VBI Vaccines (VBIV)

VBI Announces the Completion of Enrollment for Phase I Trial Evaluating CMV Vaccine Candidate

VBI Vaccines (NasdaqCM: VBIV) has announced the completion of enrollment for their Phase I trial evaluating a prophylactic vaccine against cytomegalovirus (CMV). Earlier this month, the Company also reported a positive review by the Data Safety Monitoring Board (DSMB). This provides the first indication of the vaccine’s safety in humans and represents an important de-risking moment for the program. The Company expects to report interim data from this Phase I trial in the first half of 2017 and full data in the first half of 2018. VBI also presented data at the World Vaccine Congress in Barcelona on modifications made to the gB surface antigen that is used in their vaccine candidate. This may confer stronger immunogenicity than possible with the native protein and sets VBI’s program apart from other CMV vaccine candidates.

- **Phase I Study is On Track for Interim Look in First Half of 2017.** VBI’s ongoing Phase I study is testing the safety and efficacy of their prophylactic CMV vaccine in 128 healthy, CMV-negative volunteers. The trial is also collecting data on vaccine-induced titers of neutralizing antibodies as a secondary endpoint, which will provide an important indication of the vaccine’s efficacy in protecting against CMV infection. With the completion of enrollment for the study, VBI is on track to report interim data in the first half of 2017.

- **Positive Review by DSMB is an Important Milestone for VBI.** The ongoing Phase I study is the first test of VBI’s prophylactic CMV vaccine in humans. The vaccine has been safe and well-tolerated in preclinical studies. The adjuvant is alum, the most common adjuvant in human vaccines, with a track record of safety dating back to the 1930s. The positive review by the DSMB provides an initial sign of the vaccine’s safety and tolerability in humans and an important validation of the enveloped virus-like particle (eVLP) platform.

- **Wide-Open Market Opportunity for Prophylactic CMV Vaccine.** Although generally inconsequential for healthy individuals, CMV infection during pregnancy is the leading cause of birth defects. Every year in the US, 40,000 infants are born with a CMV infection and roughly 8,000 develop symptoms or other complications. There is currently no prophylactic treatment for pregnant women to prevent congenital CMV infection and previous attempts to develop a prophylactic CMV vaccine have faltered in early stages.

Expected Upcoming Milestones

- **H2 2016 – Meeting with EMA/FDA to discuss development path for Sci-B-Vac for hepatitis B virus (HBV).**
- **H1 2017 – Interim safety, tolerability, and immunologic proof of concept data from Phase I study of VBI-1501A.**
- **H1 2017 – Initiation of Phase I trial evaluating therapeutic GBM vaccine candidate.**
- **2018 – Completion of the Phase I study of VBI-1501A, which is anticipated to be 20 months in duration.**
VBI Presented Data on Modifications to CMV Antigen to Improve Immunogenicity. VBI’s CMV vaccine candidate consists of eVLPs that contain the viral gB antigen on its surface. This protein is critically involved in the fusion process through which the virus enters cells. In its native form, the gB antigen primarily induces the production of neutralizing antibodies (nAbs) against the AD-1 epitope, which is only weakly neutralizing. Recognizing that this immunodominant epitope is only weakly neutralizing, the field has been particularly interested in modifying the gB antigen to improve its immunogenicity.

At the World Vaccine Congress earlier this month, VBI’s Chief Medical Officer, Dr. Francisco Diaz-Mitoma, presented data showing that an optimized form of the gB antigen has a greater capacity for inducing potent nAbs than the protein’s natural conformation. The modified gB protein adopts a prefusion conformation, burying the AD-1 epitope and exposing the AD-4 epitope, which is strongly neutralizing. This sets VBI’s CMV vaccine candidate apart from other attempts at using the gB antigen and may explain the superior neutralizing capacity observed in preclinical studies.

Early-Stage Clinical Development of a Prophylactic CMV Vaccine is Ongoing. Aside from VBI, there are two other CMV vaccine programs currently in clinical development. Several have halted or reverted back to preclinical development following disappointing results. Merck (NYSE: MRK) is currently testing a CMV vaccine, V160-001, in a Phase I trial, which is expected to read out interim data in the near term and full data in the first quarter of 2017. Hookipa Biotech (private) also recently launched a Phase I trial for their prophylactic vaccine candidate HB-101. Both Merck and Hookipa’s vaccine candidates are based on replication-deficient viruses. The administration of replication-deficient viruses to healthy adolescent girls may raise safety concerns that could add additional regulatory obstacles and limit their use in healthy individuals. Two other potential competitors, Pfizer (NYSE: PFE) and City of Hope (private), are both still in preclinical development and have not released any data or given clear signals as to upcoming clinical trial plans.

VBI’s Vaccine Candidate May Have Superior Neutralization Capacity. Some of the companies in this space have released preclinical data, allowing for comparison between the vaccines’ potencies. However, it is worth noting that we must be cautious because not all of these preclinical studies were conducted in the same species, so some of the observed differences may result from inter-species differences in immune response. In rabbits, three doses of Merck’s vaccine candidate induced neutralizing antibody titers that were four times lower than those induced by natural immunity. Following three doses in mice, Novartis’ (NYSE: NVS) vaccine candidate elicited titers that were eight times lower than that induced by natural immunity. Although VBI used Cytogam, an intravenous immunoglobulin (IgG) containing standardized anti-CMV titers, as its benchmark control and Merck and Novartis used seropositive human sera, a recent study has shown that the two are similar in terms of neutralization capacity. In VBI’s preclinical study, two doses of VBI-1501A were sufficient to induce higher titers than that contained in Cytogam or three doses of either of these other vaccine candidates. Since higher induced neutralizing antibody titers correlate with levels of protection, VBI’s higher potency could translate into a better efficacy profile in clinical trials.

Strategy for Commercializing a CMV Vaccine Will Likely Parallel that of HPV Market. The primary target market for prophylactic CMV vaccination is adolescent girls, similar to recommendations for vaccination against the human papilloma virus (HPV). Two virus-like particle (VLP) vaccines, Merck’s (NYSE: MRK) Gardasil and GSK’s (NYSE: GSK) Cervarix have been approved as prophylactic treatments for HPV, which causes the majority of cervical and vaginal cancers. The percentage of adolescent girls in the US aged 13-17 who have received 1, 2, or 3 doses of the HPV vaccine are shown in Figure 1.
In 2007, 5.9% of adolescent girls received the full 3 doses and a total of 25.1% of girls in this age group were given at least 1 dose. By 2015, these numbers had grown to 41.9% receiving all 3 doses and 62.8% receiving at least 1 dose. Reaching market penetration comparable to HPV coverage rates in 2015 would reflect a total market opportunity of $1.2 billion in sales for a prophylactic CMV vaccine. However, individuals may be more likely to seek a CMV vaccine than an HPV vaccine, due to the nearer-term risk and highly emotive fear of birth defects relative to the seemingly distant risk of cervical cancers. Market acceptance for HPV vaccines also faced challenges associated with vaccinating against a sexually transmitted disease (STD), which would not be relevant in the case of CMV.

**Phase I Trial Design.** The Phase I study will assess the safety and tolerability of VBI’s CMV vaccine candidate administered 3 times at months 0, 2, and 6 to 125 CMV-negative healthy adults. There will be an interim analysis at month 3. The trial will also test for the presence of anti-CMV neutralizing antibodies in fibroblasts and epithelial cells, as well as gB binding titers by ELISA, as secondary endpoints. Neutralizing antibody titers acquired after natural CMV infection afford approximately 90% protection against infection, and these levels serve as a useful benchmark for titers induced by VBI’s CMV vaccine candidate. Enrolled patients will be divided into five cohorts of 25 patients:

- Cohort 1: 0.5 µg VBI-1501A + alum.
- Cohort 2: 1.0 µg VBI-1501A + alum.
- Cohort 3: 2.0 µg VBI-1501A + alum.
- Cohort 4: 2.0 µg VBI-1501A without alum (VBI-1501).
- Cohort 5: Placebo (buffer/sucrose).
**Risk to Investment**

We consider an investment in VBI Vaccines to be a high-risk investment. While the merger is now complete, there are risks associated with VBI's plan to launch additional late-stage trials for *Sci-B-Vac*. In addition, successful clinical trials may not necessarily translate into regulatory approvals. For VBI's clinical and preclinical vaccine programs, the Company has generated positive preclinical data, but these early indications of efficacy do not necessarily translate into positive clinical results. The Company may need to raise funds to support its programs, which could be dilutive to current shareholders. There are also regulatory risks associated with vaccine development, and VBI may not receive approvals for its vaccine candidates despite significant time and financial investments. Even if VBI secures regulatory approval, there is no guarantee that expectations of market penetration and sales will come to fruition.
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