CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125509Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Summary Review
BLA #	125509
Applicant	Elusys Therapeutics, Inc.
Date of Submission	March 20, 2015
PDUFA Goal Date	March 20, 2016
Proprietary Name / Non-Proprietary Name	Anthim/Obiltoxaximab
Dosage Form/ Strength	Injection, 600 mg/6 mL/vial (100 mg/mL)
Applicant Proposed Indications	1. Treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs. 2. Prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Intended Population: Adult and pediatric patients
Recommended Action:	Approval
Recommended Indication/Population(s) (if applicable)	1. Treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs. 2. Prophylaxis of inhalational anthrax due to *B. anthracis* when alternative therapies are not available or are not appropriate. Population: Adult and pediatric patients

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Elizabeth O'Shaughnessy, MD Ramya Gopinath, MD
Statistical Review	Xianbin Li, PhD Ling Lan, PhD
Pharmacology Toxicology Review	Amy Nostrandt, DVM, PhD
OPQ Review (Team Lead)	Rashmi Rawat, PhD
Microbiology Review	Shukal Bala, PhD Lynette Berkeley, PhD
Clinical Pharmacology Review	Zhixia (Grace) Yan, PhD
OSI	Abhijit Raha, PhD Mohsen Rajabi, PhD
CDTL Review	John Alexander, MD MPH
OSE/DMEPA	Jacqueline Sheppard, PharmD Vicky Borders-Hemphill, PharmD
OSE/DRISK	Joyce Weaver, Pharm D
Labeling Review	Jibril Abdus-Samad, PharmD Shawna Hutchins, MPH, BSN, RN

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

As it is not feasible or ethical to conduct controlled clinical trials in humans with inhalational anthrax, the effectiveness of obiltoxaximab for the treatment and prophylaxis of inhalational anthrax was based on efficacy studies in animal models of inhalational anthrax (21 CFR 601, Subpart H). In four monotherapy studies, a single 16 mg/kg IV dose of obiltoxaximab showed a significant survival benefit over placebo in both the cynomolgus macaque and New Zealand White (NZW) rabbit models of inhalational anthrax. The studies in which obiltoxaximab was administered in combination with antibacterial drugs showed a numerical benefit of the combination over antibacterial drug alone. The efficacy of obiltoxaximab for the treatment of inhalational anthrax is supported by studies that demonstrated the efficacy of this product for prophylaxis against inhalational anthrax. In the majority of prophylaxis studies, obiltoxaximab was administered intramuscularly. A 16 mg/kg IM dose, administered to cynomolgus macaques and NZW rabbits within 24 hours of exposure to *B. anthracis* spores was effective in preventing inhalational anthrax. In pre-exposure studies, obiltoxaximab 16 mg/kg IM was effective when treatment was given 30 minutes and up to 72 hours prior to challenge. As exposures are lower with IM administration compared to IV administration, obiltoxaximab IV is expected to at least be as effective as the IM doses for the prophylaxis of inhalational anthrax. The finding of a statistically significant survival benefit compared to placebo in both animal models of inhalational anthrax, indicates that obiltoxaximab is reasonably likely to produce clinical benefit in humans for the treatment and prophylaxis of inhalational anthrax.

The main safety concerns of hypersensitivity reactions are adequately addressed in the Boxed Warning, Warnings and Precautions and Adverse Reactions sections of the package insert.

I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of obiltoxaximab in adult and pediatric patients for the treatment of inhalational anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs and for the prophylaxis of inhalational anthrax. I also agree with the review team that given the risk of hypersensitivity reactions, including anaphylaxis, obiltoxaximab should be approved for prophylaxis of inhalational anthrax due to *B. anthracis* when alternative therapies are not available or not appropriate. I recommend approval of BLA 125509.

I agree with the benefit-risk assessment provided by the clinical reviewers and the CDTL. The table below has been modified from the CDTL review and captures the key considerations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Anthrax is a bacterial infection caused by *B. anthracis*. Inhalational anthrax is caused by inhalation of *B. anthracis* spores and has a case fatality rate of 45-89%. *B. anthracis* is considered a category A bioterrorism agent. (http://fas.org/biosecurity/resource/documents/CDC_Bioterrorism_Agents.pdf) Protective antigen (PA) is a component of edema toxin and lethal toxin produced by *B. anthracis*. These toxins cause hemorrhage, edema, tissue necrosis, and death.	Inhalational anthrax is a life-threatening infection. PA is a component of both edema and lethal toxins that cause tissue damage.
Current Treatment Options	The current FDA-approved treatment options for inhalational anthrax include antibacterial drugs, anthrax immune globulin, and raxibacumab. Antibacterial drugs act by killing *B. anthracis* bacteria that germinate from spores and have no activity against the spores. Ciprofloxacin, levofloxacin and doxycycline are approved for post-exposure prophylaxis (PEP) and must be used for 60 days to kill bacteria that develop from spores over a period of time. There is also a concern that strains of *B. anthracis* could be engineered to be resistant to currently available antibacterial drugs. Anthrax immune globulin is purified human IgG containing polyclonal antibodies that bind PA and is approved for the treatment of inhalational anthrax in combination with antibacterial drugs. Raxibacumab is a monoclonal antibody against PA. It is approved for treatment of inhalational anthrax as an adjunct to antibacterial drugs and for prophylaxis of anthrax, when alternative therapies are not available or appropriate. Anthrax Vaccine Adsorbed (AVA) may be used for prophylaxis. As it takes time for the anthrax vaccine to provide protection, it must be used for PEP	The main treatment for inhalational anthrax is antibacterial drugs. Raxibacumab and Anthrax immune globulin are to be used with antibacterial drugs for treatment of inhalational anthrax. Since antibacterial drugs and antibodies work by different mechanisms, they are expected to work together to treat inhalational anthrax. Antibacterial drugs are approved for PEP, but need to be taken for prolonged periods of time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with antibacterial drugs initially, until an immune response has developed.	
Benefit	Because studies of humans with naturally occurring anthrax infections are not feasible, and exposing people to anthrax for studies is not ethical, the efficacy of obiltoxaximab was evaluated under the Animal Rule. Studies were done to evaluate the efficacy of obiltoxaximab for either the treatment of inhalational anthrax or for PEP. Obiltoxaximab was administered either intravenously (IV) or intramuscularly (IM). Treatment Studies: Multiple studies were conducted in NZW rabbits and cynomolgus macaques comparing obiltoxaximab to placebo. Several of these studies showed a statistically significant effect of obiltoxaximab on survival compared to placebo. However, survival rates varied widely across the studies, depending on the dose of obiltoxaximab and the route of administration. A dose of 16 mg/kg IV was determined to be the human equivalent dose. This dose is expected to provide humans with blood concentration higher than that needed to neutralize PA. In addition, studies were conducted where the efficacy of obiltoxaximab when administered in combination with an antibacterial drug was compared to antibacterial drug alone. In seven of the eight studies there were numerical improvements in survival rates for NZW rabbits and cynomolgus macaques. There did not appear to be any loss of efficacy of the antibacterial drug when obiltoxaximab was added. A meta-analysis of the combination studies suggests a small incremental benefit of adding obiltoxaximab to an antibacterial drug. However, given that there was variability among the	Obiltoxaximab 16 mg/kg IV was efficacious for the treatment of anthrax in cynomolgus macaque and NZW rabbit models of inhalational anthrax. Based on these findings it is reasonable to conclude that a dose of 16 mg/kg IV would be efficacious in humans for the treatment of inhalational anthrax. The systemic exposures achieved with obiltoxaximab 16 mg/kg IV in humans indicate that this dose should neutralize most of the circulating PA. Obiltoxaximab administered in combination with antibacterial drugs for the treatment of inhalational anthrax provided a treatment benefit and did not appear to interfere with the efficacy of antibacterial drugs. The

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	various study designs, it was difficult to quantify the magnitude of the added benefit of giving obiltoxaximab with antibacterial drugs for treatment of inhalational anthrax. Prophylaxis Studies: Post exposure prophylaxis studies were conducted in cynomolgus macaques and NZW rabbits with a range of IV and IM doses of obiltoxaximab. Obiltoxaximab IV had a statistically significant improvement in survival rates compared to placebo in NZW rabbits for prophylaxis. In cynomolgus macaques, obiltoxaximab 16 mg/kg IM showed a significant survival benefit and further support the efficacy of obiltoxaximab for prophylaxis. In addition, survival benefit was also seen in a pre-exposure model in cynomolgus macaques administered obiltoxaximab 16 mg/kg IM at different time points prior to exposure to *B. anthracis* spores.	different mechanisms of action of antibacterial drugs and obiltoxaximab suggest that combination therapy should be beneficial for the treatment of inhalational anthrax. The prophylaxis studies of IV obiltoxaximab in NZW rabbits and cynomolgus macaques showed that obiltoxaximab provides benefit in prophylaxis against inhalational anthrax.
Risk	As obiltoxaximab was developed under the Animal Rule, safety studies were conducted only in healthy adults. In the seven phase 1 trials combined, 320 healthy adults were exposed to the commercial formulation of obiltoxaximab and 70 to placebo. Hypersensitivity reaction was reported in 10.6% of the subjects; three subjects (0.9%) developed anaphylaxis. Other adverse reactions that were more common in the obiltoxaximab arm compared to placebo were headache, pruritus, urticaria, cough, nausea, upper respiratory tract infections, and vessel puncture site bruise.	As obiltoxaximab was only studied in healthy human adults, no safety data are available in patients with anthrax, children, pregnant women or patients with co-morbidities. Hypersensitivity reactions, including anaphylaxis were the major safety concern and hence this product will need to be used in closely monitored settings. As inhalational anthrax is a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		serious and life-threatening condition, the benefit of Anthim outweighs this risk.
Risk Management	Obiltoxaximab use is anticipated primarily in the event of bioterrorism. As some signs/symptoms of hypersensitivity reactions can overlap with those of inhalational anthrax, it is very important that providers be informed of this risk so that appropriate interventions can be instituted. The risk of hypersensitivity is being addressed in Boxed Warning,Warnings and Precautions, and Adverse Reactions sections of labeling.	A REMS is not necessary for this application. Labeling addresses the risk of hypersensitivity reactions including anaphylaxis and the indication for prophylaxis is limited only to situations when other options are not available or not appropriate. Due to risk of hypersensitivity, obiltoxaximab should be administered in monitored settings.

2. Background

Anthrax is a zoonosis caused by *B. anthracis*, a spore-forming, gram-positive bacterium. The disease occurs commonly in wild and domestic herbivores. The spores are the infectious form and are highly resistant to heat, cold, drought, and UV light and can persist in the environment for a prolonged period. Infection in humans is acquired primarily through exposure to infected or dying animals or their carcasses. Anthrax can occur in three forms, cutaneous, gastrointestinal or inhalational, depending on the route of exposure.

Currently, available therapies for the treatment and prophylaxis of inhalational anthrax include several antibacterial drugs, anthrax vaccine adsorbed (AVA), anthrax immune globulin intravenous (AIGIV) and raxibacumab, a monoclonal antibody targeting PA.

Obiltoxaximab (ETI-204) is a chimeric (mouse/human) affinity-enhanced monoclonal antibody of the IgG1κ isotype. Obiltoxaximab binds the free protective antigen domain 4 (PAD4) component of *B. anthracis* toxin and inhibits the binding of PA to its cellular receptors. Blocking the binding of PA to cell receptors interferes with toxin formation and works to prevent or mitigate toxin effects.

BLA 125509, obiltoxaximab for injection, was submitted by Elusys Therapeutics, Inc. on March 20, 2015, under section 351(a) of the Public Health Service Act. The product was developed under 21 CFR 601, Subpart H (Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible). The review team has completed their reviews of this application. For a detailed discussion of BLA 125509, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

3. Product Quality

The Product Quality reviewers for this BLA are Tao Xie, PhD, Bo Chi, PhD, John Metcalfe, PhD, and Donald Obenhuber, PhD. The Application Technical Lead is Rashmi Rawat, PhD.

Obiltoxaximab is produced from a recombinant DNA-derived murine myeloma cell line using standard cell culture techniques. Obiltoxaximab was engineered from the murine monoclonal antibody (14B7) gene sequences originally developed by the United States Army Medical Research Institute for Infectious Diseases (USAMRIID). Elusys obtained the original 14B7 hybridoma under a Cooperative Research and Development Agreement (CRADA) with USAMRIID. The manufacturing cell line was developed by Elusys under contract with (b) (4) . DNA sequence in variable regions on both the heavy and light chains of obiltoxaximab gene were manipulated to eliminate potential immunogenic murine sequences

and enhance the affinity of the antibody for its target. The sequence coding Fc region is human.

Obiltoxaximab is manufactured at Lonza Biologics NH, USA using standard monoclonal antibody manufacturing process. (b) (4)

Per the product quality review, the manufacturing process of obiltoxaximab is well controlled. Validation of the drug substance manufacturing process included viral clearance validation, commercial scale process validation, and (b) (4) hold time validation. An adequate microbial control strategy is also in place. (b) (4) . Bioburden and endotoxins are monitored (b) (4) .

The container closure system for obiltoxaximab BDS is (b) (4) . A proprietary extractable study has been conducted on the DS container closure system to demonstrate that the (b) (4) is safe and acceptable for storage of the BDS at the recommended storage conditions.

Data provided in the BLA support a shelf of (b) (4) months for obiltoxaximab drug substance when stored at (b) (4) °C. The post-approval stability protocols and postmarketing commitment to place (b) (4) drug substance (DS) (b) (4) each year (with production) on stability protocols were found to be acceptable.

The drug product is supplied as 600 mg/6 mL (100 mg/mL) solution in single-dose vials for intravenous injection. It is a clear to opalescent, colorless to pale yellow to pale brownish-yellow solution and may contain few translucent-to-white proteinaceous particulates. Each mL of the drug product contains 6.2 mg of L-histidine, (b) (4) mg of polysorbate 80, and 36 mg of sorbitol; (b) (4) pH to 5.5. The drug product is (b) (4) filled and finished at (b) (4)

In a review dated November 23, 2015, John Metcalfe, PhD, the product quality microbiology reviewer noted that results of the endotoxin spiking studies were still pending. The Applicant was asked to perform a study demonstrating that the DS and DP formulation did not affect the endotoxin recovery in the proposed LAL endotoxin test. The Applicant's response submitted

on February 3, 2016 was found to be adequate. Other minor issues related to product quality will be addressed as postmarketing commitments.

A pre-license inspection of the drug substance manufacturing facility at Lonza Biologics Inc., Portsmouth, NH was conducted. A seven-item Form 483 was issued. These have been adequately addressed and the overall status was acceptable.

The container closure system for the drug product includes vial, stopper and seal. The vial is a (b) (4) mL Type 1 glass with a 20 mm opening. The stopper is a 20 mm (b) (4) stopper. The seal is not in contact with the product.

The stability data in the BLA support a shelf life of 18 months for the drug product when stored at 2°C to 8°C.

I concur with the recommendations from the Product Quality reviewers to approve the BLA.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this BLA is Amy Nostrandt, DVM, Ph.D.

Tissue cross-reactivity (TCR) studies were performed in human, rat, and cynomolgus macaque tissues. In all three species, the test article stained in various cell types in most tissues examined in a similar manner. Staining was suggestive of intracellular cytoskeletal elements, and therefore was not considered relevant. In an additional study performed in a limited set of human tissues to assess TCR following the manufacturing change, there were no new findings or differences between the two products.

Two safety pharmacology studies were conducted to evaluate cardiovascular function in cynomolgus macaques. In the first study, elevation in blood pressure was seen 2 and 4 hours after IV and IM administration as well as an increase in QT interval. A second study was conducted in which no changes in blood pressure or QT prolongation was seen.

A general toxicology study was performed in 10-13 week old male Fischer rats with repeated IV and IM doses up to 2.91 mg/rat (approximately 10.6 mg/kg) of the (b) (4) antibody ((b) (4) product). Doses were administered on Days 1, 4, and 7, with sacrifice on Day 10/11. No test article-related findings were reported for mortality, clinical signs, hematology, clinical chemistry, organ weights, or gross or microscopic pathology. The No Observed Adverse Effect level (NOAEL) was determined to be 10.6 mg/kg. The second safety pharmacology study in cynomolgus macaques included limited general toxicology evaluation of test article generated in the (b) (4) cell line (Baxter product). The NOAEL was 30 mg/kg.

Pilot and definitive toxicology studies were performed in Sprague- Dawley rats. In the pilot study, no effects were noted on survival, clinical observations, body weights, clinical pathology or gross pathology suggesting that the maximum tolerated dose had not yet been reached. In the definitive study, 8 rats/sex/group were administered vehicle (saline), 3, 10, or 30 mg/kg IV of obiltoxaximab (Lonza product) on Days 1, 4, and 7. An additional high-dose (30 mg/kg) group with the Baxter product was also included. No test article-related findings were reported in clinical observations, body weights, food consumption, clinical pathology, organ weights, or macroscopic or microscopic pathology. While no differences in the toxicologic or toxicokinetic profiles were seen between the two products, increased variability in Cmax was seen with the Lonza product.

Tissue from infected macaques and infected and non-infected rabbits were examined for neuropathological changes. In macaques and rabbits exposed to inhalational anthrax that did not survive (found dead or moribund sacrificed animals), doses of ETI-204 $\geq$ 4 mg/kg were associated with a higher frequency of histological findings, consistent with a severe acute inflammatory reaction. The changes in the non-survivors, including those treated with only saline, ETI-204, or with levofloxacin, were consistent with morphologic lesions/hemorrhagic meningoencephalitis previously reported in macaques and rabbits with inhalation anthrax. Findings of hemorrhage, inflammation, and necrosis seen in non-survivors were associated with the presence of extravascular bacteria in all dose groups, including saline controls. The administration of the ETI-204 was not associated with any significant morphologic reactions in surviving animals exposed to inhaled *B. anthracis* spores. In a reproductive toxicology study, no significant neuropathological lesions were reported in rabbits administered up to 32 mg/kg IV of ETI-204.

In a developmental toxicity study in rabbits, the No-Observed-Effect Level (NOEL) for maternal and developmental toxicity was determined to be 32 mg/kg/dose, the highest dose tested. No adverse reproductive or developmental effects or maternal toxicity was observed at doses up to 32 mg/kg. Two animals were positive for antibodies to ETI-204.

Overall, in Dr. Nostrandt's assessment, a toxic dose was not reached in GLP-compliant toxicology studies in rats and macaques at doses up to 30 mg/kg and a maximum tolerated dose was not reached in a pilot study in rats at doses up to 100 mg/kg. ETI-204 does not appear to be neurotoxic in anthrax infected or in non-infected animals. Additionally, ETI-204 does not appear to always protect against anthrax-related meningitis.

Dr. Nostrandt recommends approval of the BLA from a pharmacology/toxicology perspective. I agree with her assessment.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this BLA is Zhixia (Grace) Yan, PhD.

To support the proposed dosing regimen of 16 mg/kg, the Applicant submitted clinical pharmacology data in humans and in rabbits and non-human primates. The pharmacokinetics (PK) and safety of the to-be-marketed formulation of obiltoxaximab 16 mg/kg administered IV over 90 minutes was evaluated in a single-dose PK/safety study (AH104), a repeat-dose PK/safety study (AH109) and a drug interaction study with ciprofloxacin (AH110). Single-dose PK and safety of obiltoxaximab was also assessed in studies AH101, AH102, and AH105 (doses ranged from 19 mg (~0.23 mg/kg) to 16 mg/kg) using the earlier formulation.

The dose-response relationship for obiltoxaximab was evaluated in animal models of inhalational anthrax. A survival model was used to describe time course survival using infected rabbit and macaque survival data combined as animal species was not identified as a significant factor. Simulations were performed using the final model to determine the proportion of surviving animals over a range of obiltoxaximab doses. The final model demonstrated an early linear increase in response that gradually reached a plateau beyond which additional increases in dose did not improve survival. Analysis performed by the Clinical Pharmacology review team showed that the estimated dose associated with 50% of the maximal effect (ED50) for the endpoint of survival is 1.6 mg/kg (95% confidence interval [CI]: 0.6 – 4.4 mg/kg) and the estimated dose to achieve 90% of the maximal effect (ED90) is 14.5 mg/kg (95% CI: 5.4 - 39.3 mg/kg); the estimated dose to achieve 95% of the maximal effect (ED95) is 30.5 mg/kg (95% CI: 11.4 – 83.1 mg/kg). By increasing the dose from 14.5 to 30.5 mg/kg, the probability of survival was predicted to increase by 2.8% (from 49.5% to 52.3%). Therefore, a dose of 14.5 mg/kg was determined to be the fully effective dose. The Applicant concluded that the maximum effective dose in rabbits and macaques with anthrax infection was 16 mg/kg.

Simulations showed that healthy and infected humans receiving a single 16 mg/kg IV dose will achieve similar or greater exposure to obiltoxaximab compared to infected rabbits and macaques receiving 14.5 mg/kg. Following a single 16 mg/kg IV dose, median C_{max} in humans is similar to that in rabbits and macaques. Although, the median AUC_{inf} in humans following a 16 mg/kg dose is at least 2-fold higher than that in rabbits and macaques, receiving 14.5 mg/kg, there is partial overlap in the range of AUC_{inf} between humans and macaques. Simulations suggest that a higher dose (i.e., 24 mg/kg) could result in AUC_{inf} exceeding the exposure in macaques receiving 14.5 mg/kg.

Based on predicted human PK profiles, the proposed dose of 16 mg/kg in humans would be expected to achieve maximum obiltoxaximab serum concentrations 1-2 orders of magnitude higher than the concentrations required for 99.9% (48 mcg/mL) and 99% (4.8 mcg/mL) PA

neutralization, respectively. Moreover, a molar excess of obiltoxaximab is maintained in serum for 2 to 3 weeks. More than 95% of humans administered a 16 mg/kg IV dose can be expected to achieve serum obiltoxaximab concentrations that are equimolar to or in excess of the highest observed serum PA concentration in infected rabbits and macaques for more than 3 weeks.

Dr. Yan notes that based on the relationships of dose vs. survival and exposure vs. PA concentrations, an increase from 16 mg/kg to 24 mg/kg would be expected to achieve minimal improvement in survival in humans.

Prior to treatment (PTT) bacteremia was identified as a covariate with a significant effect on response to obiltoxaximab treatment. At the lowest PTT bacteremia quartile (BLQ-3.02 log10 cfu), maximum survival was achieved at doses as low as 8 mg/kg. At higher PTT bacteremia levels, a higher dose was required to reach the response plateau. Doses of 14.5 mg/kg and greater (i.e., 16 and 32 mg/kg) remained on the response plateau in all cases. In Dr. Yan's assessment, the dose-response relationships at high PTT bacteremia levels should be considered as the worst-case scenario in determining the fully effective dose. The expected level of bacteremia in human anthrax infection is unknown.

The terminal half-life of obiltoxaximab is approximately 2 to 4 days, 3 to 4 days, 5 to 12 days, and 15 to 23 days in healthy rats, rabbits, macaques, and humans respectively. Mean obiltoxaximab steady-state volume of distribution was greater than plasma volume, suggesting some tissue distribution. Clearance values were much lower than the glomerular filtration rate indicating that there is no renal clearance.

The potential for drug-drug interaction between obiltoxaximab and ciprofloxacin was evaluated in humans. Serum obiltoxaximab concentration-time profiles were similar following administration of obiltoxaximab alone and with both oral and IV ciprofloxacin. Overall, exposure to ciprofloxacin appears to have no consistent or meaningful impact on obiltoxaximab PK. Obiltoxaximab did not alter the PK of ciprofloxacin administered orally and/or IV.

Obiltoxaximab has not been studied in children. As studies cannot be conducted in healthy children, simulations were performed to derive dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 16 mg/kg. As obiltoxaximab is eliminated by non-specific proteolysis, and a minimal effect of maturation on obiltoxaximab clearance was expected, no maturation effect was included in the simulation model. FDA analysis showed that the Applicant's proposed dosing of (b) (4) mg/kg in pediatric subjects with body weight 40 to 50 kg would result in a median AUC_{inf} (b) (4)% greater than the median AUC_{inf} in adults receiving 16 mg/kg. Dr. Yan recommends that children and adults weighing between 40 to 50 kg should receive 16 mg/kg rather than (b) (4) mg/kg. The Applicant is in agreement with the FDA proposed pediatric dosing regimen as shown in the following table:

Table 1: Dosing Recommendations

Body Weight	Dose
Greater than 40 kg	16 mg/kg
Greater than 15 kg to 40 kg	24 mg/kg
15 kg or less	32 mg/kg

Dr. Yan recommends approval of the BLA and I agree with her recommendation.

6. Clinical Microbiology

The clinical microbiology reviewers for this BLA are Shukal Bala, PhD and Lynette Berkeley, PhD.

Dr. Berkeley's review focused on the methods and validation for the following assays:

- Electrochemiluminescent (ECL) assay for detection of the PA in the sera of NZW rabbits and cynomolgus macaques and the ECL assay for quantitation of ETI-204.
- The direct and indirect Enzyme-linked Immunosorbent Assay (ELISA) for detection of PA, and anti-PA IgG antibodies respectively, in the sera of cynomolgus macaques and NZW rabbits.
- The toxin neutralization (TNA) assay for the detection of neutralizing antibodies in cynomolgus macaques and NZW rabbits.
- Culture for isolation and differentiation of *B. anthracis* from contaminating bacteria.

Dr. Berkeley notes that all assays have been validated. However, there were shortcomings in some of the parameters. Across all assays, the limits specified for the acceptance criteria were very wide. Some critical interferents that can be found in the testing of blood samples in general, including the testing of different concentrations of some of the components that might interfere with the results were not tested. The most common interferent that lacked sufficient definition was hemolysis which might interfere with the expression of an analyte at a high concentration, but not at low concentrations. Temperature stability of PA was evaluated in a few assays. In general, specimens were stable for as many as 100 days at freezing temperature (-60^{o} C to -80^{o} C).

Dr. Bala's review focuses on the natural history studies and the animal efficacy studies. Only aspects pertinent to microbiology are discussed here. The animal efficacy studies are discussed in the Clinical/Statistics section of this review.

In vitro studies showed that ETI-204 binds to PA from three strains of *B. anthracis* (Ames, Sterne, and Vollum). ETI-204 blocks the receptor binding domain 4 of PA (PAD4). Binding of ETI-204 to PAD4 prevents the cell binding of PA63-edema factor (EF) and PA63-lethal

factor (LF) complexes, thereby preventing the entry of EF and LF into the cytosol thereby preventing the downstream deleterious effects of anthrax toxins. ETI-204 was shown to inhibit the neutralizing activity of lethal toxin (LT) against murine macrophages in vitro.

For natural history studies, the Applicant referred to three published studies and four studies in DMF (b) (4). In these studies, NZW rabbits or cynomolgus macaques were challenged with approximately 200X the 50% lethal dose (LD50) spores of the Ames strain of *B. anthracis* by aerosolization.

These studies showed that both NZW rabbits and cynomolgus macaques had well-defined physiological and pathological responses to inhalational anthrax that were similar to humans. Presence of bacteremia or PA occurs early, relative to some of the other indicators of infection and detection of PA appears to be a useful trigger for intervention. In Dr. Bala's assessment, both NZW rabbits and cynomolgus macaques infected with the Ames strain of *B. anthracis* by inhalational route with approximately 200X LD50 are useful models for evaluating therapies for the treatment and prophylaxis of inhalational anthrax.

Microbiologic measurements included blood cultures and/or detection of PA by ECL assay as well as by ELISA. Blood culture methods varied among the studies and included enriched blood cultures (qualitative), qualitative blood cultures, and/or quantitative blood cultures. Overall, the enriched culture method was more sensitive compared to the other two culture methods. This could be due to a higher volume of blood used for enriched cultures compared to the other two methods as well as the anti-coagulant used. Sodium polyanethol sulfonate (SPS) was used as an anticoagulant for enriched cultures and EDTA for the other two methods. EDTA is known to have antibacterial properties and can decrease isolation of bacteria from blood.

Detection of PA in the serum by an ECL assay was used as a trigger for intervention in some studies. Measurement of PA by the ECL assay was not affected by the presence of ciprofloxacin and levofloxacin in vitro. Presence of EF, LF, or endogenous anti-PA antibodies in the serum may interfere with the detection of PA. Testing was limited to EF and LF at a concentration of 10 ng/mL. PA levels were also measured by ELISA at different time points post-challenge in many studies. The assays used varied among the different studies. Similar to the ECL assay, presence of EF, LF, or endogenous anti-PA antibodies in the serum may interfere with the detection of PA leading to false negative findings. As there was variability in the performance of the assays used in different studies, the lower limit of quantitation (LLOQ), and the upper limit of quantitation (ULOQ) varied among the assays.

The presence of PA prior to challenge was tested by the ECL assay and/or ELISA in some of the studies. Few rabbits and macaques tested positive and it is unclear whether these were false

positive results due to cross-reactivity with other organisms such as *B. cereus*, which is known to be common in animals or the animals had prior exposure to *B. anthracis*.

Dr. Bala notes that while blood culture is the most reliable method for the detection of bacteremia, it can take up to 24 to 48 hours and the disease is rapidly progressive. So, PA positivity by a screening ECL assay is an appropriate biomarker for therapeutic intervention. However, due to limitations of the performance of the ECL assay discussed above, efficacy analyses were also conducted using animals that were bacteremic.

Anti-PA IgG antibodies by ELISA or ECL assay and toxin neutralizing antibodies (TNAs) in the sera of animals were measured in some studies to assess antibody response to challenge at different time intervals post-challenge. The assays used for measuring anti-PA IgG antibodies varied among the studies. As there were several limitations with these assays, Dr. Bala notes that they are appropriate for comparing the anti-PA IgG antibody levels at different time intervals post-challenge within a study, but not for screening animals prior to challenge.
In some studies, animals were tested for anti-PA antibodies prior to challenge. Positive findings were reported in few NZW rabbits and cynomolgus macaques in some of the studies. The reason(s) for these antibody positive findings, prior to challenge is unclear.
In a re-challenge study in NZW rabbits, administration of ETI-204 with or without concurrent levofloxacin resulted in detectable anti-PA antibodies on Day 28 post-challenge which persisted up to 9 months post-challenge. The animals were protected against rechallenge.

Overall, Dr. Bala notes that the animal studies support the effectiveness of obiltoxaximab alone or in combination with an antibacterial drug for the treatment and prophylaxis of inhalational anthrax. Dr. Bala also notes that treatment with obiltoxaximab may be beneficial when alternative therapies are not available or are not appropriate e.g., in the event of an infection due to a drug resistant strain of *B. anthracis*.

Drs. Bala and Berkeley recommend approval of the BLA with labeling revisions. I agree with their assessment that there are no microbiology issues precluding approval of this BLA.

7. Clinical/Statistical-Efficacy

The clinical reviewer for the efficacy aspect of this BLA is Elizabeth O'Shaughnessy, MD. The statistical reviewers for this BLA are Xianbin Li, PhD and Ling Lan, PhD.

The studies submitted to the BLA are characterized as being treatment studies (monotherapy or combination), post-exposure prophylaxis studies, pre-exposure prophylaxis studies, or re-challenge studies, depending on the timing of administration of ETI-204 relative to exposure to *B. anthracis* spores and whether or not ETI-204 was administered alone or in combination with antibacterial drugs. The studies were conducted in cynomolgus macaques or NZW rabbits

with the exception of Study AM002, a pre-exposure prophylaxis study in mice. This study was not reviewed as part of the BLA. Three combination studies included an ETI-204 alone arm and an untreated group and are included in the monotherapy treatment studies as well. The number of animal studies undertaken in this development program is large and a more streamlined program might have allowed for assessment of efficacy with fewer animals.

The majority of studies were performed at the (b) (4)); two studies (AR035 and AR037) were performed at the (b) (4) and one (AP-10-055) at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID). In the treatment studies, the Lonza product was used only in studies AP202 and AP203. The Lonza product was also used in some post-exposure prophylaxis studies (AP301, AP307, AR035 and AR037) and in Study AP305 (pre-exposure study).

Treatment Studies

The Applicant conducted four monotherapy treatment studies in cynomolgus macaques (AP201, AP202, AP203, and AP204) and two in NZW rabbits (AR021 and AR033). In Study AP202, efficacy of the 16 mg/kg IV dose of the Lonza product versus placebo was assessed and the efficacy of the Lonza and Baxter products were also compared. In addition, there were three studies, NIAID 1030, 1045 and 1056 that contained an ETI-204 alone arm and an untreated group. (Table 2)

Table 2: Treatment Studies with ETI-204

Study and product	Design	Treatment period	Follow-up period
Cynomolgus Macaques			
AP201 Baxter	Randomized	Single dose IV	30 days
AP202 Baxter vs. Lonza	Randomized, blinded	Single dose IV	28 days
AP203 Lonza	Randomized, blinded	Single dose IV	28 days
AP204 Baxter	Randomized	Single dose IV	28 or 56 days
NIAID 1056 Baxter	Randomized, open-label	Single dose IV	28 days
NZW Rabbits			
AR021 Baxter	Randomized, open-label	Single dose IV	28 days
AR033 Baxter	Randomized, blinded	Single dose IV	28 days
NIAID 1030 Baxter	Randomized, open-label	Single dose IV	28 days
NIAID 1045 Baxter	Randomized, open-label	Single dose IV 72 hrs post-median challenge	28 days

Source: Modified from Table 1, Statistics review, Dr. Li
NIAID: National Institute of Allergy and Infectious Diseases

In these studies, animals were randomized to receive ETI-204 IV at various doses or to receive placebo or no treatment. In most studies, randomization took place prior to the challenge (target dose of 200 X LD_{50} *B. anthracis* spores). PA-ECL and/or significant increase in body temperature (SIBT) were used as treatment triggers. SIBT was defined as an increase in temperature reading of two or more standard deviations from daily baseline temperature [either three consecutive times or two consecutive times twice (measured hourly)]. SIBT was not used in macaques because of their strong diurnal temperature rhythms. If no trigger was observed, in some studies, treatment was administered at a fixed time post-challenge (54 hours in cynomolgus macaque studies and in Study AR033 and 72 hours in Study AR021). In Study NIAID 1045, ETI-204 was administered 72 hours post-challenge to all NZW rabbits, which is at a later time point than when symptoms developed in the other two rabbit treatment studies (AR021 and AR033).

The primary efficacy endpoint was survival at the end of the study (usually 28 days post-challenge). The Applicant's analyses used various populations across the different studies. Dr. Li's analyses are based on all randomized animals that received treatment (mITT population), with additional analyses in the population of bacteremic animals who received treatment.

Treatment Studies in Cynomolgus Macaques

Treatment studies conducted in cynomolgus macaques are summarized in Table 3. In Study AP202, the primary analysis was the comparison of Lonza ETI-204 with placebo and so no adjustment was needed for multiple comparisons. Four out of the five studies showed significant results at doses of ETI-204 4 mg/kg IV or higher. However, survival rates varied across the studies.

Table 3: Treatment Studies in Cynomolgus Macaques (mITT Population)

Study Product (Primary endpoint)	**Dose (mg/kg)**	**Survival n/N (%)**	**Difference in proportion [95% CI] [Adjusted 95% CI]**	**One-sided p-value (significance level)**
AP202 Lonza and Baxter (Day 28 survival)	0	0/17 (0)		
	16 (Lonza)	5/16 (31)	0.31 [0.08, 0.59]	0.0085* (0.025)
	16 (Baxter)	6/17 (35)	0.35 [0.11, 0.62]	0.0046* (0.025)
AP203 Lonza (Day 28 survival)	0	2/16 (12.50)		
	8	1/16 (6.25)	-0.063 [-0.329, 0.194] [-0.358, 0.238]	0.761
	32	6/16 (37.50)	0.25 [-0.065, 0.541] [-0.114, 0.577]	0.064
AP204 Baxter (Day 56 survival)	0	1/16 (6.3)		
	4	4/16 (25.0)	0.188 [-0.090, 0.473] [-0.135, 0.513]	0.1077
	16	8/16 (50.0)	0.438 [0.113, 0.703] [0.070, 0.733]	0.0036* (0.0125)
AP201 Baxter (Day 30 survival)	0	2/14 (14.3)		
	4	11/14 (78.6)	0.643 [0.260, 0.879] [0.206, 0.898]	0.00046* (0.0125)
	8	11/15 (73.3)	0.590 [0.207, 0.841] [0.162, 0.864]	0.00075* (0.0125)
NIAID 1056 Baxter (Day 28 survival)	0	0/8 (0)		
	8	4/8 (50)	0.50 [0.058, 0.843]	0.014* (0.025)

Source: Table 2, Statistics Review, Dr. Li

Two-sided 95% confidence interval and one-sided p-values from Boschloo's test as calculated by Dr. Li

*Statistically significant at the specified significant level with Bonferroni adjustment for multiple comparisons, if needed

The lack of significant findings in Study AP203 is concerning, especially as the Lonza product was used in this study. The Applicant attributed this finding to variability in the severity of illness just prior to treatment. Based on the results of Study AP203, the Applicant conducted Study AP202 in which both the Baxter and the Lonza products were studied at the proposed dose of 16 mg/kg IV. Numerically, survival rates in the Lonza and Baxter groups were comparable (31% versus 35%, respectively); however, the study was not powered to compare the efficacy of these two products. Both products were superior to placebo.

In these five studies, only three animals that were not bacteremic at the time of treatment. Although the survival proportions were different when only the bacteremic population was analyzed, the overall conclusions did not change.

Dr. Li performed several additional analyses as summarized here to assess the relationships between challenge dose, bacteremia, and PA-ELISA prior to treatment. As Study NIAID 1056, used untreated controls, these animals did not have "pre-treatment" bacteremia or PA-ELISA values and were not included in the analyses. There was no strong linear correlation between the challenge dose and bacteremia or PA levels. Animals with lower levels of bacteremia prior to treatment were more likely to survive. Study AP201 had the lowest pre-treatment mean bacteremia levels and the highest survival proportions in the treated group compared with other studies. Studies AP202 and AP203 had the highest geometric means for bacteremia and the lowest survival proportions in the treated groups. There was considerable variability in PA ELISA levels prior to treatment. Animals with a lower PA-ELISA level prior to treatment were more likely to survive. In Study AP201, PA-ELISA levels were the lowest compared with other studies. In Study AP203, geometric means of PA-ELISA were the highest and survival proportions were the lowest in the treated groups.

Bivariate analyses of survival with bacteremia and PA-ELISA showed that as levels of bacteremia or PA-ELISA increased, survival rates decreased. Regression analyses of survival with covariates of bacteremia and PA-ELISA were conducted to help further explore the relationship between pre-treatment severity of illness and survival. Analyses from individual treatment studies showed that bacteremia level and/or PA-ELISA were important factors for survival. However, there was considerable variability in levels of bacteremia and PA-ELISA across the five treatment studies in cynomolgus macaques.

Treatment Studies in Rabbits

All treatment studies conducted in NZW rabbits used the Baxter product and are summarized in Table 4. In Study AR021, two animals (one in the placebo group and one in the 1 mg/kg group) were inadvertently dosed with levofloxacin and survived and are included in the mITT population. Because of the inclusion of one placebo survivor, Dr. Li notes that the results are slightly conservative in the 4 mg/kg and 16 mg/kg comparisons to placebo.

Table 4: Treatment Studies in NZW rabbits (mITT Population)

Study	ETI-204 IV mg/kg	Survival n/N (%)	Difference [95% CI] [Adjusted 95% CI]	One-sided p-value (significance level)
AR021	0 (placebo)	1/10 (10)		
	1	4/10 (40.0)	0.3 [-0.107, 0.659] [-0.219, 0.732]	0.059 (0.0083)
	4	13/17 (76.5)	0.665 [0.249, 0.878] [0.155, 0.918]	0.0005* (0.0083)
	16	16/17 (94.1)	0.841 [0.443, 0.978] [0.352, 0.989]	<0.0001* (0.0083)
AR033	0	0/14		
	1	4/14 (28.6)	0.286 [0.012, 0.581] [-0.077, 0.649]	0.02081 (0.0063)
	4	6/14(42.9)	0.429 [0.135, 0.711] [0.044, 0.769]	0.003* (0.0063)
	8	10/14 (71.4)	0.714 [0.406, 0.916] [0.312, 0.944]	<0.001 (0.0063)
	16	9/14 (64.3)	0.643 [0.334, 0.872] [0.237, 0.909]	0.001* (0.0063)
NIAID 1030	0	0/6 (0)		
	8	12/16 (75)	0.75 [0.221, 0.927] [0.174, 0.941]	0.0008* (0.0125)
NIAID 1045	0	0/6 (0)		
	8	7/11 (63.6)	0.636 [0.078, 0.891] [0.022, 0.911]	0.0052* (0.0125)

*Statistically significant at the specified significant level with Bonferroni adjustment for multiple comparisons
Two-sided 95% confidence interval and one-sided p-values from Boschloo's test as calculated by Dr. Li
Source: Table 9, Statistics Review, Dr. Li

In all four studies, significant treatment benefit relative to placebo was seen in the 4, 8, and 16 mg/kg IV groups. As in the cynomolgus monkey studies, there was little correlation between challenge dose and bacteremia or PA-ELISA levels. As only limited data were available regarding bacteremia and PA-ELISA levels, no bivariate or regression analyses were performed for the NZW rabbit studies.

Summary of Treatment Studies

Overall, a single dose of obiltoxaximab 16 mg/kg IV resulted in statistically significant improvement in survival rates compared to placebo in two studies in cynomolgus macaques. A statistically significant improvement in survival rates compared to placebo was also seen in two studies in NZW rabbits receiving 16 mg/kg IV.

The following table provides the survival proportions in all randomized animals with bacteremia prior to treatment in the monotherapy treatment studies in which ETI-204 was administered at 16 mg/kg IV.

Table 5: Monotherapy Treatment Studies (ETI-204, 16 mg/kg IV)

	Proportion of Survival at Day 28[1] (# survived/n)		**p-value**[2]	**95% CI**[3]
	Placebo	**Obiltoxaximab**		
NZW Rabbits				
AR021	0 (0/9)	93% (13/14)	0.0010	(0.59, 1.00)
AR033	0 (0/13)	62% (8/13)	0.0013	(0.29, 0.86)
Cynomolgus Macaques				
AP204	6 % (1/16)	47% (7/15)	0.0058	(0.09, 0.68)
AP202[4]	0 (0/17)	31% (5/16) 35% (6/17)	0.0085 0.0046	(0.08, 0.59) (0.11, 0.62)

[1] Survival assessed 28 days after spore challenge
[2] p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma=0.001) compared to placebo
[3] Exact 95% confidence interval of difference in survival rates
[4] Anthim products manufactured at two different facilities were tested in two separate treatment arms

Post-Exposure Prophylaxis (PEP) Studies

Ten studies were conducted to evaluate the efficacy of ETI-204 for PEP, six in NZW rabbits and three in cynomolgus macaques. In addition, Phase 1 of the re-challenge study AR034 was considered a PEP study as the mean time to trigger was around 30 hours and the mean time from trigger to treatment was 1.7 hours, making it unclear if all animals in this study would have had clinical signs of disease at the time of treatment.

In the PEP studies, treatment was administered at a pre-specified fixed time point (9, 18, 24, 36, or 48 hours) post-challenge, typically before (except for the last time point) clinical signs and/or symptoms developed (approximately 37-40 hours post-challenge in cynomolgus macaques and 28 hours post-challenge in NZW rabbits). ETI-204 was administered at different doses (1, 2, 4, 8, 16, 32 mg/kg), either IV or IM (Table 6).

The primary efficacy endpoint was survival at the end of the study (usually 28 days post-challenge). All challenged animals were included in the analysis population, except in Study AP301, in which all animals that received treatment were included.

Table 6: Post-Exposure Prophylaxis Studies

Study (Manufacturer)	Design	Treatment Period	Follow-up Period
Cynomolgus Macaques			
AP107 Baxter	Randomized, open-label	Single dose 2 or 8 mg/kg IV, 4 or 8 mg/kg IM; 24 hrs post-challenge	30 days
AP301 Lonza	Randomized, blinded	Single dose 8 or 16 mg/kg IM	28 days
AP307 Lonza	Randomized, open-label	Single dose 16 mg IM	28 days
NZW Rabbits			
AR004 Elusys	Randomized	Single dose 10 mg IV	28 days
AR007 (b) (4)	Randomized, open-label	Single dose 20 mg IM or 10 mg IV, 9 hrs post-challenge	34 days
AR012 Elusys	Randomized, open-label	Single dose (2.5, 10, or 20 mg IV/animal or 5,10, 20, 40 mg IM/animal 24 hrs post-challenge	14 days
AR0315 Baxter	Randomized open-label	Single dose 4 or 16 mg/kg IM	28 days
AR035 Lonza	Randomized, open-label	Single dose 16 mg/kg IM	28 days
AR037 Lonza	Randomized, open-label	Single dose IM, 24 hrs post-challenge	28 days
AR034 Phase 1 Lonza	Open-label	Single dose IV, 30 hrs post-challenge	9 months

Source: Table 10, Statistics Review, Dr. Li

PEP studies in Cynomolgus Macaques

In StudyAP107, there were no statistically significant differences between any ETI-204 treatment group (2, 4, or 8 mg/kg) and the placebo group after Bonferroni adjustment. A 16 mg/kg IV dose was not evaluated in this study. In the IV group, survival was higher in the 8 mg/kg group compared to the 2 mg/kg group. A similar trend was not seen in the IM groups.

Studies AP301 and AP307, used the Lonza product and ETI-204 was only administered IM. Significant treatment effect was seen both in the 8 mg/kg and 16 mg/kg groups when ETI-204 was administered 18 hours or 24 hours post-challenge but not at 36 hours.

The results of the PEP studies in cynomolgus macaques are summarized in Table 7.

Table 7: PEP Studies in Cynomolgus Macaques

Study	Route	Hours post-challenge	ETI-204 mg/kg	n/N(%) Survival	Difference [Adjusted 95% CI]	One-sided p-value (sig. level)
AP107 Baxter Day 30 survival	IV or IM	24	0	1/6 (16.7)		
	IV	24	2	4/9 (44.4)	0.278 [-0.391, 0.765]	0.210 (0.0063)
	IV	24	8	6/8 (75.0)	0.583 [-0.130, 0.941]	0.020 (0.0063)
	IM	24	4	6/8 (75.0)	0.583 [-0.130 0.941]	0.020 (0.0063)
	IM	24	8	5/9 (55.6)	0.389 [-0.292, 0.835]	0.087 (0.0063)
AP301 Lonza Day 28 or 56 survival	IM	18	0	0/6 (0)		
	IM	18	8	6/6 (100)	1 [0.438, 1]	0.0012* (0.0042)
	IM	18	16	6/6 (100)	1 [0.438, 1]	0.0012* (0.0042)
	IM	24	8	5/6 (83)	0.83 [0.196, 0.998]	0.0032* (0.0042)
	IM	24	16	5/6 (83)	0.83 [0.196, 0.998]	0.0032* (0.0042)
	IM	36	8	0/6 (0)	0	1.0000 (0.0042)
	IM	36	16	3/6 (50)	0.5 [-0.069, 0.893]	0.0345 (0.0042)
AP307 Lonza Day 28 survival	IM	24	0	1/10 (10)		
	IM	24	16	13/14 (93)	0.83 [0.347, 0.987]	0.001* (0.0083)

Source: Table 11, Statistics Review, Dr. Li

PEP Studies in NZW Rabbits

In Studies AR004, AR007, and AR012, (all non-Lonza products) a statistically significant survival benefit was seen when doses of 10-20 mg (approximately 4-8 mg/kg) of ETI-204 IV were administered to NZW rabbits 9-24 hours post-challenge. In Study AR0315, a dose of 16 mg/kg IM administered 18 or 24 hours post-challenge showed a statistically significant survival benefit.

In the three studies that used the Lonza product (AR034, AR035 and AR037), survival was significantly higher than placebo in two studies (AR034 and AR035). In Phase I of Study AR034, survival was statistically higher in rabbits administered 16 mg/kg IV 30 hours post-challenge compared to the placebo group. In StudyAR035, a statistically significant treatment effect was seen when ETI-204 16 mg/kg IM was administered 18 or 24 hours post-exposure. However, no significant treatment effect was seen in Study AR037. The reason for these findings is not clear. In Dr. Li's assessment, the observed significant treatment result

in these studies is unlikely due to chance and support the overall treatment effect seen with ETI-204.

Table 8: PEP Studies in NZW Rabbits

Study	Route	Hours post-challenge	ETI-204 mg	n/N(%) Survival	Difference [Adjusted 95% CI]	One-sided p-value (Significance level)
AR004 Elusys Day 28	IV	48	0	0/9 (0)		
		24	10 mg[#]	8/10 (80.0)	0.80 [0.303, 0.986]	0.0001* (0.0083)
		36	10 mg[#]	5/10 (50.0)	0.50 [-0.017, 0.856]	0.010 (0.0083)
		48	10 mg[#]	3/7 (42.9)	0.429 [-0.084, 0.865]	0.0226 (0.0083)
AR007 (b) (4) Day 34	IV	9	0	0/9 (0)		
	IV		10 mg[#]	9/9 (100)	1 [0.568, 1]	<0.0001* (0.0125)
	IM		20 mg[#]	9/9 (100)	1 [0.568, 1]	<0.0001* (0.0125)
AR012 Elusys Day 14	IM	24	0	0/9 (0)		
	IV		2.5 mg[#]	1/9 (11.1)	0.111 [-0.436, 0.610]	0.4073 (0.0036)
			10 mg[#]	6/12 (50)	0.50 [-0.057, 0.859]	0.0074 (0.0036)
			20 mg[#]	7/12 (58.3)	0.583 [-0.018, 0.904]	0.0026* (0.0036)
	IM		5 mg[#]	1/9 (11.1)	0.111 [-0.436, 0.610]	0.4073 (0.0036)
			10 mg[#]	3/9 (33.3)	0.333 [-0.238, 0.794]	0.049 (0.0036)
			20 mg[#]	5/12 (41.7)	0.417 [-0.134, 0.806]	0.0186 (0.0036)
			40 mg	4/12 (33.3)	0.33 [-0.217, 0.749]	0.051 [0.0036]
AR0315 Baxter Day 28	IM	24	0	0/10 (0)		
		18	4 mg/kg	11/12 (91.7)	0.917 [0.425, 1]	<0.0001* (0.0063)
		24	4 mg/kg	5/12 (41.7)	0.417 [-0.058, 0.786]	0.0131 (0.0063)
		18	16 mg/kg	11/12 (91.7)	0.917 [0.425, 1]	<0.0001* (0.0063)
		24	16 mg/kg	8/12 (66.7)	0.667 [0.172, 0.934]	0.0005* (0.0063)
AR034 Phase I Lonza Day 28	IV	30	0	0/8		
			16 mg/kg	13/20 (65)	0.65 [0.300, 0.969]	0.0008* (0.0125)

Study	Route	Hours post-challenge	ETI-204 mg	n/N(%) Survival	Difference [Adjusted 95% CI]	One-sided p-value (Significance level)
AR035 Lonza Day 28	IM	18	0	0/10 (0)		
		18	16 mg/kg	6/10 (60)	0.60 [0.119, 0.912]	0.0018* (0.0083)
		24	16 mg/kg	6/10 (60)	0.60 [0.119, 0.912]	0.0018* (0.0083)
		36	16 mg/kg	0/8 (0)	0 [-0.387, 0.480]	0.5 (0.0083)
AR037 Lonza Day 28	IM	24	0	0/10		
			8 mg/kg	5/16 (31.3)	0.313 [-0.019, 0.587]^	0.33 (0.0083)
			16 mg/kg	5/16 (31.3)	0.313 [-0.019, 0.587]^	0.33 (0.0083)
			32 mg/kg	5/16 (31.3)	0.303 [-0.019, 0.587]^	0.33 (0.0083)

Source: Table 12, Statistics review, Dr. Li
#: Dose per animal
Two-sided 95% confidence interval and one-sided p-values from Boschloo's test calculated by Dr. Li
*Statistically significant at the specified significant level with Bonferroni adjustment for multiple comparisons
^Unadjusted 95 % CI

Summary of PEP Studies

In cynomolgus macaques, ETI-204 8 mg/kg or 16 mg/kg IM administered either 18 or 24 hours post-exposure provided a significant survival benefit in two studies. Survival benefit was not seen when 8 mg/kg or 16 mg/kg IM of ETI-204 was administered 36 hours post-exposure. In NZW rabbits, two studies that used 16 mg/kg IV of the Lonza product administered 18-30 hours post-exposure provided significant survival benefit. Also, lower doses (4-8 mg/kg) of the non-Lonza products administered 9-24 hours post-exposure provided significant survival benefit.

Overall, given that a significant survival benefit was seen with the 16 mg/kg IM dose, the 16 mg/kg IV dose is also likely to have at least a similar treatment effect.

Combination Studies

Eight studies were conducted to evaluate the added benefit of a single IV dose of ETI-204 when given with antibacterial drugs for treatment or PEP (Table 9). In these studies, either antibacterial therapy was delayed, or doses less than the human equivalent dose (HED) were administered or both strategies were used. The doses and timing of ETI-204 administration relative to exposure to *B. anthracis* spores varied leading to variability in the treatment effect and survival rates. In all studies, ETI-204 given in combination with antibacterial therapy was compared to antibacterial therapy alone, allowing for the assessment of the added contribution of ETI-204. The studies were open-label, randomized trials except for Study AP 10-055 which was conducted by USAMRIID and was not randomized.

Table 9: Combination Studies

Study	Test groups (number of animals) :Dose mg/kg	Treatment Initiation hours post-exposure	Follow up period
NZW Rabbit studies with antibacterial dose at HED			
AR007 (b) (4)	Levofloxacin (50): 12 Levofloxacin + ETI-204 (4 IV): 9 Levofloxacin + ETI-204 (8 IM): 9	9 ± 3	Day 28
1030 (Baxter)	Levofloxacin (50): 16 Levofloxacin + ETI-204 (8 IV): 16	96±1	Day 28
1045 (Baxter)	Levofloxacin (50): 16 Levofloxacin + ETI-204 (8 IV): 16	72±1	Day 28
AR034 (Phase I) (Lonza)	Levofloxacin (50): 20 Levofloxacin + ETI-204 (16 IV): 20	30 (re-challenge)	Month 9
NZW Rabbits studies with antibacterial dose < HED			
AR028 (Baxter)	Levofloxacin (6.5): 38 Levofloxacin + ETI-204 (16 IV): 34	72±4	Day 28
AP-10-055 (Baxter)	Doxycycline (2):10 Doxycycline + ETI-204 (8 IV): 10	ECL Positive by 30	Day 28
Cynomolgus Macaques studies with antibacterial dose < HED			
1056 (Baxter)	Ciprofloxacin (10 mg/kg): 16 Ciprofloxacin + ETI-204 (8 mg/kg IV): 16	ECL Positive + 24±12	Day 28
2469 (Baxter)	Ciprofloxacin (10 mg/kg): 16 Ciprofloxacin + ETI-204 (8 mg/kg IV): 16	ECL Positive + 24±12	Day 28

ECL: protective antigen (PA) result determined by electrochemiluminescence (ECL)
Source: Modified from Statistics Review, Dr. Lan, Table 1

NZW Rabbit Studies Using HED of Antibacterial (levofloxacin)

In Study AR007, 4 mg/kg of ETI-204 was administered IV or IM in combination with five days of HED of levofloxacin showed significant increase in survival (56%, 95% CI, 0.11, 0.82). Treatment was initiated 9 ± 3 hours following exposure.

In Study NIAID 1030, the dose of ETI-204 was 8 mg/kg IV. Treatment was delayed to 96 hours post-challenge. Only 28% of challenged animals survived to treatment (4 in the combination group and 5 in the levofloxacin alone group). In the combination group, all four animals survived compared to 2/5 (40%) in the levofloxacin group. Given the high pretreatment mortality, there was insufficient power to assess the added benefit of ETI-204.

In Study NIAID 1045, treatment was initiated about 72 hours post-exposure; 63% of animals (20/32) survived to receive treatment (11 in the combination group and 9 in the levofloxacin alone group). Similar survival rates were seen in the combination group (82%, 9/11) compared to the levofloxacin alone group (78%, 7/9).

In Study AR034, the dose of ETI-204 was 16 mg/kg IV and treatment was initiated 30 hours post-challenge. Similar survival rates were seen in both groups (95%, 19/20 in the combination group and 100%, 20/20, in the levofloxacin alone group).

Studies Using Antibacterial Dose less than HED

NZW Rabbits (levofloxacin, doxycycline)
In Study AR028, treatment was delayed to 72 hours post-exposure and 70% of animals survived to treatment. The dose of levofloxacin was 6.5 mg/kg per day orally for three days and ETI-204 was dosed at 16 mg/kg IV. In the levofloxacin alone arm, survival was 58%. Survival rates were numerically greater in the combination arm (68%, 23/34) compared to levofloxacin alone (58%).

In Study AP 10-055, NZW rabbits received doxycycline, 2 mg/kg dose twice daily for three days. Treatment was initiated at approximately 30 hours post-challenge. This was a non-randomized study and electronic data for this study were not submitted. Hence, Dr. Lan considered review of this study to be exploratory. In combination with doxycycline, ETI-204 dosed at 8 mg/kg IV had numerically higher survival rates (90%, 9/10) over doxycycline alone (50%, 5/10).

Cynomolgus Macaques (ciprofloxacin)
In Study NIAID 1056, the added benefit of ETI-204 8 mg/kg IV over oral ciprofloxacin (10 mg/kg/day for four days) was assessed in cynomolgus macaques (HED of ciprofloxacin 25.9 mg/kg). Treatment was initiated at about 24 hours following the first positive PA-ECL result, equivalent to 48 hours post-exposure. Majority of the animals, 81% (26/32), survived to receive treatment. ETI-204 provided significant added benefit in survival rates when co-administered with ciprofloxacin (62%, 8/13) compared to ciprofloxacin alone (15%, 2/13) (treatment difference 46%, 95% CI, 0.04, 0.77).

Study 2469, was similar in design to Study NIAID 1056; 84% of the animals (27/32) survived to treatment initiation (14 in the combination group and 13 in the ciprofloxacin alone group). The survival rate was numerically higher when ETI-204 was co-administered with ciprofloxacin (57%, 8/14) compared to ciprofloxacin alone (31%, 4/13).

Overall, in these four studies where antibacterial drugs were administered at doses lower than the HED showed that the combination of ETI-204 and an antibacterial drug resulted in higher survival rates compared to antibacterial drug alone. The magnitude of the treatment effect varied across the studies.

Results of the combination studies are summarized in Table 9.

Table 9: Results of the Combination Studies

Study (Manufacturer)	ETI-204 Dose IV (mg/kg)	Treatment Initiation Post Exposure (hour)	Survival % (# survived / # treated)		Difference (95%CI)
			ETI-204 + Antibacterial	Antibacterial	
NZW Rabbit studies with antibacterial dose at HED (levofloxacin)					
AR007 (b) (4)[3]	4	9 ± 3	89% (8/9)	33% (4/12)	56% (11, 82)
1030 Baxter	8	96±1	100% (4/4)	40% (2/5)	60% (-9, 95)
1045 Baxter	8	72±1	82% (9/11)	78% (7/9)	4% (-36, 44)
AR034 (Phase I) Lonza	16	30	95% (19/20)	100% (20/20)	-5% (-26, 11)
NZW Rabbits studies with antibacterial dose < HED (levofloxacin, doxycycline)					
AR028 Baxter	16	72±4	68% (23/34)	58% (22/38)	10% (-12, 32)
AP-10-055[2,3] Baxter	8	ECL[4] Positive by 30	90% (9/10)	50% (5/10)	40% (-2, 72)
Cynomolgus Monkey studies with antibacterial dose < HED (ciprofloxacin)					
1056 Baxter	8	ECL Positive + 24±12	62% (8/13)	15% (2/13)	46% (4, 77)
2469 Baxter	8	ECL Positive + 24±12	57% (8/14)	31% (4/13)	26% (-14, 60)

[1] HED: Human equivalent dose of antibacterial drug
[2] No electronic data provided (USAMRIID
[3] Doxycycline given at 2 mg/kg bid, treatment was initiated at 30 hours post-exposure or at first positive PA
[4] protective antigen (PA) result determined by electrochemiluminescence
Source: Statistics Review, Dr. Lan, Table 2

Dr. Lan performed a meta-analysis of the studies conducted to assess the added benefit of ETI 204 to an antibacterial drug using an exact fixed effect model. The primary endpoint of the meta-analysis was the difference in survival rate by the end of each study (Days 28, 29, or 30 post-exposure). The meta-analysis was stratified by animal (rabbits or macaques) and dose of antibacterial administered (HED or < HED). Key findings are summarized below:

- In NZW rabbits that received HED of an antibacterial drug, survival rates in the combination group were similar to those in the antibacterial therapy alone group [Risk difference 2%, (95% CI: -0.10, 0.53)]. The studies included were relatively heterogeneous.

- In NZW rabbits that received less than the HED of an antibacterial drug, the combination group had numerically greater survival rates than the antibacterial alone group [Risk difference 14%, (95% CI: -0.04, 0.48)] and the studies included were relatively homogenous.

- In cynomolgus macaques that received antibacterial doses less than HED, survival rates were significantly greater in those that received the combination compared to those that

received antibacterial drugs [Risk difference 36% (95%CI: 0.11, 0.61)]. The two studies had similar study designs and were homogenous.

Dr. Lan notes in her review that the results of these studies demonstrate the difficulty in showing the added benefit of ETI-204 over antibacterial alone at HED in a treatment setting. When treatment was not delayed (given at 30 hours), there was 100% survival in the antibacterial alone arm. When treatment was delayed (given at 72 hours), while the efficacy of levofloxacin alone decreased to 78%, it was difficult to show added benefit, especially when only 63% of animals survived to receive treatment. When treatment was further delayed to 96 hours, the survival rate with levofloxacin alone reduced to 40%; however, with only 28% of animals surviving to treatment, it is not feasible to power this type of study. The only study that was able to show a treatment effect of the combination over HED of levofloxacin alone was in Study AR007, where treatment was initiated 9 ± 3 hours post-exposure. However, the survival rate with levofloxacin alone was 33% as the animals were dosed only for 5 days. Dr. Lan notes that despite the limitations with these studies, these data along with the results of the studies using less than the HED of levofloxacin demonstrate the added benefit of ETI-204 when administered in combination with antibacterial drugs compared to antibacterial drugs alone in the treatment of inhalational anthrax.

Dr. O'Shaughnessy notes that the results of the eight combination studies provide limited evidence of an improvement in survival for the combination of obiltoxaximab IV plus an antibacterial drug over antibacterial drugs (levofloxacin, ciprofloxacin, and doxycycline) alone. Dr. O'Shaughnessy also notes that these studies do not negatively impact the assessment of the treatment benefit of obiltoxaximab monotherapy as there might be clinical situations where obiltoxaximab monotherapy would be necessary, for example, in the setting of infection due to multi-drug resistant *B. anthracis* or in patients with contraindications to available antibacterial drugs.

Pre-Exposure Prophylaxis Studies

AP-305: This was a randomized, blinded, placebo-controlled, study in cynomolgus macaques that evaluated the efficacy of ETI-204 16 mg/kg IM (Lonza product) administered 24, 48, or 72 hours before challenge. All cynomolgus macaques in the ETI-204 group survived ($p < 0.0001$). There was one survivor in the control group (10%). This macaque had received a challenge dose of 330 LD50 spores, had a bacteremia of 400 cfu/mL at 24 hours post-challenge and was non-bacteremic on Day 7, 14, 28, and 56.

AR-001: In this study in NZW rabbits, ETI-204 10 mg (approximately 4 mg/kg) was administered IV 30-45 minutes prior to challenge. The Elusys product was used in this study. All NZW rabbits in the ETI-204 group survived (9/9) compared to none (0/5) in the placebo group ($p < 0.0001$).

AR-003: In this study, varying doses of the ETI-204 was administered (5 groups) to NZW rabbits 35 minutes prior to exposure to *B. anthracis*. All control animals died by Day 4. There was a statistically significant difference between all the treatment groups and the placebo group, using a two-sided significance level of 0.05/5=0.01.

Re-challenge Study

Study AR034 was a randomized, controlled, open-label, re-challenge study in NZW rabbits. Healthy NZW rabbits were challenged with aerosolized *B. anthracis* spores twice, first in Phase I and nine months later in Phase II. In Phase I, rabbits were challenged and treated with ETI-204 alone, levofloxacin alone, ETI-204 + levofloxacin, or placebo. Rabbits that were treated and survived Phase 1 were included in Phase II of the study. In Phase I, study treatments were initiated 30 hours post-challenge. The Lonza product was used in this study. In Phase II, surviving animals from the treated groups were re-challenged. No monoclonal antibody or antibacterial treatment was administered in Phase II.

The survival proportions in Phase II were 100% in the ETI-204 alone group, 89% in the ETI-204 and levofloxacin group, and 95% in the levofloxacin alone group. All were statistically significantly different than the Phase II control group in which no animals survived.

The development of an immune response for the animals was assessed through measurements of anti-PA IgG levels and the functional ability of serum to neutralize *B. anthracis* lethal toxin activity (ED50/NF50 titers). Levels of Anti-PA-IgG were highest at Day 7 post-challenge, then gradually reduced until 5 days post re-challenge and increased to a level similar to the level at Day 7 post re-challenge and continued to increase through Day 21 post re-challenge indicating the development of an immune response to re-challenge with *B. anthracis* spores. The ETI-204 group (n=13) consistently exhibited an ED50 or NF50 titer following primary challenge. In addition, the titer increased by the end of the secondary challenge in-life period compared to Day 7 prior to re-challenge.

The key efficacy findings for ETI-204 at a dose of 16 mg/kg are summarized below:

- In four monotherapy studies, a single dose of ETI-204 showed a significant survival benefit over placebo in both the cynomolgus macaque and NZW rabbit models of inhalational anthrax. The lack of a treatment benefit in Study AP203 may be explained by the high bacteremia levels and high PA-ELISA levels prior to treatment observed in cynomolgus macaques in this study.
- The efficacy of ETI-204 for the treatment of inhalational anthrax is supported by studies that demonstrated the efficacy of this product for prophylaxis against

inhalational anthrax. The majority of the prophylaxis studies evaluated ETI-204 administered IM. In post-exposure prophylaxis studies, ETI-204 given early post-challenge resulted in higher survival rates than at later time points post-challenge. A 16 mg/kg IM dose, administered to cynomolgus macaques and NZW rabbits within 24 hours of exposure to *B. anthracis* spores, was effective in preventing inhalational anthrax. In pre-exposure studies, ETI-204 16 mg/kg IM was effective when treatment was given 30 minutes and up to 3 days prior to challenge. As exposures are lower with IM administration compared to IV, ETI-204 IV is expected to at least be as effective as the IM doses.

- In a re-challenge study, 100% of the NZW rabbits that were previously treated with 16 mg/kg IV ETI-204 survived a second challenge with aerosolized *B. anthracis* spores and 89% of the animals that were previously treated with ETI-204 16 mg/kg IV and levofloxacin survived a second challenge.

Drs. O'Shaughnessy, Li and Lang note that the Applicant has provided substantial evidence of effectiveness of obiltoxaximab for the treatment and prophylaxis of inhalational anthrax in the cynomolgus macaque and NZW rabbit models of inhalational anthrax. The statistically significant increase in survival rate over placebo in both models of inhalational anthrax, indicate that obiltoxaximab is reasonably likely to produce clinical benefit in humans with inhalational anthrax. They recommend approval of obiltoxaximab 16mg/kg IV single dose for the treatment of adult and pediatric patients with inhalational anthrax in combination with appropriate antibacterial drugs. However, given the risk of hypersensitivity reactions, including anaphylaxis, Dr. O'Shaughnessy recommends approval of obiltoxaximab for prophylaxis of inhalational anthrax only when alternative therapies are not available or are not appropriate.

I agree with their assessment that the Applicant has provided adequate evidence to support the efficacy of ETI-204 16 mg/kg for treatment and prophylaxis of inhalational anthrax. I also agree that given the risk of serious hypersensitivity reactions, the product should be approved for prophylaxis of inhalational anthrax only when alternative therapies are not available or are not appropriate.

8. Safety

The safety reviewer for this BLA is Ramya Gopinath, MD. As obiltoxaximab was developed under 21 CFR 601, Subpart H (Animal Rule) safety was evaluated in healthy humans. The safety of obiltoxaximab administered intravenously was evaluated in the following studies:

1. Study AH104: Single-dose of 16 mg/kg obiltoxaximab compared to placebo
2. Study AH109: Two doses of 16 mg/kg obiltoxaximab given either 14 or ≥120 days apart
3. Study AH110A: Single-dose of 16 mg/kg obiltoxaximab with or without IV ciprofloxacin followed by oral ciprofloxacin
4. Study AH101: Dose-escalation study of single doses of obiltoxaximab compared to placebo
5. Study AH102: Dose-escalation study of higher fixed doses of obiltoxaximab compared to placebo
6. Study AH105: Dose-escalation study of single-dose 4, 8, and 16 mg/kg obiltoxaximab compared to placebo

In addition, in Study AH106, the safety of a single dose of intramuscular obiltoxaximab was compared to placebo.

A total of 320 subjects received one or more IV doses of 16 mg/kg obiltoxaximab (Lonza formulation) and 30 subjects received 16 mg/kg obiltoxaximab IV of the Baxter formulation. Additionally, 27 subjects received the Lonza formulation intramuscularly at doses ranging from 4 mg/kg to 24 mg/kg. Overall, 470 subjects received IV obiltoxaximab (either formulation, doses of 4, 8 or 16 mg/kg).

Dr. Gopinath defined several different safety populations based on the formulation, the dose, number of doses and concomitant ciprofloxacin administration. The FDA Primary Study Population (PSP) was derived from the following three studies:

- Study AH104: 210 obiltoxaximab subjects and 70 placebo subjects
- Study AH110: 20 obiltoxaximab alone subjects
- Study AH109: 70 obiltoxaximab subjects in the first treatment period (Days 1-13)

The expanded safety population included 20 additional subjects who received obiltoxaximab in combination with ciprofloxacin in Study AH110 and all treatment periods in AH109. All subjects in both populations received the Lonza formulation. Diphenhydramine was administered approximately 30 minutes prior to study drug administration for all subjects enrolled in AH104, AH110, and AH109 after July 30, 2013. A total of 74 subjects in the obiltoxaximab group (66 subjects in AH104 and 8 in AH109) did not receive diphenhydramine pretreatment.

The majority of subjects were ≥ 18 years to ≤ 65 years of age, White, mean age was ~ 42 years and ~54% were males.

There were no deaths in any of the studies. There were two reports of Serious Adverse Events (SAEs), one each of ankle fracture and ovarian cyst. Both cases were assessed as unrelated to study drug administration.

In Study AH104, six subjects withdrew from the study (five in the obiltoxaximab arm and one in the placebo arm). Of these, four were lost to follow-up (all in the obiltoxaximab arm) and two withdrew consent (one in each arm). In Study AH109, 10 (14.3%) subjects withdrew from the study, five each in Sequence A and B; four were lost to follow-up, two withdrew consent, two had a protocol violation and two withdrew due to an AE. In Study AH110, one subject (2.5%) discontinued for personal reasons.

Common adverse reactions reported by ≥1.5% of subjects were headache, pruritus, infections of the upper respiratory tract, rash, urticaria, cough, vessel puncture site bruise, and infusion site swelling, nasal congestion and infusion site pain. Somnolence was reported mainly in Studies AH109 and AH110 and not in Study AH104 and was thought to be related to inconsistencies in reporting by investigators and to receipt of diphenhydramine rather than to obiltoxaximab administration.

No significant laboratory test abnormalities were reported in subjects who received obiltoxaximab.

Hypersensitivity

The main adverse reaction of concern with ETI-204 is hypersensitivity. In the expanded safety population of 320 subjects, 34 (10.6%) subjects in the obiltoxaximab arm had any clinically relevant symptom of hypersensitivity (preferred terms included various types of skin rashes, cough, hypersensitivity) compared to four (5.7%) in the placebo arm. In 8/320 (2.5%) subjects, infusion of obiltoxaximab was discontinued due to a hypersensitivity reaction. Two other subjects were withdrawn from study AH109 for hypersensitivity. Dr. Gopinath identified seven cases of anaphylaxis, while the Applicant identified only one case in which the preferred term of anaphylactic reaction was reported. Dr. Gopinath did not agree with the Applicant's assessment as use of the preferred term alone as each sign/symptom in isolation does not capture the clinical syndrome and needs to be considered in aggregate.

Dr. Kathleen Donohue, Medical Officer in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) provided a consult review regarding the risk of hypersensitivity reactions with obiltoxaximab infusion. Dr. Donohue agreed with Dr. Gopinath's assessment that seven cases met the definition for anaphylaxis for an incidence of 2.2% (7/320). All seven cases occurred during the infusion (23-90 minutes). For the one additional potential case of anaphylaxis, enough information was not available to make a

definitive determination. This patient tolerated a second dose of obiltoxaximab at study day 14 without incident, suggesting a non-IgE mediated mechanism.

Dr. Donohue notes that is DPARP's usual practice to include all cases identified as anaphylaxis by the investigator at the bedside, as well as all cases adjudicated as anaphylaxis by the first of three criteria set forth by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network. The first criterion requires 'acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:

- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence."

Dr. Donohue disagreed with the Applicant's assertion that the other cases do not represent anaphylaxis as only one subject received epinephrine, that the concomitant medications were primarily diphenhydramine and famotidine, and that there was no evidence of angioedema, wheezing, significant respiratory compromise or hypotension.

Dr. Donohue notes that the risk of anaphylaxis could have been underestimated as most patients were premedicated with diphenhydramine, which can mask or delay detection of the symptoms of anaphylaxis and secondly, obiltoxaximab is manufactured in a murine cell line known to impart an impurity galactose-alpha-1,3-galactose (alpha-gal), which has been implicated in other cases of drug-induced anaphylaxis.

In an addendum dated February 12, 2016, Dr. Lydia Gilbert-McClain, Deputy Director, DPARP, notes that the cases of anaphylaxis were re-assessed based on the Sampson criteria and only three cases met these criteria for anaphylaxis. The other four cases initially identified as anaphylaxis were considered to be equivocal based on the Sampson criteria as there was no clear finding of respiratory or cardiovascular compromise. Dr. Gilbert-McClain notes that pretreatment with diphenhydramine can alter the manifestations of anaphylaxis making the finding of these three cases (2 of whom were pretreated with diphenhydramine) all the more compelling. In Dr. Gilbert- McClain's assessment, this does not change the risk assessment for anaphylaxis and hypersensitivity for this product. Dr. Gilbert- McClain notes that the finding of at least three cases of anaphylaxis in a controlled setting in a sample size of 320 subjects (0.94%) is quite high and would warrant adequate labeling to inform prescribers about the risk and recommends a Boxed Warning for anaphylaxis and hypersensitivity reactions consistent with 21 CFR 201.57(c)(1).

The QT Interdisciplinary Review Team (QT-IRT) determined that a thorough QT study was not needed. The QT-IRT reviewed the ECG data collected in the safety studies and determined that there are no clinical or pre-clinical data to suggest that ETI-204 has the potential to delay ventricular repolarization.

Dr. Gopinath recommends approval of obiltoxaximab 16 mg/kg IV single dose for the treatment of adult and pediatric patients with inhalational anthrax in combination with appropriate antibacterial drugs. However, given the risk of hypersensitivity reactions, Dr. Gopinath recommends approval of obiltoxaximab 16 mg/kg IV single dose for prophylaxis of inhalational anthrax only when alternative therapies are not available or are not appropriate.

I agree with Dr. Gopinath's assessment.

9. Advisory Committee Meeting

This BLA was not discussed at an FDA Advisory Committee because obiltoxaximab has the same target and treatment indications as Raxibacumab, the first approved monoclonal antibody for the treatment and prophylaxis of inhalational anthrax.[1] Raxibacumab was discussed at two advisory committee meetings (October 27, 2009, and November 02, 2012).[2,3] During the review of this BLA, no new questions or concerns emerged regarding obiltoxaximab for the treatment or post-exposure prophylaxis of inhalational anthrax. The safety concerns of serious hypersensitivity reactions, including anaphylaxis have been adequately addressed in labeling.

10. Pediatrics

No pediatric studies were conducted with obiltoxaximab. Obiltoxaximab has orphan product designation for treatment of exposure to *B. anthracis* spores.[4] Therefore, the Pediatric Research Equity Act (PREA) does not apply. As pediatric dosing cannot be determined in healthy children, pediatric dosing recommendations were based on a population PK approach to provide pediatric patients with exposure comparable to the observed exposure in adults. Pediatric dosing recommendations are included in labeling. The Limitations of Use section describes the basis for pediatric dosing.

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[1] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

[2] http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/ucm188488.htm

[3] http://www.fda.gov/AdvisoryCommittees/Calendar/ucm319013.htm

[4] https://www.accessdata fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=224306

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Audits

The Office of Study Integrity and Surveillance (OSIS) audited the analytical portion of 12 nonclinical and clinical studies conducted by (b) (4). Form FDA 483 was not issued at the close-out of the inspection for the clinical studies. However, a Form FDA 483 was issued at the close-out for the nonclinical studies. The final classification for this inspection was voluntary action indicated (VAI). The overall recommendation from OSI was that the results from the analytical portion of the nonclinical and clinical studies be accepted for review. The clinical pharmacology reviewers concluded that the issues identified in the analytic inspection report are not expected to affect the observed PK of obiltoxaximab in clinical and nonclinical studies.

An inspection of the (b) (4) was also conducted by OSIS. A total of seven studies (AR021, AR033, AR201, AR202, AR203, AR204 and AR301) were audited. The field and OSIS final classification for this inspection was No Action Indicated (NAI). Overall, the audited studies were found to be acceptable. A clinical inspection of six sites was also conducted. A Form 483 was issued to Quintiles Phase One Services related to studies AH109 and AH 110. The final classification for that site was voluntary action indicated (VAI). The other five sites were classified as No Action Indicated (NAI). The overall recommendation from OSIS is that the clinical data from these sites is acceptable.

Risk Management

Dr. Joyce Weaver, Pharm D from the Division of Risk Management notes that a REMS is not required and the adverse reaction of hypersensitivity reactions can be communicated through labeling.

12. Labeling

Boxed Warning

Based on the cases of anaphylaxis and hypersensitivity reactions reported in the clinical trials, a Boxed Warning was added to labeling consistent with 21 CFR 201.57(c)(1). As noted in the Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warning sections of labeling, a Boxed Warning is appropriate when a serious reaction can be prevented

or reduced in frequency or severity by appropriate use of the product.[5] Anaphylaxis is a serious and potentially life-threatening adverse reaction that can be mitigated by early recognition and appropriate interventions. In critically ill patients with inhalational anthrax, it is important that the provider be aware of this adverse reaction; the overlap in the clinical manifestations of the illness and anaphylaxis can make it difficult in some cases to discern whether the worsening in clinical status is related to the disease or to the adverse reaction. The Boxed Warning describes the risk of anaphylaxis and hypersensitivity reactions and describes the need for close monitoring and administration in monitored settings.

Indications and Usage

Given the risk of hypersensitivity reactions including anaphylaxis, obiltoxaximab is being indicated for prophylaxis of inhalational anthrax due to *B. anthracis* only when alternative therapies are not available or not appropriate. This information is also being included in the Limitations of Use subsection (1.2). This subsection also includes limitations of use with respect to the product having been studied only in animal models and not in humans and that pediatric dosing was derived based on a population pharmacokinetic approach to provide pediatric patients with exposure comparable to the observed exposure in adults.

Dosage and Administration

The Applicant had proposed a dose of (b) (4) mg/kg in pediatric subjects with body weight 40 to 50 kg. As this would result in higher exposures than that seen in adults receiving 16 mg/kg, labeling was revised to state that children and adults weighing between 40 to 50 kg should receive 16 mg/kg.

Warning and Precautions

The Applicant had only proposed a warning on (b) (4). This was revised to hypersensitivity reactions including anaphylaxis. Further detail was provided in this section to describe the frequency of some of these events and to recommend administration of the product in monitored settings by trained personnel.

Clinical Studies

The Applicant had proposed (b) (4) This section of the labeling was revised to convey key information from studies that used the proposed dose either for treatment or for prophylaxis.

[5] Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf

Dr. Jibril Abdus-Samad, PharmD, Labeling Reviewer in the Office of Biotechnology Products notes that the carton and container labeling are adequate. The Strategic National Stockpile (SNS) labeling and repackaging process will be submitted by the Applicant post-approval.

The DMEPA reviewers for this BLA were Jacqueline Sheppard, PharmD and Vicky Borders-Hemphill, PharmD. The carton and container labels were found acceptable from a medication error standpoint. The proprietary name Anthim was acceptable. Shawna Hutchins, MPH, BSN, RN from the Division of Medical Policy Programs (DMPP) provided labeling recommendations for the Patient Package Insert (PPI).

13. Postmarketing

Postmarketing Requirements and Commitments

The Applicant will conduct the following study as a postmarketing requirement under 21 CFR 601, Subpart H.

Conduct a field study to evaluate the clinical response, pharmacokinetics, and safety profile of Anthim (obiltoxaximab) when used in the treatment of suspected or confirmed cases of inhalational anthrax due to *B. anthracis* in the United States.

Final Protocol Submission:	11/30/16
Study/Trial Completion:	To be determined should an event occur
Final Report Submission:	To be determined should an event occur

The Applicant will be performing the following studies related to product quality as postmarketing commitments:

1. Conduct a study to qualify the bioburden test for the primary recovery samples using the increased sample volume (10 mL).

2. Re-evaluate and establish final (b) (4) bioburden and endotoxin limits for all the sampling points.

3. Develop reduced and non-reduced SDS-based assays capable of providing quantitative data for the evaluation of size related product impurities and implement these assays in the release and stability program for obiltoxaximab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria. Provide the analytical procedure, validation report, proposed acceptance criteria, and data used to set the proposed acceptance criteria.

4. Conduct validation studies to confirm the shipper is suitable for maintaining critical quality attributes during shipping of obiltoxaximab drug products. This should include consideration for worst case shipping routes. The study will include monitoring of temperature during the shipment, as well as testing of pre- and post-shipping samples of obiltoxaximab drug product quality (e.g., appearance, protein concentration, and purity by SEC-HPLC, reduced and non-reduced SDS-PAGE, icIEF, visible and sub-visible particulates and potency.)

5. Conduct a study to confirm compatibility of the drug product with syringe infusion components used for administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, icIEF, visible and sub-visible particulates and potency.

6. Conduct a study to support the worst case cumulative hold times in obiltoxaximab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obiltoxaximab drug substance. These data are expected to demonstrate that there is no adverse impact to product quality when the manufacturing of a drug substance batch involves (b) (4)

7. Re-evaluate obiltoxaximab drug substance lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications.

8. Re-evaluate obiltoxaximab drug product lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications.

9. Establish a permanent control limit for (b) (4) of production (b) (4) and (b) (4) of (b) (4) unit operations after (b) (4) control points have been analyzed. The (b) (4) limits and supportive data should be submitted to the BLA.

10. Conduct drug substance specific leachable and extractable studies (b) (4)
The drug substance manufacturing processes will be optimized, as needed, based on results.

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/s/

SUMATHI NAMBIAR
03/11/2016