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RESEARCH**

*APPLICATION NUMBER:*

**125509Orig1s000**

**OFFICE DIRECTOR MEMO**

## Office Director Decisional Memo

<b>Date</b>	(electronic stamp)
<b>From</b>	Edward Cox, MD MPH
<b>Subject</b>	Office Director Decisional Memo
<b>NDA/BLA #</b>	BLA 125509
<b>Applicant Name</b>	Elusys Therapeutics, Inc.
<b>Date of Submission</b>	March 20, 2015
<b>PDUFA Goal Date</b>	March 18, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Anthim obilttoximab
<b>Dosage Forms / Strength</b>	injection, for intravenous use / 600mg/6mL
<b>Applicant Proposed Indication(s)/Populations</b>	Inhalational Anthrax Anthim (obilttoximab) is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to <i>Bacillus anthracis</i> in combination with appropriate antibacterial drugs. Anthim (obilttoximab) is also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or appropriate.
<b>Action:</b>	Approval
<b>Approved Indication(s)/Populations (if applicable)</b>	Inhalational Anthrax ANTHIM is indicated in adult and pediatric patients for the treatment of inhalational anthrax due to <i>Bacillus anthracis</i> in combination with appropriate antibacterial drugs.  ANTHIM is indicated for prophylaxis of inhalational anthrax due to <i>B. anthracis</i> when alternative therapies are not available or not appropriate

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	<b>Names of discipline reviewers</b>
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	Tao Xie, Donald Obenhuber, Bo Chi, John Metcalfe, Melinda Bauerlien, Rashmi Rawat, John Metcalfe, Patricia Hughes, Juhong Li
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
Division Director's Review	Sumati Nambiar

OND=Office of New Drugs  
 OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of 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, CDTL, and division director. The table below is from the division director review and captures the key considerations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<p>Anthrax is a bacterial infection caused by <i>B. anthracis</i>. Inhalational anthrax is caused by inhalation of <i>B. anthracis</i> spores and has a case fatality rate of 45-89%. <i>B. anthracis</i> is considered a category A bioterrorism agent. (<a href="http://fas.org/biosecurity/resource/documents/CDC_Bioterrorism_Agents.pdf">http://fas.org/biosecurity/resource/documents/CDC_Bioterrorism_Agents.pdf</a>)</p> <p>Protective antigen (PA) is a component of edema toxin and lethal toxin produced by <i>B. anthracis</i>. These toxins cause hemorrhage, edema, tissue necrosis, and death.</p>	<p>Inhalational anthrax is a life-threatening infection. PA is a component of both edema and lethal toxins that cause tissue damage.</p>
<b>Current Treatment Options</b>	<p>The current FDA-approved treatment options for inhalational anthrax include antibacterial drugs, anthrax immune globulin, and raxibacumab.</p> <p>Antibacterial drugs act by killing <i>B. anthracis</i> bacteria that germinate from spores and have no activity against the spores. Ciprofloxacin, levofloxacin and doxycycline are approved for post-exposure prophylaxis (PEP). The duration of PEP is 60 days to kill bacteria that develop from spores over a period of time. There is also a concern that strains of <i>B. anthracis</i> could be engineered to be resistant to currently available antibacterial drugs.</p> <p>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.</p> <p>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.</p>	<p>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.</p> <p>Antibacterial drugs are approved for PEP, but need to be taken for prolonged periods of time.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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 with antibacterial drugs initially, until an immune response has developed.</p>	
<p><b>Benefit</b></p>	<p>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).</p> <p><u>Treatment Studies:</u> 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.</p> <p>Obiltoxaximab 14.5 mg/kg was the fully effective dose in infected rabbits and macaques. 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.</p> <p>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</p>	<p>Obiltoxaximab 14.5 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.</p> <p>The systemic exposures achieved with obiltoxaximab 16 mg/kg IV in humans indicate that this dose should neutralize most of the circulating PA.</p> <p>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</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>antibacterial drug. However, given that there was variability among the 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.</p> <p><u>Prophylaxis Studies:</u> 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 <i>B. anthracis</i> spores.</p>	<p>different mechanisms of action of antibacterial drugs and obiltoxaximab suggest that combination therapy should be beneficial for the treatment of inhalational anthrax.</p> <p>The prophylaxis studies of IV obiltoxaximab in NZW rabbits and cynomolgus macaques showed that obiltoxaximab provides benefit in prophylaxis against inhalational anthrax.</p>
Risk	<p>As obiltoxaximab was developed under the Animal Rule, safety studies were conducted only in healthy adults. In the 3 main safety phase 1 trials combined, 320 healthy adults were exposed to the commercial formulation of obiltoxaximab and 70 to placebo.</p> <p>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.</p>	<p>As obiltoxaximab was only studied in healthy human adults, no safety data are available in patients with anthrax, children, pregnant women or patients with comorbidities.</p> <p>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</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		serious and life-threatening condition, the benefit of Anthim outweighs this risk.
<b>Risk Management</b>	Obiltoximab 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, obiltoximab should be administered in monitored settings.

# 1. Further discussion to support regulatory action

## Background

Anthim (obilttoxaximab) is a chimeric (human/mouse) IgG1 kappa monoclonal antibody directed against the protective antigen (PA) component of *B. anthracis* toxin. It binds free PA thereby inhibiting the binding of PA to its cellular receptors. Blocking the binding of PA to cell receptors interferes with toxin formation as a means to mitigate the effects of the toxin produced by *B. anthracis*.

The evaluation of the efficacy of obilttoxaximab is based on studies conducted in animals as it is not ethical or feasible to conduct studies in humans. Safety was evaluated in adult healthy volunteers who received the product.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of obilttoxaximab. For a detailed discussion of BLA 125509, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's review and the Division Director's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

## Product Quality

The Office of Pharmaceutical Quality recommends approval of obilttoxaximab. The manufacturing of obilttoxaximab is well controlled and leads to a product that is pure and potent. The information from inspections of the manufacturing sites for the product and the applicant's responses are considered acceptable. The application is also found acceptable from the standpoint of biopharmaceutics and product quality microbiology for this sterile dosage form for intravenous injection.

## Nonclinical Pharmacology/Toxicology

The recommendation from the pharmacology/toxicology reviewers is for approval. No specific target organs were identified in nonclinical studies in rats and monkeys at doses up to 30 mg/kg. Obilttoxaximab does not appear to be neurotoxic in anthrax-infected or non-infected animals. An embryo-fetal toxicity study in rabbits at doses up to 32 mg/kg did not show adverse reproductive or developmental effects. The product is labeled as pregnancy category B.

## Clinical Microbiology

The clinical microbiology review notes that obiltoxaximab is effective in improving survival in animal models of infection. In *in vitro* studies, obiltoxaximab binds the PA from the Ames, Vollum, and Sterne strains of *B. anthracis*. Studies using murine macrophages suggest that obiltoxaximab neutralizes the effects of lethal toxin.

## Clinical Pharmacology

The Clinical Pharmacology reviewers find that a human dose of 16 mg/kg for obiltoxaximab is acceptable. Based on simulations, humans should achieve a similar obiltoxaximab median  $C_{max}$  and 2-fold greater median  $AUC_{inf}$  following a single 16 mg/kg IV dose compared to infected rabbits and monkeys receiving the fully effective dose (14.5 mg/kg). Some degree of overlap in the range of human and monkey  $AUC_{inf}$  is noted at the 16 mg/kg and 14.5 mg/kg doses, respectively. Exposure response relationships suggest an increase from 16 to 24 mg/kg for human dosing would result in minimal improvements in survival. If future studies were conducted, studying a dose of 24 mg/kg could be considered in a trial where such studies were ethical; it is possible this dosing regimen could be included in an evaluation of obiltoxaximab if there were to be an anthrax event. Pediatric dosing regimens are provided based on a population pharmacokinetic approach to predict exposure comparable to the exposures in adult patients. This approach for developing dosing for pediatric patients was used because exposing healthy children to obiltoxaximab is not considered ethical.

## Clinical/Statistical – Efficacy

The clinical review of obiltoxaximab finds that substantial evidence of effectiveness has been provided and recommends approval under the animal rule for the treatment of inhalational anthrax in combination with antibacterial drugs and for the prophylaxis of inhalational anthrax when alternative therapies are not available or appropriate. The statistical reviews find that obiltoxaximab is effective in animal models of treatment and prophylaxis of inhalational anthrax in rabbits and cynomolgus monkeys. The applicant provided reports from 26 studies evaluating the efficacy of obiltoxaximab. Included among these studies were studies designed to model pre-exposure prophylaxis, post-exposure prophylaxis, and treatment (monotherapy and in combination with an antibacterial drug) of inhalational anthrax. The reviews also specifically evaluated the findings from studies where obiltoxaximab was added to antibacterial drug therapy, including studies where the antibacterial drug was administered at the human equivalent dose, and found that obiltoxaximab did not interfere with antibacterial drug efficacy and resulted in higher survival outcomes than antibacterial drug therapy alone.

Collectively the findings from these animal models of infection studies support the efficacy of obiltoxaximab for the treatment of inhaled anthrax in combination with appropriate antibacterial drugs and for the prophylaxis of inhalational anthrax when alternative therapies are not available or appropriate. The applicant undertook a number of studies to evaluate obiltoxaximab in animal models of infection, many done independent of Agency input. It is

possible that with guidance from the Agency a more efficient program could have been achieved.

## **Safety**

The safety of obiltoxaximab was assessed in 320 healthy subjects in the three main safety studies, who received one or more doses of obiltoxaximab 16 mg/kg administered intravenously. Hypersensitivity reactions were the most common adverse reactions in safety trials and were reported in 34/320 subjects. Obiltoxaximab infusion was discontinued in 8/320 subjects due to hypersensitivity reactions or anaphylaxis. Three cases of anaphylaxis occurred during or toward the end of the infusion. Testing for the development of anti-obiltoxaximab antibodies was performed and found that eight subjects (8/320) developed a treatment emergent anti-obiltoxaximab antibody response. Other commonly reported adverse reactions were headache, pruritus, infections of the upper respiratory tract, cough, vessel puncture site bruise, infusion site swelling, urticaria, nasal congestion, infusion site pain, and pain in extremity. The product labeling includes a Boxed Warning noting that hypersensitivity and anaphylaxis have been reported in patients receiving obiltoxaximab and that it should be administered in a monitored setting. There is also related information in Limitations of Use, Warnings and Precautions, and Adverse Reactions. Premedication with diphenhydramine is also included in the dosage and administration section.

## **Advisory Committee Meeting**

The application for Anthim (obiltoxaximab) was not referred to an FDA Advisory Committee because this drug is not the first monoclonal antibody directed against PA that has been approved and the animal models of infection utilized are similar to a previously approved drug. There were no specific questions regarding efficacy that warranted Advisory Committee input and the drug's safety profile can be adequately addressed in the product labeling.

## **Pediatrics**

The safety data for obiltoxaximab is exclusively from adult patients because it would be considered unethical to expose healthy pediatric patients to obiltoxaximab. The dosing recommendations for pediatric patients are based on population pharmacokinetic simulations. The product is labeled for use in all relevant pediatric populations with dosing for patients to <sup>(b)</sup><sub>(4)</sub>kg or less. Therefore, no additional pediatric studies are needed at this time. In addition, Anthim is exempt from required pediatric assessments under PREA because it has received an Orphan Drug designation for the Treatment of exposure to *B. anthracis* spores.

## **Labeling**

The product labeling includes a Boxed Warning on hypersensitivity reactions and anaphylaxis along with information to help mitigate the risk. Additional information on hypersensitivity and anaphylaxis and steps to mitigate the risk are included in Limitations of Use, Warnings and Precautions, and Adverse Reactions. The product labeling adequately describes the risks and benefits of the product. The product labeling also includes Patient Information.

### **Risk Evaluation and Mitigation Strategies (REMS)**

This application does not include a REMS. The product labeling including the package insert and patient package insert provides adequate information on the product, its risk and benefits, and recommendations on how to mitigate risks of adverse effects.

### **Postmarketing Requirements and Commitments**

The postmarketing requirements include the requirements for a field study as per requirements for approval under 21CFR Part 601 Subpart H should an anthrax event occur. There are also a number of postmarketing commitments related to product quality.

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EDWARD M COX  
03/18/2016