CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	*{See electronic stamp date}*
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader 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) [also referred to as ETI-204]
Dosage form(s) / Strength(s)	Injection Solution: 600 mg/6 mL single-dose vial
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.
Recommendation on Regulatory Action	*Approval*

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Obiltoxaximab is a monoclonal antibody that binds to protective antigen (PA), a portion of the toxins produced by the bacteria that cause anthrax infections. Elusys Therapeutics proposes to market obiltoxaximab for treatment of inhalational anthrax in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Inhalational anthrax is a life-threatening infection caused by *B. anthracis*, a category A biological warfare agent. The toxins produced by *B. anthracis* during infection cause tissue damage and death in a high proportion of people with inhalational anthrax.

Antibacterial drugs are the main treatment for anthrax, but deaths still occur despite treatment. There are antibodies approved for treatment of anthrax, raxibacumab and AIGIV. There is also an anthrax vaccine used for prophylaxis, but not treatment. Obiltoxaximab would be another treatment option to the antibody products, raxibacumab and AIGIV.

The benefits of obiltoxaximab in treatment and prophylaxis of inhalational anthrax could only be studied in animals. It is clear from the animal studies that obiltoxaximab works better than a placebo to reduce the risk of death in animals with inhalational anthrax. There appears to be enough information to support the intended dose of obiltoxaximab for humans (16 mg/kg in a single intravenous dose).

The main use of obiltoxaximab would be for treatment of inhalational anthrax in combination with antibacterial drugs. Because obiltoxaximab works in a different way from antibacterial drugs, it is reasonable to think they would work better together. The animal studies clearly show that the addition of the obiltoxaximab does not reduce the effect of the antibacterial. The animal studies of the combination of obiltoxaximab with antibacterial drugs suggest that the two together are better than the antibacterial drug alone, but the flaws in the designs of these studies make it difficult to know how much added benefit there would be for treatment of humans with inhalational anthrax. There is enough information about the benefit of obiltoxaximab in prophylaxis to think that it would be an option if antibacterial drugs or raxibacumab were not available.

There is limited safety information coming from healthy adult volunteers. The main safety risk identified in the studies is the risk of hypersensitivity reactions, including anaphylaxis. Because of the frequency of anaphylactic reactions, leading to discontinuation of obiltoxaximab infusion and other treatments, obiltoxaximab should be administered only in settings where people receiving the drug can be monitored and treated for anaphylaxis. Risk management of anaphylaxis can be addressed adequately with labeling. (b) (4)

In conclusion, I recommend approval of obiltoxaximab for treatment of inhalational anthrax in combination with antibacterial drugs. The evidence for benefit from animals suggests that obiltoxaximab would reduce the risk of death from the toxins produced in the bacterial infection. Because of the risk of anaphylaxis, it should only be administered in a setting where individuals can be monitored and treated for anaphylaxis. There is enough benefit information from animals to also support the use of obiltoxaximab for prophylaxis, but only in situations where antibacterial drugs and raxibacumab cannot be used. Because of the risk of anaphylaxis, obiltoxaximab should only be used for prophylaxis in those people with significant exposure to anthrax spores.

The benefit risk framework in the next table is modified from the one provided in the clinical review. I have no disagreement with the conclusions drawn by the clinical reviewers; the changes I made were mainly to highlight the factors that I thought were the most important in the determination of whether the application should be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Anthrax is a bacterial infection caused by *Bacillus anthracis*; Protective antigen (PA) is a component of the two toxins produced by *B. anthracis* (edema toxin and lethal toxin), which together produce the clinical manifestations of hemorrhage, edema, tissue necrosis and death. • There are 3 major forms of anthrax – cutaneous (most common), gastrointestinal and inhalational. Inhalational anthrax is a systemic infection caused by inhalation of *B. anthracis* spores, and has a case-fatality rate is 45-89%. • *B. anthracis* is a category A biological warfare agent because inhalation of the spores causes inhalational anthrax, a lethal infection.	Inhalational anthrax is a life-threatening infection caused by *B. anthracis*, which is classified as a category A biological warfare agent. The toxins produced by *B. anthracis* during infection cause tissue damage and death in a high proportion of people with inhalational anthrax.
Current Treatment Options	• The current FDA-approved treatment options for inhalational anthrax include antibacterial therapy (ABT), anthrax immune globulin (AIGIV), and raxibacumab. • ABT is used for treatment of anthrax infection, but deaths still occur despite antibacterial treatment. ABT act by killing B. anthracis bacteria that germinate from spores during anthrax infection. Antibacterial drugs are not effective against the spores themselves. Some antibacterial drugs (including ciprofloxacin, levofloxacin and doxycycline) are approved for post-exposure prophylaxis (PEP). They are very effective but must be used for a long time to kill bacteria that develop from lingering spores. Because of adverse reactions to antibacterial drugs, some people may discontinue prophylaxis. There is also a concern that strains of B. anthracis could be engineered to be resistant to antibacterial drugs. • AIGIV and raxibacumab are intended mainly for treatment of anthrax infections and intended to be used together with antibacterial drug treatment. These antibodies work by binding to PA and neutralizing or preventing the development of toxins. • AIGIV is a polyclonal preparation of anti-*B. anthracis* proteins, including anti-PA antibody, prepared from plasma of human subjects vaccinated with anthrax vaccine (AVA).	The current main treatment for inhalational anthrax is ABT, but death still occurs despite antibacterial drug treatment. Raxibacumab and AIGIV are intended to be used with ABT for treatment of inhalational anthrax. Since antibacterial drugs and antibodies work by different mechanisms, they are expected to work together in treatment to reduce the likelihood of death from inhalational anthrax. Antibacterial drugs are approved for PEP, but may be difficult for some people to take for prolonged periods due to adverse reactions. Raxibacumab is approved as an alternative to ABT for PEP, such as in situations where an individual cannot tolerate ABT or where resistance to available antibacterial drugs has been engineered. AVA may be given with ABT for PEP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Raxibacumab, a monoclonal antibody against PA given as a single intravenous dose, is approved for use as an adjunct to ABT in the treatment of inhalational anthrax. It is also approved for prophylaxis of anthrax, when alternative therapies are not available or appropriate. • AVA would not be used for treatment, but may be used in prophylaxis. AVA works be stimulating the person's immune system, so it takes time for the anthrax vaccine to provide protection. Therefore, it must be used for PEP with antibacterial drugs initially, until the person's immune system responds to the vaccine. It is unknown whether use of raxibacumab could interfere with the immune system response to AVA, if they are given together.	
Benefit	• Because studies of humans with naturally occurring anthrax infections are not feasible, and exposing people to anthrax for studies is not ethical, we must rely on animal studies to evaluate the benefits of obiltoxaximab. • Monotherapy Studies: There were multiple studies in two animal models (rabbits and macaques) comparing obiltoxaximab alone to placebo for treatment or prophylaxis of inhalational anthrax. Several of these studies showed a statistically significant effect of obiltoxaximab on reducing the death rate in the animals compared to placebo. However, the death rates varied widely across the studies, depending on the dose of obiltoxaximab given and the amount of bacteria present in the blood of the animals before treatment. • Based on simulations conducted by the clinical pharmacology team, obiltoxaximab 14.5 mg/kg IV (ED_{90}) is the maximally effective dose in infected rabbits and macaques and 16 mg/kg IV is the human equivalent dose based on modeling of systemic exposures. This human dose is expected to provide humans with blood concentration higher than needed to neutralize • Combination Studies: In seven of the eight studies where obiltoxaximab plus an antibacterial drug was compared to antibacterial drug alone, there were numerical improvements in survival rates for NZW rabbits and	The benefits of obiltoxaximab in treatment and prophylaxis of inhalational anthrax could only be studied in animals. It is reasonable to conclude that the obiltoxaximab 16 mg/kg IV dose would be an efficacious dose for treatment of anthrax in humans based on the survival rates in cynomolgus macaque and NZW rabbit models 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 protective antigen of *B. anthracis*. The combination studies demonstrated that obiltoxaximab can be administered in combination with antibacterial drugs for the treatment of inhalational anthrax with no interference in the efficacy of antibacterial drugs. The different mechanisms of action of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Cynomolgus macaques. There did not appear to be any loss of effectiveness 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, there are methodological flaws in the way that these studies were conducted, which make it unclear how much added benefit there would be when giving obiltoxaximab with antibacterial drugs for treatment of inhalational anthrax. • Prophylaxis Studies: Prophylaxis studies were conducted in cynomolgus macaques (3 studies) and NZW rabbits (six studies) with a range of intravenous and intramuscular (IM) doses of obiltoxaximab. • Obiltoxaximab IV had a statistically significant improvement in survival rates compared to placebo in NZW rabbits for prophylaxis. • (b) (4)	antimicrobial drugs and this monoclonal antibody indicate that combination therapy should be beneficial for the treatment of anthrax. The methodological flaws raise questions about what the added benefit of obiltoxaximab would be. In addition to the prophylaxis studies of IV treatment in rabbits, the data for IV obiltoxaximab for treatment supports its use as an alternative for prophylaxis. (b) (4)
Risk	Obiltoxaximab was developed under the Animal Rule—therefore, there are safety studies only in healthy human adults. Because it received Orphan Drug Designation, pediatric studies were not required or done. No studies were done in pregnant women. • Seven phase I trials were done in healthy human volunteers. There were the main studies using the commercial formulation of obiltoxaximab: studies AH104, AH109 and AH110 had a total of 320 human volunteers exposed to the commercial formulation of obiltoxaximab and 70 subjects exposed to placebo; these studies were the focus of the review. • Any symptom or sign of hypersensitivity occurred in 10.6% of the 320 subjects. Significant hypersensitivity necessitating discontinuation of obiltoxaximab infusion or discontinuation of the subject from the study due to hypersensitivity occurred in 10 subjects or 3.1%. Anaphylaxis	Because of its development under the Animal Rule, obiltoxaximab was only studied in healthy human adults; therefore no safety data is available in children, pregnant women or adults with serious co-morbidities, including actual inhalational anthrax. Hypersensitivity was the major concern, ranging from mild symptoms to anaphylaxis, and resulted in discontinuation of treatment in 3.1% of healthy subjects. Other adverse events included headache, cough, nausea and upper respiratory tract infections. The upper respiratory tract

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	occurred in 7 subjects (2.2%), and was the main safety concern. None of these 7 subjects required hospitalization, and hypersensitivity resolved with treatment. • Diphenhydramine reduced the incidence of cough and rash. • Hypersensitivity observed with obiltoxaximab was greater than that observed with raxibacumab where 0.6% of the safety population had infusion discontinued due to hypersensitivity. • Other adverse events included headache (9.1%), pruritus (4.1%), urticaria (2.5%), cough (3.1%), nausea (3.1%), upper respiratory tract infection (9.1%), and vessel puncture site bruise (2.5%). Pruritus and urticaria occurred in the context of hypersensitivity. Most of the headaches were mild in severity. • There was no clear dose-response effect with increasing doses of obiltoxaximab in the escalating-dose study, AH105. • A greater incidence of upper respiratory tract infections (URTI) was noted in the repeat-dose study, AH109. • Study AH106 was a dose-escalation study evaluating intramuscular (IM) administration of obiltoxaximab (b) (4)	infections were seen more often with obiltoxaximab than placebo in the controlled study, but it is unclear (b) (4)
Risk Management	• Obiltoxaximab is anticipated primarily in the event of bioterrorism; a risk evaluation and mitigation strategy (REMS) is not necessary. • The risk of hypersensitivity will be addressed as a warning in labeling. Because of this risk, obiltoxaximab should be administered in monitored settings, so that physicians can intervene if anaphylaxis occurs. The lack of data in pregnant women, children and adults with anthrax or other co-morbidities will be addressed in labeling. • Because of the risk of hypersensitivity, individuals should only receive obiltoxaximab for PEP if other options (including raxibacumab) are not available, and the exposure to anthrax is consider significant enough to outweigh the risks.	A REMS is not necessary for this application. Labeling addresses warnings regarding hypersensitivity and the lack of data in pregnant women, children or adults with anthrax or other co-morbidities. Use for PEP should only be considered in individuals with significant exposure to anthrax and only when other options (including raxibacumab) are not available.

2. Background

The biologics license application (BLA) 125509 for Anthim (Obiltoxaximab) was submitted in March 2015. Since clinical trials to evaluate obiltoxaximab in naturally occurring anthrax are not feasible, and it would not be ethical to expose humans to *B. anthracis* spores for studies, efficacy of obiltoxaximab could only be evaluated in animal models. Human safety studies were conducted under an IND held by Elusys Therapeutics, Inc. The BLA was submitted under the provisions of 21 CFR 601 Subpart H "Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible". The safety and efficacy findings in the BLA submission are the main topic of this memo.

3. Product Quality

The product quality review for the BLA was written by Tao Xie, PhD. The application technical lead, Rashmi Rawat, PhD, provided an integrated review from the Office of Product Quality. The other members of the quality review team are identified in the OPQ review documents. The final recommendation on approvability from OPQ is described as pending in the review documents due to outstanding issues with the methods to detect endotoxin in drug substance and drug product. The final classification of compliance status for the Lonza manufacturing site (Portsmouth, NH) was also still pending at the time of completion of the OPQ reviews.

- *General product quality considerations:*

Obiltoxaximab is a chimeric IgG1 monoclonal antibody that acts by binding to the protective antigen produced by *Bacillus anthracis*. Anthim® (obiltoxaximab) injection is formulated as a solution (600 mg/6 mL) in single-dose vials. The manufacturing process is described in detail in the OPQ review; the reviewer concluded that the data "support the conclusion that the manufacture of Anthim (obiltoxaximab, ETI-204) is well controlled and leads to a product that is pure and potent". The reviewer recommended an expiry period of 18 months for the drug product when stored at 5±3°C.

As noted in the OPQ recommendation above, there was a pending issue regarding the methods for detecting endotoxin in the drug substance and drug product. The OPQ review team requested additional information from the applicant for validation of the methods for detecting endotoxin in the drug substance and drug product. This information was not available at the time the OPQ review was completed. The OPQ team expects to receive the additional information needed and will file a review addendum once the review of this additional material is complete.

- *Facilities review/inspection:*

The OPQ integrated review by Dr. Rawat includes a table describing the various facilities and their functions in the manufacturing process for the drug substance and drug product. The final recommendation is pending for the Lonza facility in Portsmouth, NH, while the other facilities listed are approved. The Lonza facility was inspected in August 2015, and a form 483 of inspectional observations was issued at the end of the inspection on September 1, 2015. In

communication with Dr. Rawat, it is expected that the Lonza facility will be considered acceptable, but the final recommendation for this facility was still pending at the time this memo was written.

- *Other notable issues (resolved or outstanding)*:

The OPQ team has recommended several postmarketing commitments to address "minor product quality issues identified during the BLA review, which do not preclude approval of the BLA". The postmarketing commitments are listed in the OPQ integrated review by Dr. Rawat, and were conveyed to the applicant in the late cycle-meeting briefing package and a separate communication dated December 16, 2015. The applicant was asked to provide their proposed timelines for completing the postmarketing commitments during the late-cycle meeting held on December 11, 2015.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology (P/T) review was written by Dr. Amy Nostrandt. The reviewer considered the application to be approvable from the pharmacology/toxicology standpoint. The P/T review focused on the toxicology studies submitted in the application. The P/T review noted that for the animal efficacy studies, "review is limited to methods of the animal disease model and nonclinical pathology."

In the GLP-compliant toxicology studies, a toxic dose was not achieved in rats and monkeys administered doses up to 30 mg/kg. There was also a pilot study in rats where the maximum tolerated dose was not reached with doses up to 100 mg/kg. No QT prolongation was reported in two studies of cynomolgus monkeys conducted to evaluate cardiovascular function.

Carcinogenicity and genetic toxicology studies were not conducted. Reproductive toxicology studies showed no maternal toxicity or adverse reproductive or developmental effects in an embryo-fetal development study in rabbits at doses of up to 32 mg/kg.

In the PT review, there was a notable issue regarding evaluation of neuropathological changes in obiltoxaximab-treated animals from the animal efficacy studies. The review noted that administration of obiltoxaximab at doses of 4 mg/kg or higher was associated with an increased incidence of neuropathological changes in non-survivors. The changes were reported as consistent with "morphologic lesions/hemorrhagic meningoencephalitis previously reported in monkeys and rabbits with inhalational anthrax". No dose-response relationship was reported in the obiltoxaximab-treated non-survivors. There were no significant neuropathological lesions in obiltoxaximab-treated animals not exposed to *B. anthracis*. The reviewer concluded that obiltoxaximab "does not appear to be neurotoxic in anthrax-infected or in non-infected animals, but does not appear to always protect against anthrax-related meningitis." The reviewer's labeling recommendations included the proposal for an established pharmacological class; she noted concerns with the sponsor's description of the product as (b) (4), since this term is not sufficiently specific. The review also included labeling recommendations for the Pregnancy (8.1) and Nonclinical Toxicology (13) sections of labeling. These recommendations were incorporated in draft product labeling.

5. Clinical Pharmacology

Dr. Zhixia Yan was the clinical pharmacology reviewer for this application. The clinical pharmacology review identifies the clinical pharmacology team for this application, including Dr. Fang Li, the primary pharmacometrics reviewer. The reader is referred to the clinical pharmacology review for details of the clinical pharmacology team's assessment of the application. The review concluded that the clinical pharmacology information provided by the applicant was acceptable. The review stated "the proposed dose of 16 mg/kg for obiltoxaximab is acceptable for the treatment and prophylaxis of inhalational anthrax." Obiltoxaximab is proposed to be administered in a single dose.

Obiltoxaximab shows dispositions similar to other monoclonal antibodies, with virtually no renal clearance. As a monoclonal antibody, the product is expected to be catabolized to small peptides and amino acids by proteases. Terminal $t_{½}$ values were approximately 2-4 days, 3-4 days, 5-12 days, and 15-23 days in rats, rabbits, macaques, and humans, respectively.

The clinical pharmacology team determined that the fully effective dose in animals was 14.5 mg/kg based on the dose-response relationship to survival in rabbits and macaques. The proposed human dose of 16 mg/kg IV is expected to provide similar median C_{max} and median AUC_{inf} at least 2-fold higher than that in rabbits and macaques, based on simulations. There is partial overlap in the range of AUC_{inf} values in humans and macaques. The simulations suggest that a higher dose of 24 mg/kg IV could provide a range of human exposures (AUC_{inf}) that exceed the exposures in macaques. However, the 16 mg/kg dose was considered acceptable in part because this dose is expected to provide serum concentrations of obiltoxaximab two orders of magnitude higher than the concentration required for 99% neutralization of protective antigen (PA).

Because obiltoxaximab is expected to be administered in combination with antibacterial drugs for treatment of anthrax, the potential for drug-drug interactions with ciprofloxacin was evaluated in humans. Obiltoxaximab concentration-time profiles were similar when obiltoxaximab was administered alone or with IV or oral ciprofloxacin. Similarly, the PK of ciprofloxacin (IV or oral) was not altered by administration of obiltoxaximab.

Premedication with diphenhydramine is recommended for obiltoxaximab administration. The clinical pharmacology review compared obiltoxaximab PK parameters for those who received diphenhydramine with those who did not. There was no clinically meaningful effect of diphenhydramine premedication reported.

The effects of age, gender, race and weight on PK parameters were evaluated from the healthy volunteer studies. Body weight was the most significant covariate contributing to variability in obiltoxaximab PK. Since the applicant proposed weight-based dosing, the effect of this covariate is minimized. Obiltoxaximab clearance increases with increasing body weight. Lower clearance was reported for those with age ≥65 compared to younger subjects, Caucasians compared to non-Caucasians, and females compared to males. However, no dose adjustments were considered necessary for age, race or gender. There were no pediatric patients in the clinical trials of healthy volunteers, but a simulation approach was used to derive pediatric

dosing recommendations for obiltoxaximab. The clinical pharmacology team recommended changes to the weight cutoffs for weight-based doses for pediatric patients. The recommended changes were included in product labeling.

6. Clinical Microbiology

Drs. Shukal Bala and Lynette Berkeley evaluated different clinical microbiology portions of this BLA. The reader is referred to their clinical microbiology reviews for detailed information about their recommendations. The review by Dr. Berkeley focused on the methods and performance characteristics for measurement for the assays used in animal studies for measurement of protective antigen (PA), anti-PA antibodies, a toxin neutralization assay (TNA) for detection of neutralizing antibodies, and culture/identification of *B. anthracis*. Dr. Berkeley's reviews pointed out the limitations of the various assays used in the animal efficacy trials, though she did consider the assays to be "validated". The concerns that Dr. Berkeley raised about the assays were considered in the interpretation of the animal model studies by Dr. Bala.

Dr. Bala provided the main clinical microbiology review of the efficacy studies conducted in animals. Dr. Bala concluded that the BLA was approvable, pending acceptable labeling. Her recommendations included proposed labeling changes for the microbiology section of Anthim labeling. The proposed changes were included in draft labeling being sent to the applicant. The clinical microbiology review did not include any postmarketing requests.

Briefly, the in vitro data submitted in the BLA showed that obiltoxaximab binds and neutralizes PA. Obiltoxaximab binds PA produced by the 3 strains of *B. anthracis* (Ames, Sterne and Vollum), though the intensity of binding varied among the 3 strains. In vivo activity in mice was demonstrated with an earlier experimental version of the monoclonal antibody (b) (4). The (b) (4) antibody was effective in improving survival of mice infected with the Sterne strain of B. anthracis by the intratracheal route. Definitive efficacy trials were conducted in New Zealand White (NZW) rabbits and cynomolgus macaques challenged with *B. anthracis* by aerosol. Natural history studies of the NZW rabbits and cynomolgus macaques were described in the review. These studies involved aerosol challenge with 200 times the 50% lethal dose of spores of the Ames strain of *B. anthracis*. The natural history studies supported the idea that NZW rabbits and cynomolgus macaques "are useful models for evaluating treatment and prophylaxis against inhalational anthrax". The results of the definitive efficacy studies are described further in the next section of this memo.

7. Clinical/Statistical - Efficacy

The clinical review of efficacy for the BLA was conducted by Dr. Elizabeth O'Shaughnessy. There were two statistical reviews of efficacy data, by Drs. Xianbin Li and Ling Lan. Dr. Li evaluated efficacy studies where obiltoxaximab was used as monotherapy for treatment or prophylaxis, while Dr. Lan evaluated efficacy studies evaluating the added benefit of obiltoxaximab over antibacterial treatment. The reader is referred to their clinical and statistical reviews for detailed information of their findings. In their respective documents, these reviewers concluded that the studies they evaluated did support the efficacy of obiltoxaximab. I concur with their conclusions.

As noted previously, the efficacy of obiltoxaximab could only be evaluated in animal models of anthrax disease. Animal models of inhalational anthrax in cynomolgus macaques and NZW rabbits have been developed and were used previously in the approval of other drug and biological products. In both animal models, animals are exposed to lethal doses of *B. anthracis* spores, and the effects of obiltoxaximab treatment on survival are evaluated.

There were 22 monotherapy studies evaluating obiltoxaximab at a variety of doses compared to placebo. These included 9 studies evaluating treatment, 10 studies of post-exposure prophylaxis, and 3 studies of prophylaxis given prior to exposure. The main studies supporting efficacy are those evaluating treatment with obiltoxaximab after established infection in animals, as evidenced by the presence of bacteremia, protective antigen in the systemic circulation, and the development of fever (in rabbits only). The four studies included in the table below provide the main evidence to support the efficacy of obiltoxaximab in treatment of inhalational anthrax. These were studies of macaques and rabbits where one of the treatment arms included a 16 mg/kg dose, and treatment was delayed (a range 27-44 hours delay) to allow for disease to be established. In the analyses below, only animals whose blood cultures grew *B. anthracis* (providing proof of established infection) were included. It is clear from these studies that treatment with 16 mg/kg obiltoxaximab alone reduces mortality in these animal models of anthrax infection.

Animal / Study Number	**% Survivors[1] (number of survivors/n in group)**		**p-value[2]**	**95% CI[3]**
	Placebo	**Anthim 16 mg/kg IV**		
Cynomolgus Macaques				
AP202	0 (0/17)	31% (5/16)[4] 35% (6/17)	0.0085 0.0046	(0.08, 0.59) (0.11, 0.62)
AP204	6% (1/16)	47% (7/15)[5]	0.0058	(0.09, 0.68)
NZW Rabbits				
AR021	0 (0/9)[6]	93% (13/14)[7]	0.0001	(0.59, 1.00)
AR033	0 (0/13)	62% (8/13)[5]	0.0013	(0.29, 0.86)

[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] This group was treated with the to-be marketed formulation of obiltoxaximab
[5] Excluded one surviving animal that did not develop bacteremia prior to treatment
[6] Excluded one surviving placebo animal who inadvertently received levofloxacin
[7] Excluded three surviving animals that did not develop bacteremia prior to treatment

The applicant performed several treatment studies in macaques and rabbits with various doses of obiltoxaximab with the following notable findings:

- In some studies there were one or two animals in the placebo groups that survived despite what should have been a lethal exposure to *B. anthracis* spores. Some placebo animals did not develop bacteremia, but at least one placebo animal survived despite evidence of bacteremia and circulating PA.
- There is variability in the animal model results. In some studies lower doses of obiltoxaximab (4 or 8 mg/kg) also had significantly lower mortality than placebo. However, there was also one macaque study (AP203) where a higher dose of obiltoxaximab was not statistically better than the placebo. In general, there appeared to

be a dose-response with better outcomes for treatment groups receiving higher doses of obiltoxaximab, but this variability in both the rabbit and macaque models supports the need for evidence coming from more than a single animal species for this disease.

- Survival percentages in the obiltoxaximab-treated animals varied widely by study. In two trials of macaques the highest doses of obiltoxaximab (16-32 mg/kg) resulted in survival of 31-37%, while in another trial lower doses of obiltoxaximab (4-8 mg/kg) survival was 73-78%. Rabbit studies showed similar variability in the percentage of survivors.

Despite these limitations of the studies, there is substantial evidence of the efficacy of obiltoxaximab given as monotherapy in the treatment of inhalational anthrax. Obiltoxaximab does improve survival of animals with inhalational anthrax, compared to animals receiving a placebo.

Similarly for prophylaxis, there are studies showing that obiltoxaximab can reduce mortality in animals when administered after exposure to *B. anthracis* spores. The post-exposure studies generally had higher survival percentages than the treatment studies, and they also evaluated administration of obiltoxaximab for prophylaxis at varying timepoints (12, 24, 36 or 48 hours) after animal exposure to *B. anthracis* spores. It did appear in the studies with varying timepoints that survival improved with earlier obiltoxaximab administration (within 24 hours of exposure). There are also a few pre-exposure prophylaxis studies where obiltoxaximab was administered to animals prior to exposure to *B. anthracis* spores. Obiltoxaximab also appeared to reduce animal mortality when given as much as 72 hours prior to spore challenge. For more detailed information about the results of the prophylaxis studies, the reader is referred to Dr. Li's statistical review and Dr. O'Shaughnessy's clinical review.

Another important aspect of the efficacy evaluation is the review of studies evaluating the use of obiltoxaximab in combination with antibacterial treatment in the animal models of inhalational anthrax. It is expected that treatment of inhalational anthrax in humans will involve administration of both antibacterial drugs to eliminate bacteria that germinate from spores, along with administration of obiltoxaximab to bind PA and neutralize the toxin produced by the bacteria. There were six studies of NZW rabbits and two studies of cynomolgus macaques that compared the administration of obiltoxaximab in combination with antibacterial drugs to the antibacterial drug treatment alone. The two macaque studies used ciprofloxacin as the antibacterial drug; levofloxacin was the antibacterial drug in all rabbit studies except one where doxycycline was given.

There are important limitations to the designs of these combination studies that were noted by the reviewers. High survival rates are seen in the animal models when antibacterial drug treatment is given soon after exposure at an adequate dose. In order to assess the added effect of obiltoxaximab, studies used delayed treatment, antibacterial doses lower than the human equivalent dose (HED), or shorter durations of antibacterial drug treatment. The delayed treatment is problematic because a large proportion of animals die prior to the ability to intervene. It is not clear then if the animals that die prior to treatment differ from animals that survive to treatment. Studies using doses below the HED or for shorter durations are also problematic, because they artificially lower the effectiveness of the antibacterial drug. However,

animal model studies to demonstrate a statistically significant incremental benefit of a monoclonal antibody over antibacterials given at the HED are simply not feasible.

For a representation of the results of these combination studies, the reader is referred to the results of the meta-analysis in the statistical review by Dr. Lan (Figure 21 on page 68). While recognizing that the results of individual studies are variable and involve small numbers of animals, they suggest that there is a favorable effect of obiltoxaximab treatment in combination with antibacterial drugs. Both Drs. O'Shaughnessy and Lan concluded that the combination studies had adequately addressed the added benefit of obiltoxaximab over antibacterial treatment, recognizing the limitations of the studies of combination treatment.

In conclusion, the results of the monotherapy animal studies provide evidence of the effectiveness of obiltoxaximab for treatment and prophylaxis of inhalational anthrax, based on the criteria outlined for approval of biological products when human efficacy studies are not ethical or feasible (21 CFR §601.90). The combination studies provide supportive evidence of the added benefit of obiltoxaximab when used in combination with antibacterial treatment.

8. Safety

Dr. Ramya Gopinath conducted the safety review for this BLA application. The reader is referred to the medical officer review for detailed information about the safety findings.

The safety of obiltoxaximab in humans was evaluated in healthy adult volunteers, because trials of patients with naturally-occurring inhalational anthrax are not feasible. The application included 6 trials of healthy volunteers to evaluate the safety of intravenous obiltoxaximab. In addition, there was a single trial to evaluate intramuscular administration of obiltoxaximab, (b) (4) The intramuscular study included 27 subjects who received obiltoxaximab at any dose, including 6 individuals who received a 16 mg/kg IM single dose.

In total there were 497 humans who received obiltoxaximab at any dose, and 356 subjects who received a 16 mg/kg dose. The main data for safety come from three trials (AH104, AH109 and AH110) where healthy volunteers received the to-be-marketed formulation of obiltoxaximab (Lonza formulation). These three trials included 320 subjects all of whom received 16 mg/kg of obiltoxaximab. One of these trials (AH109) enrolled 70 subjects, sixty of whom received repeat administration of obiltoxaximab either 14 days or 120 days after the first dose. Comparative safety data came mainly from trial AH104, a randomized double-blind trial that enrolled 210 obiltoxaximab subjects and 70 subjects who received placebo. Drug-drug interactions were studied in AH110 – 20 subjects received obiltoxaximab alone, while 20 subjects received both obiltoxaximab and ciprofloxacin. The size of the overall safety database was considered to be adequate.

There were no deaths reported in the healthy volunteer studies. There were two serious adverse events reported in obiltoxaximab-treated subjects (ankle fracture and ovarian cyst); these SAE were considered unrelated to obiltoxaximab administration. Common adverse reactions associated with obiltoxaximab administration were headache, pruritus, infections of the upper

respiratory tract, rash, cough, vessel puncture site bruise, infusion site swelling, nasal congestion and infusion site pain.

The main safety finding of concern was the occurrence of hypersensitivity reactions in the healthy volunteers receiving obiltoxaximab. In the trials of the Lonza formulation, there were 34/320 (10.6%) obiltoxaximab-treated subjects with any clinical symptom of hypersensitivity compared to 4/70 (5.7%) placebo subjects. Of particular concern is that hypersensitivity reactions led to discontinuation of obiltoxaximab infusion in 8/320 subjects in these trials, and an additional 2 subjects in the repeat administration trial (AH109) were discontinued from the study because of concerns about hypersensitivity reactions that could recur with the second obiltoxaximab infusion. In the applicant's analysis, one subject treated with obiltoxaximab was categorized as having anaphylaxis, based on use of this preferred term by the investigator. The clinical reviewer conducted an analysis based on clinical criteria for anaphylaxis. In her analysis, Dr. Gopinath identified 7 of 320 obiltoxaximab-treated subjects who met clinical criteria for anaphylaxis, (including the individual identified by the applicant with the PT of anaphylaxis). In addition, the reviewers requested a consultation from an allergy reviewer within the Agency. Dr. Kathleen Donohue concurred with Dr. Gopinath's assessment of anaphylaxis cases with obiltoxaximab administration. The review team has proposed labeling revisions to highlight the risks of anaphylaxis, including the need to administer obiltoxaximab in a monitored setting by personnel trained and equipped to manage anaphylaxis.

9. Advisory Committee Meeting

This application was not discussed at an advisory committee (AC) meeting. As pointed out in the appendix of the medical officer review, the AC meeting held for raxibacumab addressed similar questions to those presented in this BLA. No new questions requiring public discussion at an AC meeting were raised in the initial filing/review of the obiltoxaximab BLA. Therefore, it was not considered necessary to have an AC meeting specifically for the obiltoxaximab BLA.

10. Pediatrics

No pediatric studies of obiltoxaximab have been conducted. Anthim has received orphan designation for treatment of anthrax. Therefore, the Pediatric Research Equity Act (PREA) does not apply. Inhalational anthrax is an extremely rare disease, so pediatric studies of this condition would not be feasible in any case. As noted in the clinical pharmacology section of this memo, pediatric dose recommendations for obiltoxaximab were derived using a simulation approach based on exposure data in adults receiving 16 mg/kg of obiltoxaximab and modeling of the effects of weight on obiltoxaximab clearance. These pediatric dose recommendations are included in the proposed labeling for obiltoxaximab, along with appropriate caveats regarding the lack of any pediatric PK or safety data. The approach is similar to that taken for pediatric labeling of another anthrax monoclonal antibody, raxibacumab.

11. Other Relevant Regulatory Issues

The applicant provided financial disclosure information for the investigators in the human trials. There were no significant financial arrangements or proprietary interests reported for any of the investigators in these trials.

A bioanalytical inspection report was completed by Dr. Mohsen Rajabi. The Office of Scientific Integrity and Surveillance audited analytical portions of 12 nonclinical and clinical studies conducted by (b) (4). A form 483 was issued at the close-out for the nonclinical studies. The firm provided responses to the items in the form 483. The inspection report concludes that the analytical data were found to be reliable. The report recommended accepting the analytical data for agency review with consideration of some limitations identified in the report. These limitations were addressed subsequent to the clinical pharmacology review.

12. Labeling

Proposed product labeling was reviewed by the review team, including representatives from the Division of Medication Errors and Prevention Analysis, the Office of Prescription Drug Promotion, and the Division of Medical Policy Programs (review of patient labeling).

In general, the prescribing information (PI) proposed by the applicant was consistent with the PI for the previously approved monoclonal antibody, raxibacumab. The PI for obiltoxaximab included specific statements regarding the reliance on efficacy studies in animal models and other limitations of use in the PI for raxibacumab.

Because of the safety findings regarding anaphylaxis/hypersensitivity reactions, the labeling revisions conveyed to the applicant included warnings regarding anaphylaxis. The warnings include information on the rate of anaphylaxis seen in clinical trials and the recommendation to administer obiltoxaximab "in (b) (4) monitored settings by personnel trained and equipped to manage anaphylaxis". Infusion of obiltoxaximab should be stopped if anaphylaxis or serious hypersensitivity occurs.

The review team's proposed labeling revisions for the PI, patient labeling, and carton and container labeling have been conveyed to the applicant, but discussion with the applicant and final agreement on product labeling is still pending.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The applicant did not propose REMS for this BLA application. A review was conducted by the Dr. Joyce Weaver of the Division of Risk Management Review. The reviewer concluded that a REMS program was not necessary to ensure the benefits of obiltoxaximab outweigh the risks.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The applicant has agreed to conduct a field study to evaluate the use of obiltoxaximab in the treatment of individuals with confirmed or suspected inhalational anthrax. This field study is required under 21 CFR 601.91 (b)(1) to evaluate the product's clinical benefit and assess its safety when used as indicated. The applicant is expected to provide a timeline for submission of a final protocol for this field study. However, timelines for completion of the study and submission of a final report would be dependent on the occurrence of an anthrax event.

The office of product quality has also proposed a list of postmarketing commitments and the applicant has agreed to conduct these studies and submit the data.

A postmarketing commitment (PMC) to evaluate the effect of concomitant administration of obiltoxaximab on anthrax vaccine was considered, but I do not recommend including this as a postmarketing commitment. Given the frequency of hypersensitivity reactions in the clinical trial database for obiltoxaximab, I think the risk of harm to the healthy volunteers is not justified in comparison to the knowledge to be gained regarding the effect of obiltoxaximab on immune response to anthrax vaccine. The previously approved monoclonal antibody (raxibacumab) does have a PMC to evaluate the effect of raxibacumab on antibody response to the vaccine. Therefore, there will be some information available regarding the effect of another monoclonal antibody on anthrax vaccine immune response.

14. Recommended Comments to the Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J ALEXANDER
02/05/2016