Summary Basis for Regulatory Action Template

Date: November 11, 2015

From: CDR Elizabeth J. Valenti, Chair of the Review Committee

BLA/ STN#: 103821/5344

Applicant Name: Emergent BioDefense Operations Lansing LLC

Date of Submission: October 30, 2014

PDUFA Goal Date: November 29, 2015

Proprietary Name/ Established Name: BioThrax®, Anthrax Vaccine Adsorbed

Indication:
BioThrax is a vaccine indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis* in persons 18 through 65 years of age. BioThrax is approved for:
1. Pre-exposure prophylaxis of disease in persons at high risk of exposure.
2. Post-exposure prophylaxis of disease following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

X **I concur with the summary review.**
□ **I concur with the summary review and include a separate review to add further analysis.**
□ **I do not concur with the summary review and include a separate review.**

Material Reviewed/Consulted; Specific documentation used in developing the SBRA	Reviewer Name	Document Date
Clinical Review	A. Worobec	November 11, 2015
Nonclinical Studies Review	D. Burns	August 25, 2015
Statistical Review	T. Lin	November 3, 2015
Assay Review	L. Wager	October 13, 2015
Pharmacology/ Toxicology Review	A. O'Carroll	January 29, 2015
Bioresearch Monitoring Review	D. Cato	September 2, 2015
Environmental Assessment Review	C. Harman	May 13, 2015
Pharmacovigilance Plan Review	J. Woo	May 27, 2015
Labeling Review	K. Khuc	April 29, 2015

1. Introduction

While naturally occurring anthrax disease in humans is rare, the potential for use of *Bacillus anthracis* as a bioweapon has significantly increased the level of concern about the disease. Anthrax is one of the most feared of all bioweapons, primarily because the spores are very stable and very easy to disperse. The disease, especially the inhalation form of the disease, is often fatal if not promptly treated. With this form of the disease, spores are inhaled. Once in the lungs, the spores are trafficked to the lymph nodes, where they germinate.

Anthrax Vaccine Adsorbed (AVA), BioThrax® is the only vaccine approved in the U.S. for the prevention of anthrax disease. Initial U.S. approval was granted in 1970. BioThrax is currently licensed for active immunization for the prevention of disease caused by *Bacillus anthracis* in persons 18 through 65 years of age at high risk of exposure. On October 30, 2014 Emergent BioDefense Operations Lansing LLC (Applicant) submitted a supplemental Biologics License Application (sBLA) to broaden the indication to include post-exposure prophylaxis (PEP) of disease following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs in persons 18 through 65 years of age.

Clinical field trials to demonstrate effectiveness of an anthrax vaccine in a post-exposure setting are not feasible and human challenge studies are not ethical because of the rapid progression and fatal nature of the disease. Therefore, animal protection data was used as a basis for demonstration of effectiveness of the product for the proposed indication, per the Animal Rule, 21 CFR 601 Subpart H.

In November 2010, a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held in which a pathway for demonstrating effectiveness of PA-based anthrax vaccines in post-exposure setting using animal data was affirmed. The VRBPAC agreed with the strategy for demonstration of effectiveness of PA-based anthrax vaccines in a post-exposure setting in which protective antibody levels are determined in rabbit and non-human primate studies followed by extrapolation of these protective levels to humans in order to estimate effectiveness of the vaccine in a post-exposure setting. Protective antibody levels in the animals would be determined using the General Use Prophylaxis (GUP) study design in which animals are first vaccinated and then challenged with a lethal aerosol dose of anthrax bacilli.

At that meeting, the VRBPAC also affirmed that animal studies, using a post-exposure prophylaxis design, in which animals are first challenged and then vaccinated, would serve as proof -of-concept that vaccine could have added benefit over antimicrobials alone in a post-exposure setting. The VRBPAC agreed that complexities encountered with the PEP model, which are not encountered with the GUP model, confound estimates of protective antibody levels. Therefore, animal PEP studies were not used to derive protective antibody levels. The VRBPAC further agreed that passive immunization protection studies in animals would serve to support the use of antibodies to bridge animal protection data to humans.

The Animal Rule states that a biological product may be licensed when adequate and well-controlled animal studies are conducted and the results of those animal studies establish that the biological product is "reasonably likely to produce clinical benefit in humans." Licensure of

BioThrax for the PEP indication under the Animal Rule is thereby predicated on demonstration that the anthrax vaccine dose administered to humans can elicit an immune response comparable to that in animals protected from challenge by the vaccine. Toxin neutralizing antibody (TNA) levels represent functional antibody that binds and inactivates anthrax toxin and thus, are considered the most appropriate for measurement of protective activity against anthrax. To demonstrate effectiveness of the vaccines in a post-exposure setting, protective TNA levels were estimated in animal GUP studies; these TNA levels were then extrapolated to humans in order to bridge and estimate effectiveness. The FDA concluded that protective TNA thresholds corresponding to a 70% probability of survival in animal models of inhalational anthrax predict a reasonable survival benefit. Vaccine protection in humans was determined by the percentage of clinical study subjects that achieve a TNA level that corresponds to a 70% probability of survival in the animal models.

Emergent provided data from animal studies in support of the requested post-exposure prophylaxis indication for BioThrax. The animal models chosen were rabbits and monkeys, as they closely mimic human anthrax disease. Two pivotal animal studies (Rabbit Study 646-N107247 and Non-Human Primate Study 844-N109502) used to determine the protective TNA antibody level were conducted. Logistic regression analysis of data from these studies demonstrated that a 70% probability of survival was associated with a TNA NF_{50} (50% neutralization factor) level of 0.56 in rabbits and 0.29 in NHPs   ). A strong relationship was observed between pre-challenge serum TNA levels and survival in each respective animal model (rabbit and NHP), thus it is reasonable to conclude that demonstration of similar antibody titers in human subjects are likely to produce clinical benefit, i.e., enhanced survival in a post-exposure setting. The more conservative of the protective TNA level estimates derived from the animal studies was extrapolated to humans and used to estimate clinical protection.

Emergent also provided supportive rabbit studies in which animals were first challenged and then immunized. These studies serve as proof-of-concept that vaccine can offer a benefit over antimicrobials alone in a post-exposure setting. Data were also provided from animal passive immunization protection studies. These studies serve as proof-of-concept that antibodies, in the absence of other components of the immune response, can provide protection against anthrax.

Emergent included three human clinical studies, two of which (EBS.AVA.005 and EBS.AVA.006) exclusively evaluated the immunogenicity of BioThrax. The third study (EBS.AVA.009) evaluated the potential interference of BioThrax on the pharmacokinetics of ciprofloxacin, and conversely the effect of ciprofloxacin on the immune response to BioThrax when given using the PEP schedule and subcutaneous (SC) route of administration. No new safety issues, beyond those identified in previous clinical studies and noted in the labeling, were observed.

During the review cycle, CBER identified deficiencies with the data to support the addition of PEP to the indication. The prominent issue involved incorrectly recorded Day 69 TNA raw data results, expressed as NF_{50}, for one animal in the pivotal Rabbit Study (646). These deficiencies were resolved through information requests and subsequent revisions to immunogenicity data and analyses for Rabbit Study 646 and for Clinical Studies 005 and 006.

2. Background

Product Description

BioThrax is a sterile suspension made from cell-free filtrates of cultures of an avirulent, non-encapsulated strain of *Bacillus anthracis*. Protective antigen (PA) is a predominant antigen found in these cell-free filtrates. The final product is formulated to contain 1.2 mg/ml aluminum, added as aluminum hydroxide in 0.85% sodium chloride, 25 mcg/ml benzethonium chloride, and 100 mcg/ml formaldehyde (the latter two components are added as preservatives).

Regulatory History

BioThrax, the only anthrax vaccine currently approved for use in the U.S., was originally approved in the 1970s. The original approval was for a six-dose regimen (Week 0, 2, and 4; and Month 6, 12, and 18) administered subcutaneously to prevent disease caused by *Bacillus anthracis* in persons 18 through 65 years of age at high risk of exposure. On December 11, 2008 the FDA approved a change to an intramuscularly (IM) administered five-dose primary series (Week 0 and 4; and Month 6, 12, and 18) followed by an annual booster thereafter.

A further change in dosing schedule for BioThrax was approved on May 17, 2012. This approval changed the schedule to a three-dose primary series (Month 0, 1, and 6), followed by booster injections at 12 and 18 months, and an annual booster thereafter.

With the approval of this supplement BioThrax will be the first vaccine to be approved for an indication based on the Animal Rule. The indication and schedules will be revised to read:

BioThrax is a vaccine indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis* in persons 18 through 65 years of age. BioThrax is approved for:

1. Pre-exposure prophylaxis of disease in persons at high risk of exposure.

Schedule	Route of Administration	Dosing Schedule
Primary Series	Intramuscular	0,1, and 6 months
Booster Series	Intramuscular	6 and 12 months after completion of the primary series and at 12-month intervals thereafter

2. Post-exposure prophylaxis of disease following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs.

Schedule	Route of Administration	Dosing Schedule
Primary Series	Subcutaneous	0, 2, and 4 weeks post-exposure combined with antimicrobial therapy

On April 11, 2014 Emergent received orphan drug-designation for the indication of "post-exposure prophylaxis of anthrax disease resulting from suspected or confirmed exposure to *Bacillus anthracis*."

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

BioThrax is a licensed vaccine. No new manufacturing processes, product quality data, methods, specifications, or results of product tests were submitted for review. The product formulation used in the animal and human studies to support the PEP indication is identical to the formulation described in and approved with the original BLA and subsequent approved changes to the license.

b) CBER Lot Release

There are no pending lots or issue that would preclude approval of this supplement.

c) Facilities review/inspection

No new facility inspections were conducted in support of this supplement. No ongoing or impending investigations or compliance actions with respect to Emergent's facilities or products are in effect.

d) Environmental Assessment

The BLA supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Emergent submitted a single, supportive, non-pivotal, limited, non-GLP toxicology study (2017-11139) that was conducted to study the safety and immunogenicity of BioThrax when given in conjunction with an ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ Rabbits. This study assessed interaction between BioThrax ▓▓▓▓▓▓ Animals were dosed with either anthrax vaccine adsorbed or saline control on Days 1 and 8 and were given a single infusion of either ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ or the reference substance Gamunex® on Day 1. Clinical observations and body weight were measured for a 29 day period at which point all animals were sacrificed. ▓▓▓▓▓ had an attenuation effect on the rabbit endogenous immune response to BioThrax. No significant toxicological findings were reported in this study.

5. Clinical Pharmacology

No new pharmacology data were submitted as part of this supplement.

6. Clinical/ Statistical

a) Clinical Program

Overview

To demonstrate effectiveness of PA-based anthrax vaccines in a post-exposure setting, animal data from a General Use Prophylaxis (GUP) study was used to estimate protective antibody levels in animals. These protective antibody levels were then extrapolated to humans in order to bridge and estimate efficacy for a post-exposure prophylaxis indication where the vaccine is administered in order to protect against disease resulting from residual spores that remain after completion of the recommended course of antimicrobial therapy.

Non-Clinical Animal Studies

To provide evidence of effectiveness as stipulated in the Animal Rule, Emergent conducted two pivotal animal studies to demonstrate that the vaccine could provide protection in a post-exposure setting against exposure to *Bacillus anthracis*.

646-N107247 (Pivotal Rabbit General Use Prophylaxis Study)

Rabbit Study 646 was a pivotal GUP study that included 108 ▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮ Rabbits (50% male, 50% female) weighing between 2.2 kg and 2.7 kg. Animals were randomized into four groups of 24 (Groups 1-4) and one group of 12 (Group 5). On Days 0 and 28, animals were vaccinated intramuscularly with 0.5 ml dilutions of BioThrax or with ▮▮▮▮▮▮▮▮▮▮. The vaccine dilutions for each group were as follows:

- Group 1 AVA 1:4
- Group 2 AVA 1:16
- Group 3 AVA 1:64
- Group 4 AVA 1:256
- Group 5 Saline ▮▮▮▮▮▮▮▮

On Day 70, animals were challenged with an aerosolized aqueous suspension of *Bacillus anthracis* spores (▮▮▮▮▮▮).

The three stated study objectives were 1) to determine the correlation between the dose of vaccine administered in a two-dose pre-exposure vaccine regimen and animal survival following a lethal aerosol challenge of *Bacillus anthracis* spores, 2) to compare measured vaccine-induced levels of anti-PA TNA using the TNA assay in vaccinated and control animals, and to determine the protective TNA level, and 3) to evaluate additional study endpoints including time to death after challenge, body temperature, body weight, clinical observations, the presence/absence of bacteremia, and gross necropsy results.

All Group 1 rabbits survived the lethal challenge and 96% of the Group 2 rabbits survived. Survival percentages for Group 3 and 4 were 63% and 13%, respectively. All animals died that received [redacted] alone (Group 5).

The relationship between antibody levels (as measured by TNA NF_{50}) and survival for the vaccine treated groups in Rabbit Study 646 was investigated using logistic regression analysis. A statistically significant relationship was observed between animal survival and TNA titers (NF_{50}) measured just prior to challenge. Point estimates and confidence intervals for the TNA NF_{50} value corresponding to various survival probabilities were calculated. A pre-exposure NF_{50} level of 0.56 at Day 69 corresponds to a 70% probability of survival. The relationship between TNA NF_{50} levels and survival of the animals was used to extrapolate the animal protection data to humans. The study used an animal model that is essentially identical to the one developed by the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) that was discussed at the November 2010 VRBPAC meeting and it is appropriate for evaluation of PA-based anthrax vaccines.

844-N109502 (Pivotal Non-Human Primate General Use Prophylaxis Study)

Non-Human Primate Study 844 was a pivotal GUP study that included 48 [redacted] [redacted] (50% male, 50% female) that were 1.5-2.6 kg (2.3-3.5 years old). Only animals negative for anti-PA IgG were included in the study. NHPs were randomized into five vaccine groups and one phosphate-buffered saline (PBS) control group. Each group consisted of eight animals. Animals were randomized to one of three aerosol challenge days. Animals were vaccinated intramuscularly with 0.5 ml dilutions of BioThrax or with PBS. The vaccine dilutions for each group were as follows:

- Group 1   Undiluted
- Group 2   AVA 1:4
- Group 3   AVA 1:16
- Group 4   AVA 1:64
- Group 5   AVA 1:256
- Group 6   PBS

NHPs in Groups 1-5 were vaccinated on Days 0 and 28. Animals in Group 6 were placebo-vaccinated on Days 0 and 28. NHPs were challenged via the inhalation route with *Bacillus anthracis* ([redacted]) on Day 70. Serum TNA titers were determined for all animals in the study prior to challenge on Days 0, 14, 28, 42, 56, and 70 and post-challenge on Days 84 and 133.

All animals receiving undiluted vaccine (Group 1) survived; a clear dose response relationship between vaccine dose and survival was noted. A statistically significant relationship was observed between animal survival and TNA titers (NF_{50}) measured just prior to challenge. This study used an animal model that is essentially identical to the one developed by NIH/NIAID that was discussed at the November 2010 VRBPAC meeting and it is appropriate for evaluation of PA-based anthrax vaccines.

Conclusion

The derived estimate for the TNA titer that protects 70% of NHPs (NF_{50} titer of 0.29) is similar to that derived from the rabbit model (NF_{50} titer of 0.56). The finding that the estimated protective levels for two very different animal species are similar provides substantial support for extrapolating animal protective levels to humans.

Human Clinical Studies

To provide evidence of effectiveness as stipulated in the Animal Rule, Emergent conducted two clinical immunogencity studies to demonstrate that the vaccine could provide protection in a post-exposure setting against exposure to *Bacillus anthracis*. One of these studies (EBS.AVA.005) was a pilot study used to inform the design of the pivotal immunogenicity study (EBS.AVA.006). A third study (EBS.AVA.009) was conducted to evaluate the potential interference of BioThrax on the pharmacokinetics of ciprofloxacin, and conversely the effect of ciprofloxacin on the immune response to BioThrax when given using the PEP schedule (Weeks 0, 2, and 4) via the SC route of administration.

EBS.AVA.005 (Immunogenicity Study of a Three-Dose Subcutaneous BioThrax Regimen for Post-exposure Prophylaxis in Healthy Adults)

EBS.AVA.005 was an open-label, multi-center Phase 3 study evaluating a Week 0, 2, and 4 schedule of BioThrax administered as a 0.5 mL SC injection. One hundred and fifty (150) subjects 18 to 65 years of age were enrolled and stratified 1:1 by sex to permit comparison of the immune response of females and males. The primary purpose was to determine the timing and peak of the TNA level that is shown to be protective in a lethal-dose challenge model in animals following three doses of BioThrax given SC on Weeks 0, 2, and 4. Study results were used to design the pivotal Phase 3 study (EBS.AVA.006, below) to support licensure of BioThrax for a PEP indication.

The primary immunogenicity endpoint for this study was the antibody titer measured on study Days 35, 42, 49, and 56 using the TNA assay, assessed by seroconversion rates and geometric mean titers (GMTs).

At the initial vaccination visit (Day 0), subjects received the first dose of BioThrax. Additional vaccination visits occurred on Days 14 and 28. Immunogenicity evaluations occurred at Screening and on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, and 100. TNA assays were performed on blood samples collected at each of these time points. Safety assessments occurred at these same study time points and evaluated local and systemic reactogenicity, along with unsolicited adverse events through subject diary card follow-up and at in-clinic visits. Routine follow-up laboratory testing was performed at select study time points.

Results were reported for the Intent-to-Treat (ITT) (all subjects who were enrolled and received at least one vaccination) and per protocol (PP) populations (all subjects in the ITT population who received all three BioThrax vaccinations within pre-specified time windows

and had follow-up visits with evaluations within the protocol windows). All enrolled subjects received at least one 0.5 mL SC dose of BioThrax, and 138 (92%) completed the study. Of the 150 subjects enrolled in the study, 121 (80.7%) were included in the PP population. The majority of enrolled subjects were white, non-Hispanic, and in the 18-30 year age range.

The study's primary and secondary endpoints were met and support the approval of this application. At Days 35 to 56, > 96% of subjects had at least a four-fold increase in TNA titer, based on [redacted] and NF_{50} TNA data. Results of study EBS.AVA.005 suggested that subjects develop a robust immune response following the second and third vaccinations of BioThrax, using a PEP schedule of 0.5 mL BioThrax given SC on Week 0, 2, and 4. Additionally, the data suggested that the peak immune response occurred at around Day 42 (2 weeks after the third administration of vaccine). All subjects seroconverted by Day 42, as assessed by TNA NF_{50}. The peak GMT as assessed by TNA NF_{50} was 1.672 on Day 42 in the PP population, and peak ELISA was 454.3 µg/mL.

Safety data indicated that the PEP schedule of BioThrax was well tolerated and had an overall acceptable safety profile. No unusual side effects were observed with this dosing schedule. The most common AEs reported were those related to local and systemic reactogenicity and were generally mild to moderate in severity. No significant changes in laboratory parameters or physical examinations were reported. No deaths or SAEs were reported.

EBS.AVA.006 (Immunogenicity and Safety Study of a Three-Dose BioThrax Regimen for Post-Exposure Prophylaxis in Healthy Adults)

EBS.AVA.006 was a Phase 3, open-label, uncontrolled, multi-center immunogenicity and safety study evaluating a three-dose schedule (Week 0, 2, and 4) of 0.5 mL BioThrax administered SC to 200 healthy adult subjects, 18-65 years of age. Eligible subjects were enrolled at four sites in the U.S. Enrollment was stratified by sex with an equal number of males and females. Additionally, within each sex, enrollment was stratified by age with 50% of subjects between the ages of 18-30 years and 50% between 31-65 years.

The primary immunogenicity endpoint was the proportion of subjects achieving a TNA response of at least 0.56 at Day 63 (five weeks following the third vaccination on Day 28).

At the initial vaccination visit (Day 0), subjects received the first dose of BioThrax. Additional vaccination visits occurred on Days 14 and 28. Subjects were required to fill out a seven-day diary card after each vaccination. Safety and immunogenicity data were collected at Screening and on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, and 100. Safety follow-up was performed through Study Day 100, because substantial safety data were already available following SC injection of BioThrax at 0, 2, and 4 weeks from Studies EBS.AVA.000 (to support the currently licensed schedule) and EBS.AVA.005 (above).

The primary analysis of immunogenicity was performed on the PP population (subjects who received three vaccinations within the study-specified time windows and had a blood draw

for immunogenicity within the study-specified time windows on the specific day(s) summarized, including Day 63), with supportive analysis performed on the ITT population (all subjects who received at least one vaccination of BioThrax). Analyses of the TNA, anti-PA antibody level, the proportion of subjects achieving a TNA response of at least 0.56 at pre-specified time points in the study, and predicted vaccine efficacy at pre-specified time points in the study included the number of subjects, mean, standard deviation (SD), median, minimum, maximum, and 95% CI for the mean. For TNA and anti-PA IgG levels, geometric mean titer (GMT, for TNA; GMC for anti-PA IgG) and corresponding 95% CIs were also reported. For dichotomous variables (yes or no, 0 or 1), the following were included: number and percentage of subjects and its corresponding 95% CI with the characteristic of interest.

Multiplicity was addressed for the primary and secondary immunogenicity endpoints, using a hierarchical stepwise procedure. The primary immunogenicity endpoint was assessed first; if the predefined success criteria were met, then the first two secondary immunogenicity endpoints were assessed in order, without adjustment of the α level. Other endpoints were reported using descriptive statistics, as indicated in the Statistical Analysis Plan.

The study's primary endpoint (lower bound of $\geq 40\%$ for the 2-sided 95% CI for the proportion of subjects who achieved a TNA NF_{50} value ≥ 0.56 at Day 63) was met and supports the approval of this application. Overall, 71.2% of subjects achieved a TNA NF_{50} value ≥ 0.56 at Day 63.

The success criteria for the first two secondary immunogenicity endpoints were met and support approval of this application. The proportion of subjects achieving a TNA NF_{50} value ≥ 0.56 on Day 70 was 57.9% (95% CI, 50.4%, 65.2%), and the mean proportion of subjects achieving a TNA NF_{50} value ≥ 0.56 between Days 63 to 100 (inclusive) was 47.9% (95% CI, 40.6%, 54.5%). The lower bounds of the 95% CIs for both values were $\geq 40\%$.

Safety monitoring for this Phase 3 study comprised of complete or symptom-directed physical exams at each study visit, a review of any new adverse events and concomitant medications at each study visit, completion and evaluations of diary cards for local and systemic reactogenicity for seven days after each vaccination, and in-clinic evaluations for local and systemic reactogenicity.

The most common solicited adverse reactions reported seven days after each vaccination comprised local reactions, including symptoms of lump, tenderness, and erythema. The most common solicited systemic reactions comprised fatigue, headache, and myalgia. Of the subjects that reported local and systemic solicited reactions, $\geq 98\%$ required minimal or no treatment and resulted in little to no interference with subjects' daily activity. The most common ($> 2.0\%$) unsolicited related adverse reactions reported following at least one dose up to 100 days after the third dose were: headache (4.0%), fatigue (3.5%), skin hyperpigmentation (3.5%), decreased joint range of motion (2.5%), myalgia (2.5%). No new safety signals were identified in Study EVS.AVA.006.

EBS.AVA.009: A Study of the Effects of Co-administering Ciprofloxacin and BioThrax on the Pharmacokinetics of Ciprofloxacin in Healthy Adults

EBS.AVA.009 was a Phase 2, randomized, open-label, multi-center study to evaluate the potential interaction of ciprofloxacin and BioThrax by examining the pharmacokinetics (PK) of ciprofloxacin before and after administration of three SC vaccinations of BioThrax at 0, 2, and 4 weeks (PEP schedule) and evaluating the immunogenicity of BioThrax when co-administered with ciprofloxacin given as an oral dose of 500 mg every 12 hours. In this study, 154 subjects 18 to 45 years of age were stratified by sex and age, with a minimum of 40% of subjects being in each of the two age strata: 18 to 30 years of age, and 31 to 45 years of age. Subjects were randomized into three study arms:

- Arm 1: Ciprofloxacin plus BioThrax with ciprofloxacin PK
- Arm 2: Ciprofloxacin plus BioThrax without ciprofloxacin PK
- Arm 3: BioThrax alone

Ciprofloxacin PK assessments were performed at prespecified time points for Arm 1. Arms 1 and 2 were compared to Arm 3.

The study's primary endpoints were the AUC_{0-12h} (area under the serum concentration-time curve (12 hours)) and C_{max} (maximum observed concentration) achieved once ciprofloxacin concentrations had reached steady-state. The study's secondary immunogenicity endpoint was the TNA GMT measured two weeks after the last vaccination.

Ciprofloxacin plasma concentrations were analyzed in human serum using a validated ▢▢ ▢▢ bioanalytical assay which had a linear range in human serum from 50 to 10,000 ng/mL with a lower limit of quantitation (LLOQ) of ▢▢ . Ciprofloxacin exposure, based on C_{max}, AUC_{0-12h} and $AUC_{0-\infty}$, was comparable pre- and post-vaccination.

The study's primary endpoints (geometric mean ratios of C_{max} and AU_{0-12h} of ciprofloxacin) were met. The 90% CIs for systemic ratios fell entirely within the equivalence range of 80-125%. The ciprofloxacin PK data showed that BioThrax administration did not have an impact on the single dose or steady-state pharmacokinetics of ciprofloxacin.

The study's secondary endpoint analysis was met. The study demonstrated that subjects that received BioThrax plus ciprofloxacin (Arms 1 + 2) had an immune response that was non-inferior to BioThrax (Arm 3) only subjects, two weeks after the last vaccination. The lower bound of the 95% CI was 0.8984, which met the success criterion (> 0.67).

The observed reactogenicity profile for BioThrax with ciprofloxacin was relatively similar to that of BioThrax alone, with the majority of reported adverse events local reactogenicity events, most of which were mild in severity. Systemic reactions were also reported for the BioThrax arm and the Ciprofloxacin plus BioThrax arm, but were less frequent than local reactions. The proportion of subjects reporting local and systemic reactions were fairly similar between the two treatment arms and between collection methods, when evaluated in-clinic and via the e-diary, with most reactions rated as mild in severity. No new safety concerns were identified in the safety database of EBS.AVA.009 that would warrant changes to the current package insert (PI).

Conclusion

Data from two clinical studies support the safety and effectiveness of BioThrax for the PEP indication against anthrax in healthy adult subjects 18-65 years of age. EBS.AVA.005 was designed to determine the appropriate dosing schedule of BioThrax for the PEP indication and evaluate different immunogenicity endpoints that would be bridged to animal immunogenicity and survival data to determine a threshold of protection. Using information obtained from study EBS.AVA.005, both anti-PA antibody levels and TNA NF_{50} levels were further evaluated in a larger, pivotal Phase 3 study (EBS.AVA.006) where human TNA antibody levels were used to bridge to TNA antibody levels in animals (rabbits and NHPs) that were vaccinated with the proposed BioThrax PEP schedule and survived challenge. These data were used to support licensure under the Animal Rule.

The primary immunogenicity endpoint in EBS.AVA.006, defined as the proportion of subjects achieving a TNA response of at least 0.56 at Day 63 and correlated to a 70% survival rate of rabbits against oral inhalational anthrax challenge of 200 LD_{50}, met the pre-specified success criteria. Pre-defined secondary endpoints were also met.

A third clinical study, EBS.AVA.009, evaluated potential interference of BioThrax administration on the pharmacokinetic profile of ciprofloxacin and conversely, the effect of ciprofloxacin administration on the immune response after vaccination with the PEP schedule of BioThrax. Interference of BioThrax on the PK of ciprofloxacin was not shown. Ciprofloxacin was shown not to adversely affect the immunogenicity of BioThrax when dosed using the PEP schedule.

Bioresearch Monitoring

FDA conducted Bioresearch Monitoring Inspections at two clinical study sites and one nonclinical laboratory. The inspections at the two clinical study sites did not reveal problems that impact the data submitted by Emergent for this supplement. The nonclinical laboratory inspection was conducted at and focused on Rabbit Study 646. The only significant issue that was identified during that inspection was that the Day 69 TNA NF_{50} raw data for one animal did not match the final study report that was submitted in the supplement. On May 27, 2015 CBER sent an information request to Emergent asking them to submit an amendment with the corrected immunogenicity data and revised analyses for the study using the correct TNA NF_{50} value for the animal on Day 69, and to verify that NF_{50} values presented in the remainder of the supplement match the raw data results for all animals. Emergent submitted this information in an amendment. Their reanalysis of the data changed the Rabbit NF_{50} threshold very slightly from 0.56065 to 0.56387 for Day 69. This correction had no effect on the overall conclusions of the study.

NHP Study 844 was not conducted as a GLP study. During the IND review, CBER determined that many, but not all, aspects of GLP compliance were followed. To assess whether any deviations from GLP were a concern for Study 844, FDA conducted a

Bioresearch Monitoring Inspection of ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ focusing on NHP Study 844. No significant adverse findings were found and it was concluded that the GLP deviations did not affect study results.

Toxin Neutralizing Antibody Assay

The anthrax TNA assay, which measures functional antibody response, is species independent; therefore, it can be used to directly compare functional immune response across species. The assay was originally developed by the Centers for Disease Control and Prevention (CDC) and further developed by ▮▮▮▮ and the National Institute of Allergy and Infectious Disease (NIAID) at the National Institutes of Health (NIH). An inter-laboratory study sponsored by NIAID directly demonstrated the consistent accuracy and precision of the TNA assay. The study also provided evidence that the TNA assay is an appropriately rugged pan-species assay, which allows for comparisons between species (e.g., rabbit, NHP, and human). The data from this study support the utility of the TNA assay for use in bridging the efficacy of the anthrax vaccine from the animal models to the human immunogenicity studies. The assay includes nine test samples per plate and each sample is tested at least twice, in independent assays.

All assays were performed by ▮▮▮▮ three clinical studies in support of the PEP indication (EBS.AVA.005, EBS.AVA.006, EBS.AVA.009), two pre-exposure animal studies (Rabbit Study 646, NHP Study 844), and four supportive rabbit studies (AVA-104-RBT, AVA-105-RBT, AVA-106-RBT, and AVA-107-RBT). A human serum reference standard was used for TNA testing of the three pivotal and two supportive studies. Non-clinical, supportive rabbit studies were noted to have utilized a different human reference serum than that used in the pivotal studies to determine protective antibody levels; however, data were provided to demonstrate adequate comparability between the two references.

Data were submitted that demonstrated that the assay was well-controlled, stable, and performed consistently over time. The data support adequate performance parameters of the TNA assay to generate data for clinical and non-clinical studies. No issues with the validation reports were noted.

b) Pediatrics

On April 11, 2014 Emergent received orphan drug-designation for the indication of "post-exposure prophylaxis of anthrax disease resulting from suspected or confirmed exposure to *Bacillus anthracis*." Under the Orphan Drug Law, this supplement qualified for a waiver of the requirements under PREA based on Section 526 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360bb).

7. Safety

The safety data from three clinical studies, combined with extensive postmarketing experience with BioThrax in the military population, do not suggest any new safety concerns that the

proposed indication might raise. The safety profile of BioThrax is well-characterized since the vaccine was licensed in the U.S. in the 1970s.

In the studies submitted to support this proposed indication, no deaths were reported. Of the two serious adverse events (SAEs) reported, neither were considered to be related to vaccination. There were no pregnancies reported or subject withdrawals due to adverse events. Review of the safety data for 504 subjects who participated in studies EBS.AVA.005, EBS.AVA.006, and EBS.AVA.009 did not reveal any new safety signals or adverse events that are not already described in the package insert for BioThrax.

8. Advisory Committee Meeting and Workshops

Using the Animal Rule, the FDA may license a biological product, for which safety has been established in humans, based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is "reasonably likely to produce clinical benefit in humans." The Animal Rule stipulates that the FDA can rely on data from animal studies to provide evidence of effectiveness of a product if four criteria are fulfilled. The four criteria are:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.

2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans.

3. The animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity.

4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Previously, CBER partnered with other U.S. Government agencies, including the NIH/NIAID and the Department of Defense, in sponsoring workshops to discuss implementation of the Animal Rule for anthrax vaccines. The first workshop, titled Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity, was held in April 2002. A second workshop, titled Anthrax: Bridging Correlates of Protection in Animals to Immunogenicity in Humans, was held in November 2007. At these workshops, scientific consensus was reached in certain important areas. First, pathogenic mechanisms of *Bacillus anthracis* were reviewed and were thought to be reasonably well understood. Second, NHPs and rabbits were determined to be appropriate animal models to use to generate the pivotal animal data that would serve as a basis for assessing efficacy of PA-based anthrax vaccines. Third, animal protection study designs were discussed for PA-based vaccines in which survival of animals following an anthrax challenge could be

tested. Scientific consensus was achieved that the first three criteria of the Animal Rule had been met in regard to PA-based anthrax vaccines.

The fourth criterion of the Rule focuses on establishing a scientifically sound bridge between animal protection data and the human immune response in order to determine an effective human dose. CBER's stated position is that the anthrax vaccine dose used in humans should elicit an immune response in humans comparable to that of animals protected by the vaccine. The question of which immune response and what study design should be used to determine protective antibody levels in the animals that could be extrapolated to humans for a post-exposure prophylaxis indication was discussed at the VRBPAC held on November 16, 2010. At that meeting, a scientific strategy for bridging animal protection data to humans for PA-based vaccines, including BioThrax, was agreed upon. In particular, three study designs were discussed: a GUP design, a PEP design, and a passive immunization study design. The three study designs were presented and evaluated along with the pros and cons of each model for predicting the immune response that would be protective in humans for a post-exposure prophylaxis indication.

The GUP study design was judged by the VRBPAC to be the most appropriate design to estimate protective TNA antibody levels in animals and to extrapolate these to vaccine induced TNA levels in humans via an antibody bridge to support a post-exposure prophylaxis indication.   The VRBPAC acknowledged that animal studies using a PEP study design and passive immunization studies in animal models could serve as further proof-of-concept that the vaccine can protect in a post-exposure setting and that use of antibodies to bridge animal protection data to humans is appropriate. However, the VRBPAC agreed that data from such studies would not be pivotal and would not be used to estimate protective antibody levels since complexities encountered with PEP and passive immunization studies confound estimates of protective antibody levels and preclude accurate estimations of such levels.

Emergent conducted two pivotal GUP studies as well as additional supportive PEP and passive immunization studies.

9. Other Relevant Regulatory Issues

None.

10. Labeling

The package insert (PI) and Patient Package Insert (PPI) content were reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch. Major changes to the PI include the addition of an indication, and dosage and administration for post-exposure prophylaxis (Sections 1 and 2); the presentation of the human clinical data (Section 6.1) and animal data (Sections 13.2 and 14.2) to support these changes, as well as information about co-administration with Ciprofloxacin (Sections 7.1 and 14.3). The PPI was updated to inform patients on the use of BioThrax after an exposure or suspected exposure, and that the effectiveness after exposure has only been studied in animals.

CBER comments and recommendations regarding the PI and PPI were initially conveyed to Emergent on July 16, 2015, and further revised throughout the months of July to October 2015. Final versions of the PI and PPI submitted to the BLA on October 9, 2015, were considered acceptable. All issues were acceptably resolved after exchange of information and discussions with the applicant.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The data provided in this supplement demonstrated the benefit of BioThrax in post-exposure prophylaxis of disease following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs. Therefore, the Committee recommends approval of this supplement to update the BioThrax Package Insert with results from the studies.

b) Risk/ Benefit Assessment

Data submitted to this efficacy supplement establish a substantial likelihood of benefit when BioThrax is administered in conjunction with recommended antibacterial drugs, for PEP of disease resulting from suspected or confirmed *Bacillus anthracis* exposure in persons 18 to 65 years of age.

Although BioThrax administration has been associated with a high frequency of local reactogenicity events in individuals vaccinated with the PEP regimen, the severity of most local reactions are mild to moderate. In addition, these data associated with the PEP regimen are similar to those collected during previous studies of BioThrax. Studies to support the proposed PEP indication did not reveal any new safety signals or adverse events, beyond those identified in the previous clinical studies and noted in the labeling.

The benefit of protection against a fatal disease significantly outweighs the risk of cutaneous reactions at the injection site. PEP immunization likely protects against disease resulting from residual spores that remain after completion of the recommended course of antibacterial drugs. Furthermore, addition of BioThrax to antibiotics for post-exposure prophylaxis may provide substantial benefit in preventing anthrax disease for individuals where poor compliance with antimicrobial therapy is documented.

c) Recommendation for Postmarketing Risk Management Activities

The reviewed safety data of the Pharmacovigilance Plan for BioThrax do not suggest a need for a postmarketing study or Risk Evaluation and Mitigation Strategy (REMS) beyond the required Animal Rule postmarketing requirement (PMR), per 21 CFR 601.91(b).

d) Recommendation for Postmarketing Activities

Emergent's existing Pregnancy Registry and routine pharmacovigilance plan will continue.

As required under 21 CFR 601.91(b), Emergent submitted a draft protocol synopsis to assess the clinical benefit and safety of BioThrax in a post-exposure setting should an anthrax event occur in the United States.

Emergent has agreed to the following Postmarketing Requirement (PMR):

1. To conduct a field study to evaluate the efficacy and safety of BioThrax for the post-exposure prophylaxis indication when administered concurrently with a licensed regimen of antimicrobials following a suspected and/or confirmed exposure to *Bacillus anthracis*.

    Final Protocol Submission: November 30, 2016

    Study/Trial Completion: To be determined should an event occur.

    Final Report Submission: To be determined should an event occur.