregate, with the performance of his duties and responsibilities to Blue Water Vaccines Inc. Accordingly, although Mr. Hernandez's primary occupation is his service to Blue Water Vaccines Inc., he also holds certain management positions and directorships of other companies, and may allocate his time to such other businesses, thereby causing conflicts of interest in his determination as to how much time to devote to our affairs. Additionally, our Chief Financial Officer, Jon Garfield, is engaged in other business endeavors for which he may be entitled to substantial compensation, which may result in a conflict of interest in allocating his time between our operations and his other businesses. Pursuant to Mr. Garfield's employment agreement, Mr. Garfield shall be employed with the Company on a full-time basis, but shall be permitted to participate in certain limited business activities, subject to the restrictions imposed on Mr. Hernandez as described above. Accordingly, Mr. Garfield holds certain management positions and directorships of other companies, and may allocate his time to such other businesses, thereby causing conflicts of interest in his determination as to how much time to devote to our affairs. Each of Messrs. Hernandez and Garfield may also have competitive fiduciary obligations and pecuniary interests relating to their other business ventures that conflict with our interests. Each of Messrs. Hernandez and Garfield's employment agreement contains certain restrictive covenants while they are employed at Blue Water Vaccines Inc. These restrictive covenants, generally, restrict Messrs. Hernandez and Garfield from engaging in any other business or occupation that (x) conflicts with the interests of the Company, (y) interferes with the proper and efficient performance of his duties for the Company, or (z) interferes with his exercise of judgment in the Company's best interests. Messrs. Hernandez and Garfield are further subject to general restrictions regarding the solicitation of employees, certain customers, as well as the use or disclosure of any confidential information, of the business of Blue Water Vaccines Inc. Notwithstanding the foregoing, to the extent that these additional activities may have a conflict between their interests and ours, this could have a negative impact on our ability to implement our plan of operations. Certain significant personnel may allocate their time to other businesses, which may cause conflicts of interest in their determination as to how much time to devote to our affairs and potentially competitive fiduciary and pecuniary interests that conflict with our interests. Our executive officers are supported by Ali Fattom and Andrew Skibo, who provide valuable technical and strategic capabilities to us. They are not currently required to commit their full time to our affairs. As such, they may allocate their time to other businesses. From time to time, those other commitments may limit the nature of services that Messrs. Fattom and Skibo provide to our Company, for instance, where such activities may involve overlapping industries and products. If these individuals' other business affairs require them to devote substantial amounts of time to such affairs in excess of their current commitment levels, it could limit their ability to devote time or resources to our affairs, which may have a negative impact on our ability to complete our plan of operations. Members of our management team and board of directors have significant experience as founders, board members, officers, or executives of other companies. As a result, certain of those persons people have been and may become involved in proceedings, investigations and litigation relating to the business affairs of the companies with which they were, are, or may in the future be, affiliated. This may have an adverse effect on us, could damage our reputation and business. During the course of their careers, members of our management team and board Board of directors have had significant experience as founders, board members, officers or executives of other companies. As a result of their involvement and positions in these companies, certain persons were, are now, or may in the future become, involved in litigation, investigations or other proceedings relating to the business affairs of such companies or transactions entered into by such companies. Any such litigation, investigations or other proceedings may divert our management team's and board's attention and resources away from our affairs and may negatively affect our reputation and our business. Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent review of regulatory submissions new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business. The ability of the FDA to review regulatory submissions and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new drugs regulatory submissions to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018, the U. S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, in our operations as a public company, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations. We may be adversely affected by natural disasters, pandemics and other catastrophic events, and by man-made problems such as terrorism and acts of war, that could disrupt our business operations and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster. If a disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as enterprise financial systems, manufacturing resource planning or enterprise quality systems, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. Our contract manufacturers' and suppliers' facilities are located in multiple locations, where other natural disasters or similar events, such as blizzards, tornadoes, fires, explosions or large-scale accidents or power outages, and other public health emergencies could severely disrupt our operations and have a material adverse effect on our business, financial condition, operating results and prospects. For example, the recent COVID-19 pandemic may cause significant disruption to our business operations, the



operations of our third-party contractors and suppliers and the operations of our clinical trials, including as a result of significant restrictions or bans on travel into and within the geographic areas in which our manufacturers produce our product candidates or where we conduct our clinical trials. A public health emergency could also affect the operations of the FDA and other regulatory or public health authorities, resulting in delays to meetings related to planned or completed clinical trials and ultimately of reviews, **review** and approvals of our product candidates. Such disruption could impede, delay, limit or prevent our employees and third-party contractors from beginning or continuing research and development or clinical trial-related activities, which may impede, delay, limit or prevent initiation or completion of our ongoing clinical trials and preclinical research and ultimately lead to the delay or denial of regulatory **submissions** approval of our product candidates, which could seriously harm our operations and financial condition. Our employees, independent contractors, principal investigators, consultants, **and** vendors and clinical research organizations, or CROs, may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements. We are exposed to the risk that our employees, independent contractors, **principal investigators**, consultants, **and** vendors **and** CROs may engage in fraudulent or other illegal activity. Misconduct by these persons could include intentional, reckless, or negligent conduct or unauthorized activity that violates laws or regulations, including those laws requiring the reporting of true, complete and accurate information to the FDA or foreign regulatory authorities; manufacturing standards; federal, state and foreign healthcare fraud and abuse laws and data privacy; or laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and other business arrangements in the healthcare industry are subject to extensive laws intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws may restrict or prohibit a wide range of business activities, including research, manufacturing, distribution, pricing, discounting, marketing and promotion, sales commission, customer incentive programs, **patient rebate programs**, and other business arrangements. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials, or illegal misappropriation of drug product, which could result in regulatory sanctions or other actions or lawsuits stemming from a failure to comply with such laws or regulations, and serious harm to our reputation. In addition, federal procurement laws impose substantial penalties for misconduct in connection with government contracts and require certain contractors to maintain a code of business ethics and conduct. If any such actions are instituted against us, we may have to terminate employees or others involved and the impact of such termination can result in our experiencing delays and additional costs associated with replacing the services being provided. If we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, FDA debarment, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our operating results. Macroeconomic pressures in the markets in which we operate, including, but not limited to, the **effect of the COVID-19 pandemic and the current conflict** **conflicts between in** Ukraine and **Russia the Middle East** may alter the ways in which we conduct our business operations and manage our financial capacities. To varying degrees, the ways in which we conduct our business operations and manage our financial capacities are influenced by macroeconomic conditions that affect companies directly involved in or providing services related to the drug **and biological product** development. For example, real GDP growth, business and investor confidence, the **COVID-19 pandemic, the conflict** **conflicts between in** Ukraine and **Russia the Middle East**, inflation, employment levels, oil prices, interest rates, tax rates, availability of consumer and business financing, housing market conditions, foreign currency exchange rate fluctuations, costs for items such as fuel and food and other macroeconomic trends can adversely affect not only our decisions and ability to engage in research and development and clinical trials, but also those of our management, employees, third-party contractors, manufacturers and suppliers, competitors, stockholders and regulatory authorities. In addition, geopolitical issues around the world and how our markets are positioned can also impact the macroeconomic conditions and could have a material adverse impact on our financial results. Economic uncertainty may adversely affect our access to capital, cost of capital and ability to execute our business plan as scheduled. Generally, worldwide economic conditions remain uncertain. Access to capital markets is critical to our ability to operate. Traditionally, biotechnology companies have funded their research **and** development **and** **commercialization** expenditures through raising capital in the equity markets. Declines and uncertainties in these markets in the past have severely restricted raising new capital and have affected companies' ability to continue to expand or fund existing research **and** development, **and commercialization** efforts. We require significant capital for **the commercialization of** research and development for our **products** vaccine candidates and clinical trials. The general economic and capital market conditions, both in the U. S. and worldwide, have been volatile in the past and at times have adversely affected our access to capital and increased the cost of capital. There is no certainty that the capital and credit markets will be available to raise additional capital on favorable terms. If economic conditions become worse, our future cost of equity or debt capital and access to the capital markets could be adversely affected. In addition, if we are unable to access the capital markets on favorable terms, our ability to execute our business plan as scheduled would be compromised. Moreover, we rely and intend to rely on third-parties, including **CROs** clinical research organizations, **CMOs** contract manufacturing organizations and other important vendors and consultants. Global economic conditions may result in a disruption or delay in the performance of our third-party contractors and suppliers. If such third-parties are unable to adequately satisfy their contractual commitments to us in a timely manner, our business could be adversely affected. **Conditions in the global economy may adversely affect our business, financial condition and results of operations. Although demand for in vitro diagnostics is considered inelastic in developed economies, the in vitro diagnostic industry that we sell to may be affected by material changes in supply, market prices, exchange rates and general economic conditions. Delays or reductions in our customers' purchasing or shifts to lower-cost alternatives that result from tighter economic market conditions would reduce demand for our products and services and could, consequently, have a material adverse effect on our business, financial condition, and**

results of operations. Misconduct and errors by our current and former employees and our third- party service providers could cause a material adverse effect on our business and reputation. Our employees and third- party service providers are integral to our business operations, including confidential information. If any such information were leaked to unintended recipients due to human error, theft, malicious sabotage or fraudulent manipulation, we may be subject to liability for loss of such information. Further, if any of our employees or third- party service providers absconded with our proprietary data or know- how in order to compete with us, our competitive position may be materially and adversely affected. Any improper conduct or use of funds by any of our employees or third- party service providers in contravention of our protocols and policies may lead to regulatory and disciplinary proceedings involving us. We may be perceived to have facilitated or participated in such conduct and we could be subject to liability, damages, penalties and reputational damage. It is impossible to completely identify and eradicate all risks of misconduct or human errors, and our precautionary measures may not be able to effectively detect and prevent such risks from happening. The occurrence of any of the above risks could result in a material adverse effect on our business and results of operations, as we are exposed to potential liability to borrowers and investors, reputational damage, regulatory intervention, financial harm. Our ability to attract new and retain existing borrowers and investors and operate as an ongoing concern may be impaired. Our industry is subject to rapid change, which could make our solutions and the diagnostic tests we develop and services we offer, obsolete. If we are unable to continue to innovate and improve our diagnostic tests and services, we could lose customers or market share. Our industry is characterized by rapid changes, including technological and scientific breakthroughs, frequent new product introductions and enhancements and evolving industry standards, all of which could make our current diagnostic tests and others we are developing obsolete. Our future success will depend on our ability to keep pace with the evolving needs of our customers on a timely and cost- effective basis and to pursue new market opportunities that develop as a result of scientific and technological advances. In recent years, there have been numerous advances in technologies relating to the diagnosis and treatment of cancer. There have also been advances in methods used to analyze very large amounts of molecular information as well as new imaging- based technologies used of the early assessment and monitoring of disease. We must continuously enhance our offerings and develop new and improved diagnostic tests to keep pace with evolving standards of care. If we do not leverage or scale our sample and data biobank, discover new diagnostic biomarkers or applications, or update our diagnostic tests to reflect new scientific knowledge, including about prostate cancer biology, and information about new cancer therapies or relevant clinical trials, our diagnostic tests could become obsolete and sales of our current diagnostic tests and any new tests we develop could decline or fail to grow as expected. This failure to make continuous improvements to our diagnostic tests to keep ahead of those of our competitors could result in the loss of customers or market share that would adversely affect our business, financial condition, and results of operations. The development of new liquid biopsy and imaging technologies could negatively impact demand for our products. In the event that our products are the subject of guidelines, clinical studies or scientific publications that are unhelpful or damaging, or otherwise call into question the benefits of our products, we may have difficulty in convincing prospective customers to adopt our test. Moreover, the perception by the investment community or shareholders that recommendations, guidelines, or studies will result in decreased use of our products could adversely affect the prevailing market price for our common stock. Similar challenges apply to all of the products in our pipeline. We face competition from many sources, including larger companies, and we may be unable to compete successfully. There are a number of diagnostic solutions companies in the United States, Europe and Asia. Notable competitors in the United States include, but are not limited to OPKO Health, Beckman Coulter, BioTechne, MdxHealth, A3P Biomedical AB. These competitors all provide diagnostic tests or testing services to hospitals, researchers, clinicians, laboratories, and other medical facilities. Many of these organizations are significantly larger with greater financial and personnel resources than us and enjoy significantly greater market share and have greater resources than we do. As a consequence, they may be able to spend more on product development, marketing, sales and other product initiatives than we can. Some of our competitors have: • substantially greater name recognition; • broader, deeper, or longer- term relations with healthcare professionals, customers, and third- party payers; • more established distribution networks; • additional lines of diagnostic tests and the ability to offer rebates or bundle them to offer greater discounts or other incentives to gain a competitive advantage; • greater experience in conducting research and development, manufacturing, clinical trials, marketing and obtaining regulatory clearance or approval for diagnostic tests; and • greater financial and human resources for product development, mergers and acquisitions, sales and marketing and possible patent litigation. Our continued success depends on our ability to: • Further penetrate the diagnostic solutions market and increase utilization of our diagnostic tests; • attract and retain a sufficient number of qualified employees; • maintain and widen our technology lead over competitors by continuing to innovate and deliver new product enhancements on a continuous basis; and • cost- effectively manufacture our diagnostic tests and their component parts as well as drive down the cost of service. As we attain greater commercial success, our competitors are likely to develop diagnostic tests that offer features and functionality similar to our diagnostic tests that are currently on the market. Improvements in existing competitive diagnostic tests or the introduction of new competitive diagnostic tests may make it more difficult for us to compete for sales, particularly if those competitive diagnostic tests demonstrate better reliability, convenience or effectiveness or are offered at lower prices. Performance issues, service interruptions or price increases by our shipping carriers and warehousing providers could adversely affect our business and harm our reputation and ability to provide our services on a timely basis. Expedited, reliable shipping and delivery services and secure warehousing are essential to our operations. We rely heavily on providers of transport services for reliable and secure point- to- point transport of our diagnostic tests to our customers and for tracking of these shipments, and from time to time require warehousing for

our diagnostic tests, sample collection kits and supplies. Should a carrier encounter delivery performance issues such as loss, damage, or destruction of any systems, it would be costly to replace such systems in a timely manner and such occurrences may damage our reputation and lead to decreased demand for our diagnostic tests and increased cost and expense to our business. In addition, any significant increase in shipping or warehousing rates could adversely affect our operating margins and results of operations. Similarly, strikes, severe weather, natural disasters, civil unrest and disturbances or other service interruptions affecting delivery or warehousing services we use would adversely affect our ability to process orders for our diagnostic tests on a timely basis. For our clinical studies, we rely on commercial courier delivery services to transport samples to our laboratory facility in a timely and cost-efficient manner and if these delivery services are disrupted, our business will be harmed. Disruptions in delivery service, whether due to labor disruptions, bad weather, natural disaster, civil unrest or disturbances, terrorist acts or threats or for other reasons could adversely affect specimen integrity and our ability to process samples in a timely manner and to service our customers, and ultimately our reputation and our business. In addition, if we are unable to continue to obtain expedited delivery services on commercially reasonable terms, our operating results may be adversely affected. We rely on software hosting our online risk calculator needed to be accessed by the user to calculate the test result. Any internet service interruption or hardware failure could affect availability of the online resource and thus negatively impact our business. Cost-containment efforts of our customers, purchasing groups and governmental purchasing organizations could have a material adverse effect on our future sales and profitability. In an effort to reduce costs, many hospitals in the United States have become members of GPOs and Integrated Delivery Networks (IDNs). GPOs and IDNs negotiate pricing arrangements with medical device companies and distributors and then offer these negotiated prices to affiliated hospitals and other members. GPOs and IDNs typically award contracts on a category-by-category basis through a competitive bidding process. Bids are generally solicited from multiple providers with the intention of driving down pricing or reducing the number of vendors. Due to the highly competitive nature of the GPO and IDN contracting processes, we may not be able to obtain new contract positions with major GPOs and IDNs. Furthermore, the increasing leverage of organized buying groups may reduce market prices for our diagnostic tests, thereby reducing our revenue and margins. While having a contract with a GPO or IDN for a given product category can facilitate sales to members of that GPO or IDN, such contract positions can offer no assurance that any level of sales will be achieved, as sales are typically made pursuant to individual purchase orders. Even when a provider is the sole contracted supplier of a GPO or IDN for a certain product category, members of the GPO or IDN are generally free to purchase from other suppliers. Furthermore, GPO and IDN contracts typically are terminable without cause by the GPO or IDN upon 60 to 90 days' notice. Accordingly, the members of such groups may choose to purchase alternative diagnostic tests due to the price or quality offered by other companies, which could result in a decline in our revenue. We are highly dependent on our senior management team and key personnel, and our business could be harmed if we are unable to attract and retain the personnel necessary for our success. We are highly dependent on our senior management and other key personnel. Our success will depend on our ability to retain senior management and to attract and retain qualified personnel in the future, including sales and marketing professionals, scientists, clinical specialists, and other highly skilled personnel and to integrate current and additional personnel in all departments. The loss of members of our senior management, sales and marketing professionals, scientists, clinical and regulatory specialists could result in delays in product development and harm our business. If we are not successful in attracting and retaining highly qualified personnel, it would have a material adverse effect on our business, financial condition, and results of operations. Our laboratory operations depend on our ability to attract and retain highly skilled scientists and technicians. We may not be able to attract or retain qualified scientists and technicians in the future due to the competition for qualified personnel among life science businesses, particularly near our laboratory facility in Zurich-Schlieren, Switzerland. We also face competition from universities and public and private research institutions in recruiting and retaining highly qualified scientific personnel. We may also have difficulties locating, recruiting, or retaining qualified salespeople. Recruiting and retention difficulties can limit our ability to support our research and development and sales programs. To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have issued and may continue to issue equity awards that vest over time. Our employment arrangements with our employees provide for at-will employment, which means that any of our employees could leave our employment at any time, with or without notice, which may lead to more difficulty in retaining qualified salespeople and other talent. We depend on our information technology systems and any failure of these systems could harm our business. We depend on information technology and telecommunications systems, including third-party cloud computing infrastructure and operating systems, for significant elements of our operations, including our online risk analysis software. We have installed, and expect to expand, a number of enterprise software systems that affect a broad range of business processes and functional areas, including systems handling human resources, financial controls and reporting, contract management, regulatory compliance and other infrastructure operations. Information technology and telecommunications systems are vulnerable to damage from a variety of sources, including telecommunications or network failures, malicious human acts (such as ransomware) and natural disasters. Moreover, despite network security and back-up measures, some of our external servers are potentially vulnerable to physical or electronic break-ins, computer viruses and similar disruptive problems. Despite the precautionary measures we have taken to prevent unanticipated problems that could affect our information technology and telecommunications systems, failures or significant downtime of these systems or those used by our partners or subcontractors could prevent us from conducting our diagnostic products development, preparing and providing reports to researchers, clinicians and our partners, billing payors, handling enquiries, and managing the administrative aspects of our business. Any disruption or loss of information technology or telecommunications systems



**on which critical aspects of our operations depend could have an adverse effect on our business and our reputation, and we may be unable to regain or repair our reputation in the future.** Risks Related to Our Intellectual Property It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection. If our patent position does not adequately protect our **products and / or** product candidates, others could compete against us more directly, which would harm our business, possibly materially. Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of our current product candidates and future product candidates, the processes used to manufacture them and the methods for using them, as well as successfully defending these patents against third- party challenges. Our ability to stop third parties from making, using, selling, offering to sell or importing our **products and / or** product candidates is dependent upon the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. The patent positions of biotechnology and pharmaceutical companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the U. S. or in foreign jurisdictions outside of the U. S. Changes in either the patent laws or interpretations of patent laws in the U. S. and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be enforced in the patents that may be issued from the applications we currently license or may in the future own or license from third parties. Further, if any patents we obtain or license are deemed invalid and unenforceable, our ability to commercialize or license our **products and / or** product candidates or technology could be adversely affected. Others may file patent applications covering products and technologies that are similar, identical, or competitive to ours or important to our business. We cannot be certain that any patent application owned by a third party will not have priority over patent applications filed or in- licensed by us, or that we or our licensors will not be involved in interference, opposition, re- examination, review, reissue, post grant review or invalidity proceedings before U. S. or non- U. S. patent offices. Such proceedings are also expensive and time consuming. The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example: • others may be able to make compounds / **assays** that are similar to our **products and / or** product candidates **and / or assays**, but that are not covered by the claims of our licensed patents; • any patents that we obtain from licensing or otherwise may not provide us with any competitive advantages; • any granted patents that we rely upon may be held invalid or unenforceable as a result of legal challenges by third parties; and • the patents of others may have an adverse effect on our business. We are dependent on licensed intellectual property. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing our **products and / or** product candidates, if approved. If we breach any of the agreements under which we license the use, development, and commercialization rights to our **products and / or** product candidates or technology from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business. **We Proteomedix owns the patents and patent applications detailed above in the chapter entitled “ Intellectual Property ”. Apart from this we** do not currently own any **further** patents, and we are heavily reliant upon a number of license agreements under which we are granted rights to intellectual property that are important to our business, and we may need or choose to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose on us, various development, regulatory and / or commercial diligence obligations, payment of milestones and / or royalties and other obligations. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license. Our business could suffer, for example, if any current or future licenses terminate, if the licensors fail to abide by the terms of the license, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms. Licensing of intellectual property is of critical importance to our business and involves complex legal, business, and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including: • the scope of rights granted under the license agreement and other interpretation- related issues; • whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement; • our right to sublicense patent and other rights to third parties; • our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our **products and / or** product candidates, and what activities satisfy those diligence obligations; • our obligation to pursue or license others to pursue development of indications we are not currently pursuing; • the ownership of inventions and know- how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; • our right to transfer or assign the license; and • the effects of termination. If disputes over intellectual property that we **own or** have licensed prevent or impair our ability to maintain our **patents or** current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected **products and / or** product candidates. We have entered into several licenses to support our various programs. Termination of any of these license agreements would have a material adverse impact on our ability to develop and commercialize derived products under each respective agreement. We may enter into additional licenses to third- party intellectual property that are necessary or useful to our business. Our current licenses and any future licenses that we may enter into impose various royalty payment, milestone, and other obligations on us. Under some license agreements, we may not control prosecution of the licensed intellectual property, or may not have the first right to enforce the intellectual property. In those cases, we may not be able to adequately influence patent prosecution or enforcement, or prevent inadvertent lapses of coverage due to failure to pay maintenance fees. If we fail to comply with any of our obligations under a current or future license agreement, the licensor may allege that we have breached our license agreement, and may accordingly seek to terminate our license. Termination of any of our current or future licenses could result in our loss of the right to use the licensed intellectual property, which could materially adversely affect our ability to develop and commercialize a product candidate or product, if approved, as well as harm our competitive business

position and our business prospects. Under some license agreements, termination may also result in the transfer of or granting in rights under certain of our intellectual property and information related to the product candidate being developed under the license, such as regulatory information. The agreements under which we license intellectual property or technology to or from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected **products and / or** product candidates. In addition, if our licensors fail to abide by the terms of the license, if the licensors fail to prevent infringement by third parties, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms, our business could suffer. Moreover, our licensors may own or control intellectual property that has not been licensed to us, and, as a result, we may be subject to claims, regardless of their merit, that we are infringing, misappropriating or otherwise violating the licensor's rights. Similarly, if we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to seek alternative options, such as developing new **products and / or** product candidates with design-around technologies, which may require more time and investment, or abandon development of the relevant research programs or **products and / or** product candidates and our business, financial condition, results of operations and prospects could suffer. Some of the intellectual property **owned by Proteomedix and / or** covered by our licenses concerns patent applications and provisional applications. We cannot assure investors that any of the currently pending or future patent applications will result in granted patents, nor can we predict how long it will take for such patents to be granted. Some of intellectual property covered by our licenses concerns certain unspecified patent rights (including patent applications, provisional patent applications and PCT patent applications). While in some instances, the licensors have agreed to assume responsibility for the preparation, filing, prosecution and maintenance of patent applications covered by the licensed patent rights, we cannot be certain as to when or if final patents will be issued for those patent applications covered by the licensed patent rights. However, the licensors may not successfully prosecute certain patent applications, the prosecution of which they control, under which we are only a licensee and on which our business substantially depends. Even if patents issue from these applications, there is no assurance that the patents will be free from defects or survive validity or enforceability challenges, the licensors may fail to maintain these patents, may decide not to pursue litigation against third-party infringers, may fail to prove infringement or may fail to defend against counterclaims of patent invalidity or unenforceability. Moreover, it is possible that the **patent applications owned by Proteomedix and / or** licensed pending patent applications will not result in granted patents, and even if such pending patent applications grant as patents, they may not provide a basis for intellectual property protection of commercially viable vaccine products or may not provide us with any competitive advantages. Further, it is possible that, for any of the patents that may be granted in the future, others will design around the licensed patent rights or identify methods of **diagnosis or** for preventing or treating infectious diseases that do not concern the rights covered by our **patents and / or** licenses. Further, we cannot assure investors that other parties will not challenge any patents granted to **Proteomedix or** the licensors or that courts or regulatory agencies will hold **Proteomedix and / or** licensor's patents to be valid or enforceable. We cannot guarantee investors that, if required to defend the covered patents, we will have the funds to or be successful in defending challenges made against the **Proteomedix and / or** licensed patents and patent applications. Any successful third-party challenge to the **Proteomedix and / or** licensed patents could result in the unenforceability or invalidity of such patents, or to such patents being interpreted narrowly or otherwise in a manner adverse to our interests. Our ability to establish or maintain a technological or competitive advantage over our competitors may be diminished because of these uncertainties. Even if patents are issued based on patent applications to which we have been granted a license **or owned by Proteomedix**, because the patent positions of **diagnostic methods and / or** pharmaceutical and biotechnology products are complex and uncertain, we cannot predict the scope and extent of patent protection for our **products and / or** product candidates. Any patents that may be issued based on patent applications that we have been granted licenses to **or owned by Proteomedix** will not ensure sufficient protection with respect to our activities for a number of reasons, including without limitation the following: ● any issued patents may not be broad or strong enough to prevent competition from other **diagnostic and / or** vaccine products including identical or similar products; ● if patents are not issued or if issued patents expire, there would be no protections against competitors making generic equivalents; ● there may be prior art of which we are not aware that may affect the validity or enforceability of a patent claim; ● there may be other patents existing, now or in the future, in the patent landscape for our **products and / or** product candidates that we seek to commercialize or develop, if any, that will affect our freedom to operate; ● if patents that we have been granted licenses to are challenged, a court could determine that they are not valid or enforceable; ● a court could determine that a competitor's technology or product does not infringe patents that we have been granted licenses to; ● patents to which we have been granted licenses could irretrievably lapse due to failure to pay fees or otherwise comply with regulations, or could be subject to compulsory licensing; and ● if we encounter delays in our development or clinical trials, the period of time during which we could market our products under patent protection would be reduced. Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and patent protection could be reduced or eliminated for noncompliance with these requirements. Periodic maintenance fees on any issued patent are due to be paid to the United States Patent and Trademark Office ( "USPTO " ) and foreign Intellectual Property Offices in several stages over the term of the patent. Maintenance fees are also due for pending patent applications in some countries. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent

application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to office actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business. The life of patent protection is limited, and third parties could develop and commercialize **methods, products,** and technologies similar or identical to ours and compete directly with us after the patent licensed to us expires, which could materially and adversely affect our ability to commercialize our products and technologies. The life of a patent and the protection it affords is limited. For example, in the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U. S. non-provisional filing date. In Europe, the expiration of an invention patent is 20 years from its filing date. Even if we successfully obtain patent protection for **a diagnostic method and / or** an approved vaccine candidate, it may face competition, **e. g.,** from biosimilar medications. **Diagnostic companies or Manufacturers-manufacturers** of biosimilar drugs may challenge the scope, validity or enforceability of the patents underlying our technology in court or before a patent office, and the patent holder may not be successful in enforcing or defending those intellectual property rights and, as a result, we may not be able to develop or market the relevant **method /** product candidate exclusively, which would materially adversely affect any potential sales of that product. Given the amount of time required for the development, testing and regulatory review of new **diagnostic methods and / or** vaccine candidates, patents protecting such **diagnostic methods and / or** vaccine candidates might expire before or shortly after such **methods or** vaccine candidates are commercialized. As a result, the patents and patent applications **owned or** licensed to us may not provide us with sufficient rights to exclude others from commercializing **methods /** products similar or identical to ours. Even if we believe that the patents involved are eligible for certain (and time-limited) patent term extensions, there can be no assurance that the applicable authorities, including the FDA and the USPTO, and any equivalent regulatory authority in other countries, will agree with our assessment of whether such extensions are available, and such authorities may refuse to grant extensions to such patents, or may grant more limited extensions than requested. For example, depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of the U. S. patents licensed to us may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than requested. If we are unable to obtain patent term extension or term of any such extension is less than requested, our competitors may obtain approval of competing products following our patent expiration, and our business could be harmed. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The patents and pending patent applications licensed to us for our **diagnostic methods and** product candidates are expected to expire on various dates. Upon the expiration, we will not be able to assert such licensed patent rights against potential competitors, which would materially adversely affect our business, financial condition, results of operations and prospects. We may need to license intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms or at all. There may be intellectual property rights existing now, or in the future, relevant to our **methods and / or products and / or** product candidates that we seek to commercialize or develop, if any, that may affect our ability to commercialize such **methods and / or products and / or** product candidates. Although the Company is not aware of any such intellectual property rights, a third-party may hold intellectual property rights, including patent rights, that are important or necessary to the development or manufacture of our **methods and / or products and / or** product candidates. Even if all our main **methods and / or products and / or** product candidates are covered by patents, it may be necessary for us to use the patented or proprietary technology of third parties to commercialize our **methods and / or products and / or** product candidates, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms, or at all, and we could be forced to accept unfavorable contractual terms. In that event, we may be required to expend significant time and resources to redesign our technology, **methods and / or products and / or** product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, our business could be harmed. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have a material adverse effect on our business, financial condition, results of operations, and prospects. We may infringe the intellectual property rights of others, which may prevent or delay our **method and / or** product development efforts and stop us

from commercializing or increase the costs of commercializing our **methods and / or products and / or** product candidates. Our success will depend in part on our ability to operate without infringing the proprietary rights of third parties. We are not aware of any third-party proprietary rights that our planned **methods and / or** products will infringe or misappropriate, but we have not conducted any freedom to operate study as we are in the earliest stages of development. We thus cannot guarantee that our **methods and / or products and / or** product candidates, or manufacture or use of our **products and / or** product candidates, will not infringe third-party patents. Furthermore, a third party may claim that we are using inventions covered by the third party's patent rights and may go to court to stop us from engaging in our normal operations and activities, including making or selling our **methods and / or products and / or** product candidates. These lawsuits are costly and could affect our results of operations and divert the attention of managerial and scientific personnel. Some of these third parties may be better capitalized and have more resources than us. There is a risk that a court would decide that we are infringing the third party's patents and would order us to stop the activities covered by the patents. In that event, we may not have a viable way around the patent and may need to halt commercialization of our **methods and / or products and / or** product candidates. In addition, there is a risk that a court will order us to pay the other party damages for having violated the other party's patents. In addition, we may be obligated to indemnify our licensors and collaborators against certain intellectual property infringement claims brought by third parties, which could require us to expend additional resources. The **diagnostic**, pharmaceutical and biotechnology industries have produced a proliferation of patents, and it is not always clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our **products and / or** product candidates or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid, and we may not be able to do this. Proving invalidity is difficult. For example, in the U. S., proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and diversion of management's time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, which may not be available, defend an infringement action or challenge the validity of the patents in court. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, if we do not obtain a license, develop or obtain non-infringing technology, fail to defend an infringement action successfully or have infringed patents declared invalid, we may incur substantial monetary damages, encounter significant delays in bringing our **methods and / or products and / or** product candidates to market and be precluded from manufacturing or selling our **products and / or** product candidates. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than us or the third parties from whom we license intellectual property because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations. We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful. In addition to the possibility of litigation relating to infringement claims asserted against it, we may become a party to other patent litigation and other proceedings, including inter partes review proceedings, post-grant review proceedings, derivation proceedings declared by the USPTO and similar proceedings in foreign countries, regarding intellectual property rights with respect to our current or future technologies or **methods and / or products and / or** product candidates or products. The cost to us of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Patent litigation and other proceedings may also absorb significant management time. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could impair our ability to compete in the marketplace. Competitors may infringe or otherwise violate our intellectual property, including patents that may ~~be issue~~ **issued** to be licensed by us. As a result, we may be required to file claims in an effort to stop third-party infringement or unauthorized use. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights, and / or that any of our intellectual property, including licensed intellectual property, is invalid and / or unenforceable. This can be prohibitively expensive, particularly for a company of our size, and time-consuming, and even if we are successful, any award of monetary damages or other remedy we may receive may not be commercially valuable. In addition, in an infringement proceeding, a court may decide that our asserted intellectual property is not valid or is unenforceable ~~or~~ may refuse to stop the other party from using the technology at issue on the grounds that our intellectual property does not cover its technology. An adverse determination in any litigation or defense proceedings could put our intellectual property at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not ~~issuing~~ **being issued**. If the breadth or strength of our patent or other intellectual property rights is compromised or threatened, it could allow third parties to exploit and, in particular, commercialize our technology or **methods and / or** products or result in our inability to exploit and / or commercialize our technology and **methods and / or** products without infringing third-party intellectual property rights. Further, third parties may be dissuaded from collaborating with us. Interference or derivation proceedings brought by the USPTO, or its foreign counterparts may be necessary to determine the priority of inventions with respect to our patent applications, and we may also become involved in other proceedings, such as re-examination proceedings, before the USPTO or its foreign counterparts. Due to the substantial competition in the pharmaceutical space, the number of such proceedings may increase. This could delay the prosecution of our pending patent applications or impact the validity and enforceability of any future patents that we may obtain. In addition, any such litigation, submission or proceeding may be resolved adversely to us and, even if successful, may result in substantial costs and distraction to our management. If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our technology and product could be significantly diminished. We also rely on



trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers, and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its transparency initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position. We may be subject to claims that our employees or consultants have wrongfully used or disclosed alleged trade secrets. As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees and consultants do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees or consultants have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. If we fail ~~in to defending~~ **defend** any such claims, in addition to paying monetary damages, we could lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. Our intellectual property may not be sufficient to protect our **methods and / or products and / or** product candidates from competition, which may negatively affect our business as well as limit our partnership or acquisition appeal. We may be subject to competition despite the existence of intellectual property we license **or own** or may in the future own. We can give no assurances that our intellectual property claims will be sufficient to prevent third parties from designing around patents we own or license and developing and commercializing competitive products. The existence of competitive products that avoid our intellectual property could materially adversely affect our operating results and financial condition. Furthermore, limitations, or perceived limitations, in our intellectual property may limit the interest of third parties to partner, collaborate or otherwise transact with us, if third parties perceive a higher than acceptable risk to commercialization of our **methods and / or products and / or** product candidates or future **products and / or** product candidates. We may elect to sue a third party, or otherwise make a claim, alleging infringement or other violation of patents, trademarks, trade dress, copyrights, trade secrets, domain names or other intellectual property rights that we either own or license from a third party. If we do not prevail in enforcing our intellectual property rights in this type of litigation, we may be subject to: • paying monetary damages related to the legal expenses of the third party; • facing additional competition that may have a significant adverse effect on our product pricing, market share, business operations, financial condition, and the commercial viability of our product; and • restructuring our company or delaying or terminating select business opportunities, including, but not limited to, research and development, clinical trial, and commercialization activities, due to a potential deterioration of our financial condition or market competitiveness. A third party may also challenge the validity, enforceability, or scope of the intellectual property rights that we license or own and the result of these challenges may narrow the scope or claims of or invalidate patents that are integral to our **products and / or** product candidates in the future. There can be no assurance that we will be able to successfully defend patents we own or license in an action against third parties due to the unpredictability of litigation and the high costs associated with intellectual property litigation, amongst other factors. Intellectual property rights may be less extensive and enforcement more difficult in jurisdictions outside of the U. S. Therefore, we may not be able to protect our intellectual property and third parties may be able to market competitive products that may use some or all of our intellectual property. **Intellectual property rights do not necessarily address all potential threats to our competitive advantage and** ~~Changes changes to in patent law laws, including~~ **or patent jurisprudence could diminish the Leahy value of patents in general, thereby impairing our ability to protect our products. The America Invents Act ("AIA") has been enacted in the United States, resulting in significant changes to the U. S. patent system. An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a "first** ~~Smith America Invests Act of 2011 and the~~ **to- file" system for deciding which party should be granted a** ~~Patent patent when two or more~~ **Patent patent when two or more** ~~Reform Act of 2009 and other future article of legislation, may substantially change the regulations and procedures surrounding patent applications, issuance~~ **are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application, but circumstances could prevent us from promptly filing patent applications on our inventions. Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and provide opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U. S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U. S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. The AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued** ~~patents. We can give no assurances~~ **patents. Additionally, the U. S. Supreme Court has ruled on several patent**

cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. This is in particular the case in the field of diagnostic patents based on biomarkers (Mayo v. Prometheus, 566 U. S. 66 (2012)), where Proteomedix is active. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U. S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents of our- or to enforce licensor can be defended or our will-existing patents and patents that we might obtain in the future. Any inability of us to protect our competitive advantage with regard to any of our product candidates may prevent us from successfully monetizing such product candidate against future intellectual property challenges, particularly as they pertain to changes in patent law and future patent law interpretations this could materially adversely affect our business, prospects, financial condition and results of operations.

Risks Related to Healthcare Compliance and Other Regulations If we fail to comply with healthcare regulations, we could face substantial enforcement actions, including administrative, civil, and criminal penalties and our business, operations and financial condition could be adversely affected. We could be subject to healthcare fraud and abuse laws and patient health information privacy and security laws of both the federal government and the states in which we conduct our business. The laws include:

- the U. S. federal healthcare program anti-Anti-kickback-Kickback law-Statute, which prohibits, among other things, persons from soliciting, receiving, or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;
- federal Federal civil and criminal false claims laws and civil monetary penalties laws, including the federal civil False Claims Act, which can be enforced by individuals through civil whistleblower and qui tam actions, prohibit any person or entity from, among other things, individuals or entities from knowingly presenting, or causing to be presented, a false claims- claim for payment from to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government.;
- The federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made third-party payers that are false or fraudulent, and which may apply to physicians entities like us which provide coding and billing information teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to customers report annually to CMS ownership and investment interests held by Covered Recipients, as defined at 42 CFR Part 403, Subpart I;
- HIPAA which prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statements- statement relating to in connection with the delivery of or payment for healthcare matters-benefits, items or services, and which also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information and certain notification requirements and criminal and civil penalties for failure to comply with those requirements;
- the FDCA which among other things, strictly regulates drug manufacturing and product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts. If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including administrative, civil, and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security and fraud laws may prove costly. Healthcare reform in the United States has been implemented in the past, and we expect further changes to be proposed in the future, leading to potential uncertainty in the healthcare industry. Violations of healthcare laws can have an adverse impact on our ability to advance ENTADFI our product candidates and our operating results. In the United States, there have been, and continue to be, a number of legislative and regulatory changes and proposed changes to the healthcare system that could affect the future results of pharmaceutical manufactures' operations. In particular, there have been and continue to be a number of initiatives at the federal and state levels that seek to reduce healthcare costs. For example, the Affordable Care Act, or the ACA, which was originally enacted in March 2010 and subsequently amended, includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA of greatest importance to the pharmaceutical and biotechnology industry are the following:

  - an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
  - implementation of the federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act";
  - a licensure framework for follow-on biologic products;
  - a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
  - establishment of a Center for Medicare Innovation at the Centers for Medicare



& Medicaid Services to test innovative payment and service delivery models to lower Medicare and Medicaid spending; potentially including prescription drug spending; • an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price; • a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics, including our product candidates, that are inhaled, infused, instilled, implanted or injected; • extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations; • expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; • a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and • expansion of the entities eligible for discounts under the Public Health program. Some of the provisions of the ACA have yet to be implemented, and there have been legal and political challenges to certain aspects of the ACA. The former Trump administration issued certain executive orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the ACA. Concurrently, Congress considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed repeal legislation, the Tax Cuts and Jobs Act of 2017 included a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Congress may consider other legislation to repeal or replace elements of the ACA. Many of the details regarding the implementation of the ACA are yet to be determined, and at this time, the full effect that the ACA would have on a pharmaceutical manufacturer remains unclear. In particular, there is uncertainty surrounding the applicability of the biosimilars provisions under the ACA. This uncertainty is heightened by President Biden's January 28, 2021 Executive Order on Strengthening Medicaid and the Affordable Care Act, which indicates that the Biden administration may significantly modify the ACA and potentially revoke any changes implemented by the Trump administration. In August 2022, President Biden signed the Inflation Reduction Act, which extended enhanced subsidies, passed as part of the American Rescue Plan Act in 2021, and prevented insurance companies from imposing significant increases in healthcare premiums for low income exchange customers through 2025. In addition, under this legislation, Medicare will have the ability to negotiate drug prices for a select list of pharmaceuticals in Medicare Part D drugs, with the list of included drugs expected to increase over the coming years and incorporate drugs in Medicare Parts B and D. The FDA has issued several guidance documents, but no implementing regulations, on biosimilars. A number of biosimilar applications have been approved over the past few years. The regulations that are ultimately promulgated and their implementation are likely to have considerable impact on the way pharmaceutical manufacturers conduct their business and may require changes to current strategies. A biosimilar is a biological product that is highly similar to an approved drug notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the approved drug in terms of the safety, purity, and potency of the product. Individual states have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and marketing cost disclosure and transparency measures, and to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm a pharmaceutical manufacturer's business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce ultimate demand for certain products or put pressure product pricing, which could negatively affect a pharmaceutical manufacturer's business, results of operations, financial condition and prospects. It is also possible that President Biden will further reform the ACA and other federal programs in a manner that may impact our operations. For example, the Biden administration has indicated that a goal of its administration is to expand and support Medicaid and the ACA and to make high-quality healthcare accessible and affordable. The potential increase in patients covered by government funded insurance may impact our pricing. Further, it is possible that the Biden administration may further increase the scrutiny on drug pricing, including a recent provision of the 2023 Inflation Reduction Act, allowing Medicare to negotiate pharmaceutical prices directly with drug manufacturers. In addition, given recent federal and state government initiatives directed at lowering the total cost of healthcare, the Biden administration, Congress and state legislatures will likely continue to focus on healthcare reform, the cost of prescription drugs and biologics and the reform of the Medicare and Medicaid programs. For example, there have been several recent U. S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. Further, in July 2020, former President Trump issued a number of executive orders that are intended to lower the costs of prescription drug products including one that directs HHS to finalize the rulemaking process on modifying the anti-kickback law safe harbors for discounts for plans, pharmacies, and pharmaceutical benefit managers. No assurance can be given whether these orders will remain in effect under the Biden administration. While no one can predict the full outcome of any such legislation, it may result in decreased reimbursement for drugs and biologics, which may further exacerbate industry-wide pressure to reduce prescription drug prices. This could harm a pharmaceutical manufacturer's ability to generate revenue. Increases in importation or re-importation of pharmaceutical products from foreign countries into the United States could put competitive pressure on a

pharmaceutical manufacturer's ability to profitably price products, which, in turn, could adversely affect business, results of operations, financial condition and prospects. A pharmaceutical manufacturer might elect not to seek approval for or market products in foreign jurisdictions in order to minimize the risk of re-importation, which could also reduce the revenue generated from product sales. It is also possible that other legislative proposals having similar effects will be adopted. Furthermore, regulatory authorities' assessment of the data and results required to demonstrate safety and efficacy can change over time and can be affected by many factors, such as the emergence of new information, including on other products, changing policies and agency funding, staffing and leadership. We cannot be sure whether future changes to the regulatory environment will be favorable or unfavorable to our business prospects. For example, average review times at the FDA for marketing approval applications can be affected by a variety of factors, including budget and funding levels and statutory, regulatory and policy changes. Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation. We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. ~~Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation.~~ It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and integrity oversight and reporting obligations. We may rely on government funding and collaboration with government entities for our **vaccine product** development, which adds uncertainty to our research and development efforts and may impose requirements that increase the costs of development, commercialization and production of any programs developed under those government- funded programs. Because we anticipate the resources necessary to develop our **vaccine products and / or** product candidates will be substantial, we may explore funding and development collaboration opportunities with the U. S. government and its agencies. For example, we may apply for certain grant funding from BARDA, the NIH or other government agencies to further the research, development, manufacture, testing, and regulatory approval of our **vaccine products and / or** product candidates. We have no control or input over whether an application for BARDA grant funding or any other funding will be accepted or approved, in full or in part, and we cannot provide investors with any assurances that we will receive such funding. Contracts and grants funded by the U. S. government and its agencies, contain provisions that reflect the government's substantial rights and remedies, many of which are not typically found in commercial contracts, including powers of the government to: • reduce or modify the government's obligations under such agreements without the consent of the other party; • claim rights, including Intellectual Property rights, in products and data developed under such agreements; • audit contract- related costs and fees, including allocated indirect costs; • suspend the contractor or grantee from receiving new contracts pending resolution of alleged violations of procurement laws or regulations. • impose U. S. manufacturing requirements for products that embody inventions conceived or first reduced to practice under such agreements; • suspend or debar the contractor or grantee from doing future business with the government; • control and potentially prohibit the export of products; • pursue criminal or civil remedies under the False Claims Act, False Statements Act, and similar remedy provisions specific to government agreements; and • limit the government's financial liability to amounts appropriated by the U. S. Congress on a fiscal- year basis, thereby leaving some uncertainty about the future availability of funding for a program even after it has been funded for an initial period. If we received such grants or agreements, we may not have the right to prohibit the U. S. government from using certain technologies developed by us, and we may not be able to prohibit third -parties, including our competitors, from using those technologies in providing products and services to the U. S. government. Further, under such agreements we could be subject to obligations to and the rights of the U. S. government set forth in the Bayh- Dole Act of 1980, meaning the U. S. government may have rights in certain inventions developed under these government- funded agreements, including a non- exclusive, non- transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U. S. government could have the right to require us to grant exclusive, partially exclusive, or nonexclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations, also referred to as " march- in rights. " Although the U. S. government's historic restraint with respect to these rights indicates they are unlikely to be used, any exercise of the march- in rights could harm our competitive position, business, financial condition, results of operations -and prospects. In the event we would be subject to the U. S. government's exercise such march- in rights, we may receive compensation that is deemed reasonable by the U. S. government in its sole discretion, which may be less than what we might be able to obtain in the open market. Additionally, the U. S. government requires that any products embodying any invention generated through the use of U. S. government funding be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U. S. manufacturers may limit our ability to contract with non- U. S. manufacturers

for products covered by such intellectual property. Although we may need to comply with some of these obligations, not all of the aforementioned obligations may be applicable to us unless and only to the extent that we receive a government grant, contract or other agreement. However, as an organization, we are relatively new to government contracting and new to the regulatory compliance obligations that such contracting entails. If we were to fail to maintain compliance with those obligations, we may be subject to potential liability and to termination of our contracts, which may have a materially adverse effect on our ability to develop our **vaccine products and / or** product candidates. We are subject to U. S. and certain foreign export and import controls, sanctions, embargoes, anti- corruption laws and anti- money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business. We are subject to export control and import laws and regulations, including the U. S. Export Administration Regulations, U. S. Customs regulations, various economic and trade sanctions regulations administered by the U. S. Treasury Department's Office of Foreign Assets Controls, the U. S. Foreign Corrupt Practices Act of 1977, as amended, the U. S. domestic bribery statute contained in 18 U. S. C. § 201, the U. S. Travel Act, the USA PATRIOT Act and other state and national anti- bribery and anti- money laundering laws in the countries in which we conduct activities. Anti- corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties for clinical trials outside of the United States, to sell our products abroad once we enter a commercialization phase and / or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government- affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences.

**Risks Related to Owning our Common Stock**

The market price of our common stock has been extremely volatile and may continue to be highly volatile due to numerous circumstances beyond our control, and stockholders could lose all or part of their investment. The market price of our common stock may be highly volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, which include:

- whether we achieve our anticipated corporate objectives;
- actual or anticipated fluctuations in our financial condition and operating results;
- changes in financial or operational estimates or projections;
- **the development status of our product candidates and when our products receive regulatory approval;**
- our execution of our sales and marketing, manufacturing and other aspects of our business plan;
- performance of third parties on whom we rely to manufacture our products, **and** product components **and product candidates**, including their ability to comply with regulatory requirements;
- **the results of our clinical studies and clinical trials;**
- results of operations that vary from those of our competitors and the expectations of securities analysts and investors;
- changes in expectations as to our future financial performance, including financial estimates by securities analysts and investors;
- our announcement of significant contracts, acquisitions, or capital commitments;
- announcements by our competitors of competing products or other initiatives;
- announcements by third parties of significant claims or proceedings against us;
- regulatory and reimbursement developments in the United States and abroad;
- future sales of our common stock;
- product liability claims;
- healthcare reform measures in the United States;
- additions or departures of key personnel; and
- general economic or political conditions in the United States or elsewhere.

In addition, the stock market in general, and the stock of medical biotechnology companies like ours, in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the issuer. For example, on ~~March 15~~ **February 14, 2022-2023** and ~~November 9~~ **December 21, 2022-2023**, the closing price of our common stock on Nasdaq was \$ ~~67.1~~ **90.56** and \$ ~~0.92-18~~, respectively, and daily trading volume on these days was approximately ~~42,90,326~~, 500 and ~~236,534~~, **500-300** shares, respectively. ~~Additionally, our intraday trading prices have experienced extreme fluctuation. On April 7, 2022, the difference between our high and low trading price was \$ 52.10.~~ These broad market fluctuations may adversely affect the trading price of our common stock. In particular, a proportion of our common stock may be traded by short sellers which may put pressure on the supply and demand for our common stock, further influencing volatility in its market price. Additionally, these and other external factors have caused and may continue to cause the market price and demand for our common stock to fluctuate, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of our common stock. While the market price of our common stock may respond to developments regarding operating performance and prospects, expansion plans, developments regarding our participation in direct contracting, ~~the impacts of COVID-19~~, and developments regarding our industry, we believe that the extreme volatility we experienced in recent periods reflects market and trading dynamics unrelated to our underlying business, our actual or expected operating performance, our financial condition, or macro or industry fundamentals, and we do not know if these dynamics will continue or how long they will last. Under these circumstances, we caution you against investing in our common stock, unless you are prepared to incur the risk of losing all or a substantial portion of your investment. We may be subject to securities litigation, which is expensive and could divert our management's attention. The market price of our securities may be volatile, and in the past, companies that have experienced volatility in the market price of their securities have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business. **We may have violated Section 13 (k) of the Exchange Act (implementing Section 402 of the Sarbanes- Oxley Act of 2002) and may be subject to sanctions as a result. Section 13 (k) of the Exchange Act provides that it is unlawful for a company that has a class of securities registered under Section 12 of the Exchange Act to, directly or indirectly, including through any subsidiary, extend or maintain credit in the form of a personal loan to or for any of**

its directors or executive officers. In the fiscal year ended December 31, 2022 and the nine months ended September 30, 2023, we paid certain expenses of our former Chief Executive Officer and Chairman of the Board, which may be deemed to be personal loans made by us to our former Chief Executive Officer and Chairman of the Board that are not permissible under Section 13 (k) of the Exchange Act. Specifically, after a review completed by the Audit Committee, it was determined that our former CEO and an accounting employee charged certain personal expenses on their corporate credit cards that were not recorded as related party receivables. The aggregate amount of such unauthorized charges ranged from approximately (i) \$ 257, 000 to \$ 405, 000 for all of 2022, (ii) \$ 86, 000 to \$ 122, 000 for the quarter ended March 31, 2023 and (iii) \$ 79, 000 to \$ 150, 000 for the quarter ended June 30, 2023. The accounting employee was also the CEO's assistant and had roles in the Company's system of internal control over financial reporting, including controls relating to the Company's corporate credit cards. Issuers that are found to have violated Section 13 (k) of the Exchange Act may be subject to civil sanctions, including injunctive remedies and monetary penalties, as well as criminal sanctions. The imposition of any of such sanctions on us could have a material adverse effect on our business, financial position, results of operations or cash flows. If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired. We have identified weaknesses in our internal controls, and we cannot provide assurances that these weaknesses will be effectively remediated, or that additional material weaknesses will not occur in the future. We are subject to the reporting requirements of the Exchange Act, the Sarbanes- Oxley Act and Nasdaq rules and regulations. The Sarbanes- Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. We must perform system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting in our Annual Report on Form 10- K for each year, as required by Section 404 of the Sarbanes- Oxley Act (" Section 404 "). This requires significant management efforts and requires us to incur substantial professional fees and internal costs to expand our accounting and finance functions. Any failure to implement required new or improved controls, or difficulties encountered in their implementation, could cause us to fail to meet our reporting obligations. In addition, any testing by us, as and when required, conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, as and when required, may reveal deficiencies in our internal controls over financial reporting that are deemed to be significant deficiencies or material weaknesses or that may require prospective or retroactive changes to our financial statements, or may identify other areas for further attention or improvement. Furthermore, we cannot be certain that our efforts will be sufficient to remediate or prevent future material weaknesses or significant deficiencies from occurring. We do not yet have effective disclosure controls and procedures, or internal controls over all aspects of our financial reporting. Specifically, we have identified the following control deficiencies which we believe are material weaknesses. • We did not maintain an effective control environment as there was an inadequate segregation of duties with respect to certain cash disbursements. The processing and the approval for payment of credit card transactions and certain bank wires were being handled by the former CEO and an accounting employee, and the accounting employee was responsible for the reconciliation of credit card statements and bank statements. This allowed these individuals to submit unauthorized payments to unauthorized third parties. • We do not have an effective risk assessment process or effective monitoring of compliance with established accounting policies and procedures, and do not demonstrate a sufficient level of precision in the application of our controls. • Our controls over the approval and reporting of expenses paid with the Company's credit cards and certain bank wires were not designed and maintained to achieve the Company's objectives. • We have insufficient accounting resources to maintain adequate segregation of duties, maintain adequate controls over the approval and posting of journal entries, and to provide optimal levels of oversight in order to process financial information in a timely manner, analyze and account for complex, non- routine transactions, and prepare financial statements. • We do not yet have adequate internal controls in place for the timely identification, approval or reporting of related party transactions. • The Company did not design, implement, and maintain effective controls to ensure information technology (" IT ") policies and procedures set the tone at the top, to mitigate the risks to the achievement of IT objectives and ITGCs in the change management, logical security and computer operations domains. Specifically, the design and implementation of user authentication, user access privileges, data backup and data recovery controls as well as the monitoring controls of excessive user access and elevated privileged access to financial applications and data were not appropriately designed and maintained. In addition, these inadequate ITGC controls combined with the use of personal devices to conduct business, can lead to an IT control environment vulnerable to breaches and social engineering persuasion. We cannot provide assurances that these weaknesses will be effectively remediated, or that additional material weaknesses will not occur in the future. As a result of the material weaknesses in our internal controls over financial reporting described above, and other matters raised or that may in the future be raised by the SEC, we may face for the prospect of litigation or other disputes which may include, among others, claims invoking the federal and state securities laws, contractual claims or other claims arising from the material weaknesses in our internal control over financial reporting and the preparation of our financial statements, any of which claims could result in adverse effects to our business. As of the date hereof, we have no knowledge of any such litigation or dispute. Our Amended and Restated Certificate of Incorporation requires, to the fullest extent permitted by law, that derivative actions brought in our name, actions against our directors, officers, other employees or stockholders for breach of fiduciary duty and other similar actions may be brought only in the Court of Chancery in the State of Delaware and, if brought outside of Delaware, the stockholder bringing the suit will be deemed to have consented to service of process on such stockholder's counsel, which may have the effect of discouraging lawsuits against



our directors, officers, other employees or stockholders. Our Amended and Restated Certificate of Incorporation requires, to the fullest extent permitted by law, that derivative actions brought in our name, actions against our directors, officers, other employees or stockholders for breach of fiduciary duty and other similar actions may be brought only in the Court of Chancery in the State of Delaware and, if brought outside of Delaware, the stockholder bringing the suit will be deemed to have consented to service of process on such stockholder's counsel except any action (A) as to which the Court of Chancery in the State of Delaware determines that there is an indispensable party not subject to the jurisdiction of the Court of Chancery (and the indispensable party does not consent to the personal jurisdiction of the Court of Chancery within ten days following such determination), (B) which is vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery, (C) for which the Court of Chancery does not have subject matter jurisdiction, or (D) any action arising under the Securities Act, as to which the Court of Chancery and the federal district court for the District of Delaware shall have concurrent jurisdiction. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and consented to the forum provisions in our Amended and Restated Certificate of Incorporation. This choice of forum provision may make it more costly for a stockholder to bring a claim, and it may also limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, other employees or stockholders, which may discourage lawsuits with respect to such claims, although our stockholders cannot waive our compliance with federal securities laws and the rules and regulations thereunder. Alternatively, if a court were to find the choice of forum provision contained in our Amended and Restated Certificate of Incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, operating results and financial condition. Our Amended and Restated Certificate of Incorporation provides that the exclusive forum provision will be applicable to the fullest extent permitted by applicable law. Section 27 of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction. In addition, our Amended and Restated Certificate of Incorporation provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act of 1933, as amended, or the rules and regulations promulgated thereunder. We note, however, that there is uncertainty as to whether a court would enforce this provision and that investors cannot waive compliance with the federal securities laws and the rules and regulations thereunder. Section 22 of the Securities Act creates concurrent jurisdiction for state and federal courts over all suits brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. An active trading market for our common stock may not develop or be sustained. Prior to the commencement of trading of our common stock on February 18, 2022, no public market for our common stock existed. Although our common stock is listed on The Nasdaq Capital Market, an active trading market for our common stock may not develop, or if developed, be sustained. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair value of your shares. Further, an inactive market may also impair our ability to raise capital by selling shares of our common stock may impair our ability to enter into strategic partnerships or acquire companies or products by using our shares of common stock as consideration. Our principal stockholders and management own a significant percentage of our capital stock and will be able to exert a controlling influence over our business affairs and matters submitted to stockholders for approval. As of ~~March 6, 2023~~ **April 5, 2024**, our officers and directors, together with holders of 5% or more of our outstanding common stock and their respective affiliates, beneficially own or control ~~10,540,376, 600,959~~ **10,540,376, 600,959** shares of our common stock, which in the aggregate represents approximately ~~65.26~~ **40**% of the outstanding shares of our common stock. As a result, if some of these persons or entities act together, they will have the ability to exercise significant influence over matters submitted to our stockholders for approval, including the election and removal of directors, amendments to our Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws, the approval of any business combination and any other significant corporate transaction. These actions may be taken even if they are opposed by other stockholders. This concentration of ownership may also have the effect of delaying or preventing a change of control of our company or discouraging others from making tender offers for our shares, which could prevent our stockholders from receiving a premium for their shares. Some of these persons or entities who make up our principal stockholders may have interests different from yours. There can be no assurance that we will be able to comply with the continued listing standards of Nasdaq. Our continued eligibility for listing on Nasdaq depends on our ability to comply with Nasdaq's continued listing requirements. **On September 18, 2023, we received notice from Nasdaq staff indicating that, based upon the closing bid price of the Common Stock for the prior 30 consecutive business days, we were not in compliance with the requirement to maintain a minimum bid price of \$ 1.00 per share for continued listing on Nasdaq, as set forth in Nasdaq Listing Rule 5550 (a) (2). We have 180 days from September 18, 2023, or through March 16, 2024, to regain compliance with the Bid Price Rule. On March 13, 2024, we submitted a plan of compliance to Nasdaq to discuss our plans to evidence compliance with the Bid Price Rule and we received an additional 180-day period, or until September 16, 2024, to regain compliance with the Bid Price Rule.** If Nasdaq delists ~~the our~~ common stock from trading on its exchange for failure to meet the **Bid Price Rule or any other** listing standards, we and our stockholders could face significant material adverse consequences including: • a limited availability of market quotations for our securities; • a determination that our common stock is a "penny stock," which will require brokers trading in our common stock to adhere to more stringent rules, possibly resulting in a reduced level of trading activity in the secondary trading market for our common stock; • a limited amount of analyst coverage; and • a decreased ability to issue additional securities or obtain additional financing in the future. If our shares become subject to the penny stock rules, it would become more difficult to trade our shares. The SEC has adopted rules that regulate broker-dealer practices in



connection with transactions in penny stocks. Penny stocks are generally equity securities with a price of less than \$ 5.00, other than securities registered on certain national securities exchanges or authorized for quotation on certain automated quotation systems, provided that current price and volume information with respect to transactions in such securities is provided by the exchange or system. If we do not retain a listing on Nasdaq and if the price of our common stock is less than \$ 5.00, our common stock will be deemed a penny stock. The penny stock rules require a broker-dealer, before a transaction in a penny stock not otherwise exempt from those rules, to deliver a standardized risk disclosure document containing specified information. In addition, the penny stock rules require that before effecting any transaction in a penny stock not otherwise exempt from those rules, a broker-dealer must make a special written determination that the penny stock is a suitable investment for the purchaser and receive (i) the purchaser's written acknowledgment of the receipt of a risk disclosure statement; (ii) a written agreement to transactions involving penny stocks; and (iii) a signed and dated copy of a written suitability statement. These disclosure requirements may have the effect of reducing the trading activity in the secondary market for our common stock, and therefore stockholders may have difficulty selling their shares. Future sales of our shares by existing stockholders could cause our stock price to decline. If we or our existing stockholders, directors and officers sell, or indicate an intent to sell, substantial amounts of our common stock or securities convertible into our common stock in the public market after contractual lock-up and other legal restrictions on resale lapse, the trading price of our common stock could decline significantly and could decline below the initial public offering price. We have outstanding ~~15-22~~, ~~911-324~~, ~~868-576~~ shares of common stock as of the date hereof, assuming no exercise of outstanding options or warrants, are or will be freely tradable, without restriction, in the public market. If our existing stockholders sell substantial amounts of our common stock in the public market, or if the public perceives that such sales could occur, this could have an adverse impact on the market price of our common stock, even if there is no relationship between such sales and the performance of our business. We have previously registered 2, ~~600-330~~, ~~000-640~~ shares of common stock under our equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and lock-up agreements. Upon issuance, the 1, ~~470-322~~, ~~040-504~~ shares subject to outstanding options under our stock option plan and the shares reserved for future issuance under our stock option plan will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. If our existing stockholders sell substantial amounts of our common stock in the public market, or if the public perceives that such sales could occur, this could have an adverse impact on the market price of our common stock, even if there is no relationship between such sales and the performance of our business. If we fail to maintain an effective system of internal controls, we may not be able to accurately report our financial results or prevent fraud which could subject us to regulatory sanctions, harm our business and operating results and cause the trading price of our stock to decline. Effective internal controls required under Section 404 of the Sarbanes-Oxley Act, are necessary for us to provide reliable financial reports and effectively prevent fraud. If we cannot provide reliable financial reports or prevent fraud, our business, reputation and operating results could be harmed. We have discovered, and may in the future discover, areas of our internal controls that need improvement. We cannot be certain that the measures we have taken or intend to take will ensure that we maintain adequate controls over our financial processes and reporting in the future. Any failure to implement the required new or improved controls or difficulties encountered in their implementation could subject us to regulatory sanctions, harm our business and operating results or cause us to fail to meet our reporting obligations. Inferior internal controls could also harm our reputation and cause investors to lose confidence in our reported financial information, which could have a negative impact on the trading price of our stock. We are an "emerging growth company" and the reduced disclosure requirements applicable to emerging growth companies could make our common stock less attractive to investors. We are an "emerging growth company," as defined in the JOBS Act. We may remain an "emerging growth company" until as late as December 31, 2027 (the fiscal year-end following the fifth anniversary of the completion of our initial public offering, which closed during February 2022), though we may cease to be an "emerging growth company" earlier under certain circumstances, including (1) if the market value of our common stock that is held by nonaffiliates exceeds \$ 700 million as of any June 30, in which case we would cease to be an "emerging growth company" as of the following December 31, or (2) if our gross revenue exceeds \$ 1.235 billion in any fiscal year. "Emerging growth companies" may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. Investors could find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. In addition, Section 102 of the JOBS Act also provides that an "emerging growth company" can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act, for complying with new or revised accounting standards. An "emerging growth company" can therefore delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We are subject to increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives. As a public company, we incur significant legal, accounting, and other expenses that we did not incur as a private company, including costs associated with public company reporting requirements. The Sarbanes-Oxley Act of 2002, as amended, or Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and The Nasdaq Capital Market to implement provisions of the Sarbanes-Oxley Act, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas, such as "say on

pay” and proxy access. Emerging growth companies may implement many of these requirements over a longer period of up to five years from the pricing of their initial public offering. We intend to take advantage of these extended transition periods but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel will devote a substantial amount of time to these compliance programs and monitoring of public company reporting obligations and as a result of the new corporate governance and executive compensation related rules, regulations and guidelines prompted by the Dodd- Frank Act and further regulations and disclosure obligations expected in the future, we will likely need to devote additional time and costs to comply with such compliance programs and rules. These rules and regulations will cause us to incur significant legal and financial compliance costs and will make some activities more time-consuming and costly. To comply with the requirements of being a public company, we may need to undertake various actions, including implementing new internal controls and procedures and hiring new accounting or internal audit staff. The Sarbanes-Oxley Act requires that we maintain effective disclosure controls and procedures and internal control over financial reporting. We are continuing to develop and refine our disclosure controls and other procedures that are designed to ensure that information required to be disclosed by us in the reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms, and that information required to be disclosed in reports under the Securities Exchange Act of 1934, as amended, or the Exchange Act, is accumulated and communicated to our principal executive and financial officers. Our current controls and any new controls that we develop may become inadequate and weaknesses in our internal control over financial reporting may be discovered in the future. Any failure to develop or maintain effective controls when we become subject to this requirement could negatively impact the results of periodic management evaluations and annual independent registered public accounting firm attestation reports regarding the effectiveness of our internal control over financial reporting that we may be required to include in our periodic reports we will file with the SEC under Section 404 of the Sarbanes- Oxley Act of 2002, or the Sarbanes- Oxley Act, harm our operating results, cause us to fail to meet our reporting obligations or result in a restatement of our prior period financial statements. In the event that we are not able to demonstrate compliance with the Sarbanes- Oxley Act, that our internal control over financial reporting is perceived as inadequate or that we are unable to produce timely or accurate financial statements, investors may lose confidence in our operating results and the price of our common stock could decline. In addition, if we are unable to continue to meet these requirements, we may not be able to remain listed on Nasdaq. The rules and regulations applicable to public companies have substantially increased our legal and financial compliance costs and make some activities more time- consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition, and results of operations. The increased costs will decrease our net income and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, these rules and regulations made it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs in the future to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. Our management team has limited experience managing a public company. **Most** **Several** members of our management team have limited experience managing a publicly- traded company, interacting with public company investors and complying with the increasingly complex laws pertaining to public companies. Our management team may not successfully or efficiently manage our transition to being a public company subject to significant regulatory oversight and reporting obligations under the federal securities laws and the continuous scrutiny of securities analysts and investors. These new obligations and constituents require significant attention from our senior management and could divert their attention away from the day- to- day management of our business, which could adversely affect our business, financial condition and operating results . **If we fail to maintain an..... on the trading price of our stock** . If securities or industry analysts do not publish research, or publish inaccurate or unfavorable research, about our business, our stock price and our trading volume could decline. The trading market for our common stock depends, in part, on the research and reports that securities or industry analysts publish about us or our business. While we currently have certain analyst coverage, if one or more of the analysts who cover us downgrade our common stock or publish inaccurate or unfavorable research about our business, our stock price could decline. In addition, if our operating results fail to meet the forecast of analysts, our stock price could decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, demand for our common stock could decrease, which might cause our stock price and trading volume to decline. Our stock repurchase program may adversely affect our liquidity and cause fluctuations in our stock price. On November 8, 2022, our Board authorized a stock repurchase program pursuant to which the Company may repurchase up to 5 million shares of our common stock, with a maximum price of \$ 1. 00 per share, with discretion to management to make purchases subject to market conditions. On November 18, 2022, our Board approved an increase to the maximum price to \$ 2. 00 per share. Potential future stock repurchases under the stock share repurchase program could be funded by operating cash flow or excess cash balances. The maximum number of shares of the Company’ s common stock that may yet be repurchased under the share repurchase program is 4. 5 million. Repurchases under the stock repurchase program may adversely affect our liquidity, which in turn could impact our profitability, financial condition and results of operations. In addition, repurchases under the stock repurchase program will reduce the number of shares of our common stock available for purchase and sale in the public market, which could affect the market price of our common stock. Furthermore, the Inflation Reduction Act of 2022, which was signed into law in August 2022, imposes a non- deductible 1 % excise tax on the fair market value of stock repurchases after December 31, 2022 , that exceed \$ 1. 0 million in a taxable year,

which may impact the tax efficiency of our stock repurchase program. Failure in, or security breaches or incidents impacting, our information technology or storage systems could significantly disrupt our operations and our research and development efforts. Our ability to execute our business strategy will depend, in part, on the continued and uninterrupted performance of our information technology, or IT, systems, which support our operations, including at our proposed clinical laboratories ~~and our research and development efforts~~. We are dependent on our IT systems for many aspects of our business, including our needs to retain and store our confidential and proprietary business information and to receive and process test orders, securely store patient health records and deliver the results of our tests. The integrity and protection of our own data, and that of our customers and employees, is critical to our business. The regulatory environment governing information, security and privacy and data protection laws is increasingly demanding and continues to evolve. IT systems are vulnerable to damage from a variety of sources, including telecommunications or network failures, cyberattacks (including ransomware attacks) and other malicious human acts from criminal hackers, hacktivists, state- sponsored intrusions and other attacks, industrial espionage and employee malfeasance, breaches and incidents due to employee error or negligence, and natural disasters. Moreover, despite network security and back- up measures, some of our servers are potentially vulnerable to physical or electronic break- ins, computer viruses and other malicious code ~~or similar disruptive problems~~. **Proclarix is comprised of two components: Proclarix Assays and Proclarix Risk Calculator. The Proclarix Risk Calculator is cloud- based software to integrate the results from Proclarix Assays for THBS1 and CTSD together with age, total and free PSA (from third party manufacturers) to calculate the Proclarix Risk Score. When entering the Patient ID, a warning indicates that the Patient ID shall not contain any sensitive personal patient data. After the risk report is generated, the patient data including values for THBS1, CTSD, total and free PSA together with age and Patient ID is stored for six months and is then automatically deleted.** High- profile security breaches and incidents at other companies and in government agencies have increased in recent years, **particularly in the healthcare sector**, and security industry experts and government officials have warned about the risks of hackers and cyber- attacks targeting businesses such as ours. Cyber- attacks are becoming more sophisticated and frequent, and in some cases have caused significant harm. Computer hackers and others routinely attempt to breach the security of technology products, services, ~~and systems, and to fraudulently induce employees, customers, or others to disclose~~ **disclose** information or unwittingly provide access to systems or data. Much of our workforce currently works remotely rather than in our offices, and we may be more susceptible to security breaches and incidents as a result. Our service providers **also may accommodate remote workers and therefore** may be more susceptible to security breaches and other security incidents ~~while social distancing measures restrict the ability of their employees to work at offices to combat the COVID- 19 pandemic~~. We **have experienced and** may in the future experience attempted or successful cyber- attacks of our IT systems or networks. To date, we have not experienced any material cyber- attacks. However, any security breach or incident ~~impacting~~, or interruption could compromise our networks and the information stored therein, including algorithms relating to our products, could be accessed by unauthorized parties, publicly disclosed, lost, **rendered** inaccessible or unavailable, corrupted, or stolen. Despite the precautionary measures we have taken to prevent unanticipated problems that could affect our IT systems, unauthorized access to our systems, or disruptions or other security breaches impacting our IT systems, ~~and any unauthorized access to, or, loss, inaccessibility, unavailability, corruption, theft, or disclosure could also disrupt our operations, including our ability to:~~

- process tests, provide test results, bill payors or patients;
- process claims and appeals;
- provide customer assistance services;
- conduct research and development activities;
- collect, process and prepare company financial information;
- provide information about our tests and other patient and healthcare provider education and outreach efforts through our website; and
- ~~and~~ manage the administrative aspects of our business and damage our reputation. Any such breach, incident, or other compromise of IT systems or data, or the perception that any of these has occurred, could result in ~~legal claims or proceedings~~, liability under laws that protect the privacy of personal information, such as the Health Insurance Portability and Accountability Act of 1996, **as amended by the Health Information Technology or for Economic and Clinical Health Act of 2009 (collectively, “HIPAA ”)**, similar U. S. state data ~~protection~~ **privacy and security laws and** regulations, and other regulations, ~~as well as the breach of which could result in legal claims, complaints, regulatory investigations or other proceedings, and significant fines, or other penalties, and or other~~ **the liability requirement to enter into a multi- year settlement and remediation agreement with federal or state agencies**. We also may be required to incur significant costs in an effort to **prevent, detect, and prevent-remediate** security breaches and other security- related incidents. Additionally, information obtained by third parties in connection with past or future cyberattacks, ~~or other security breaches or incidents could be used in ways that adversely affect our company or our stockholders. Further, third- party service providers who support our operations, and our independent contractors (including CROs), consultants, collaborators, and service providers also may suffer interruptions and disruptions of systems and other breaches, incidents, or other compromises of~~ ~~or impacting~~ their IT systems or data that they process or maintain for us, which may lead to any of the foregoing. We and our third- party service providers may not have the resources or technical sophistication to anticipate or prevent all cyberattacks or other sources of security breaches or incidents, and we or they may face difficulties or delays in identifying and responding to cyberattacks and data security breaches and incidents. In addition, the interpretation and application of consumer ~~or health related~~ **and data** security, privacy and ~~data~~ protection laws in the United States, Europe and elsewhere are often uncertain, contradictory and in flux, such as in the area of international transfers of personal data. Complying with these various laws ~~and satisfying healthcare providers’ and patients’ evolving expectations with respect to data protection, could cause us to incur substantial costs or require us to change our business practices and compliance procedures in a manner adverse to our business. We do not maintain insurance policies for cybersecurity- related matters, data handling or data security liabilities. The successful assertion of one or more large claims against us could have a material adverse effect on our business, including our financial condition, operating results, and reputation.~~ **Our Amended and Restated Certificate of Incorporation and our Amended and Restated Bylaws and Delaware law may have anti- takeover effects that could discourage, delay or prevent a change in control, which may cause our**

stock price to decline. Our Amended and Restated Certificate of Incorporation and our Amended and Restated Bylaws and Delaware law could make it more difficult for a third party to acquire us, even if closing such a transaction would be beneficial to our stockholders. Our Amended and Restated Certificate of Incorporation authorizes us to issue up to 10 million shares of preferred stock. This preferred stock may be issued in one or more series, the terms of which may be determined at the time of issuance by our board of directors without further action by stockholders. The terms of any series of preferred stock may include voting rights (including the right to vote as a series on particular matters), preferences as to dividend, liquidation, conversion and redemption rights and sinking fund provisions. The issuance of any preferred stock could materially adversely affect the rights of the holders of our common stock, and therefore, reduce the value of our common stock. In particular, specific rights granted to future holders of preferred stock could be used to restrict our ability to merge with, or sell our assets to, a third party and thereby preserve control by the present management. Provisions of our Amended and Restated Certificate of Incorporation, our Amended and Restated Bylaws and Delaware law also could have the effect of discouraging potential acquisition proposals or making a tender offer or delaying or preventing a change in control, including changes a stockholder might consider favorable. Such provisions may also prevent or frustrate attempts by our stockholders to replace or remove our management. In particular, our Amended and Restated Certificate of Incorporation, our Amended and Restated Bylaws and Delaware law, as applicable, among other things: • provide the board of directors with the ability to alter the bylaws without stockholder approval; • place limitations on the removal of directors; • establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings; and • provide that vacancies on the board of directors may be filled by a majority of directors in office, although less than a quorum. These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management. As a Delaware corporation, we are also subject to provisions of Delaware law, including Section 203 of the Delaware General Corporation law, which prevents certain stockholders holding more than 15 % of our outstanding capital stock from engaging in certain business combinations without approval of the holders of at least two-thirds of our outstanding common stock not held by such stockholder. Any provision of our Amended and Restated Certificate of Incorporation, Amended and Restated Bylaws or Delaware law that has the effect of delaying, preventing, or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our capital stock, and could also affect the price that some investors are willing to pay for our common stock. We do not anticipate paying any cash dividends on our common stock in the foreseeable future and, as such, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. We have never declared or paid cash dividends on our common stock. We do not anticipate paying any cash dividends on our common stock in the foreseeable future. We currently intend to retain all available funds and any future earnings to fund the development and growth of our business. In addition, ~~and~~ any future loan arrangements we enter into may contain ~~terms~~ prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. As a result, capital appreciation, if any, of our common stock, which may never occur, will be your sole source of gain for the foreseeable future. Environmental, social and governance matters may impact our business and reputation. Increasingly, in addition to the importance of their financial performance, companies are being judged by their performance on a variety of environmental, social and governance (“ ESG ”) matters, which are considered to contribute to the long- term sustainability of companies’ performance. A variety of organizations measure the performance of companies on such ESG topics, and the results of these assessments are widely publicized. In addition, investment in funds that specialize in companies that perform well in such assessments are increasingly popular, and major institutional investors have publicly emphasized the importance of such ESG measures to their investment decisions. Topics taken into account in such assessments include, among others, the company’ s efforts and impacts on climate change and human rights, ethics and compliance with law, and the role of the company’ s board of directors in supervising various sustainability issues. In addition to the topics typically considered in such assessments, in the healthcare industry, issues of the public’ s ability to access our medicines are of particular importance. In light of investors’ increased focus on ESG matters, there can be no certainty that we will manage such issues successfully, or that we will successfully meet society’ s expectations as to our proper role. Any failure or perceived failure by us in this regard could have a material adverse effect on our reputation and on our business, share price, financial condition, or results of operations, including the sustainability of our business over time. A possible “ short squeeze ” due to a sudden increase in demand of our common stock that largely exceeds supply may lead to price volatility in our common stock. Investors may purchase our common stock to hedge existing exposure in our common stock or to speculate on the price of our common stock. Speculation on the price of our common stock may involve long and short exposures. To the extent aggregate short exposure exceeds the number of shares of our common stock available for purchase in the open market, investors with short exposure may have to pay a premium to repurchase our common stock for delivery to lenders of our common stock. Those repurchases may in turn ~~;~~ dramatically increase the price of our common stock until investors with short exposure are able to purchase additional common shares to cover their short position. This is often referred to as a “ short squeeze. ” A short squeeze could lead to volatile price movements in our common stock that are not directly correlated to the performance, or prospects of our company and once investors purchase the shares of common stock necessary to cover their short position the price of our common stock may decline.