CLINICAL REVIEW

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Priority or Standard	Standard
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Division/Office	Division of Anti-Infective Products
Reviewer Names	Ramya Gopinath, M.D., Elizabeth O'Shaughnessy, M.D.
Review Completion Date	12/18/15
Established Name	Obiltoxaximab
Trade Name	Anthim®
Applicant	Elusys Therapeutics Inc., Pine Brook , NJ 07058
Formulation	Solution for Injection
Dosing Regimen	Single-dose 16mg/kg intravenous infusion over 90 minutes
Proposed Indications	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.
Intended Populations	Adult and pediatric patients with confirmed or suspected exposure to inhalational *Bacillus anthracis*.
Recommendation on Regulatory Action	Recommend approval of obiltoxaximab 16mg/kg IV single dose.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AIGIV	Anthrax Immunoglobulin Intravenous
ATA	anti-therapeutic antibodies
AVA	Anthrax Vaccine Adsorbed
[redacted]	(b) (4)
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CCRU	Clinical Data Analysis and Reporting Organization
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CTSC	Clinical Trial Steering Committee
CMC	chemistry, manufacturing, and controls
CFU	colony forming unit
CRF	case report form
CRO	Contract Research Organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
eCTD	electronic common technical document
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
HED	human equivalent dose
ICF	informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
LOD	limit of detection
LLOD	lower limit of detection
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MAED	MedDRA-Based Event Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
NZW	New Zealand White (rabbits)
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PA	Protective Antigen
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	post marketing commitment
PMR	post marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
PT	preferred term
PTT	prior to treatment
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SIBT	significant increase in body temperature
SOC	System Organ Class
TEAE	treatment emergent adverse event
WHO	World Health Organization

1 Executive Summary

1.1 Product Introduction

Anthim® (obiltoxaximab, [code name ETI-204]) is a deimmunized IgG1 monoclonal antibody (mAb) that binds the protective antigen (PA) component of the exotoxins produced by *Bacillus anthracis,* the causative agent of anthrax. Obiltoxaximab is formulated as a liquid solution to be administered as a single intravenous (IV) infusion of 16 mg/kg over 90 minutes; (b) (4) The Applicant, Elusys Therapeutics Inc., developed obiltoxaximab under the Animal Rule [1] for the following proposed indications: a) the treatment of adult and pediatric patients with inhalational anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs, and b) for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness of obiltoxaximab (Anthim®) for the treatment of inhalational anthrax in the cynomolgus macaque (*Macaca fascicularis*) and New Zealand White rabbit (*Oryctolagus cuniculus)* models of inhalational anthrax under the Animal Rule regulations.[1] Obiltoxaximab 16 mg/kg IV, single-dose, monotherapy, demonstrated a statistically significant increase in survival rate over placebo in the cynomolgus macaque and the New Zealand White (NZW) rabbit models of inhalational anthrax. The results of these animal studies indicate that this anti-PA monoclonal antibody is reasonably likely to produce clinical benefit in humans with inhalational anthrax.

The clinical reviewers recommend approval of obiltoxaximab 16mg/kg IV single dose for the indication: *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*. The hypersensitivity rate of 3.1% associated with obiltoxaximab infusion in the phase I studies in healthy humans is acceptable for treatment of inhalational anthrax given the life-threatening nature of the disease and high case-fatality rate. However, obiltoxaximab should be used for prophylaxis against anthrax in situations when no other therapies are available.

[1] 21 CFR 601 Subpart H – Approval of Biological Products When Human Studies Are Not Ethical or Feasible

1.3 Benefit-Risk Assessment

Benefit Risk Summary and Assessment

Obiltoxaximab (ETI-204/Anthim®) is a deimmunized IgG1 monoclonal antibody targeting the protective antigen (PA) component of the exotoxins produced by *Bacillus anthracis,* the causative agent of anthrax. It was developed under the Animal Rule by Elusys Therapeutics Inc., for the following indication: the treatment of adult and pediatric patients with inhalational anthrax due to *B. anthracis* in combination with antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. We recommend approval of Anthim® for the treatment of inhalational anthrax with cautions regarding its use for prophylaxis.

Anthrax is a zoonosis caused by the spore-forming *B. anthracis* and most commonly occurs in wild and domestic herbivores. Humans can acquire the disease when they are exposed to infected animals or their products, or when they are directly exposed to the spores of *B. anthracis.* The clinical manifestations of disease are primarily caused by the two toxins, edema toxin and lethal toxin, produced by the bacterium; these toxins are complexes of PA with edema factor and lethal factor respectively. Although endemic in other parts of the world, human anthrax is sporadic in the U.S; there were 242 naturally occurring cases reported to the CDC from 1955 to 2007. Inhalational anthrax, the most serious form of the disease, has a case-fatality rate of 45-86%.[2] *B. anthracis* is classified as a category A biological warfare agent due to the ability of its spores to persist in the environment, their ability to readily cause infection via inhalation, and the high resultant mortality. Current therapies consist of antibacterial therapy with doxycycline, ciprofloxacin or intramuscular (IM) procaine penicillin for 60 days (to cover ongoing spore germination) for treatment and post-exposure prophylaxis, anthrax immune globulin for post-exposure prophylaxis, and anthrax vaccine adsorbed (administered as a five-dose IM series) for pre-exposure prophylaxis. Compliance with recommended antibacterial therapy was found to be only 21-42% in the at-risk population of 10,000 people after the bioterrorism event of 2001; most stopped therapy due to adverse reactions. Therefore, there is need for alternative and adjunctive measures for prophylaxis and treatment of anthrax.

In this application, obiltoxaximab, administered as a single intravenous (IV) dose, demonstrated a significant improvement in survival in four of five monotherapy efficacy studies in the non-human primate (cynomolgus macaque)

model of inhalational anthrax and in two studies in the New Zealand White (NZW) rabbit model of inhalational anthrax. In these animal studies, 14.5mg/kg IV of obiltoxaximab was found to be the fully effective dose; based on modeling, 16mg/kg IV was determined to be the human equivalent dose. The natural history of inhalational anthrax in nonhuman primates is comparable to human disease; therefore, based on the Animal Rule criteria, we determined that obiltoxaximab 16mg/kg IV is likely to be efficacious in human inhalational anthrax.

The efficacy data in seven of eight combination studies demonstrated improvements in survival rates for the combination of obiltoxaximab IV plus an antibacterial drug over antibacterial drugs (levofloxacin, ciprofloxacin, doxycycline) alone in cynomolgus macaques and in NZW rabbits. The studies were not powered to show differences between the two arms. 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. Despite the limited evidence of significant added-benefit of obiltoxaximab IV plus an antibacterial drug versus an antibacterial drug alone, one must take into account the high mortality rate observed with antibacterial drugs in human inhalational anthrax. Obiltoxaximab neutralizes PA, a critical component of *B. anthracis* toxins, and therefore it is biologically plausible that the combination of obiltoxaximab IV plus an antibacterial drug IV would be beneficial for treatment of human inhalational anthrax due to their different mechanisms of action. Obiltoxaximab IV monotherapy would also be of benefit in the setting of infection due to multi-drug resistant *B. anthracis* or in patients with contraindications to available antibacterial drugs.

The fully effective dose of obiltoxaximab in animals was determined to be 14.5 mg/kg. The pharmacokinetics of obiltoxaximab in humans and animals demonstrates some overlap in C_{max} and AUC, and based on modeling, the proposed human equivalent dose is 16 mg/kg. Because FDA Guidance on the Animal Rule recommends clear separation of the pharmacokinetic parameters, C_{max} and AUC, between animals and humans, post-market studies of a higher dose of obiltoxaximab could be considered.

Hypersensitivity to obiltoxaximab was the greatest safety concern, and occurred in 3.1% of the safety population; 2.2% had anaphylaxis though no subject required hospitalization. By contrast, the incidence of hypersensitivity in phase 1 human studies of raxibacumab was 0.6%. Although it did not prevent anaphylaxis, diphenhydramine premedication reduced its incidence as well as the incidence of cough and rash, therefore, diphenhydramine is recommended prior to

infusion of obiltoxaximab. Less serious adverse reactions with obiltoxaximab included headache, cough, vessel puncture site bruise and upper respiratory tract infection. Because obiltoxaximab was developed under the Animal Rule, safety studies are available only in healthy human adults; obiltoxaximab has not been studied in pregnant women, children or humans with serious co-morbidities. Studies in rabbits and nonhuman primates did not demonstrate teratogenicity with administration of obiltoxaximab to pregnant females, but unanticipated safety concerns may arise when the product is administered to children, adults with significant co-morbidities including immunosuppression, or any person with inhalational anthrax.

We recommend approval of obiltoxaximab 16mg/kg IV single-dose for treatment of inhalational anthrax. The survival outcomes in this Application support the conclusion that the benefits of obiltoxaximab outweigh its risks for treatment of this life-threatening disease. Because obiltoxaximab binds and neutralizes a critical component of the toxins produced by *B. anthracis,* it would provide a valuable adjunct to antibacterial drugs in the treatment of inhalational anthrax, and may indeed be one of the few options available in the event of dissemination of a drug-resistant strain of *B. anthracis*. The risk of hypersensitivity drives our recommendation for use of obiltoxaximab as second- or third-line therapy for prophylaxis and only in situations in which other treatments for prophylaxis are not available or appropriate because adequate medical supervision is unlikely to be available to all recipients of obiltoxaximab in a mass casualty event. A Risk Evaluation and Mitigation Strategy (REMS) is not applicable because this drug is intended only for use as a single dose in the event of a bioterrorism attack with intentional release of *B. anthracis.* Although 16 mg/kg IV was determined to be the human equivalent of the fully effective dose of obiltoxaximab for treatment of inhalational anthrax in animals in this application, there is some uncertainty about whether a higher dose could be more efficacious in infected humans. Therefore, a PMR may be considered to address the risk of hypersensitivity with a higher dose of obiltoxaximab; however, a human pharmacokinetic/safety study raises ethical concerns about the safety of study participants.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Anthrax is a zoonosis caused by *Bacillus anthracis*; humans acquire the disease naturally when exposed to infected animals or their products, or when directly exposed to the spores of *B. anthracis*. • There are 3 major forms – cutaneous (most common), gastrointestinal and inhalational. Inhalational anthrax is a systemic infection caused by inhalation of *B. anthracis* spores; the estimated incubation period is 4.5 days and the case-fatality rate is 45-89%. The lethal dose is estimated to range from 2,500 to 760,000 spores in non-human primates. • 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. • Initial signs and symptoms of inhalational anthrax include sore throat, fever and muscle aches, but in untreated cases, progressive illness characterized by shortness of breath, mediastinitis, low blood pressure, prostration and shock follow in 2-3 days. • *B. anthracis* is classified as a category A biological warfare agent due to the ability of its spores to persist in the environment, their ability to readily cause infection via inhalation, and the high resultant mortality.	Inhalational anthrax is a life-threatening infection with a case-fatality rate of 45-89%. It is caused by *B. anthracis* which is classified as a category A biological warfare agent due to the ability of its spores to persist in the environment, its ability to easily cause infection, and the high resultant mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The current FDA-approved treatment options for inhalational anthrax include antibacterial therapy (ABT), anthrax vaccine adsorbed (AVA), anthrax immune globulin (AIGIV), and raxibacumab, a monoclonal antibody active against the PA of *B. anthracis*. Various combinations of these are recommended for pre (PrEP) - and post (PEP)-exposure prophylaxis and treatment of anthrax. • Treatment with ciprofloxacin, doxycycline or intramuscular procaine penicillin for 60 days is recommended following exposure to *B. anthracis* spores, along with AVA for post-exposure prophylaxis and supportive care as needed in established cases. • AVA is a PA-based vaccine used for pre-exposure vaccination as a series of 5 intramuscular injections over 18 months in persons at high-risk for spore inhalation. For post-exposure prophylaxis, AVA is recommended as a 3-dose subcutaneous series at 0, 2 and 4 weeks (under Emergency Use Authorization) along with ABT for 60 days. • AIGIV is a polyclonal preparation of anti-*B. anthracis* proteins, including anti-PA antibody, prepared from plasma of human subjects vaccinated with AVA. It confers passive immunity. • Raxibacumab, a monoclonal antibody against PA given as a	The current main treatment options each have limitations – ABT is limited by occurrence of adverse reactions and the potential use of drug-resistant strains of *B. anthracis* for bioterrorism, and AVA is limited by the duration of time needed to develop a robust antibody response, and AIGIV by potential hypersensitivity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	single intravenous dose, is approved for use as an adjunct to ABT in the treatment and prophylaxis of inhalational anthrax. • Studies in nonhuman primates suggest that dormant spores can exist in the lung up to 100 days after exposure and cause delayed disease. Because maintenance of ABT until both germinating and dormant spores are cleared is needed for prevention of disease, the recommended duration of therapy is 60 days. • The limitations of ABT in a bioterrorism setting include lack of effectiveness against drug-resistant strains of *B. anthracis*, or adverse events related to ABT, which include diarrhea, headache, nausea, or tendonitis or tendon tears with fluoroquinolone therapy	
Benefit	Six monotherapy efficacy studies of intravenous obiltoxaximab (ETI-204) were conducted in the nonhuman primate model, cynomolgus macaque, (4 studies) and New Zealand White (NZW) rabbit (2 studies) models of inhalational anthrax because clinical studies are not ethical to conduct in humans. The primary endpoint, survival rate compared to placebo, is a clinically relevant endpoint. Treatment/monotherapy studies: • A statistically significant improvement in survival rates with obiltoxaximab 16mg/kg IV single-dose (31% and 50%) versus placebo (0% and 6.5%), respectively, was observed in two studies in cynomolgus macaques. Similarly, obiltoxaximab 16mg/kg IV	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 could neutralize protective antigen of *B. anthracis* (ref. section 4.5).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demonstrated a statistically significant improvement in survival rates of 64% and 94%, compared to placebo (0% an 10%), respectively, in two NZW rabbit studies. • Overall, four of five Cynomolgus macaque studies and two NZW rabbit studies demonstrated a significant improvement in survival rates over placebo at doses of obiltoxaximab at or less than 16mg/kg IV, (ref. section 7.3 for additional detail). • Cynomolgus macaques and NZW rabbits with the lowest bacteremia and PA levels prior to treatment had the highest survival rates. • No recurrence of anthrax occurred in the NZW rabbits or macaques once bacteremia was initially cleared. • 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. Treatment /Combination Studies: • In seven of the eight studies, there were numerical improvements in survival rates for NZW rabbits and Cynomolgus macaques treated with the combination of obiltoxaximab plus an antibacterial drug versus the antibacterial drug alone for the treatment of inhalational anthrax. • No statistically significant improvements in survival rates were observed in studies in which initiation of treatment with obiltoxaximab was delayed longer than 24±12 hours after the first	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 antimicrobial drugs and this monoclonal antibody indicate that combination therapy would be efficacious for the treatment of anthrax. Obiltoxaximab 16mg/kg IV may be used for prophylaxis because it is effective for treatment of inhalational anthrax. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	positive PA (about 48 hours post-challenge with *B. anthracis*). • There was no significant difference in survival rates between obiltoxaximab 16mg/kg IV administered with levofloxacin human equivalent dose (HED) 50mg/kg oral, compared with levofloxacin (alone (95%, 19/20 versus 100%, 20/20, respectively). 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 16mg/kg IM had a statistically significant improvement in survival rates compared to placebo in NZW rabbits and macaques when administered within 24 hours post-challenge with *B. anthracis*. • The Applicant compared systemic exposures of obiltoxaximab in humans to those in macaques at the efficacious dose for prophylaxis, (b) (4)	The data for intravenous obiltoxaximab supports its use for the proposed indication: Treatment of inhalational anthrax in adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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 humans. Studies AH101, AH102, and AH105 used a non-commercial formulation of obiltoxaximab, while 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 9.2% 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 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, rash and anaphylaxis though these were not prevented. • Hypersensitivity observed with obiltoxaximab was greater than that observed with raxibacumab where 0.6% of the safety	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. Under the Animal Rule, the human safety database for the IV administration of obiltoxaximab is adequate. 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, but no cardiac toxicity or drug-drug interactions are anticipated. Because single-dose obiltoxaximab is proposed in the indication for treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 (3.7%), 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. • There was no cardiac toxicity associated with obiltoxaximab. • No alteration in PK of either obiltoxaximab or ciprofloxacin was noted in the drug-drug interaction study, AH110. • 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)	of inhalational anthrax, the finding of increased URTI with repeat doses may not be clinically relevant. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4)	
Risk Management	• Because the use of obiltoxaximab is anticipated primarily in the event of bioterrorism, a risk mitigation strategy is not applicable. • The risk of hypersensitivity will be addressed as a warning in labeling. Because of this risk, the use of obiltoxaximab in non-monitored settings should be reserved for situations where there are no other therapeutic options. • The lack of data in pregnant women, children and adults with significant co-morbidities will be addressed in labeling. • Although 14.5 mg/kg IV is the fully effective dose in animals and the PK data support the use of 16 mg/kg IV as the equivalent dose in humans, it is possible that a higher dose may be more efficacious in infected humans.	A Risk Evaluation and Mitigation Strategy (REMS) is not applicable. Labeling addresses the recommended indication for use of obiltoxaximab IV as treatment of inhalational anthrax, and precautions for its use for prophylaxis. Labeling also notes the lack of data in pregnant women, children or adults with co-morbidities, and IM use of this product has been removed. A PMR to study a higher dose in humans could be considered but needs to be weighed against the potential risk of hypersensitivity in study participants. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		(b) (4)

2 Therapeutic Context

2.1 Analysis of Condition

Anthrax is a zoonosis caused by the spore-forming, gram-positive bacteria, *B. anthracis* and most commonly occurs in wild and domestic herbivores. The infectious forms are spores, which are highly resistant to heat, cold, drought, UV light, gamma radiation and can persist in the environment for a prolonged period. Infection in humans is acquired primarily through agricultural or veterinary exposure to infected or dying animals or their carcasses, and industrial exposure to spores during the cleaning and processing of contaminated hides, hair, or wool from infected animals. Depending on the route of exposure, anthrax can occur in three forms, i.e., cutaneous, gastrointestinal or inhalational. Although endemic in other parts of the world, human anthrax is sporadic in the U.S.; there were only 242 naturally occurring cases reported to the CDC from 1955-2007.[2] Of these, 232 (96%) were cutaneous, 10 (4%) were inhalational, and none were gastrointestinal.

Though appropriately-treated cutaneous anthrax has a case-fatality rate of <1%, inhalational anthrax is associated with a case-fatality rate of 45-89%.[2] A case-fatality rate of 86% was reported in the outbreak following accidental release of *B. anthracis* spores from a military facility in Sverdlosk, in the former Soviet Union in 1979. In the U.S. bioterrorism event of 2001, 22 confirmed or suspected human cases of anthrax occurred when *B. anthracis* spores were sent as a powder by envelope to news media companies and congressional leaders – 11 cases were inhalational anthrax, and 11 were cutaneous. Despite aggressive antibacterial therapy and supportive care, 5 of 11 patients died with inhalational anthrax resulting in a case-fatality rate of 45%.

Inhalational anthrax follows the inhalation of *B. anthracis* spores and their deposition in alveoli; the inoculum of spores leading to disease in non-human primates ranged from 2,500 to 760,000 colony forming units. The average incubation period was 4.5 days. Spores are engulfed by dendritic cells and macrophages and transported to the draining lymph nodes, especially in the mediastinum. The primary manifestation of inhalational anthrax is not pneumonia, but rather mediastinitis, local hemorrhage, edema and necrosis, followed by bacteremia, shock and death in the absence of appropriate and aggressive treatment. Meningitis is also common in systemic anthrax. *B. anthracis* spores germinate both in the lymph nodes and at the primary

[2] Wright JG, Quinn CP, Shadomy S., *et al*. Use of anthrax vaccine in the United States: recommendations of the advisory committee on immunization practices (ACIP), 2009. MMWR Recomm Rep. 2010 July 23; 59 (RR-6)1- 30.

site of infection, releasing two exotoxins which are mainly responsible for the pathogenesis of the disease. Once inhaled, spores can stay dormant within the lung for up to 100 days, and cause delayed disease, for example, after the completion of an initial course of antibacterial drugs.

The capsule of *B. anthracis* is a virulence factor, but the major damage is done by production of edema toxin, a complex of protective antigen (PA) and edema factor, and lethal toxin, a complex of protective antigen and lethal factor. Edema toxin increases host intracellular cyclic adenosine monophospate (cAMP) levels, resulting in cytokine modulation, upregulation of the anthrax toxin receptor, and disruption of interstitial fluid balance.[3] Lethal toxin inactivates members of the mitogen-activated protein kinase -kinase (MAPKK) family, causing an imbalance in the production or release of a range of cytokines.[4]
Protective antigen, a component of both exotoxins, mediates entry of each complex into the cytosol of the cell where they exert their pathogenic effects. Blocking the binding of PA to cell receptors interferes with toxin formation and works to prevent or mitigate toxin effects; this explains the effectiveness of vaccination with PA (AVA) or passive immunization with anti-PA serum. PA has therefore become the main target of vaccine and monoclonal antibody development for prevention and treatment of inhalational anthrax.

The Centers for Disease Control (CDC) classifies *B. anthracis* as a category A biological warfare agent due to the ability of its spores to persist in the environment, their ability to readily cause infection via inhalation, and the high resultant mortality. In 2008, the Department of Homeland Security stated that anthrax posed a threat sufficient to affect U.S. national security. The WHO has estimated that 100 kg of spores released upwind of the Washington DC metropolitan area would result in an estimated 130,000 to 3 million deaths (Office of Technology Assessment, 1993). Furthermore, a strain of *B. anthracis* engineered for bio-warfare or bioterrorism might be resistant to antimicrobial therapy with increased dispersion capabilities. Following the bioterrorism event of 2001, the creation and implementation of bioterrorism preparedness plans, public health mechanisms for the distribution and administration of drugs and vaccines and research initiatives for the development of additional therapeutic options have been emphasized. Because of the life-threatening nature of inhalational anthrax, it is not ethical to test new products through studies in infected humans. The pathogenesis of disease in cynomolgus macaques[5] and New Zealand White rabbits[6] in natural history studies were found

[3] Cui X, et al. (2007). Bacillus anthracis edema and lethal toxin have different hemodynamic effects but function together to worsen shock and outcome in a rat model. *J Infect Dis*, 195: 572-80.

[4] Duesbery NS, et al. (1998). Proteolytic inactivation of MAP-kinase-kinase by anthrax lethal factor. *Science*, 280: 734-7.

[5] Henning LN, *et al*. Development of an Inhalational *Bacillus anthracis* Exposure Therapeutic Model in Cynomolgus Macaques. Clin Vaccine Immunol 2012; 19(11): 1765-1775.

to be similar to that in humans; therefore, new therapies such as monoclonal antibodies are developed under the Animal Rule.

2.2 Analysis of Current Treatment Options

Currently, there are four major forms of therapy for treatment and prophylaxis of inhalational anthrax – antibacterial therapy (ABT), anthrax vaccine adsorbed (AVA), anthrax immune globulin intravenous (AIGIV) and a monoclonal antibody targeting PA, raxibacumab. Characteristics of the disease such as production of toxin and frequent occurrence of meningitis, and other factors such as the persistence of spores and potential for antimicrobial drug resistance influence the specific recommendations for prophylaxis and treatment.

Antibacterial therapy (ABT): Doxycycline, ciprofloxacin, and levofloxacin are FDA-approved for ABT for inhalation anthrax in adults 18 years of age or older; the first two drugs are recommended as first-line agents. Alternatives include amoxicillin, IM procaine penicillin or clindamycin if the isolate is susceptible. [7] When choosing a regime, several factors must be considered. A combination of antimicrobial drugs that includes at least one bactericidal agent and one that inhibits protein synthesis (for potential antitoxin effects) is recommended.[7] Combination antibacterial drug regimens were used in all eight survivors of inhalational anthrax during the 2001 bioterrorism event.[8] Naturally occurring *B. anthracis* has variable β-lactam resistance, particularly to cephalosporins and this class of antimicrobials is therefore relatively contraindicated. Multidrug resistance has been reported in naturally occurring strains of *B. anthracis* and can be induced *in vitro*. The use of β-lactams for a strain that was originally susceptible could potentially induce β-lactam-resistance during prophylaxis especially if compliance with therapy is poor. Meningitis and hemorrhagic brain parenchymal infection is observed in up to 50% of human cases[9], so ABT that provides good CNS penetration is necessary. Finally, the presence of the spore form of *B. anthracis* mandates prolonged prophylaxis with ABT because incubation periods of up to 43 days have been observed in humans[10] and viable spores have been detected in lungs of NHPs for up to 100 days after

[6] Comer JE, *et al*. Characterization of a Therapeutic Model of Inhalational Anthrax using an increase in Body Temperature in New Zealand White Rabbits as a Trigger for Treatment. Clin Vaccine Immunol 2012;19(9): 1517-1525.

[7] Hendricks KA, et al. Centers for Disease Control and Prevention Expert Panel Meetings on Prevention and Treatment of Anthrax in Adults. Emerg Infect Dis 2014; 20(2): e130687.

[8] Sprenkle MD, et al. Lethal factor and anti-protective antigen IgG levels associated with inhalation anthrax. Emerg Infect Dis 2014; 20: 310-4.

[9] Sejvar JJ, et al. Management of anthrax meningitis. Lancet Infect Dis 2005; 5:287-95.

[10] Meselson M, G. et al. The Sverdlovsk anthrax outbreak of 1979. Science 1994; 266:1202-8.

aerosol exposure.[11] Therefore, the recommended duration of post-exposure prophylaxis for inhalational anthrax is 60 days. Because ABT acts primarily to kill *B. anthracis*, there would be an expected benefit to combine ABT with an agent that targets toxin, such as obiltoxaximab.

The potential adverse events of ABT are well-understood and will not be reviewed in detail here. Briefly, they include diarrhea, nausea, headache, photosensitivity, and *C. difficile* colitis, and were responsible for a significant rate of ABT non-compliance after the bioterrorism event in 2001.

Anthrax vaccine adsorbed (AVA)/Biothrax®: AVA is an acellular vaccine prepared from cell-free culture filtrates of a toxigenic, nonencapsulated strain of *B. anthracis*; this filtrate includes the protein PA (83 kDa), and contains no dead or live bacteria. It was initially developed for pre-exposure prophylaxis of anthrax in humans who are at risk of acquiring this infection, i.e., veterinarians, abattoir workers, and military personnel. It is given as a series of five IM injections at 0, 1, 6, 12 and 18 months with a booster dose recommended yearly. AVA is generally well-tolerated; the most common post-market adverse reactions included arthralgias, headache, pruritus, pain, injection-site erythema, myalgia, fever, and rash. Seroconversion, defined as a fourfold rise in anti-PA IgG titers occurred in 85%-100% of adults receiving two and three doses of subcutaneous (SQ) or intramuscular (IM) AVA.[12] For post-exposure prophylaxis however, the ACIP recommends AVA as a series of three subcutaneous (SQ) injections at 0, 2 and 4 weeks, since this regimen results in rapid and high-level antibody production[13] and provides a useful adjunct to ABT.

Anthrax Immune Globulin (AIGIV): This is a preparation of polyclonal antibodies against the PA of *B. anthracis* made from pooled plasma of healthy humans vaccinated with AVA. In animal studies, AIGIV increased survival when administered without an antimicrobial drug.[7] AIGIV is part of the Strategic National Stockpile and would be made available under the IND or an EUA in an emergency setting to provide immediate passive immunity to protective antigen. The BLA for Anthrasil® (Anthrax Immune Globulin Intravenous) was approved in March 2015.

Raxibacumab: Raxibacumab is a recombinant, fully humanized, anti-PA IgG1λ monoclonal

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[11] Henderson DW et al. Observations on the prophylaxis of experimental pulmonary anthrax in the monkey. J Hyg 1956;54:28-36.

[12] Singer DE, et al. Serum IgG antibody response to the protective antigen (PA) of Bacillus anthracis induced by anthrax vaccine adsorbed (AVA) among U.S. military personnel. *Vaccine 2008;*26: 869-73.

[13] Pittman PR, et al. Anthrax vaccine: immunogenicity and safety of a dose-reduction, route-change comparison study in humans. Vaccine 2002;20: 1412-20.

antibody which was approved by the FDA -in 2012, for treatment of inhalational anthrax and prophylaxis when other treatments are not available or not appropriate. Though the treatment indication was primarily as an adjunct to ABT, the MAb could potentially also be used as primary treatment when anthrax is caused by antibacterial drug-resistant strains, or when antibacterial drug therapy is contraindicated or not tolerated. Adverse reactions include headache and urticaria but these were mild and easily managed in the human trials. Raxibacumab is part of the SNS.

Table 2.1 summarizes the available modalities of treatment of anthrax. Given the inability to perform clinical trials in human infection, recommendations for therapy are based on limited clinical data from observational and animal studies, the lessons learned in the bioterrorism event in 2001, and on biological plausibility.

Table 2.1. Summary of Available Therapies for Anthrax According to Indication

Indication	Available Agents
Pre-exposure Prophylaxis	AVA*
Post-exposure Prophylaxis	ABT, AVA, AIGIV, Raxibacumab
Treatment of established infection	ABT, AVA, AIGIV, Raxibacumab

*This refers to prophylaxis in a non-emergent situation, such as for veterinarians, military personnel or others with potential occupational exposure to anthrax.

Development of Obiltoxaximab*:* The development of obiltoxaximab was initiated soon after the bioterrorism-related anthrax outbreak in 2001. The development approach is briefly summarized: (b) (4)

The Applicant compared obiltoxaximab with raxibacumab and found three significant differences:

1) the amino acid sequences of the complementarity-determining regions (CDR) within the variable regions of both the heavy (V_H) and light (V_L) chains are different.

2) the light chain type (b) (4)

3) the functional binding affinity.

PA is an 83 KDa protein that undergoes proteolytic cleavage to 63 KDa (PA63) and 20 KDa (PA20) proteins. Obiltoxaximab binds domain 4 of PA63, the domain responsible for cellular receptor recognition, with a KD of 0.33 nM, thereby inhibiting toxin binding and internalization. According to published reports (Chen Z, 2011), raxibacumab binds its target with an affinity of 2.78 nM, ~1-log lower than obiltoxaximab.

Combination Therapy: Because clinical deterioration occurs rapidly in inhalational anthrax, early initiation of effective ABT is critical. During the 2001 outbreak, all six patients with inhalational anthrax who received IV ABT during the prodromal phase of the disease survived, while all five who received ABT after the prodromal phase died.[14] In 2009, the US Advisory Committee on Immunization Practices recommended 60 days of ABT for immediate protection in combination with a 3-dose series of SQ AVA (Biothrax®) for longer-term protection.[2] The CDC Expert Panel further recommended that everyone exposed to aerosolized *B. anthracis* should receive ABT for 60 days even if fully or partially vaccinated.[7] In addition, the panel emphasized the importance of aggressive supportive care and management of pleural effusions in the treatment of inhalational anthrax, and gave detailed recommendations for choice of ABT based on the presence or absence of meningitis.

Though agents with activity against PA (raxibacumab, AIGIV) appear to have a role in treatment of systemic anthrax, the optimal time to administer them is unknown. The consensus of the CDC Expert Panel was that given the high case-fatality rate of systemic anthrax and the low relative risk for raxibacumab or AIGIV, the potential benefit to adding one of these agents to combination ABT outweighed the potential risk. Thus, an anti-PA product should be added to combination ABT for any patient in whom there is a high clinical suspicion for anthrax.[7] This group did not clearly determine that AIGIV would be superior to raxibacumab or vice versa, and did not address the possibility of using both.

After the bioterrorism event in 2001, compliance with recommended ABT was found to be only 21-42% in the at-risk population of 10,000 people; most stopped therapy due to adverse events. Further, despite the emphasis on effective combinations of ABT for treatment or post-

[14] Jernigan JA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. Emerg Inf Dis 2001; 7: 933-44.

exposure prophylaxis, these agents would potentially be of little use in the event of dispersal of multidrug-resistant *B. anthracis* in a bioterrorism event. In such a situation, the urgent deployment of therapeutic agents to effectively counter the effect of the toxins of *B. anthracis* may offer the only hope of survival. Therefore, there is a medical need for alternative and adjunctive measures for prophylaxis and treatment of inhalational anthrax.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Obiltoxaximab is a new molecular entity (NME) and it is not marketed in the United States. The development program for obiltoxaximab was designed to meet the criteria described in the draft *FDA Guidance for Industry: Animal Models – Essential Elements to Address Efficacy under the Animal Rule to Support the Licensure of Obiltoxaximab for Treatment and Prophylaxis of Inhalational Anthrax in Humans.*[15]

3.2 Summary of Presubmission/Submission Regulatory Activity

Key regulatory milestones and discussions with FDA during the obiltoxaximab/ETI-204 development program between 2003 and 2014 are summarized in Table 3.1**.**

[15] Animal Rule Guidance:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf

Table 3.1. Obiltoxaximab/ETI-204 Regulatory History

Regulatory Milestone	Description	Date
Pre-IND meeting		03 Nov 2003
IND filing	For the treatment of exposure to *B. anthracis* spores by IV or IM administration (post-exposure prophylaxis)	24 Feb 2005
IND effective		04 Aug 2005
Fast track designation	Post-exposure/presumed exposed and adjunctive treatment of symptomatic inhalational anthrax, including disease caused by antibiotic-resistant organisms	06 May 2006
Orphan drug designation	For the treatment of exposure to *B. anthracis* spores	09 Jun 2006
FDA meeting – Development Plan discussion	Development plan revised in line with NIAID funding and NIAID request to focus on a treatment indication and IV administration only	07 Aug 2007
End-of-Phase 1 meeting	Pursuing treatment indication with IV or IM administration with intent to add on additional indication of post-exposure	30 Sep 2009
FDA meeting –development plan discussion	Development plan aligned with BARDA funding/contract. Submitted development plan for treatment of inhalational anthrax by IV administration as initial indication	10 May 2011
FDA meeting – development plan discussion	Discussion of approach to IV dose selection, added benefit study design, and exploratory discussions related to IM development program	27 Nov 2012
FDA Feedback - Manufacturing	Bulk Drug Substance Process Validation Master Plan	25 Jan 2013
End-of-Phase 2 (clinical/nonclinical) meeting	Discussion of the dose and design selected for pivotal Phase 3 nonclinical studies, the dose and design selected for the IV clinical studies, the size and composition of the clinical safety database to support registration of ETI-204 for the indication sought, the adequacy of existing nonclinical safety pharmacology and toxicology studies to support registration of ETI-204, and the adequacy of the bioanalytical methods in place to support the planned Phase 3 program	15 Mar 2013
Added Benefit Teleconference	Briefing package outlining available nonclinical data on ETI-204 in combination with antibiotics was submitted to the IND. Following 15 March 2013 Pre-BLA meeting, the added benefit meeting was cancelled and converted to an informal telephone call between R Conrad from Elusys and Dr. Alexander from FDA	20 Mar 2013
End-of-Phase 2 (CMC) meeting	Key CMC aspects of drug development which include: comparability data to support a new drug substance manufacturing process, drug substance/product registration stability plans, container closure integrity and extractable testing, acceptability of analytical methods for testing identity, purity and potency of drug substance and product and drug product process validation master plan	7 May 2013
FDA (teleconference) - Efficacy	FDA requested an additional nonclinical efficacy study be conducted with the final commercial material.	3 July 2013
Pre-BLA meeting (including CMC)	Key aspects of rolling submission filing format, content, and timelines were discussed	30 July 2013
SPA Agreement	Special Protocol Assessment Agreement on design of nonclinical efficacy study AP202: Three Armed Trigger-to-Treat Efficacy Study of Intravenously Administered ETI-204 in Cynomolgus Monkeys with Inhalational Anthrax	23 Dec 2013
Teleconference to discuss AP202 results	Reviewed results of special protocol assessment study AP202 and confirmed outcome is adequate for Biologics License Application filing, comparability of commercial (Lonza BDS) and previous (Baxter BDS) product. Agency noted recently (May 2014) issued draft guidance document and requested dose justification for the proposed human dose of 16 mg/kg submission in advance of BLA submission	3 July 2014

BARDA: Biomedical Advanced Research and Development Authority; BDS: bulk drug substance; CMC: Chemistry, Manufacturing, and Controls; IND: Investigational New Drug; NIAID: National Institute of Allergy and Infectious Diseases.

Source: BLA 125509: Table 2 from the Applicant's Clinical Overview

<u>Dr. Gopinath's Comment</u>: There were other important milestones during the development of obiltoxaximab and these are summarized below:

1. There was a change in cell type in which the product was produced. For AH101, obiltoxaximab was produced in a NS0 research cell line and designated (b) (4)*. A new cell line,* (b) (4)*, was subsequently used for the production of the monoclonal antibody with small differences in* (b) (4)*. An additional study AH102, was conducted to evaluate the safety profile with doses rangingfrom ~1.5 to~4.5 mg/kg.*

2. In the discussion of the Development Plan on 8/7/2007, FDA specified that safety and tolerability data should be available in 300 individuals to exclude serious or fatal adverse events (AEs) with 1% frequency and to evaluate - AEs that occur with frequency >1%.

3. At the EOP1 meeting on 9/30/2009, FDA noted that they no longer recommended a study of the simultaneous administration of anthrax vaccine with ETI-204 to support a treatment indication. There was also discussion about (b) (4)*. There was no such study submitted in the Application. An information request was sent and the Applicant clarified that this study was never done.*

4. Following the completion of study AH105, manufacturing of the product was switched to Lonza. In July 2014, the FDA agreed that ETI-204 manufactured by Baxter and Lonza were comparable. There was also discussion about the appropriateness of 16 mg/kg IV as the human equivalent dose.

3.3 Foreign Regulatory Actions and Marketing History

Obiltoxaximab, Anthim® is not marketed anywhere in or outside of the United States.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

OSI audit reports are pending and will be included in an addendum to this review.

4.2 Product Quality

The product quality reviewer, Tao Xie, Ph.D. found no significant concerns that would impact approval. The following information is excerpted from Dr. Xie's review: The data submitted in this BLA 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 product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs at both drug substance and drug product manufacturing sites.

The reviewers recommend that Anthim® (obiltoxaximab) be approved for human use under conditions specified in the package insert. They recommend an expiry period of (b) (4) months for obiltoxaximab drug substance when stored at (b) (4) °C and they recommend an expiry period of 18 months for Anthim® drug product when stored at 5±3°C. The stability protocols were acceptable and extension of expiry based on additional real time stability data can be reported to the BLA in an Annual Report.

4.3 **Clinical Microbiology**

The clinical microbiology reviewers, Shukal Bala, Ph.D. and Lynette Berkeley, Ph.D. found no significant concerns that would impact approval of obiltoxaximab. The following information is from Dr. Bala's review:

Natural History Studies: The applicant referred to three published studies[16,17,18] and four studies in the DMF (b) (4) to support the choice of New Zealand White (NZW) rabbits (*Oryctolagus cuniculus*) and cynomolgus monkeys (*Macaca fascicularis*) challenged with approximately 200x the 50% lethal dose (LD_{50}) of *B. anthracis* spores (Ames strain) by aerosolization for measuring the efficacy of ETI-204. The studies show that both NZW rabbits and cynomolgus monkeys have well defined physiological and pathological responses to inhalational anthrax that are similar to humans. Due to the high mortality rate and rapid time to death, the NZW rabbit model is a more stringent model than the cynomolgus macaque model. Gross lesions and histological findings observed in rabbits and cynomolgus macaques were similar to those of inhalational anthrax in humans. Presence of bacteremia or PA occurs early relative to some of the other indicators of infection. Detection of PA appears to be a trigger for intervention. Both NZW rabbit and cynomolgus macaques infected with *B. anthracis* (Ames strain) by the inhalational route with approximately 200x LD_{50} meet the essential elements of an animal model and are

[16] Vasconcelos D., *et al*. Pathology of inhalation anthrax in cynomolgus monkeys (*Macaca fascicularis*). Lab Invest 2003;83:1201-1209.
[17] Yee SB, *et al*. Aerosolized *B. anthracis* infection in New Zealand white rabbits: Natural history and intravenous levofloxacin treatment. Comparative Medicine 2010; 60(6): 461-468.
[18] Zaucha GM, *et al.* The pathology of experimental *B. anthracis* in rabbits exposed by inhalation and subcutaneous inoculation. Pathol Lab Med 1998; 122:982-992.

appropriate models for evaluating treatment and prophylaxis against inhalational anthrax (for full details, see microbiology review by Shukal Bala, Ph.D.).

Microbiological Measurements: Microbiological measurements included in the studies were blood cultures and detection of PA by an electrochemiluminescence (ECL) assay and /or by an enzyme linked immunosorbent assay (ELISA). The performance characteristics of the ECL assay and other experimental assays in the BLA submission were reviewed by Lynette Berkeley, Ph.D.

Blood cultures: Methods used to detect and measure bacteremia in different studies included enriched blood cultures (qualitative), qualitative blood cultures, and/or quantitative blood cultures. Enriched (qualitative) cultures were performed by inoculating 1 mL of blood in brain heart infusion (BHI) broth or other appropriate culture broth at an approximate 1:10 dilution for a minimum of 24 hours and up to 64 hours at 37°C. A portion (~40 µL) of this broth culture was plated on blood agar plates to determine (qualitatively) the presence or absence of colony morphology consistent with *B. anthracis*. Another type of qualitative blood culture were performed by inoculating either 10 µL or 40 µL of blood in EDTA onto tryptic soy agar (TSA) plates. Quantitative blood cultures were performed by plating of 100 µL of whole blood (collected in EDTA tubes) and a series of dilutions in triplicate on TSA plates. Blood samples were stored at room temperature until diluted and plated; typically samples were plated within 6 hours of collection with the exception of terminal samples which were held longer. The results were expressed as colony forming units per milliliter, CFU/mL. The majority of the colony counts were based on 2 of 3 replicates. The lower limit of detection (LLOD) by quantitative culture method varied in different studies. Dr. Bala concluded that, overall, the studies showed that the enriched blood culture method was more sensitive compared to the other two blood culture methods. This could be due to higher volume of blood used for enriched cultures compared to the other two methods as well as the anti-coagulant used. 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.

Protective antigen (PA): Detection of PA in the sera of NZW rabbits and cynomolgus macaques by an ECL assay was used as a trigger-for intervention in some of the studies.PA levels at different time points post-challenge were measured by ELISA in many of the NZW rabbit and cynomolgus macaque studies. The ELISA assay used in some of the studies was based on a rabbit anti-PA antibody serum which detected the whole molecule of PA (PA83) as well as its fragments; the PA measured in such an assay was termed as total PA. In some of the other studies, ETI-204 was used as the capture antibody that detected only the PA63 fragment of the PA molecule; the PA detected by such a method was termed as free PA (for full details see Dr. Lynette Berkeley's microbiology review, 12/16/15, in DARRTS). Due to the variability in the assays used in different studies, the LLOD, lower limit of quantitation (LLOQ), and upper limit of quantitation (ULOQ) varied among the assays.

The presence of PA was tested by the ECL assay or ELISA in animals, prior to challenge, in some of the studies and a small number of rabbits and macaques tested positive. It remains unclear whether the positive PA results were false positives due to cross-reactivity with other *Bacillus* species or the animals had prior exposure to *B. anthracis*.

Blood culture is the most reliable method for the detection of bacteremia; however, the culture can take up to 24 to 48 hours to become positive. Dr. Bala noted that PA detected by a screening ECL assay is an appropriate marker for therapeutic intervention due to the rapid progression of disease after inhalation of *B. anthracis* spores.

Measurement of immunologic parameters: The Applicant measured anti-PA IgG antibodies by ELISA or ECL assay and toxin neutralizing antibodies (TNAs) in the sera of animals in some of the NZW rabbit and cynomolgus macaque studies. The purpose of these assays was to measure anti-PA antibody response post-challenge at different time intervals to compare to prior-to-challenge (baseline) results. The assays used for measuring anti-PA IgG antibodies varied among the studies. In some assays, anti-rabbit IgG or anti-monkey IgG polyclonal antibodies were used as the capture agent; these assays were designed to measure endogenous anti-PA IgG antibodies. In others assays, PA and non-specific Protein A/G reagent were used as the capture agent; although these assays were designed to measure concentrations of obiltoxaximab, endogenous anti-PA IgG antibodies were also detected. However, **if** the obiltoxaximab is known to be absent in the sera of animals e.g., prior to administration of obiltoxaximab, or is measured after several half-lives of obiltoxaximab then a positive result would reflect the presence of an endogenous anti-PA IgG antibody response. The microbiology reviewer, Dr. Berkeley, concluded that these assays 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. Dr. Berkeley suggested that a polyclonal antibody against *B. anthracis* lysate be used for screening of animals to ensure absence of any past-exposure to *B. anthracis*. A toxin neutralizing assay (TNA) was used to measure neutralizing antibodies. The assay did not distinguish between obiltoxaximab and the animals' endogenous antibody response. Based on the half-life of obiltoxaximab in infected rabbits (~3 to 4 days) and macaques (~5 to 12 days), the antibodies measured at Day 28 should be a reflection of antibody response and not obiltoxaximab (for additional details, see microbiology review by Lynette Berkeley, Ph.D.).

4.4 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Amy Nostrandt DVM,found no significant concerns that would impact approval of obiltoxaximab. The following information is taken from Dr. Nostrandt's review: Tissue cross-reactivity (TCR) studies were performed in panels of human,

rat, and cynomolgus macaque tissues. The only observed tissue staining was reported to be cytoplasmic (not relevant because cytoplasm would not be accessible to the antibody in vivo), and no membrane staining was reported. An additional TCR study was performed in a limited set of human tissues to compare antibody derived from (b) (4) and (b) (4) cell lines after a manufacturing change from the former to the latter. Staining was reported to be similar for both test articles, and consistent with previous findings for the (b) (4) antibody. There was very little tissue cross-reactivity however, ETI-204 concentrations of 1-10 µg/mL were used in these studies, which are lower than concentrations seen in humans treated with ETI-204 at doses of 16 mg/kg IV.

Two safety pharmacology studies were conducted to evaluate cardiovascular function in cynomolgus macaques. In the first study, compound-related elevation in blood pressure at 2 and 4 hours after IV and IM administration was seen, as well as apparent increase in QT interval on ECG. The reviewer concluded that a more rigorous study was needed. In the second study, the changes in blood pressure were not seen; blood pressures were in the normal range for this species. No QT interval prolongation was reported.

General toxicology studies were performed in rats and cynomolgus macaques. The initial study No. ARR002 ((b) (4) study no. 03553) was performed in 10-13 week old male Fischer 344 rats at repeated IV and IM doses up to 2.91 mg/rat (approximately 10.6 mg/kg) of the (b) (4) antibody. 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 NOAEL was determined to be the high dose, 10.6 mg/kg.
The second safety pharmacology study in cynomolgus macaques included general toxicology evaluation of test article generated in the (b) (4) cell line. The NOAEL was 30 mg/kg, which resulted in an AUC of approximately 150,000 µg·hr/mL.
More recently, pilot and definitive toxicology studies were performed in Sprague-Dawley rats. In the pilot study, doses of vehicle (saline), 10, 30, or 100 mg/kg were administered by slow IV bolus injection on Days 1, 4, and 7 to five male rats per group. No effects were noted on survival, clinical observations, body weights, clinical pathology or gross pathology. The study concluded 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 by IV injection on Days 1, 4, and 7. The test article was the new material manufactured by Lonza, and this study included an additional high dose (30 mg/kg) group utilizing material manufactured by Baxter in order to compare material made by the two manufacturers. Additional satellite groups were used for pharmacokinetics. No test article-related findings were reported in clinical observations, body weights, food consumption, clinical pathology, organ weights, or in macroscopic or microscopic pathology. While no differences between materials made by the

two manufacturers were reported in the toxicologic or toxicokinetic profiles, the report did note increased variability in C_{max} with the Lonza material.
Central nervous system (CNS) lesions (bacteria, inflammation, hemorrhage and occasionally necrosis) were seen in anthrax infected non-surviving rabbits and monkeys administered IV obiltoxaximab (≥4 mg/kg) or control at the time of PA toxemia. Microscopic changes in the non-surviving animals that received obiltoxaximab were due to the presence of extravascular bacteria and not the effect of obiltoxaximab. No dose-response relationship for brain histopathology was identified. No treatment-related brain lesions were shown in anthrax-treated surviving rabbits (at Day 28) or macaques (up to Day 56) after a single administration of obiltoxaximab at doses up to 16 mg/kg and up to 32 mg/kg/dose, respectively. No obiltoxaximab-related neurobehavioral effects were observed in surviving anthrax infected macaques following treatment with obiltoxaximab.

An assessment for neuropathological changes was performed on tissue from studies in infected macaques and in infected and non-infected rabbits. In primates and rabbits exposed to inhalational anthrax *that did not survive* (found dead or moribund sacrificed animals), administration of obiltoxaximab at doses at and above 4 mg/kg was associated with an increased incidence (frequency) of histological findings, consistent with a severe acute inflammatory reaction. The changes in the non-survivors, including those treated with only saline, with obiltoxaximab, or with levofloxacin, were stated to be consistent with morphologic lesions/hemorrhagic meningoencephalitis previously reported in monkeys and rabbits with inhalational anthrax. Biologically significant reactions (hemorrhage, inflammation, necrosis) in non-survivors were associated with the presence of extravascular bacteria in all dose groups, including saline controls. The occurrence of an acute inflammatory response in the obiltoxaximab treated non-survivors did not exhibit a dose response relationship (i.e., changes were not more pronounced at higher doses). The administration of the obiltoxaximab was not associated with any biologically significant morphologic reactions in surviving animals exposed to inhaled *B. anthracis*. Similarly, no significant neuropathological lesions were reported in rabbits not exposed to anthrax spores and given up to 32 mg/kg intravenous obiltoxaximab in a reproductive toxicology study.

4.5 Clinical Pharmacology

The clinical pharmacology reviewers, Zhixia (Grace) Yan, Ph.D., and Fang Li, Ph.D., found no significant issues that would impact approval of obiltoxaximab. The following information is taken from Dr. Yan's review.

4.5.1 Mechanism of Action

Obiltoxaximab targets *B. anthracis* protective antigen (PA), the cell-binding component of anthrax toxins. *In vitro* studies suggest that obiltoxaximab binds protective antigen (PA) with a dissociation constant (K_D) of 0.33 nM i.e., 48.8 pg/mL and neutralizes PA. Obiltoxaximab blocked the receptor binding domain 4 of PA (PAD4) to the capillary morphogenesis gene -2 (CMG-2), an anthrax toxin receptor; such an effect was concentration dependent. The CMG-2 has higher affinity for PA than TEM-8. Binding of PA63 to the anti-PA polyclonal antibody was inhibited by obiltoxaximab. Binding of obiltoxaximab to PAD4 is known to prevent the cell binding of PA63-edema factor (EF) and PA63-lethal factor (LF) complexes that prevents the entry of EF and LF into the cytosol, thereby preventing the downstream deleterious effects of anthrax toxins, the main pathophysiological drivers of morbidity and mortality.

4.5.2 Pharmacodynamics

Administration of obiltoxaximab post-challenge with *B. anthracis* spores did not interfere with the development of adaptive immunity to *B. anthracis* in animal models of inhalational anthrax. In the human studies, administration of obiltoxaximab was not associated with significant immunogenicity; this is further discussed in Section 8.4.10.

4.5.3 Pharmacokinetics

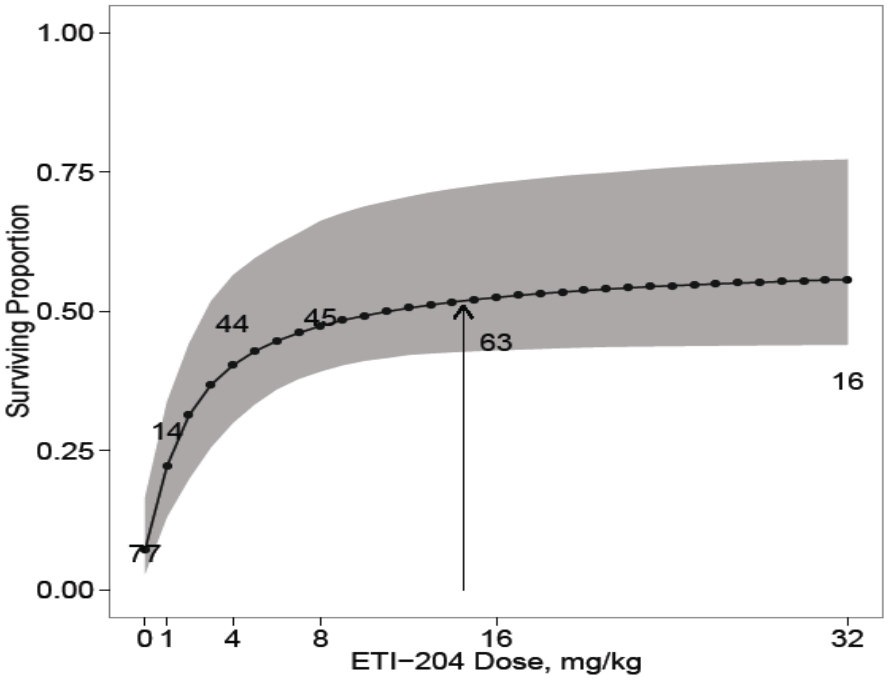
The pharmacokinetics of obiltoxaximab were defined in rabbits, cynomolgus macaques and humans. Obiltoxaximab dose selection is supported by a cross-species comparison of exposure and dose-response (D/R) relationships described in *in vivo* animal models of inhalation anthrax infection. These studies show that obiltoxaximab demonstrates the following clinical pharmacology characteristics:

- The disposition of obiltoxaximab IV is similar to that of other mAbs. Serum concentrations decline in a bi- or multi-exponential fashion after IV administration, with terminal $t_{1/2}$ values of approximately 2 to 4 days, 3 to 4 days, 5 to 12 days, and 15 to 23 days in healthy rats, rabbits, monkeys, and humans, respectively. The mean obiltoxaximab steady-state volume of distribution was greater than plasma volume, suggesting some tissue distribution. Clearance values were much smaller than the glomerular filtration rate indicating that there is virtually no renal clearance of obiltoxaximab.

- No significant differences in mean estimates of Cmax, AUC_{inf}, CL, or half-life of obiltoxaximab between two doses administered ≥4 months apart were observed.
- Administration of ciprofloxacin (PO and IV) and obiltoxaximab together did not alter the PK of either drug.

- In the macaque and rabbit studies with the endpoint of survival, a dose of 14.5 mg/kg (ED_{90}) was identified as the fully effective dose in infected animals according to the Animal Rule guidance.
- Simulations show that humans (healthy and infected) achieve similar to or greater exposure to obiltoxaximab with a single 16 mg/kg IV dose compared to infected rabbits and macaques receiving the fully effective dose (14.5 mg/kg), with partial overlap of the AUC_{inf}. These simulations also suggest that a higher dose (i.e., 24 mg/kg) could result in the full-range of human exposure (AUC_{inf}) exceeding the exposure in macaques with the fully effective dose, 14.5 mg/kg.
- The proposed dose of 16 mg/kg in humans would be expected to maintain effective concentrations of obiltoxaximab in serum for 2 to 3 weeks.
- More than 95% of humans administered a 16 mg/kg dose can be expected to achieve an obiltoxaximab serum concentration equal or greater than the highest observed PA concentrations in the animal studies.
- In summary, the clinical pharmacology data provided by the Applicant supports the use of 16 mg/kg of obiltoxaximab in humans, but future trials with a higher dose of 24 mg/kg are suggested to minimize overlap in exposure with the fully effective dose in animals, provided that such studies are ethical to conduct in healthy human subjects. The dose-response was similar in cynomolgus macaques and NZW rabbit monotherapy studies and results for both species are combined in the following dose-response graph, Figure 4.1.

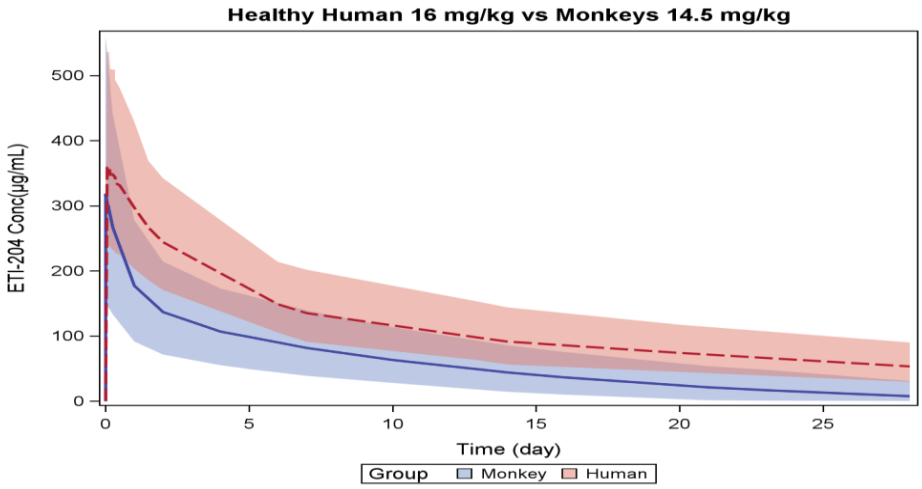
Figure 4.1. ETI-204 Dose Response in NZW Rabbits and Cynomolgus Macaques



Source: Clinical pharmacology review by Grace Yan, Ph.D.

The 16 mg/kg IV in humans did not achieve exposures with the 5th percentile of AUC exceeding the 95th percentile of AUC in cynomolgus macaques for the fully effective dose, Figure 4.2. Median C_{max} values were comparable (i.e., human exposures do not exceed animal exposures). The clinical pharmacology reviewers estimated that a higher human dose of 24 mg/kg would be needed to achieve human AUC exposures (5th percentile) exceeding the AUC (95th percentile) of the fully effective dose.

Figure 4.2. Simulated Concentration Profile of ETI-204: Human 16 mg/kg vs. Monkeys 14.5 mg/kg



Source: Clinical pharmacology review by Fang Li, Ph.D.

Reviewer Comment: The clinical reviewers agree with the clinical pharmacology reviewer's recommendation for approval of the obiltoxaximab 16mg/kg IV dose in humans. One must consider the risk of hypersensitivity in healthy volunteers if one were to conduct an additional PK/safety study to evaluate single-doses greater than 16mg/kg. All adverse reactions leading to discontinuation of ETI-204 IV infusion were hypersensitivity reactions; the FDA analysis conducted by Ramya Gopinath, M.D. identified 7 (2.2%) subjects who had symptoms/signs of anaphylaxis. There was no apparent dose-response for hypersensitivity. In my opinion, it would not be ethical to conduct another PK/safety study in healthy human adults with higher doses of obiltoxaximab for the following reasons: the rate of significant hypersensitivity of 3.1% with obiltoxaximab and that there was a gain of approximately 3% in survival observed at the higher doses, 24 or 32mg/kg, of obiltoxaximab modeled from animal studies. A study of higher doses of obiltoxaximab could be conducted in a field study if, unfortunately, cases of inhalational anthrax were to occur. Please refer to the ethics consultation (12/8/15) from Kevin Prohaska, D.O., M.P.H., for further information regarding the safety concerns of testing a higher dose of obiltoxaximab in humans. See section 8 for the review of safety of obiltoxaximab in healthy humans.

4.6 Devices and Companion Diagnostic Issues

Not applicable.

4.7 Consumer Study Reviews

Not applicable.

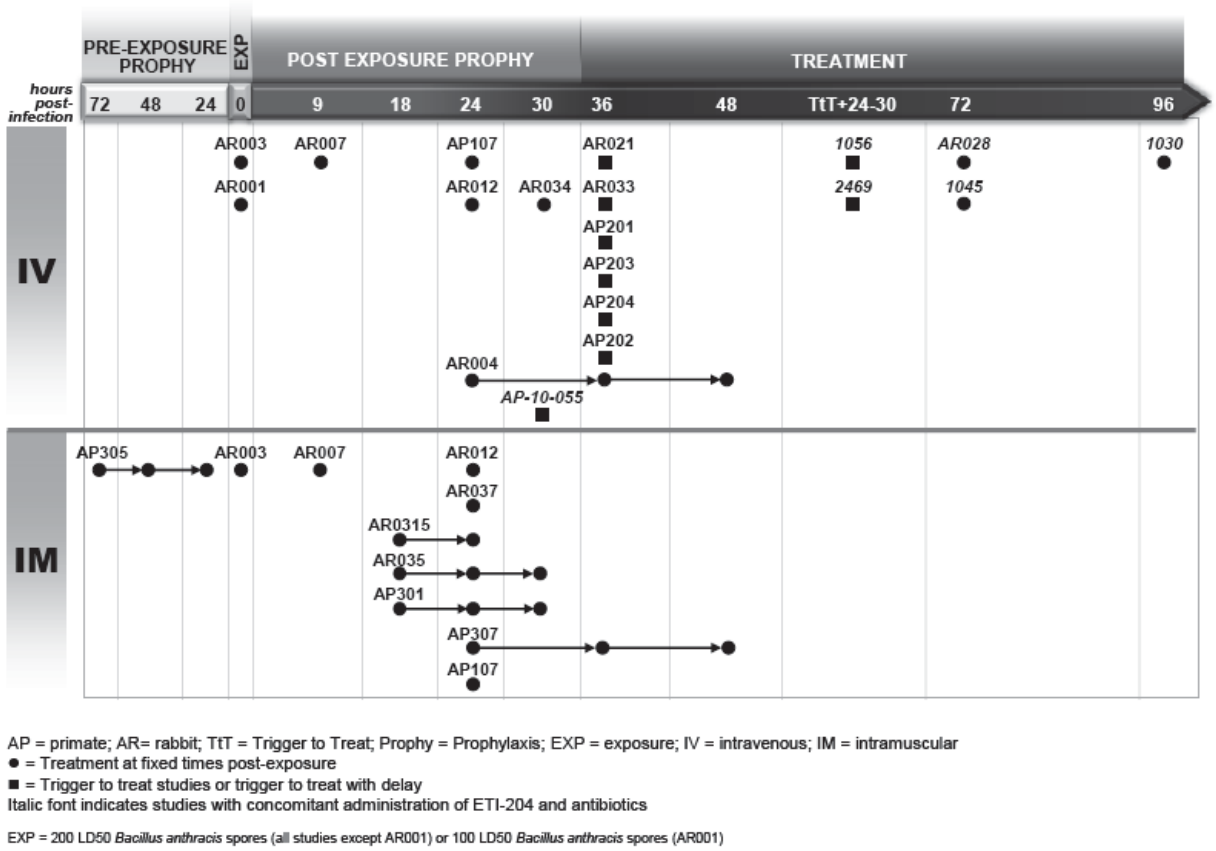
5 Sources of Clinical Data and Review Strategy

5.1 Nonclinical Studies

Clinical studies of inhalational anthrax are unethical to conduct in humans. Therefore, under the Animal Rule, the Applicant evaluated obiltoxaximab (ETI-204) for the treatment, and prophylaxis of inhalational anthrax in the nonhuman primate (cynomolgus macaques) and New Zealand white (NZW) rabbit models of inhalational anthrax.

The studies included treatment studies with IV monotherapy, obiltoxaximab in combination with antibacterial drug, and pre- and post-exposure prophylaxis studies. All studies, except three NZW rabbit 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). The 25 nonclinical studies conducted during the development program for obiltoxaximab are summarized in Figure 5.1.

Figure 5.1. Nonclinical Studies with Obiltoxaximab in Nonhuman Primates and Rabbits



AP = primate; AR= rabbit; TtT = Trigger to Treat; Prophy = Prophylaxis; EXP = exposure; IV = intravenous; IM = intramuscular
● = Treatment at fixed times post-exposure
■ = Trigger to treat studies or trigger to treat with delay
Italic font indicates studies with concomitant administration of ETI-204 and antibiotics

EXP = 200 LD50 *Bacillus anthracis* spores (all studies except AR001) or 100 LD50 *Bacillus anthracis* spores (AR001)

Source: BLA 125509, SDN 1: Study report, AP202, Summary of Clinical Efficacy - Treatment of Inhalational Anthrax, section 2.7.3 , Fig.2, p.15.

The to-be-marketed formulation of obiltoxaximab is manufactured by Lonza Pharmaceuticals. Treatment, pre-exposure, post-exposure prophylaxis studies are summarized in Table 5.1. All studies were randomized and all except one rabbit study, AR021, were blinded.

Table 5.1. BLA 125509: Treatment, Pre-exposure, Post-exposure Prophylaxis Studies

Type of Study	Study #	ETI-204 Manufacturer	IV	IM
Treatment				
Cynomolgus macaque	AP201	Baxter	X	
	AP202	Baxter vs. Lonza	X	
	AP203	Lonza	X	
	AP204	Baxter	X	

NZW Rabbit	AR021	Baxter	X	
	AR033	Baxter	X	
Combination Studies				
NZW rabbit	NIAID 1030	Baxter	X	
	NIAID 1045	Baxter	X	
	AR028	Baxter	X	
	AR007	(b) (4)	X	X
	AP10-055	Baxter	X	
	AR 034 Phase 1	Lonza	X	
Cynomolgus macaque	NIAID 1056	Baxter	X	
	NIAID 2469	Baxter	X	
Post-exposure prophylaxis				
Cynomolgus macaque	AP301	Lonza		X
	AP307	Lonza		X
NZW Rabbit	AR004	Elusys	X	
	AR012	Elusys	X	X
	AR0315	Baxter		X
	AR035	Lonza		X
	AR037	Lonza		X
Pre-exposure prophylaxis				
Cynomolgus macaque	AP305	Lonza		X
NZW Rabbit	AR001	Elusys	X	
	AR003	Elusys	X	X
Re-challenge study				
NZW Rabbit	AR034 Phase II	Lonza	X	

Reviewer Comment: In addition to the six monotherapy treatment studies, the results of three studies sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), study NIAID 1030, 1045 (New Zealand White rabbits) and 1056 (cynomolgus macaques) were submitted in the BLA. The goal of these studies was to investigate the added benefit of obiltoxaximab combined with an anti-bacterial drug versus an antibacterial drug alone to treat inhalational anthrax; these studies also contained an obiltoxaximab treatment arm and a placebo arm.

Obiltoxaximab IV Monotherapy Studies

Six studies were conducted by the Applicant to evaluate the efficacy of a single intravenous dose of obiltoxaximab for the treatment of inhalational anthrax in two animal species. Four monotherapy studies, Studies AP201, AP202, AP203, and AP204, were conducted in cynomolgus macaques, and two monotherapy studies in NZW rabbits, studies AR021 and AR033. All of the ETI-204 IV monotherapy studies were randomized, placebo-controlled, parallel-group studies conducted with good laboratory practices (GLP) in which IV ETI-204 single-dose was administered to rabbits or monkeys that were exhibiting signs of anthrax. Doses ranging from 1 to 16 mg /kg were evaluated in NZW rabbits and the highest dose studied in cynomolgus macaques was 32 mg/kg (single-dose) in Study AP203. Two of the nonhuman primate studies, AP202 and AP204, and two rabbit studies, AR021 and AR033, evaluated a single-dose of 16 mg/kg IV which is the proposed treatment dose in humans. The target challenge dose in all of the studies was 200 LD_{50} of *B. anthracis* spores. The trigger to treat was a positive protective antigen (PA) level by electrochemiluminescence (ECL) in cynomolgus macaques or a positive PA-ECL or a significant increase in body temperature (SIBT) in NZW rabbits. All of the studies were conducted at the (b) (4) . The study designs for six intravenous monotherapy efficacy studies in cynomolgus macaques and NZW rabbit are outlined in Table 5.2.

Table 5.2. Obiltoxaximab Monotherapy Studies for the Treatment of Inhalational Anthrax in Cynomolgus Macaques and New Zealand White Rabbits

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals[1]
AR021 GLP	Rabbit/NZW	Randomized, open-label, placebo- and positive-controlled (levofloxacin), parallel group, trigger-to-treat (dosing upon positive PA-ECL, elevated body temperature, or time), dose-ranging study in anthrax-challenged animals	ETI-204 IV: 0 mg/kg 1 mg/kg 4 mg/kg 16 mg/kg levofloxacin: 50 mg/kg/day po for 5 days	 9 9 17 17 10
AR033 GLP	Rabbit/NZW	Randomized, blinded, placebo-controlled, parallel group, trigger-to-treat (dosing upon positive PA-ECL, elevated body temperature, or time), dose-ranging study in anthrax-challenged animals	ETI-204 IV: 0 mg/kg 1 mg/kg 4 mg/kg 8 mg/kg 16 mg/kg	 14 14 14 14 14
AP201 GLP	Monkey/cynomolgus	Randomized, blinded-to-group, placebo-controlled, parallel-group, trigger-to-treat (dosing upon positive PA-ECL or time), dose-ranging study in anthrax-challenged animals	ETI-204 IV: 0 mg/kg 4 mg/kg 8 mg/kg	 14 14 15
AP204 GLP	Monkey/cynomolgus	Randomized, blinded-to-group, placebo-controlled, parallel-group, trigger-to-treat (dosing upon positive PA-ECL or time), dose-ranging study in anthrax-challenged animals	ETI-204 IV: 0 mg/kg 4 mg/kg 16 mg/kg	 16 16 16
AP203 GLP	Monkey/cynomolgus	Randomized, blinded, placebo-controlled, parallel-group, trigger-to-treat (dosing upon positive PA-ECL or time), dose-ranging study in anthrax-challenged animals	ETI-204 IV: 0 mg/kg 8 mg/kg 32 mg/kg	 16 16 16
AP202 GLP	Monkey/cynomolgus	Randomized, blinded, placebo-controlled, parallel-group, trigger-to-treat (dosing upon positive PA-ECL or time) study of drug products made from Lonza and Baxter BDS	ETI-204 IV: 0 mg/kg 16 mg/kg (B) 16 mg/kg (L)	 17 17 16

[1]Total number of animals randomized to treatment.
GLP: Good Laboratory Practices; NZW: New Zealand White; PA-ECL: protective antigen electrochemiluminescence; IV: intravenous; mg/kg: milligram/kilogram; po: oral; BDS: bulk drug substance; B: Baxter; L: Lonza.

Source: BLA 125509, Study Report AP 202, Summary of Clinical Efficacy - Treatment of Inhalational Anthrax, Section 2.7.3, Table 1. p.18.

Reviewer Comment: The clinical reviewer considers the six randomized, placebo-controlled, parallel-group studies as the pivotal studies supporting the efficacy of obiltoxaximab monotherapy for the treatment of inhalational anthrax and they are the main focus of this review.

Combination Studies - Obiltoxaximab combined with an antibacterial drug
The following combination studies of obiltoxaximab and antibacterial drugs were designed to evaluate the added-benefit (survival rate) of obiltoxaximab to antibacterial drug therapy versus the antibacterial drug alone, Table 5.3. Six studies evaluated obiltoxaximab as an 8 mg/kg IV single-dose with antibacterial drugs. Obiltoxaximab 16 mg/kg IV single-dose (the proposed human dose) was evaluated with levofloxacin in two rabbit studies.

Studies that evaluated human equivalent dose (HED) are considered the primary studies in support of the efficacy of ETI-204 in combination with antibacterial drugs. Four studies evaluated ETI-204 with a a HED of an antibacterial drug in NZW rabbits:
• AR034 (Phase 1)
• NIAID 1030
• NIAID 1045
• AR007

Studies with less than human equivalent doses are considered supportive of the efficacy of ETI-204 in combination with antibiotics. Four studies with less than human equivalent dose (< HED) of an antibacterial drug were conducted in nonhuman primates and rabbits:

- Study AR028 in NZW rabbits
- NIAID Study AP-10-055 in NZW rabbits
- Study 1056 in cynomolgus macaques
- Study 2469 in cynomolgus macaques

Table 5.3. Combination Studies of ETI-204 with Antibacterial Drugs

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals[1]
Human Equivalent Dosing				
NIAID Study 1030 (1030-G607604) Non-GLP	Rabbit/NZW	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at 96 hours after anthrax exposure	ETI-204 IV: Untreated 8 mg/kg 8 mg/kg + levo 50 mg/kg/day x 3 days po levo 50 mg/kg/day x 3 days po	 6 16 16 16
NIAID Study 1045 (1045-G607604) Non-GLP	Rabbit/NZW	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at 72 hours after anthrax exposure	ETI-204 IV: Untreated 8 mg/kg 8 mg/kg + levo 50 mg/kg/day x 3 days po levo 50 mg/kg/day x 3 days po	 6 16 16 16
AR034 (Phase 1) non-GLP	Rabbit/NZW	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at 30 hours after anthrax exposure	ETI-204 IV: 0 mg/kg plus no levo 0 mg/kg + levo 50 mg/kg/day po 16 mg/kg 16 mg/kg + levo 50 mg/kg/day x 3 days po	 8 20 20 20
AR007 GLP	Rabbit/NZW	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at 9 hours after anthrax exposure	ETI-204[2]: 0 mg/kg ~4 mg/kg IV ~4 mg/kg IV + levo 50 mg/kg/day x 5 days po ~8 mg/kg IM ~8 mg/kg IM+ levo 50 mg/kg/day x 5 days po levo 50 mg/kg/day x 5 days po	 9 9 9 9 9 12

[1]Total number of animals randomized to treatment.
[2]ETI-204 was given at fixed dose. The body weights of rabbits in this study ranged from 2.2 to 2.7 kg. The actual doses administered were 10 and 20 mg/rabbit, which were approximately equal to 4 and 8 mg/kg.
GLP: Good Laboratory PracticesIM: intramuscular; IV: intravenous; kg: kilogram; levo: levofloxacin; mg: milligram; NIAID: National Institute of Allergy and Infectious Disease; NZW: New Zealand White; po: oral.

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals[1]
Lower than Human Equivalent Dosing				
AR028 non-GLP	Rabbit/NZW	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at 72 hours after anthrax exposure	ETI-204 IV: 0 mg/kg 16 mg/kg + levo 6.5 mg/kg x 3 days po levo 6.5 mg/kg/day x 3 days po	 12 34 38
NIAID Study AP-10-055 non-GLP	Rabbit/NZW	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at detection of elevated PA	Saline control Doxy 2 mg/kg/day x 3 days bid IV ETI-204 8 mg/kg + doxy 2 mg/kg/day x 3 days bid IV	4 10 10
NIAID Study 1056 (1056-G607605) non-GLP	Monkey/cynomolgus	Randomized, controlled, open-label, parallel-group, factorial design study; dose received upon positive PA-ECL (ETI-204 only treatment) or 24±12 hours after positive PA-ECL (ETI-204 + cipro; cipro alone)	ETI-204 IV: Untreated 8 mg/kg 8 mg/kg + cipro 10 mg/kg/day x 4 days po cipro 10 mg/kg x 4 days po	 8 8 16 16
NIAID Study 2469 (2469-G937901) non-GLP	Monkey/cynomolgus	Randomized, controlled, open-label, parallel-group, factorial design study; dose received at 24±12 hours after positive PA-ECL. Included both ETI-204 and another Sponsor's antitoxin	Untreated ETI-204 8 mg/kg IV + cipro 10 mg/kg/day x 4 days Antitoxin "A" 10 mg/kg/day + cipro 10 mg/kg/ day x 4 days Cipro po 10 mg/kg/day x 4 days Cipro po 26 mg/kg/day x 4 days	8 16 16 16 16

[1]Total number of animals randomized to treatment.
cipro: ciprofloxacin; doxy: doxycycline; GLP: Good Laboratory Practices; IM: intramuscular; IV: intravenous; kg: kilogram; levo: levofloxacin; mg: milligram; NIAID: National Institute of Allergy and Infectious Disease; NZW: New Zealand White; PA: protective antigen; po: oral; USAMRIID: United States Army Medical Research Institute for Infectious Diseases.

Rechallenge Study AR034

The objective of Study AR034 was to demonstrate that protective endogenous immunity develops in animals that survive a primary *B. anthracis* infection following administration of IV ETI-204 either alone or in combination with antibacterial drugs (phase 1). Protective immunity was measured by increased survival in the absence of treatment following a secondary challenge with *B. anthracis* spores (phase 2).

Post-Exposure Prophylaxis Studies

The Applicant conducted nine post-exposure prophylaxis studies with intravenous or intramuscular single doses of obiltoxaximab. Three randomized, placebo-controlled, parallel-group studies in cynomolgus macaques, i.e., Study AP107 (open- label), AP301 (blinded), and AP307 (open-label), are considered the primary studies in support of the use of obiltoxaximab for post-exposure prophylaxis.
Six studies, i.e., AR004, AR007, AR012, AR035, and AR0315 were conducted in NZW rabbits and are considered supportive because anthrax in rabbits transitions rapidly to advanced systemic

disease and the time window for intervention is often too narrow to allow for an evaluation of the efficacy especially of drug administered by the intramuscular (IM) route which has slower absorption than IV drug.

Table 5.4. Post-Exposure Prophylaxis Studies

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals[1]
Pivotal Studies				
AP107 GLP	Monkey/cynomolgus	Randomized, open-label, placebo-controlled, parallel group, IV and IM ETI-204 dose-ranging study (dosing at 24 hrs following *B. anthracis* spore exposure)	ETI-204: 0 mg/kg IV 2 mg/kg IV 8 mg/kg IV 4 mg/kg IM 8 mg/kg IM	 6 9 9 8 9
AP301 GLP	Monkey/cynomolgus	Randomized, blinded, placebo-controlled, parallel group, IM ETI-204 dose-ranging study (dosing at 18, 24, and 36 hrs following *B. anthracis* spore exposure)	ETI-204 IM: 0 mg/kg (18 hrs) 8 mg/kg (18 hrs) 16 mg.kg (18 hrs) 8 mg/kg (24 hrs) 16 mg/kg (24 hrs) 8 mg/kg (36 hrs) 16 mg/kg (36 hrs)	 6 6 6 6 6 6 6
AP307 Non-GLP	Monkey/cynomolgus	Randomized, open-label, placebo-controlled, parallel group, IM ETI-204 study (dosing at 24, 36, and 48 hrs following *B. anthracis* spore exposure)	ETI-204 IM: 0 mg/kg (24 hrs) 16 mg/kg (24 hrs) 16 mg/kg (36 hrs) 16 mg/kg (48 hrs)	 10 14 14 16

[1]Total number of animals randomized to treatment.
B. anthracis: *Bacillus anthracis*; GLP: Good Laboratory Practices; hrs: hours; IM: intramuscular; IV: intravenous; kg: kilogram; mg: milligram.

Post-Exposure Prophylaxis Studies, cont.

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals[1]
Supportive Studies				
AR004 Non-GLP	Rabbit/NZW	Randomized, open-label, placebo-controlled, parallel group, IV ETI-204 study (dosing at 24, 36, and 48 hrs following *B. anthracis* spore exposure)	ETI-204 IV[2]: 0 mg/kg (24 hrs) ~4 mg/kg (24 hrs) ~4 mg/kg (36 hrs) ~4 mg/kg (48 hrs)	 10 10 10 10
AR007 GLP	Rabbit/NZW	Randomized, open-label, placebo-controlled, parallel group, IV and IM ETI-204 study in combination with a human equivalent dose of antibiotic (dosing at 9 hrs following *B. anthracis* spore exposure)	ETI-204[3]: 0 mg/kg IV 0 mg/kg IV+ levo[4] ~4 mg/kg IV ~4 mg/kg IV + levo[3] ~8 mg/kg IM ~8 mg/kg IM + levo[3] levo[1]	 9 12 9 9 9 9
AR012 GLP	Rabbit/NZW	Randomized, open-label, placebo-controlled, parallel group, IV and IM ETI-204 dose-ranging study (dosing at 24 hrs following *B. anthracis* spore exposure)	ETI-204[5]: 0 mg/kg IM ~1 mg/kg IV ~4 mg/kg IV ~8 mg/kg IV ~2 mg/kg IM ~4 mg/kg IM ~8 mg/kg IM ~15 mg/kg IM	 9 9 12 12 9 9 12 12
AR0315 Non-GLP	Rabbit/NZW	Randomized, open-label, placebo-controlled, parallel group, IM ETI-204 dose-ranging study (dosing at 18 and 24 hrs following *B. anthracis* spore exposure)	ETI-204 IM: 0 mg/kg (24 hrs) 4 mg/kg (18 hrs) 16 mg/kg (18 hrs) 4 mg/kg (24 hrs) 16 mg/kg (24 hrs)	 10 12 12 12 12

[1]Total number of animals randomized to treatment.
[2]ETI-204 was given at fixed dose. The body weights of rabbits in this study ranged from 2 to 2.8 kg at the time of randomization. The actual dose administered was 10 mg/rabbit,which was approximately equal to 4 mg/kg.
[3]ETI-204 was given at fixed dose. The body weights of rabbits in this study ranged from 2.2 to 2.7 kg. The actual dose administered were 10 and 20 mg/rabbit, which were approximately equal to 4 and 8 mg/kg.
[4]Levofloxacin dose was 50 mg/kg/day oral gavage x 5 days.
[5]ETI-204 was given at fixed dose. The body weights of rabbits in this study ranged from 2.3-3.0 kg. The actual dose administered was 2.5, 5, 10, 20 or 40 mg/rabbit, which was approximately equal to 1, 2, 4, 8. or 15 mg/kg.
GLP: Good Laboratory Practices; hrs: hours; IM: intramuscular; IV: intravenous; kg: kilogram; levo: levofloxacin; mg: milligram; NZW: New Zealand White

Post-Exposure Prophylaxis Studies, cont.

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals
Supportive Studies				
AR035 GLP	Rabbit/NZW	Randomized, open-label, placebo-controlled, parallel group, IM ETI-204 study (dosing at 18, 24, and 30 hrs following *B. anthracis* spore exposure)	ETI-204 IM: 0 mg/kg (18 hrs) 16 mg/kg (18 hrs) 16 mg/kg (24 hrs) 16 mg/kg (30 hrs)	 10 10 10 10
AR037 GLP	Rabbit/NZW	Randomized, open-label, placebo-controlled, parallel group, IM ETI-204 dose-ranging study (dosing at 24 hrs following *B. anthracis* spore exposure)	ETI-204 IM: 0 mg/kg 8 mg/kg 16 mg/kg 32 mg/kg	 10 16 16 16

GLP: Good Laboratory Practices; IM: intramuscular; kg: kilogram; mg: milligram; NZW: New Zealand White.

Pre-Exposure Prophylaxis Studies

The efficacy of ETI-204 as a monotherapy for pre-exposure prophylaxis of inhalational anthrax was evaluated in the following three studies:
Cynomolgus macaques: Study AP305
New Zealand white rabbits: Study AR001 and AR003

Study AM002, was conducted in the mouse model of inhalational anthrax, using an intraperitoneal inoculation route with a different strain of *B. anthracis* (Sterne) and is not discussed in this review.
These nonhuman primate and rabbit studies were randomized, controlled, parallel-group studies to evaluate the effects of dose and timing relative to *B. anthracis* spore challenge on survival when given intravenously or intramuscularly before *B. anthracis* spore exposure. All of the studies were conducted at the (b) (4).

Table 5.5. Pre-Exposure Prophylaxis Studies

Study Number	Species/Strain	Study Design	Treatment Regimen and Dose	Total No. Animals[1]
Primary Studies				
AR001 (357-G004819) Non-GLP	NZW/rabbit	Randomized, placebo-controlled, open-label, parallel-group study with treatment received 30 to 45 minutes before anthrax spore challenge	ETI-204 IV: 0 mg/kg ~4 mg/kg	 5 10
AR003 (397-G004957) Non-GLP	NZW/rabbit	Randomized, placebo-controlled, open-label, dose-ranging, parallel-group study with treatment received within 35 minutes before anthrax spore challenge	ETI-204: 0 mg/kg IV ~0.5 mg/kg IV ~1 mg/kg IV ~2 mg/kg IV ~4 mg/kg IV ~8 mg/kg IM	 8 8 8 8 8 8
AP305 2778-100018326 GLP	Monkey/cynomolgus	Randomized, blinded, placebo-controlled, time-ranging. parallel-group study with treatment received within 24, 48, and 72 hrs before anthrax spore challenge	ETI-204 IM: 0 mg/kg (24 hrs) 16 mg/kg (24 hrs) 16 mg/kg (48 hrs) 16 mg/kg (72 hrs)	 10 14 14 15
Supportive Studies				
AM002 Non-GLP	Mouse/ DBA/2	Randomized, placebo-controlled, open-label, parallel-group study with treatment received immediately before anthrax spore challenge	0 mg/kg IP ETI-204: 0.5 mg IP 14B7: 0.5 mg IP	5 5 5

[1]Total number of animals randomized to treatment.
hrs: hours; IM: intramuscular; IP: intraperitoneal; IV: intravenous; kg: kilogram; mg: milligram; NZW: New Zealand White.

Data Quality and Integrity: Sponsor's Assurance
The Applicant provided a quality assurance statement that the studies were inspected by the Quality Assurance Unit. The Good Laboratory Practice (GLP) statement noted that the GLP studies were performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58). Non-GLP studies were conducted according to the study protocols as amended and (b) (4) standard operating procedures (SOPs).

5.2 Review Strategy

Obiltoxaximab Monotherapy Studies (Table 5.2): Survival outcomes will be assessed from the submitted datasets for the six randomized, placebo-controlled, monotherapy studies conducted under good laboratory practices to evaluate the efficacy of intravenous obiltoxaximab monotherapy for the treatment of inhalational anthrax.

Combination or "Added-benefit" Studies (Table 5.3): Survival outcomes will be assessed from the submitted datasets for the eight studies to address the question of the added-benefit of obiltoxaximab combined with an antibacterial drug versus antibacterial drug alone for the treatment of inhalational anthrax.

Prophylaxis Studies (Table 5.4 and Table 5.5): Survival outcomes will be assessed in pre- and post-exposure prophylaxis studies to evaluate the efficacy of obiltoxaximab for 1) preemptive treatment pre-exposure and 2) delayed treatment post-exposure for the prevention of anthrax disease in patients exposed to *B. anthracis*. The indication for prophylaxis will hinge on whether obiltoxaximab monotherapy significantly improves survival over placebo for treatment of inhalational anthrax.

Note: Obiltoxaximab and its code name, ETI-204, are used interchangeably throughout the document. The Application was reviewed by two medical officers, Elizabeth O'Shaughnessy, MD reviewed the animal efficacy data and Ramya Gopinath, MD reviewed the human safety data. Graphics and tables were constructed in collaboration with biostatistics reviewers, Xianbin Li, Ph.D. and Ling Lan, Ph.D.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1 Study AP202

6.1.1 Study Design

Overview and Objective

Study AP202 was a randomized, blinded, placebo- controlled, parallel group, trigger-to treat-study of obiltoxaximab products manufactured by Lonza and Baxter in cynomolgus macaques with inhalational anthrax.

The primary objective was to evaluate the efficacy of a single intravenous dose of obiltoxaximab (manufactured at Lonza) on survival rate compared to placebo control in cynomolgus macaques with inhalational anthrax.
The secondary objective was to provide survival data from a treatment arm using obiltoxaximab manufactured at Baxter to compare to a treatment arm using obiltoxaximab manufactured at Lonza.

Reviewer Comment: Study AP202 was conducted after studies AP201, AP203, and AP204. Studies AP201 and AP204 tested the obiltoxaximab/Baxter product in the cynomolgus macaque model of inhalational anthrax and they demonstrated a survival benefit. Study AP203 tested the Lonza product and it failed to demonstrate a survival benefit. The differences in survival rates among studies AP201, AP203, and AP204 were likely due to differences in the severity of anthrax as demonstrated by pre-treatment bacteremia and PA levels in the cynomolgus macaques. However, for completeness, a study that included the Lonza and the Baxter product was recommended by the Agency because the only nonhuman primate monotherapy efficacy study done with the obiltoxaximab/Lonza product at that time was study AP203 and it failed to show a survival benefit over placebo.

Synopsis of Study Design

A total of 53 young adult/adult cynomolgus macaques, 2 to 5 years of age, were included in the study. Fifty-one cynomolgus macaques were placed on study with the remaining two animals (one male and one female) serving as potential replacements. Fifty-one animals were to be randomized to the following treatment groups (17 subjects per group) per protocol, however, one animal died following spore challenge but prior to randomization to a treatment group. See Figure 6.1 for an overview of the study design.

The planned treatment groups and ETI-204 doses are as follows:

Group	ETI-204 Dose	No. of cynomolgus macaques	Description
1	0 mg/kg	17	Placebo (saline) control
2	16 mg/kg	16*	Lonza
3	16 mg/kg	17	Baxter

*One animal died following spore challenge but prior to treatment.

Study Population: Healthy young adult and adult cynomolgus macaques with a negative screen for infectious diseases (tuberculosis, SIV, STLV-1, Herpes B, SRV1 and SRV2) were included in the study.

Animal History Records: An animal history record was compiled for each of the animals in the study.

Randomization: The cynomolgus macaques were stratified by sex to one of three challenge days and were also randomized to challenge order. Animals were also randomized to treatment in an effort to balance the onset of disease among the three groups. Randomization was not considered complete until an animal received treatment. The dosing order and assignment were determined by the order in which animals triggered for treatment.

Blinding: The study director, Applicant, microbiologists, pathologist, and technicians performing the dosing and all technicians assessing subjects were blinded to a treatment group, challenge day, and challenge order.

Challenge Dose: On the day of aerosol-challenge, animals were exposed via a head-only inhalation exposure chamber to aerosolized *Bacillus anthracis* spores with a target exposure of 200 LD_{50}.

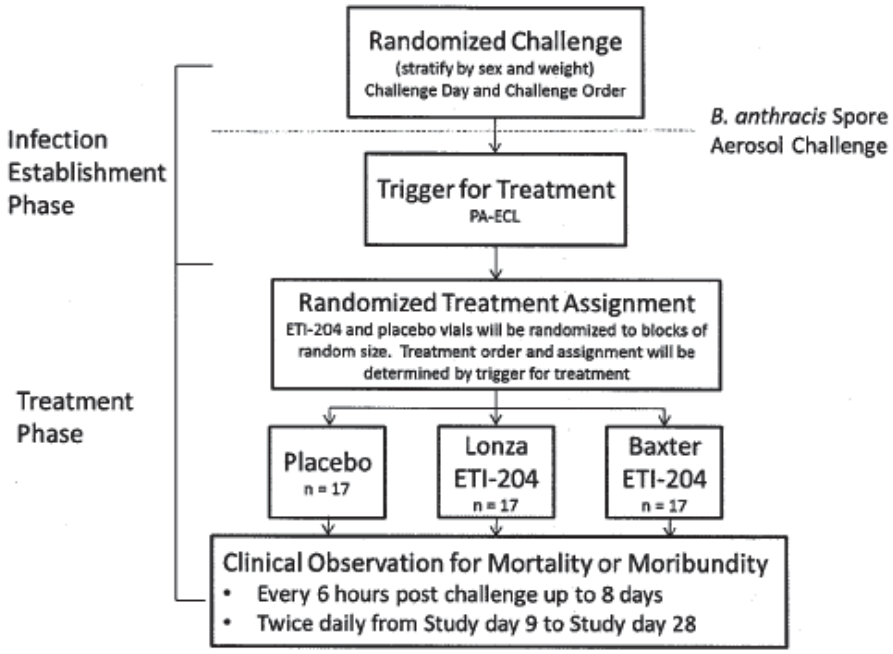
Trigger to Treat: A positive serum protective antigen (PA) result via the electrochemiluminescence (ECL) assay run on-site was the criterion for trigger-to-treat with blinded study drugs.

Treatment: On the day of challenge, animals were exposed to aerosolized *B. anthracis* at a target inoculum of 200 LD_{50} and then later treated with saline IV or obiltoxaximab IV. Animals received one dose of obiltoxaximab (Lonza or Baxter) 16 mg/kg IV or IV normal saline (placebo) based on a positive serum PA-ECL assay (trigger for treatment). Animals that did not have a

positive serum PA-ELISA screening assay after obtaining results from the 54 hours post-challenge time point were to be treated with study drugs, per the study protocol.

Monitoring: Animals exposed to aerosolized *B. anthracis* were observed for signs of inhalational anthrax. Observations were performed every six hours beginning ~24 hours post-challenge up to study Day 8 and twice-daily from Day 9 through Day 28. On study Day 28, clinical observations were recorded once (prior to euthanasia) in survival animals. Macaques were observed for clinical signs including anorexia, lethargy, respiratory distress, decreased activity (recumbent, weak, or unresponsive), seizures, moribundity, and other abnormal clinical signs. In addition, appetite was monitored twice daily during the observation period.

Figure 6.1. Study AP202: Overview of Study Design



Source: BLA 125509, SDN 1: AP202 Study protocol.

Blood cultures and Protective Antigen Assays

Quantitative blood cultures, enriched blood cultures, and assays for PA were performed at intervals pre- and post-challenge with *B. anthracis* spores and up to and on the day of scheduled (Day 28) or unscheduled termination. The collections of blood samples were scheduled based on either post- treatment (PT) or post- challenge times. Blood samples for enriched blood culture and protective antigen by ECL were collected at Study Day -7, and at 24, 30, 36, 42, 48, and 54 hours post-challenge.

The limit of detection (LOD) for quantitative bacteremia was 3 cfu/mL in this study. Quantitative bacteremia levels less than the LOD or reported as "zero" were replaced with one half of the LOD rounded to the nearest integer (2 cfu/mL) for the statistical analysis.

Blood collected in EDTA tubes were used for assessment of quantitative bacteremia (cfu/mL blood). For enriched bacteremia, approximately 1.0 mL of whole blood was collected in a SPS tube. The whole blood sample was cultured in brain heart infusion (BHI) at an approximate 1: 10 dilution (i.e., 9 mL of BHI broth for 1 mL of whole blood) between 24 and 64 hours at 37 ± 2°C. A portion (approx. 40µL) of this broth culture was plated on blood agar plates to determine qualitatively the presence or absence of colony morphology consistent with *B. anthracis.*

The Rapid Protective Antigen Screening Assay, produced by MesoScale Discovery (MSD, Gaithersburg, MD), is a 96-well ECL assay (qualitative) designed to detect the presence or absence of *B. anthracis* PA. This result of this test was used as a trigger for treatment.

The PA-ELISA was designed to run to quantify circulating PA levels. The lower limit of quantitation (LLOQ) for PA-ELISA was 5ng/mL. PA-ELISA values reported as less than the limit of quantitation (LLOQ) were replaced with one half of the LLOQ (2.5 ng/mL) for the statistical analysis. This test was used to monitor PA levels during the study period. The schedule of pre-treatment and post-treatment sample collection and testing is summarized in **Table 6.1**.

Table 6.1. Study AP202: Blood Collection and Assay Schedule

Target Time Point		Blood Tube type/ Approximate Blood volume	Quantitative Bacteremia (Culture)*	Enriched Bacteremia (Culture)#	Serum for PA-ECL	Serum for PA-ELISA	Serum for ETI-204 Concentration
Before Treatment[a]	Study Day -7	EDTA ~0.5 ml SPS ~1.0 ml SST ~4.0 ml	X	X	X	X	X
	^24 hr PC	SPS ~1.0 ml SST ~1.0 ml	-	X	X	-	-
	^30 hr PC	SPS ~1.0 ml SST ~1.0 ml	-	X	X	-	-
	^36 hr PC	SPS ~1.0 ml SST ~1.0 ml	-	X	X	-	-
	^42 hr PC	SPS ~1.0 ml SST ~1.0 ml	-	X	X	-	-
	^48 hr PC	SPS ~1.0 ml SST ~1.0 ml	-	X	X	-	-
	^54 hr PC	SPS ~1.0 ml SST ~1.0 ml	-	X	X	-	-
	PTT	EDTA ~0.5 ml SPS ~1.0 ml SST ~1.0 ml	X	X	-	X	-
Post Treatment	15 min PT	SPS ~1.0 ml SST ~2.5 ml	-	X	-	X	X
	96 hr PT	EDTA ~0.5 ml SPS ~1.0 ml SST ~1.5 ml	X	X	-	-	X
	7 days PT	EDTA ~0.5 ml SPS ~1.0 ml SST ~1.5 ml	X	X	-	-	X
	Day 28 PC (day of scheduled termination)	EDTA ~1.5 ml SPS ~1.0 ml SST ~4.0 ml	X	X	-	X	X
	Unscheduled Termination[b]	EDTA ~1.5 ml SPS ~1.0 ml SST ~2.0 ml	X	X	-	X	-

The day of spore challenge is Study Day 0, PC = Post Challenge, PTT = Prior to Treatment, PT = Post Treatment

* Post challenge pre-treatment bleed time points are relative to a median challenge time for a challenge cohort. Post treatment bleed times are calculated from the time each animal's IV treatment ends. Blood samples will occur within ±60 minutes of the calculated time, except for the 15 min PT and 96 hr PT samples which will occur within 5 min and 3 hr of the their calculated times respectively. The Study Day -7 bloods will be relative to the day of challenge and the 7 days PT blood samples will be relative to the day of treatment.

[b] If collection is possible.

^ Post Challenge, pre-treatment sampling stops once decision to treat has been made.

Bacteremia enrichment performed on sample collected in sodium polyanethol sulfonate (SPS) tube

* Quantitative Bacteremia performed on sample collected in EDTA tube

Priority of sample analysis and approximate target volumes:

PC: PA ECL (150 µL serum), enriched bacteremia (1.0 mL whole blood)

PTT: enriched bacteremia (1.0 mL whole blood), quantitative bacteremia (0.5 mL whole blood), quantitative PA (ELISA) (400 µL serum)

PT: quantitative bacteremia (0.5 mL whole blood), enriched bacteremia (1.0 mL whole blood), ETI-204 concentration (400 µL serum), quantitative PA (ELISA) (400 µL serum)

Source: BLA 125509, SDN 1: AP202 Study Protocol.

Criteria for Euthanasia:

Clinical signs of inhalational anthrax in cynomolgus macaques usually preceded death by 1 to 4 days. The presence of any of the following criteria was established for immediate euthanasia:

- Presence of any seizure denoting primary central nervous system disease
- Respiratory distress, dyspnea, or forced abdominal respirations
- Unresponsive to touch or external stimuli
- Moribundity

If the clinical signs listed below were observed in macaques, the infection was considered irreversible and euthanasia was performed:

- Recumbency and weakness
- > 20% body- weight loss
- Total anorexia with duration longer than 48 hours

Reviewer Comment: The euthanasia criteria are standard and similar criteria were used in the other nonhuman primate studies.

Histopathology: Gross necropsy was performed on all macaques that were found dead or euthanized including those that survived and were euthanized on study Day 28. At the time of gross necropsy, a section was obtained from the desired tissue and was processed for bacterial culture. Sections of target tissues including but not limited to brain/meninges, lungs, liver, spleen, spinal cord, kidney, and mediastinal and bronchial lymph nodes, as well as gross lesions were preserved in 10% neutral buffered formalin. All of these tissues, except for brain and spinal cord, were processed to blocks and slides, stained with hematoxylin and eosin (H&E), and evaluated microscopically at (b) (4) by a board-certified veterinary pathologist who was blinded to study group assignment until completion of the initial pathology interpretation was documented. Sections of the spinal cord were stored in formalin and archived for potential future use. Each brain was cut into hemispheres. The left hemisphere was placed in 10% formalin for neuropathologic examination. The right hemisphere was fixed in 10% formalin for 24-48 hours, transferred to 70% ethanol for additional fixation for 2-7 days, and then trimmed. Each section was cut in approximately 5 mm thickness and embedded in paraffin blocks. The paraffin blocks were stored to allow for further evaluations.

Study Endpoints

The primary efficacy endpoint was survival to Day 28 post-challenge with *B. anthracis* spores in cynomolgus macaques treated with obiltoxaximab (Lonza) compared to placebo-control animals. The secondary endpoint was survival to Day 28 post-challenge in the treatment arm using obiltoxaximab (Baxter) compared to the treatment arm using obiltoxaximab (Lonza).

Statistical Analysis Plan

Two analysis populations were defined:

Intent to treat population, ITT: All animals assigned to treatment regardless of bacteremia status prior to treatment.
Modified intent to treat population, mITT: All animals assigned to treatment excluding those animals with negative blood cultures by enriched culture at any time prior to dosing with obiltoxaximab or placebo. The primary analysis population is the mITT population.

Reviewer Comment: All animals were bacteremic prior to dosing therefore the mITT and ITT population are the same in Study AP202.

The primary comparison was survival rates for the animals treated with the obiltoxaximab/ Lonza product versus placebo. Survival proportion in the obiltoxaximab/ Lonza treatment group was compared to the placebo group using a one-sided test 0.025 level using a Bonferroni-Holm adjustment for multiple comparisons. The study was not powered to demonstrate noninferiority of the Lonza product to the Baxter product. The Sponsor submitted a statistical analysis plan (SAP) and the Agency agreed with the SAP. The Applicant proposed that 17 animals per dose group would provide 83.5% power to detect a difference in survival proportions between the obiltoxaximab-treated group and placebo-control group. This assumes that the probability of survival in the obiltoxaximab- treated group is 55% and that in the placebo-control group is 10%.

Missing values: It was planned that missing values were not to be included in the statistical analysis.

Reviewer Comment: The clinical and biostatistics reviewers agree with the primary endpoint and the statistical analysis plan in the study protocol. The study was not powered to demonstrate noninferiority of the Lonza product to the Baxter product. Differences between the survival rates for the two products will be described using descriptive statistics. For further details, see the biostatistics reviews (in DARRTS) of IND 12,285 by Lan Zeng, Ph.D. and of BLA 125509 by Xianbin Li, Ph.D.

Protocol Amendments

Three amendments to the protocol for Study AP202 are outlined below.

Protocol Amendment #1: This amendment clarified that the Lonza product is filled at (b) (4) . The sponsor requested that the target concentration be used for all dose formulation preparation calculation purposes. Other minor changes were included.

Protocol Amendment #2: This amendment clarified that the determination of obiltoxaximab serum concentrations and concentration of the drug in the dosing formulations will be performed by (b) (4)

Protocol Amendment #3: The protocol was amended to clarify that analysis of the stock obiltoxaximab samples was not required.

Reviewer Comment: These amendments did not make substantial changes to the original protocol and do not appear to have impacted the integrity of the study.

Data Quality and Integrity: Sponsor's Assurance

The Applicant provided a quality assurance statement that the study was inspected by the Quality Assurance Unit. The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58). The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

6.1.2 Study Results

Compliance with Good Laboratory Practices

The Applicant submitted a statement that Study AP202 was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21CFR Part 58).

Animal History Records

The Applicant provided an animal history record for each of the cynomolgus macaques in the study. The cynomolgus macaques where of (b) (4) origin and were bred at (b) (4) . The age of each animal was estimated based on its dentition. During the screening period, the animals were routinely weighed, underwent physical examinations, and were screened for evidence of B-virus, SRV, SIV, STLV -1, fecal ova & parasites, tuberculosis, and *Klebsiella* sp. at regular intervals. Animals were treated with panacur, albendazole or

fenbendazole, ivermectin, azithromycin, and insecticide dust. Each animal received a tetanus and hepatitis A vaccine. Animals were tested for measles titers and received measles vaccine if they were negative for measles antibodies

Reviewer Comment: The animal history records indicate that all the animals enrolled in this study were healthy and experimentally naïve.

Patient Disposition

APPEARS THIS WAY ON ORIGINAL

Fifty-one cynomolgus macaques were challenged with an inhalational inoculum of *B. anthracis* 200 LD_{50}. Fifty macaques were randomized to three treatment groups; group 1 (17 animals), group 2 (16 animals), and group 3 (17 animals). Animal, C59383* died post-challenge before it received treatment and it was excluded from the analysis of the primary endpoint. The three treatment groups are described in Table 6.2.

Table 6.2. Study AP202: Overview of Treatment Groups

Treatment Group	Single-Dose IV	No. of cynomolgus macaques; N=50
1. Placebo control	Normal Saline	17
2. Obiltoxaximab (Lonza)	16 mg/kg	16*
3. Obiltoxaximab (Baxter)	16 mg/kg	17

*Animal C59383 died following spore challenge but prior to treatment.

Reviewer Comment: Animal C59383 appeared to be healthy prior to challenge with B. anthracis; the Animal Record indicated that it was negative for B-virus, SRV, SIV, STLV -1, fecal ova & parasites, tuberculosis, and Klebsiella sp. It had a positive PA-ECL at 36 hours post-challenge and it was found moribund before treatment and it died after anesthesia for terminal blood collection..*

Protocol Violations/Deviations

The Applicant reports eight study deviations that occurred at (b) (4). These deviations were related to omissions in data entry for an individual animal or omissions in data entry for the test article. The Applicant states that corrective action was taken for each of the deviations for example, study personnel were required to review standard operating procedures. One animal, C58715, was bacteremic (enriched blood culture) with gram-positive cocci (not consistent with *Bacillus anthracis*) in two separate blood culture samples during screening, Day -7. The quantitative blood culture was negative and the enriched blood culture was positive however, the cause of the positive enriched blood culture result was not determined. Animal C58715 was replaced with animal C58888.

Reviewer Comment: This clinical reviewer agrees with the Applicant's assessment that none of the protocol deviations impacted the integrity of the study.

Table of Demographic Characteristics

Fifty macaques received treatment with obiltoxaximab/Baxter, obiltoxaximab/Lonza, or IV saline/placebo. The animals were evenly distributed among the treatment groups with respect to age range (2 to 5 years) and mean body weight of 3 kg (2 to 5 kg) across all dose groups. There were more males in the Lonza group and more females in the Baxter group. The mean inoculum was 256 ± 49 LD_{50} of *B. anthracis* was similar across the three treatment groups. Eight (16%) animals received an inoculum lower than the target challenge inhalational dose of 200 LD_{50}, however, all animals were bacteremic with *B. anthracis* prior to treatment. All animals except one, i.e., 49 (98%) animals had a positive PA by ECL (PA-ECL) prior to treatment. The baseline characteristics and demographics of the study population are summarized in Table 6.3.

Table 6.3. Study AP202: Demographic Variables and Baseline Characteristics of the Primary Efficacy Population

	Placebo IV (N=17)	Lonza ETI-204 16 mg/kg IV (N=16)	Baxter ETI-204 16 mg/kg IV (N=17)	All (N=50)
Age (years) estimated range	2.7-5	2.7-5	2.7-5	2.7-5
Gender [n (%)]				
Male	8 (47.1)	10 (62.5)	6 (35.3)	24 (48.0)
Female	9 (52.9)	6 (37.5)	11 (64.7)	26 (52.0)
Body weight (kg)				
Mean (SD)	2.91 (0.52)	2.88 (0.42)	2.85 (0.37)	2.88 (0.4)
Range	2.5, 4.6	2.2, 3.7	2.4, 3.9	2.2, 4.6
CHALLENGE with *B. anthracis*				
Challenge dose (LD_{50})				
Mean (SD)	247.6 (52.6)	270.2 (54.8)	254.4 (41.0)	257.1 (49.6)
Range	172.0, 318.0	166.0, 402.0	182.0, 323.0	166.0, 402.0
Challenge dose (LD_{50}) [n (%)]				
<200	4 (23.5)	1 (6.3)	3 (16.7)	8 (16.0)
200 or higher	13 (76.5)	15 (93.8)	14 (82.4)	42 (84.0)
Challenge dose (x 10^7 cfu)				
Mean (SD)	1.53 (0.33)	1.67 (0.34)	1.57 (0.25)	1.59 (0.31)
Range	1.06, 1.97	[1.02, 2.49]	[1.13, 2.00]	[1.02, 2.49]
BACTEREMIA				
Bacteremic subjects [n (%)]; qualitative and quantitative prior to treatment	17 (100)	16 (100)	17 (100)	50 (100)
Log_{10} bacteremia prior to treatment (cfu/mL) *of B. anthracis)*				
Mean (SD)	4.95 (1.11)	5.52 (1.24)	5.08 (1.60)	5.18 (1.33)
Range	3.73, 8.13	2.76, 7.66	2.82, 8.56	2.76, 8.56
Bacteremia (cfu/mL x 10^4) prior to treatment				
Geometric mean	9.0	32.8	12.1	15.0
95% confidence interval	2.4, 33.2	7.1, 150.7	1.8, 80.1	6.3, 35.8
Range	0.5, 13500	0.058, 460	0.7, 36300	0.0570, 36300
PROTECTIVE ANTIGEN				
No. of subjects [n(%)]with PA-ECL (qualitative) positive	17 (100)	15 (93.8)*	17 (100)	49 (98.0)
No. of subjects [n(%)]with positive PA-ELISA (quantitative)	13(76)	13(81)	14(82)	40(80)

prior to treatment				
PA-ELISA prior to treatment (ng/mL) Geometric mean 95% confidence interval	15.9 5.4, 46.9	31.9 10, 101.5	30.7 7.4, 127.2	24.8 12.8, 48.3
Log_{10} PA-ELISA prior to treatment Mean (SD) Range	1.2 (0.92) 0.4, 3.93	1.5 (0.94) 0.4, 3.71	1.49 (1.2) 0.4, 4.31	1.39 (1.02) 0.4, 4.31

***Animal C60822 had a negative PA-ECL; Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Mean levels of *B. anthracis* (CFU/mL) in blood were similar between the obiltoxaximab/Baxter group and the placebo group. The obiltoxaximab/Lonza group had a slightly higher mean log_{10} and geometric mean bacteremia levels but it was not statistically significant. These differences may have an effect on time to death but are unlikely to have affected the overall survival rates. The PA levels in the two obiltoxaximab groups were slightly higher than the placebo group prior to treatment.

Reviewer Comment: The biostatistics reviewer, Dr. Xianbin Li, conducted an analysis of variance (ANOVA) of log $_{10}$ bacteremia levels prior to treatment and found no differences between the three treatment groups.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Not applicable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable. Animals did not receive medications other than test drugs during the study period.

Efficacy Results – Primary Endpoint

The primary analysis was a comparison of survival in the IV obiltoxaximab/Lonza group compared to IV placebo at Day 28. The survival rate in animals treated with obiltoxaximab/Lonza was significantly higher than placebo, 31% versus 0%, respectively at Day 28. A secondary analysis indicated that the Baxter product also had a significantly higher survival rate (35%) compared to the placebo rate (0%). There was no statistically significant difference in survival rates between the obiltoxaximab/Lonza and obiltoxaximab/Baxter groups indicating similar efficacy of the two products. The mean survival rate in both obiltoxaximab treatment groups combined was 11/33 (33%). The survival rates at Day 28 for each treatment group are summarized in Table 6.4.

Table 6.4. Study AP202: Survival at Day 28 Post-Challenge with *B. anthracis*

	Placebo (N=17)	**Lonza ETI-204 16 mg/kg IV (N=16)**	**Baxter ETI-204 16 mg/kg IV (N=17)**	**All (N=50)**
N (%)	0 (0)	5 (31)	6 (35)	11 (22)
Difference in survival proportion compared with placebo [95% CI] p-value*		0.31 [0.08, 0.59] 0.0085	0.35 [0.11, 0.62] 0.0046	

***** *Two-sided 95% confidence interval and one-sided p-values from Boschloo's test were calculated by the biostatistics reviewer, Xianbin Li, Ph.D.*

Kaplan-Meier Graph

All animals in the placebo group (n=17) died of anthrax by Day 7 post-challenge with *B. anthracis*. In the obiltoxaximab/Lonza group, 11 animals died of anthrax within the first eight days post-challenge and the remaining five (31%) animals survived to the end of the study, Day 28. In the obiltoxaximab/Baxter group, 11 animals died within the first six days post-challenge and six (35%) animals survived to, Day 28.

The following Kaplan-Meier curves and 95% confidence interval band summarizes the time to death by treatment group up to Day 28, *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

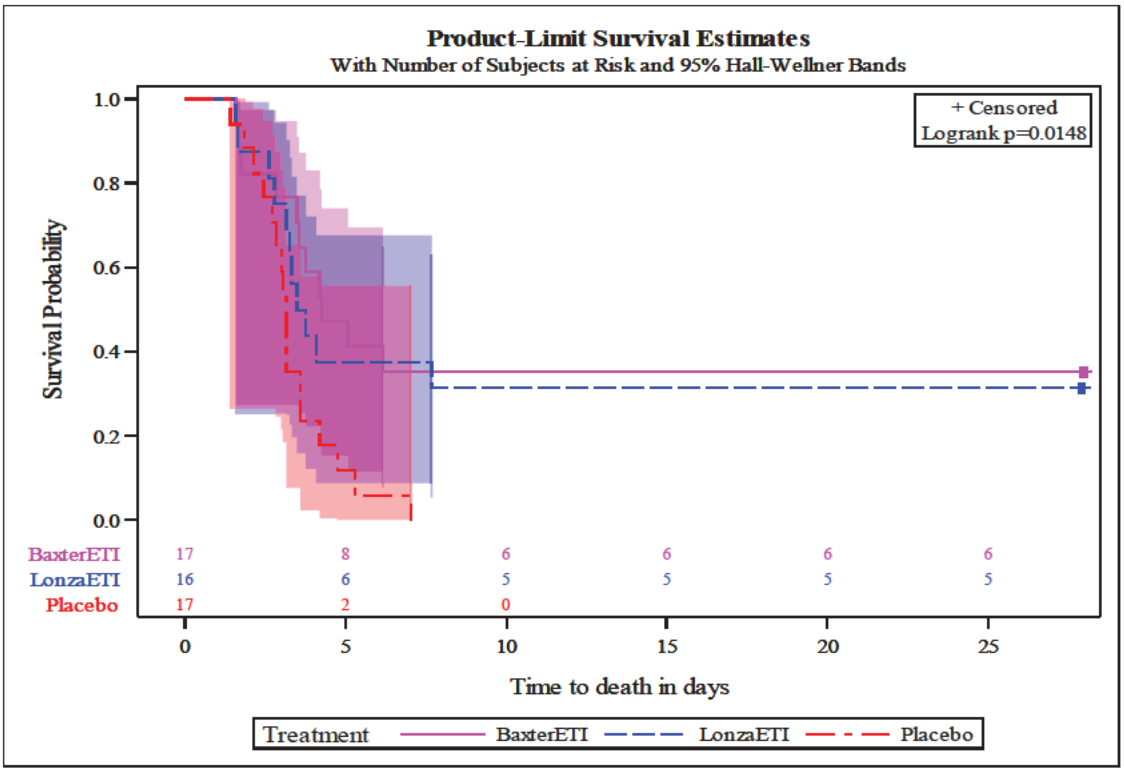
Figure 6.2. The p-value was 0.0148 for the comparison of the three groups. The survival results indicate that obiltoxaximab /Lonza and obiltoxaximab/Baxter demonstrated a significant treatment effect compared to placebo in the cynomolgus macaque model. The p-value was 0.026 for the comparison of the Lonza ETI-204 and placebo group and 0.0073 for the comparison of the Baxter ETI-204 and placebo group, **Table 6.3.**

Table 6.5. Study AP202: Two-sided p-values of pairwise log-rank tests comparing time from challenge to death among groups

	Lonza ETI-204 16 mg/kg IV (N=16)	**Baxter ETI-204 16 mg/kg IV (N=17)**
Placebo	0.026	0.0073
Lonza ETI-204		0.6409

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Figure 6.2. Study AP202: Kaplan-Meier Curve - Time to Death by Treatment Arm



Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

The results for a proportional hazards model on time to death with treatment and $\log_{10}$ bacteremia prior to treatment are shown in **Table** 6.8. Both obiltoxaximab treatment groups had a significantly reduced risk of death compared to the placebo group. Bacteremia prior to treatment was significantly associated with an increased risk of death. No interaction terms between treatment and bacteremia were statistically significant. Log_{10} PA-ELISA and challenge inoculum of *B. anthracis* were not statistically significantly associated with survival in this model. Bacteremia and $\log_{10}$ PA-ELISA levels were highly correlated therefore, this correlation may likely explain why there is no statistical association between PA-ELISA levels and survival.

Table 6.6. Study AP202: Log Hazard Ratio Estimates from a Proportional Hazards Regression Model on Time from Challenge to Death

Parameter	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio
Lonza ETI-204	-1.58741	0.42812	13.7485	0.0002	0.204
Baxter ETI-204	-1.35765	0.41845	10.5264	0.0012	0.257
Log_{10} bacteremia prior to treatment	1.12175	0.18408	37.1346	<.0001	3.070

Source: Table excerpted from the biostatistics review by Dr. Xianbin Li.

Reviewer Comment: A similar number of deaths occurred in the treatment groups that used the Lonza and Baxter products and there appeared to be no significant difference in the times to death post-challenge between the two obiltoxaximab treatment groups as indicated in the Kaplan-Meier graph. Other factors such as time to trigger (PA), time to bacteremia, and time from trigger to treatment were similar between the treatment groups. This reviewer concludes that obiltoxaximab manufactured by Lonza and Baxter are similar products based on the survival results of Study AP202 and the ONDQA reviewer's assessment of the structural similarity of the products. Therefore, the survival data from the studies that used the Baxter product may be used to support the efficacy of obiltoxaximab.

Data Quality and Integrity – Reviewers' Assessment

The submitted data was of high quality. All data sets were submitted in AdaM and SEND standard format. The review of the study report did not reveal any issues of concern related to the integrity of the study data. The clinical reviewer in collaboration with the biostatistics reviewer was able to replicate the survival results of the study by an independent assessment of the submitted datasets for all studies.

Efficacy Results – Secondary and other relevant endpoints

The trigger for treatment was a positive PA level by ECL (PA-ECL). Time to the trigger with a positive PA, time from trigger to treatment, and time to bacteremia was measured to test for any differences between the three arms of the study, Table 6.7. The mean time to trigger, i.e., PA-ECL positivity, was approximately 35 hours post-challenge and it was similar across the three treatment groups. The mean time to treatment with obiltoxaximab (Lonza or Baxter) or placebo was approximately 39 hours post-challenge across the three treatment groups. The mean time from trigger to treatment with obiltoxaximab IV or placebo IV was 4.3 hours across the three treatment groups.

There was no significant difference with regard to time to trigger (PA), time to bacteremia, or time from trigger to treatment between the three treatment groups, i.e. obiltoxaximab-Baxter, obiltoxaximab-Lonza, or placebo control. It should be noted that there was one measurement of bacteremia between challenge and prior to treatment therefore, the time interval from challenge to bacteremia was very close to the time interval from challenge to treatment and may not reflect the actual time to development of bacteremia.

Table 6.7. Study AP202: Time to Challenge, Trigger (positive PA ECL) and Treatment

	Placebo	**Lonza ETI-204 16 mg/kg IV**	**Baxter ETI-204 16 mg/kg IV**	**Total No. of Subjects**
Time (hours) to bacteremia **N** **Mean (SD) [Range]**	17 38.8 (5.4) 28.3, 51.9	16 39.2 (5.6) 31.0, 53.1	16 39.2 (4.3) 32.3, 46.0	50 39.1 (5) 28.3, 53.1
Time (hours) to trigger (PA-ECL) **N** **Mean (SD)** **[Range]**	17 34.5 (5.5) [24.8, 48.5]	15* 34.1 (4.6) [27.1, 43.1]	17 35.1 (4.5) [28.4, 42.8]	49 34.6 (4.8) [24.8, 48.5]
Time (hours) from trigger to treatment **N** **Mean (SD)** **[Range]**	17 4.3 (0.8) [3.2, 6.2]	15* 4.2 (0.8) [3.2, 5.8]	17 4.2 (0.7) [3.3, 5.8]	49 4.3 (0.7) [3.2, 6.2]

*Animal C60822 did not have a positive PA-ECL and was not included in the calculations. This animal was bacteremic, it was treated at 54 hours and it survived.
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Deaths in Treatment and Placebo Arms during Study Period

One animal was found dead post-challenge before treatment. Twenty-two animals died in the test arms, 11 animals each in the obiltoxaximab/ Baxter and obiltoxaximab/ Lonza treatment groups. The 11(22%) survivors (6 animals in the Baxter group and 5 animals in the Lonza group) were sacrificed at the end of the study i.e., terminal sacrifice at Day 28.

Table 6.8. Study AP202: Deaths of Nonhuman Primates in Treatment and Placebo Arms

OUTCOME	Disposition Event	Baxter ETI-204, 16 mg/kg N=17	Control (Placebo), 0 mg/kg IV N=17	Lonza ETI-204, 16 mg/kg IV N=16	Subjects N=50
Survived	Terminal Sacrifice	6	0	5	11 (22%)
Died	Moribund Sacrifice	5	5	4	14 (27%)
	Found Dead	6	12	7	25 (50%)

Source: Table by constructed by clinical reviewer using JReview 9.2

Reviewer Comment: The first week post-challenge is the timeframe when the animals were expected to show signs of inhalational anthrax. Fifty percent of the macaques in the study were found dead in the first week post-challenge. The animals were monitored every six hours (per protocol) for the first eight days post-challenge therefore 50% appears to be a rather high percentage of animals that were found dead. One would expect more animals to be found moribund than found dead with a monitoring schedule at six hourly intervals. This finding indicates that once animals demonstrated clinical signs, many of them succumbed quickly to anthrax. Future study protocols should consider monitoring at intervals less than six hours apart to reduce suffering of infected animals.

Dose/Dose Response

Not applicable.

Durability of Response

A single dose of obiltoxaximab (Baxter or Lonza products) was effective in preventing death in 11 (33%) of the animals up to Day 28 (end of study) at which time these animals were terminally sacrificed per protocol.

Persistence of Effect

Obiltoxaximab provided persistent inhibition of PA and with no recurrence of bacteremia or signs of disease up to the end of the study, Day 28.

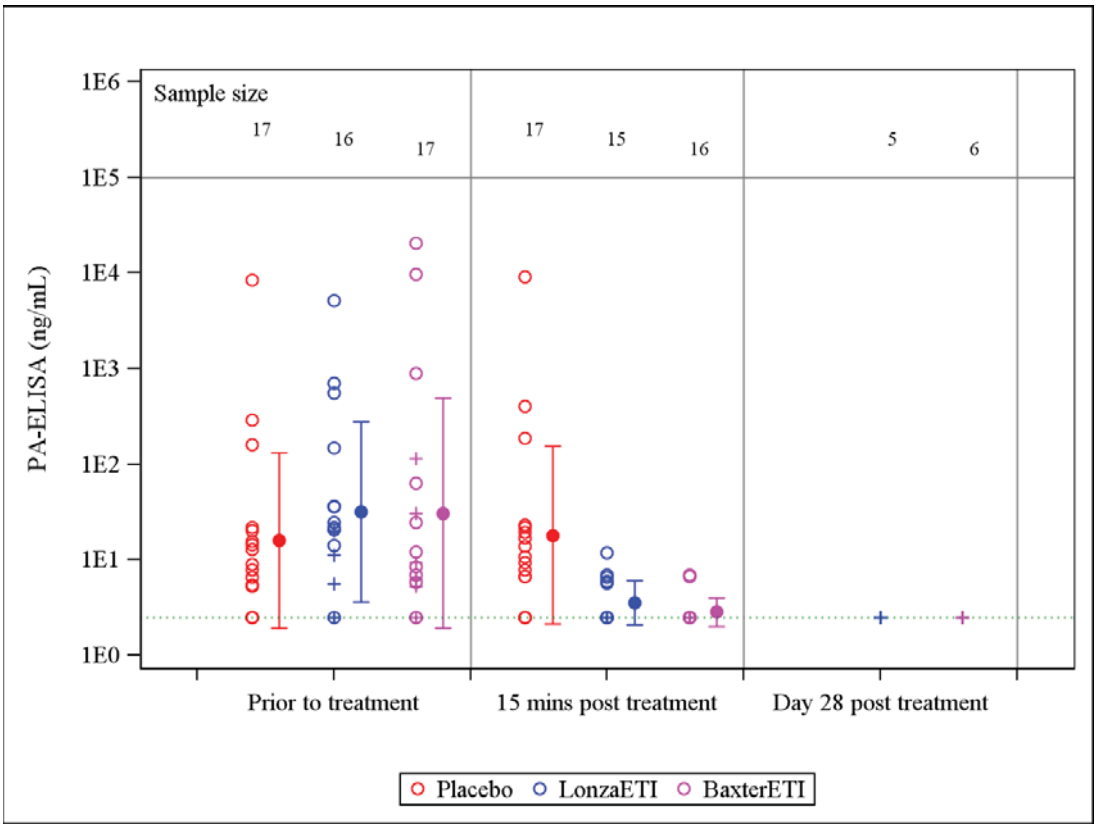
Additional Analyses Conducted on the Individual Trial

Protective Antigen Levels

PA levels were evaluated at intervals, i.e. prior to challenge, prior to treatment with obiltoxaximab or placebo, 15 minutes post treatment, and at Day 28. PA-ELISA levels over time by treatment group are plotted in Figure 6.3.

Prior to treatment, all animals had elevated levels of PA. At 15 minutes post treatment, PA levels decreased significantly for the two treatment groups and some animals already had a PA level below below the limit of detection (LOD). The placebo group had no reductions in PA levels.
PA levels increased over time in the placebo group and decreased over time in the obiltoxaximab- treated groups. At the end of the study, all survivors in the obiltoxaximab/Lonza and obiltoxaximab/Baxter treatment groups had PA levels below the LOD.

Figure 6.3. Study AP202: Protective Antigen over Time for Individual Animals

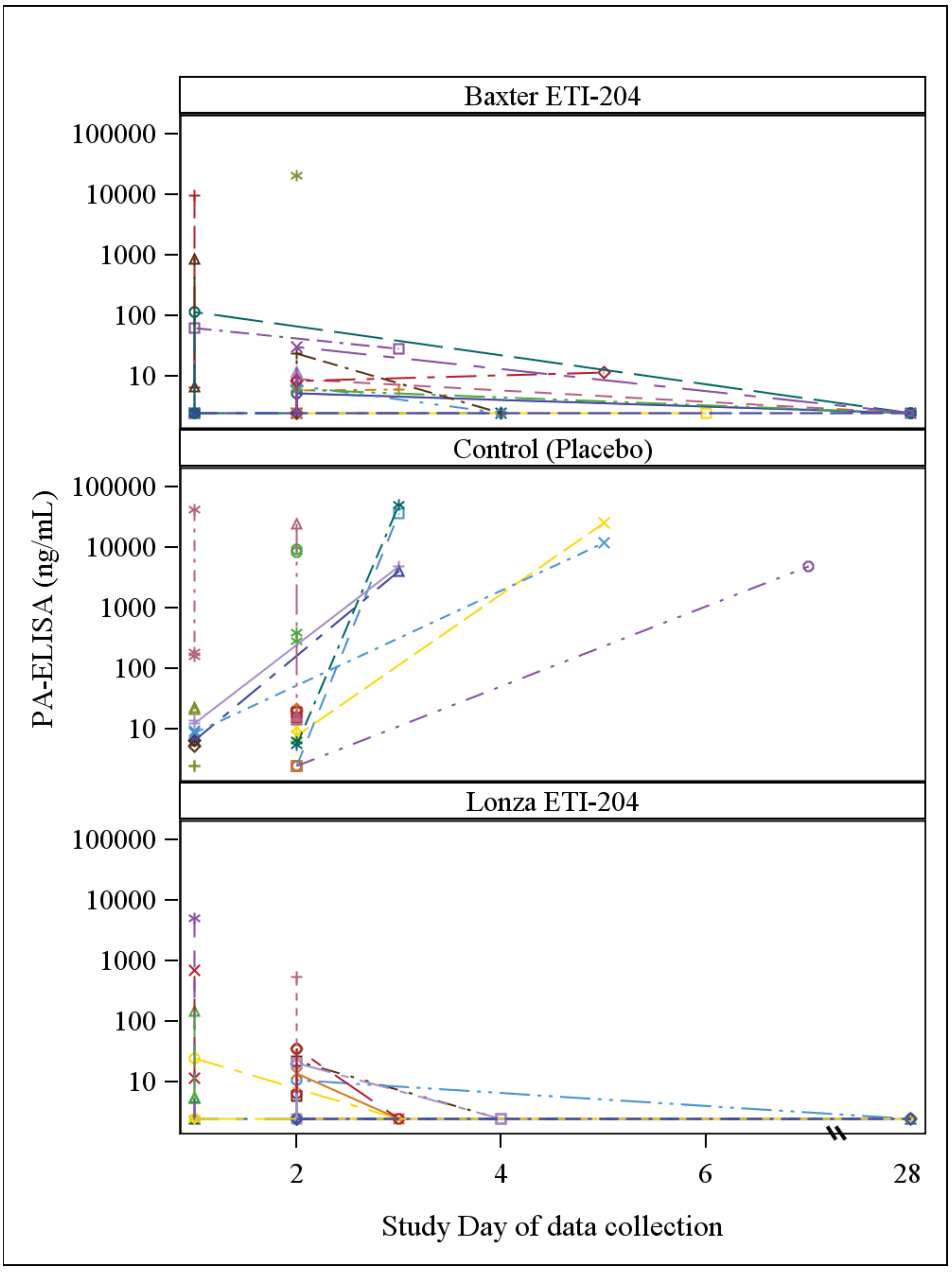


+ (plus sign) =survived to Day 28; o (circle) = died before Day 28. The dotted green line is the reference line for 2.5 ng/mL i.e., below the limit of detection of PA.

Note: There is overlap among the subjects for levels of protective antigen therefore discrete data points are not always visible on the graph. Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

PA levels measured by ELISA (PA-ELISA) levels for each animal over time starting from challenge are summarized in Figure 6.4. At Day 2 post-challenge, the PA levels reduced in the obiltoxaximab-treatment groups. The pattern was similar to the graph of bacteremia over time, Figure 6.5.

Figure 6.4. Study AP 202: PA-ELISA over time by Animal and Treatment Group

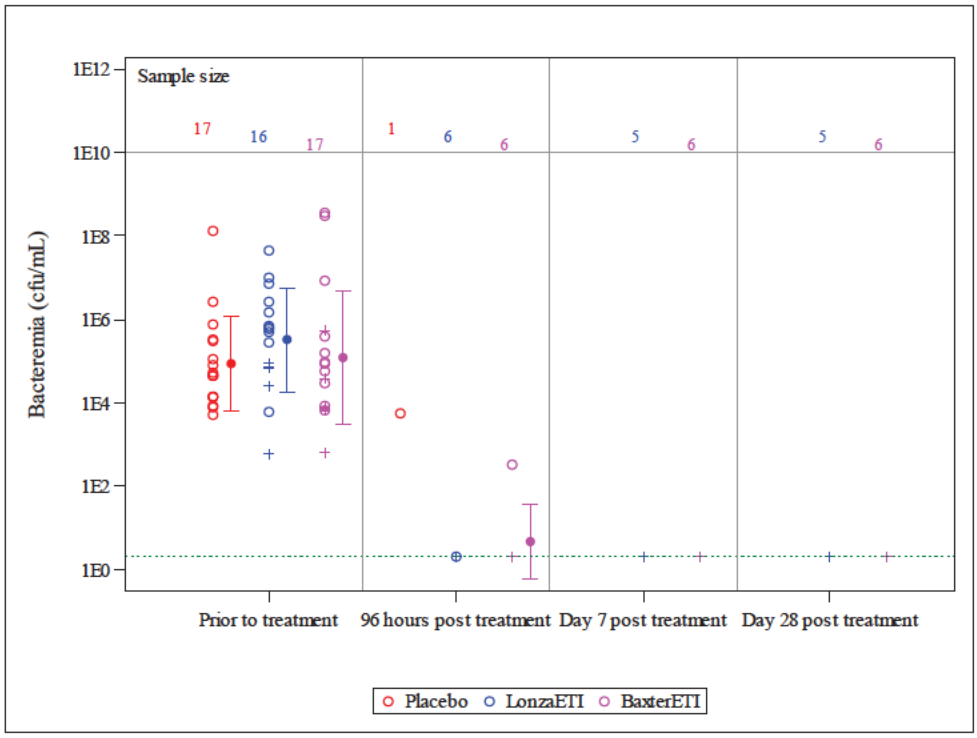


Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Bacteremia

Bacteremia levels (*geometric mean)* at selected time points by treatment group and survival status are summarized in Figure 6.5. Prior to treatment, bacteremia levels ranged from approximately 10^4 to > 10^8 CFU/mL. Levels of bacteremia decreased significantly by 96 hours post-treatment with obiltoxaximab and at seven days post to treatment, all surviving animals had negative blood cultures (below the LOD, 2 CFU/mL).

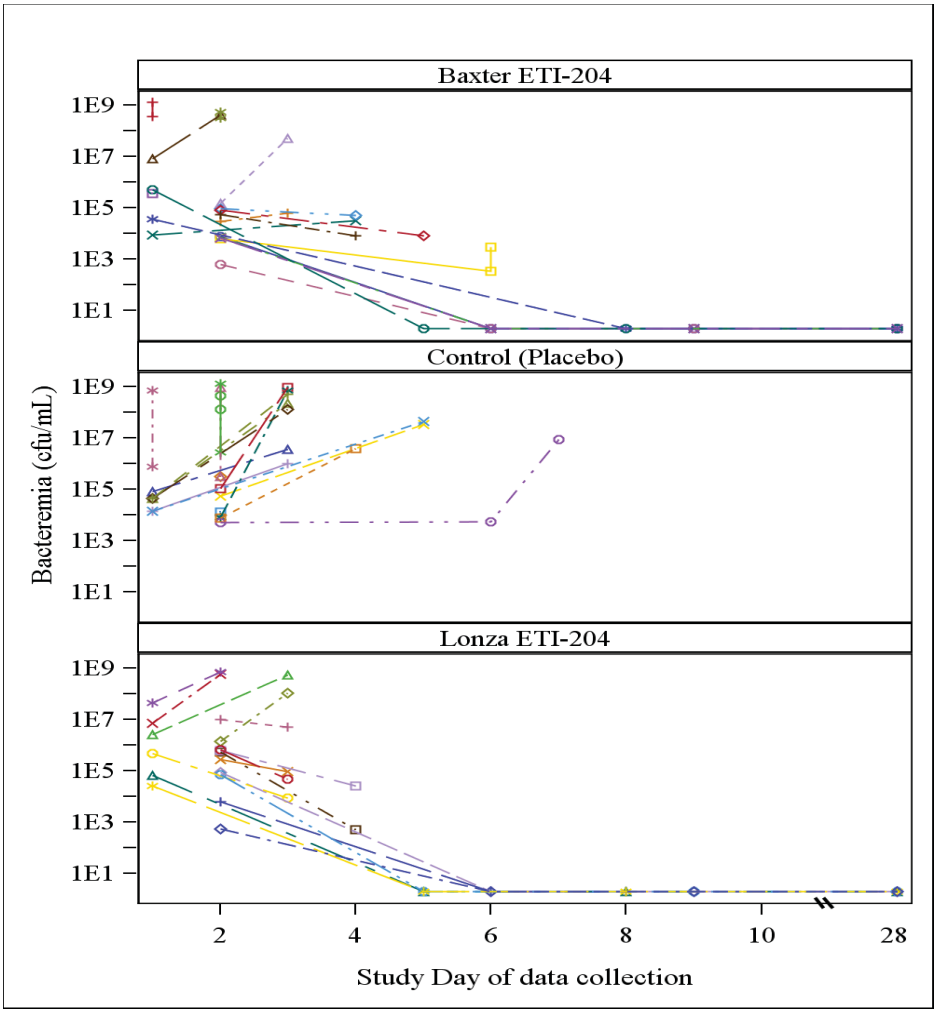
Figure 6.5. Study AP202: Bacteremia Levels by Survival Status to Day 28



+ (plus sign) =survived to Day 28; o (circle) = death before Day 28.
The dotted green line is the reference line for the lower limit of detection, 2 CFU/mL
Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Bacteremia levels (CFU/mL) for individual animals by treatment group are plotted against time up to Day 28, Figure 6.6. Animals in the placebo group had ongoing bacteremia until their death. Animals in the treatment groups had decreased levels of bacteremia over time after initiation of treatment with obiltoxaximab at approximately 39 hours or 1.6 days post-treatment.

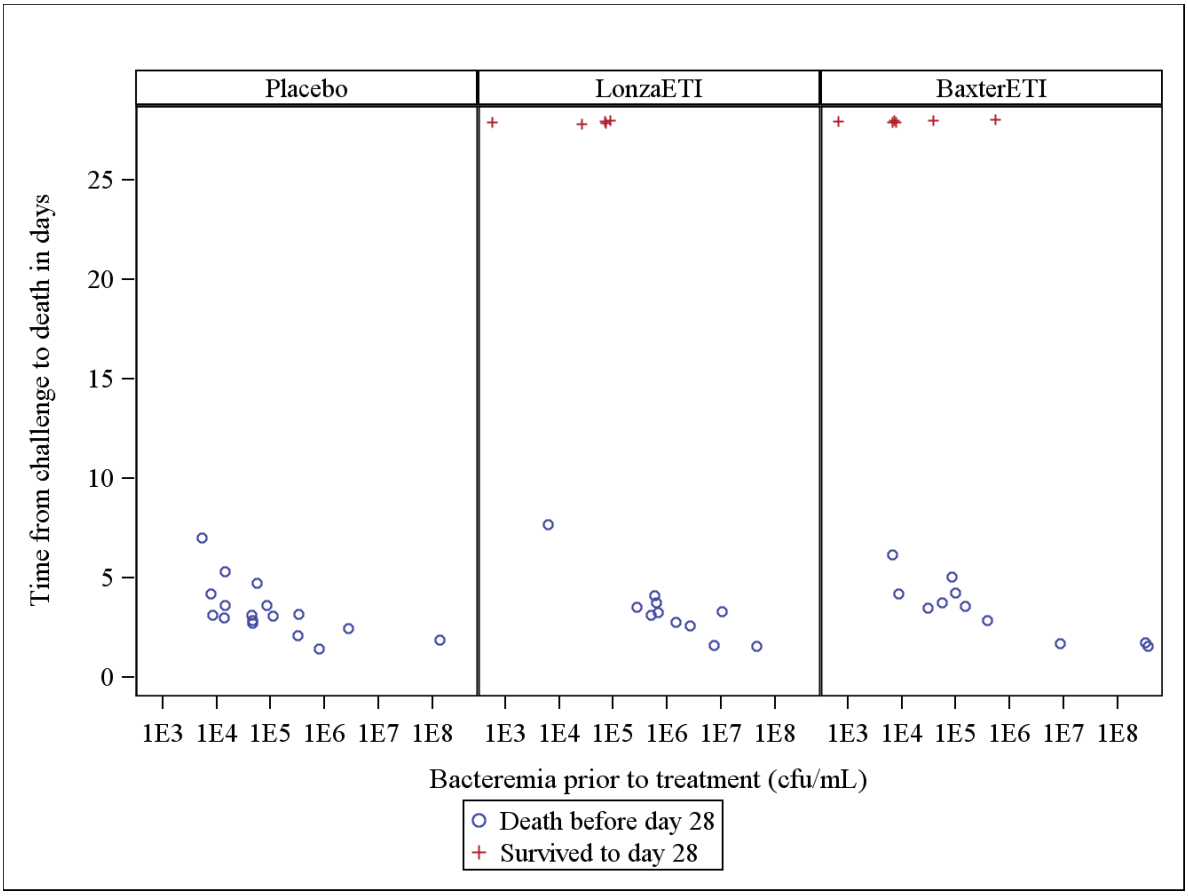
Figure 6.6. Study AP202: Bacteremia over Time by Animal and Treatment Group



This graph includes all available bacteremia data including terminal bacteremia. *Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Time to death versus bacteremia prior to treatment by treatment group and survival status up to Day 28 is summarized in **Figure 6.7**. Animals with the highest levels of bacteremia died earlier in the course of the study.

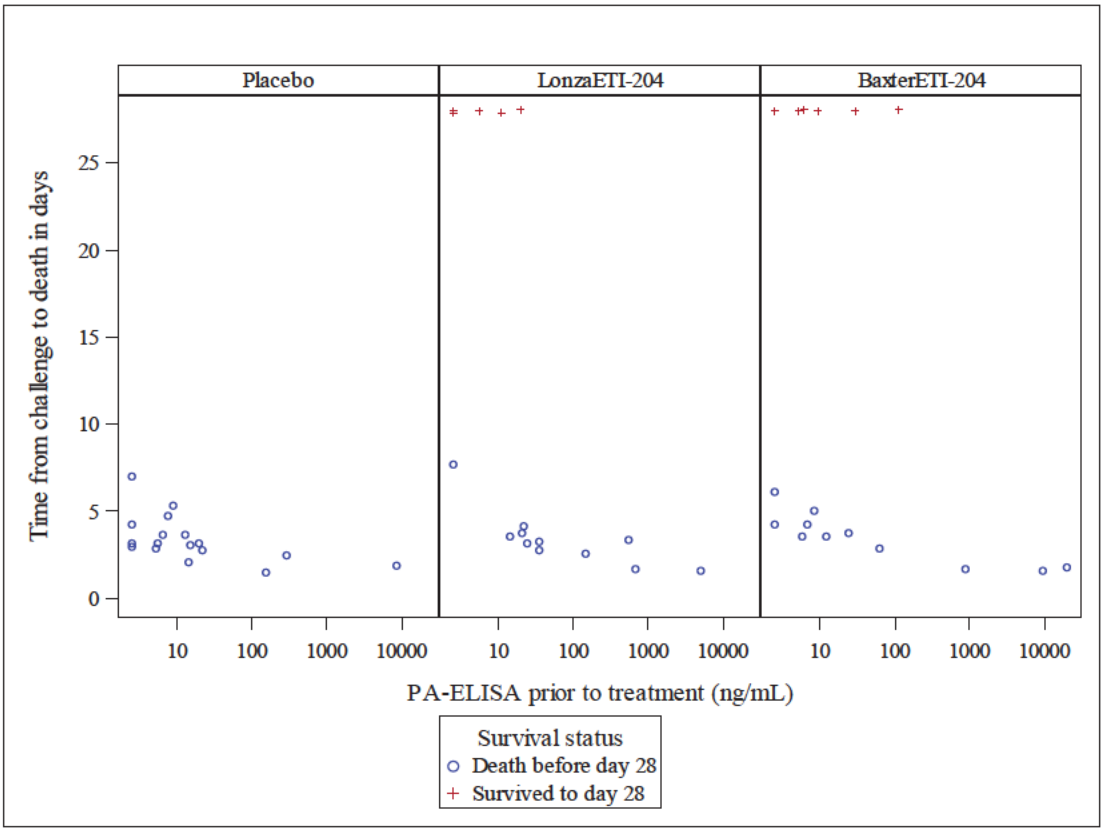
Figure 6.7. Study AP202: Time to Death versus Bacteremia PTT by Survival Status at Day 28



PTT: prior to treatment
Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Time to death versus protective antigen (PA) prior to treatment by treatment group and survival status up to Day 28 is summarized in Figure 6.8. In the two obiltoxaximab treatment groups, animals with a lower PA-ELISA level were more likely to survive to Day 28. Animals with the highest levels of PA died earlier in the course of the study. Animals with a PA-ELISA level greater than approximately 1,000 ng/mL died in the two treatment groups.

Figure 6.8. Study AP202: Time to Death versus PA-ELISA PTT by Survival Status at Day 28

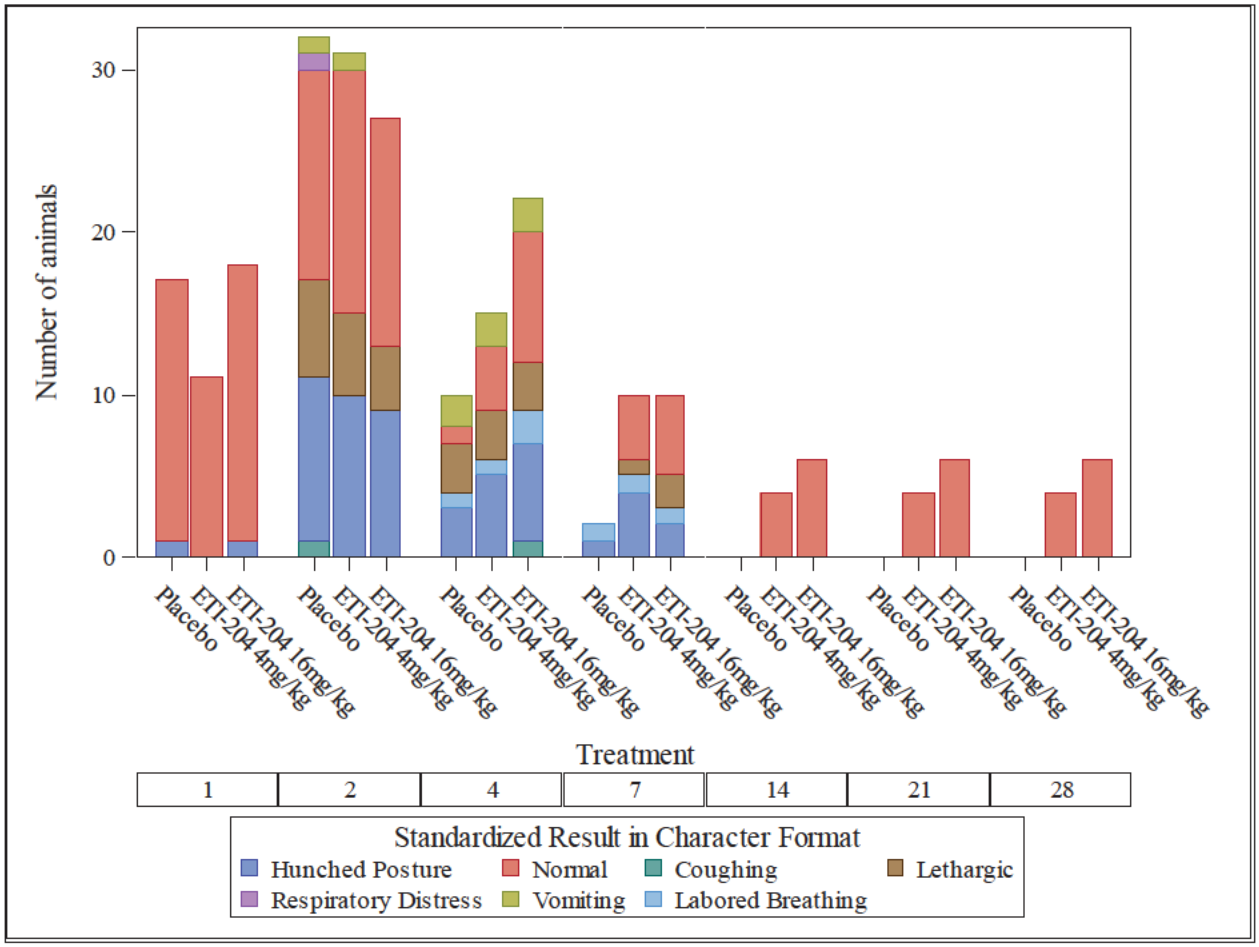


PTT: prior to treatment
Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Clinical Observations

In animals that survived to the end of the study, body weights on Day 28 were greater than or equal to body weights on Day 0. Stool abnormalities, respiratory abnormalities, lethargy, and hunched posture were noted in all challenged animals. Survivors cleared their clinical signs of disease such as coughing, vomiting, hunched posture, labored breathing, respiratory distress, by Day 14 post-challenge, Figure 6.9. In the obiltoxaximab-treated animals that survived to the end of the study, all abnormal clinical observations were no longer noted after Day 22 post-challenge. The Applicant noted that some animas did have sporadic stool abnormalities which are not uncommon in laboratory-housed nonhuman primates.

Figure 6.9. Study AP202: Clinical Observations in Animals Exposed to *B. anthracis*



Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph. D.

Survival at Day 28 by Gender, Challenge Dose, Bacteremia

The relationship between survival and challenge dose, bacteremia levels prior to treatment, and PA levels is summarized in Table 6.9. The target challenge inoculum was 200 LD_{50} *B. anthracis* spores. Animals received a mean inoculum of 250 LD_{50} *B. anthracis*. Eight macaques received less than 200 $LD_{50,}$ however, all these placebo animals were bacteremic and died from anthrax. High levels (arbitrary cut-off ≥ 10^4 cfu/mL) of bacteremia and PA (arbitrary cut-off ≥ 50ng/mL) were associated with decreased survival in the two treatment groups. The survival proportions in females in the two treatment groups were higher than in males, however, these differences were not statistically significant.

In the two obiltoxaximab treatment groups, high levels of bacteremia, and relatively high PA levels were associated with a lower survival rate. Results show that the level of bacteremia did not correlate with the size of the challenge dose [challenge dose was not correlated with bacteremia or PA-ELISA, with non-statistically significant correlation coefficients of 0.014 and

0.008, respectively]. These sample sizes were small and the Fischer's exact test did not demonstrate statistical significance (two-sided p-value =1).

Table 6.9. Study AP202: Survival at Day 28 by Gender, and Challenge Dose, Log_{10} Bacteremia, and PA Prior to Treatment

	Placebo (N=17)	Lonza ETI-204 16 mg/kg IV (N=16)	Baxter ETI-204 16 mg/kg IV (N=17)	All (N=50)
Gender				
Female	0/9	3/6 (50)	5/11 (45)	8/26 (31)
Male	0/8	2/10 (20)	1/6 (17)	3/24 (12)
Challenge dose (LD_{50}), n/N(%)				
<250	0/9 (0)	1/5 (20)	2/7 (29)	3/21 (14)
250 or higher	0/8 (0)	4/11 (36)	4/10 (59)	8/29 (28)
Bacteremia prior to treatment (cfu/mL) n/N (%)	0/3 (0) 0/12 (0) 0/17 (0)	1/2 (50) 4/9 (44) 0/5 (0)	4/6 (67) 2/8 (25.0) 0/3 (0)	5/11 (45) 6/29 (21) 0/10 (0)
PA-ELISA prior to treatment (ng/mL)				
0 - < 10	0/9 (0)	3/4 (75.0)	4/9 (44)	22 (44.0)
10 - < 50	0/5 (0)	2/8 (25.0)	1/3 (33)	16 (32.0)
50 or higher	0/3 (0)	0/4 (0)	1/5 (20.0)	12 (24.0)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Summary of Key Findings

Study AP202 was primarily designed to test the effect of the Lonza product versus placebo, but to also descriptively compare the Lonza product with the Baxter product. Obiltoxaximab manufactured at Lonza is the to- be-marketed product. The survival results indicate that Lonza and Baxter products demonstrate a similar significant treatment effect of obiltoxaximab compared to placebo in the cynomolgus macaque model of inhalational anthrax. The survival rate of 31% in the obiltoxaximab/Lonza 16 mg/kg IV group was statistically significantly higher than placebo (0%) at the end of the study, Day 28. The survival rate of 35% in the obiltoxaximab/Baxter 16 mg/kg IV group was statistically significantly higher than placebo (0%) at Day 28. Furthermore, the ONDQA reviewer concluded that there were no significant differences in the chemistry of the Lonza and the Baxter products. This study showed that severity of disease as measured by bacteremia and PA-ELISA affected the probability of surviving in the obiltoxaximab treatment arms. The results of study AP202 provide adequate evidence that the Baxter and Lonza products are the same and allow for studies that used the Baxter product to support the efficacy of obiltoxaximab.

6.2 Study AP203

6.2.1 Study Design

Overview and Objective

Study AP203 was a randomized, blinded, placebo-controlled, parallel group, trigger-to-treat, dose-ranging study of obiltoxaximab (manufactured by Lonza) in *B. anthracis*-challenged cynomolgus macaques.
The primary objective was to evaluate the efficacy of intravenous obiltoxaximab against lethality due to inhalational anthrax in cynomolgus macaques. The goal of this study was to evaluate the efficacy of a higher dose of obiltoxaximab (32 mg/kg) than the doses evaluated in prior studies (AP201 and AP204). Study AP203 was conducted at the (b) (4) in 2012.

Trial Design

The study design and primary endpoint were similar to prior studies, AP201 and AP204, therefore the protocol will not be discussed in detail. The target inhalational dose was 200 LD_{50} of *B. anthracis* (Ames strain) spores, the primary endpoint was survival at Day 28 i.e., end of study. The trigger for treatment was serum protective antigen (qualitative) by ECL assay. Animals were to be administered intravenous obiltoxaximab (0, 8, or 32mg/kg) within three hours of a positive PA-ECL, per protocol.
Forty-eight healthy cynomolgus macaques were randomized by weight into the three groups of 16 animals, each containing 50% males and 50% females: 16 animals in the placebo group (Group 1), 16 animals in the 8 mg/kg ETI-204 group (Group 2), and 16 animals in the 32 mg/kg ETI-204 group (Group 3). The 32 mg/kg dose was selected to determine if increasing the dose four-fold would increase the survival rate. The 8 mg/kg dose, used in prior studies, was selected to provide data on the consistency of obiltoxaximab in the treatment of inhalational anthrax. The three treatment groups are summarized in Table 6.11.

Table 6.10. Study AP203: Overview of Treatment Groups

Treatment Groups	No. of cynomolgus macaques	Obiltoxaximab/ETI-204 IV single dose	Description
1	16	0 mg/kg	Placebo (normal saline)
2	16	8 mg/kg	Obiltoxaximab
3	16	32 mg/kg	Obiltoxaximab

Study Endpoints

The primary endpoint is the proportion of animals that survived to Day 28 post-challenge with *B. anthracis* spores.

Study Schedule of Assessments

Blood cultures and PA-ELISA assays were performed on each animal at intervals pre- and post-challenge and up to and on the day of scheduled (Day 28) or unscheduled termination. The collections of samples were scheduled based on either post- treatment or post- challenge times. The inflammatory marker, C-reactive protein (CRP) was measured in this study, at baseline at Days 16, 23, 28 post challenge and, when possible, when the animal died.

Statistical Analysis Plan

Analysis Populations
There were three study populations defined in the protocol:
The protocol defined dataset (PDD) was based on the treatment animals received and excluded animals with a negative enriched blood culture prior to treatment.
The intent to treat (ITT) dataset included all challenged animals regardless of bacteremia status and excluded animals that died prior to treatment.
The modified intent to treat (mITT) dataset included animals that were positive for bacteremia at any time point prior to treatment and excluded animals that died prior to treatment.

The study director, applicant, microbiologists, pathologist, and technicians performing the dosing and all technicians assessing subjects were blinded to animals randomized to a group, challenge day, and challenge order. The primary efficacy endpoint, survival rate, was summarized in descriptive statistics (%; n/N with 95% confidence intervals) on the PDD population. For treatment group comparison, the survival data from each treatment group was compared to the control group using a one-sided Fisher's exact test (0.025 level) using a Bonferroni-Holm adjustment for multiple comparisons using the PDD dataset.

Reviewer Comment: No animals were excluded from this PDD population because all were bacteremic prior to treatment. This review used adjustment for multiple comparisons in the analysis of the survival endpoint.

Secondary analyses
Secondary analyses were the same as primary analysis but using mITT and ITT populations. No animals were excluded from mITT and ITT population, the PDD is the same as the ITT, therefore no secondary analyses were conducted for these two analysis populations.

Protocol Amendments

There were nine protocol amendments made during the study period. In protocol amendment #1, 50 replacement cynomolgus macaques were procured from the vendor because the original group was infected with parasites. Some protocol procedures had commenced in the original group of animals therefore an amendment was needed to include all the study activities which would take place with the replacement animals. Amendment #2 contained updates to the information on the test article with regard to storage conditions and shipment. Amendment#3 and #4 contained clarifications about the acceptance criteria for the PA-ECL assay. Amendment #5 contained an update on the location of testing facilities. Amendment #6 contained a minor update to the PA-ELISA standard operating procedure (SOP). Amendment #7 included an update in the statistical analysis plan. The statistical analysis used to analyze survival results was changed from a two-sided Fisher's exact test at the 0.05 level to a one-sided Fisher's exact test at the 0.025 level. The two-sided Fisher's exact test at the 0.05 level remained in the sample size justification because the Fisher's exact test was used to determine the power calculation for the number of animals to be used per group on study. Amendment #8 contained minor editorial changes. Amendment #9 noted that anti-drug antibody results would be reported in an amendment to the final study report.

6.2.2 Study Results

Compliance with Good Laboratory Practices

The Applicant submitted a statement that Study AP202 was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21CFR Part 58).

Patient Disposition

See demographics and baseline characteristics, **Table 6.11**.

Protocol Violations/Deviations

The protocol contained 37 reported deviations. The original animals procured for this study were infected with parasites therefore they were replaced with a new cohort of 50 cynomolgus macaques and an amendment was written to allow for replacement of the animals. Other deviations included occasional failure to record dates, inclusion of the wrong days of sample collection, or failure to perform clinical observations on time but animals were still observed four times per day. There were reported failures to document that the animals were acclimatized to chair restraint prior to challenge. Some terminal collection of blood samples were done after euthanasia and not prior to euthanasia as per protocol. There were some failures to record lot numbers of water and pipettes and to label correctly a PA-ELISA sample from one animal at 48 hours post-challenge and the sample was discarded.

Clinical Comment: These deviations do not appear to have impacted the conduct or integrity of the study.

Table of Demographic Characteristics

Baseline characteristics and demographic characteristics of the macaques in the three dose groups are described in **Table 6.11**. Animals (50% males, 50% females) of similar age and body weight were distributed evenly among each of the dose groups.

The mean challenge dose was 288 LD_{50} was similar across the three dose groups. Three animals received less than 200 $LD_{50,}$ one in each dose group, however, all animals were bacteremic post-challenge. All animals had a positive PA by ECL prior to therapy.

All animals (48, 100%) were bacteremic prior to treatment with obiltoxaximab. The mean bacteremia level and mean PA-ELISA level prior to treatment for all animals were 5.6×10^4 CFU/mL and 473 ng/mL, respectively. The obiltoxaximab 8 mg/kg dose group had a slightly higher mean bacteremia level = 1.19×10^5 and mean PA level = 865 ng/mL prior to treatment compared to the placebo and 32 mg /kg dose groups.

Table 6.11. Study AP203: Demographics and Baseline Characteristics

	Placebo (N=16)	**ETI-204 8 mg/kg IV (N=16)**	**ETI-204 32 mg/kg IV (N=16)**	**All Animals (N=48)**
Age (yrs) mean (SD) Range	4.4 (0.6) 3.0, 5.0	4.3 (0.6) 3.0, 5.0	4.4 (0.6) 3.0, 5.0	4.3 (0.6) 3.0, 5.0
Gender [n (%)]				
Male	8 (50%)	8 (50%)	8 (50%)	24 (50%)
Female	8 (50%)	8 (50%)	8 (50%)	24 (50%)
Body Weight kg Mean (SD) [Range]	3.88 (0.56) [3.00, 4.70]	3.83 (0.64) [2.9, 4.9]	3.99 (0.62) [3.0, 4.8]	3. 9 (0.6) [2.9, 4.9]
CHALLENGE DOSE				
Challenge LD_{50}				

Mean (SD) [Range]	294.6(76.7) [166, 462.0]	279.4 (59.2) [185.0, 430.0]	291.8 (79.7) [185.0, 430.0]	288 (71.2) [160.0, 462.0]
Challenge dose (LD_{50}) [n(%)] < 200 LD_{50}	1(6.3%)	1(6.3%)	1(6.3%)	3 (6.3%)
Challenge dose ($x10^7$ cfu) Mean (SD) Range	1.53 (0.33) [1.06, 1.97]	1.67 (0.34) [1.02, 2.49]	1.57(0.25) [1.13, 2.00]	1.59 (0.31) [1.02, 2.49]
BACTEREMIA				
Bacteremic (enriched) prior to treatment [n (%)]	16	16	16	48
Bacteremic (qualitative) prior to treatment [n (%)]	16 (100)	16 (100)	15(93.8)	48 (100)
Log_{10} Bacteremia cfu/mL Mean (SD) [Range]	4.77 (1.08) [3.21, 6.93]	5.07 (1.30) [3.26, 7.72]	4.67(1.29) [0.30, 6.61]*	4.84 (1.21) [0.30, 7.72]
Bacteremia prior to treatment (cfu/mL) Geometric mean 95% CI	$5.90x10^4$ ($1.57x10^4$, $2.21x10^5$)	$1.19x10^5$ ($2.42x10^4$, $5.83x10^5$)	$2.48x10^{4*}$ ($3.25x10^3$, $1.89x10^{5**}$)	$5.57x10^4$ ($2.24x10^4$, $1.39x10^5$)
PROTECTIVE ANTIGEN				
PA-ECL at Trigger, n(%)	16 (100)	16 (100)	16 (100)	48 (100)
No. of subjects n(%) with Positive PA-ELISA PTT	15 (94)	15 (94)	14 (87)	44 (92)
Log_{10} PA-ELISA PTT Mean (SD) [Range]	1.97 (0. 66)	2.22 (0.8)	2.14(0.6)	2.11(0.69)

	[1.2, 3.3]	[1.1, 3.9]	[1.2, 3.3]	[1.1, 3.9]
Positive with PA-ELISA, ng/mL PTT Geometric mean 95% CI Range	 93.32 40.1, 217.2 15.5, 1810	 166.34 59.8, 462.9 12.8, 8630	 137.22 61.5, 306.2 16.8, 2000	 128.48 79.3, 208.1 12.8, 8630
Positive PA-ELISA (ng/mL) PTT Mean (SD) [Range]	 320.0 (571.6) [15.5, 1810]	 864.5 (2174.9) [12.8, 8630]	 350.7 (563.7) 16.8, 2000]	 515.4 (1344.3) [12.8, 8630]

PA: Protective Antigen; PTT = prior to treatment
*C40915 was negative for bacteremia (quantitative). If this animal was excluded, the mean (SD) would to be 4.67 (1.29), range: 2.18, 6.61. Geometric mean was 4.64 $x10^4$ [95% CI: 8974, 239867].
The less than lower limit of detection (<LLOQ) equals 4.84 ng/mL (50% of the lower limit of detection equals 9.68 ng/mL).

Efficacy Results - Primary Endpoint

Survival to Day 28 post-challenge with *B. anthracis* was the primary endpoint for this study. The survival rates were 13% in the placebo group, 6% in the 8mg/kg, and 38% in the 32mg/kg obiltoxaximab groups. The survival rate in the 8 mg/kg dose group was lower than placebo. One animal C44168 (female) survived in the 8mg/kg dose group. In this animal, the inoculum of *B. anthracis* was 359 LD_{50} and the maximum PA level was 35.8ng/mL on Day 1. Blood cultures grew < 10 CFU /mL *B. anthracis* at 24 hours and 5.77 x 10^2 CFU/mL at 30 hours post-challenge and there were no subsequent blood cultures. In fact, there was no statistically significance difference in survival rates between any obiltoxaximab group and the control group, in all animals or in bacteremic only animals. Survival outcomes at Day 28 post-challenge are summarized in Table 6.12.

Table 6.12. Study AP203: Survival Outcomes in Cynomolgus Macaques at Day 28 by Treatment Group

Study AP203	**Placebo (Normal saline) N=16**	**Obiltoxaximab 8mg/kg IV N=16**	**Obiltoxaximab 32mg/kg IV N=16**
N (%)	2 (13)	1 (6)	6 (38)
Difference in survival Proportion [95% CI] *p-value* versus control*		0.887 [-32.9, 19.4] *0.761**	0.11 [- 6.5, 54.1] *0.064**
Adjusted exact 95% confidence interval		-0.358, 0.238	-0.114, 0.577
Including only quantitatively bacteremic animals			
N%	same	same as above	5/15 (33.3)
Difference in survival proportion [exact 95% confidence interval] one-sided p-value compared with control		same as above	0.208 [-0.104, 0.510] 0.104
Adjusted exact 95% confidence interval		same as above	0.148, 0.550

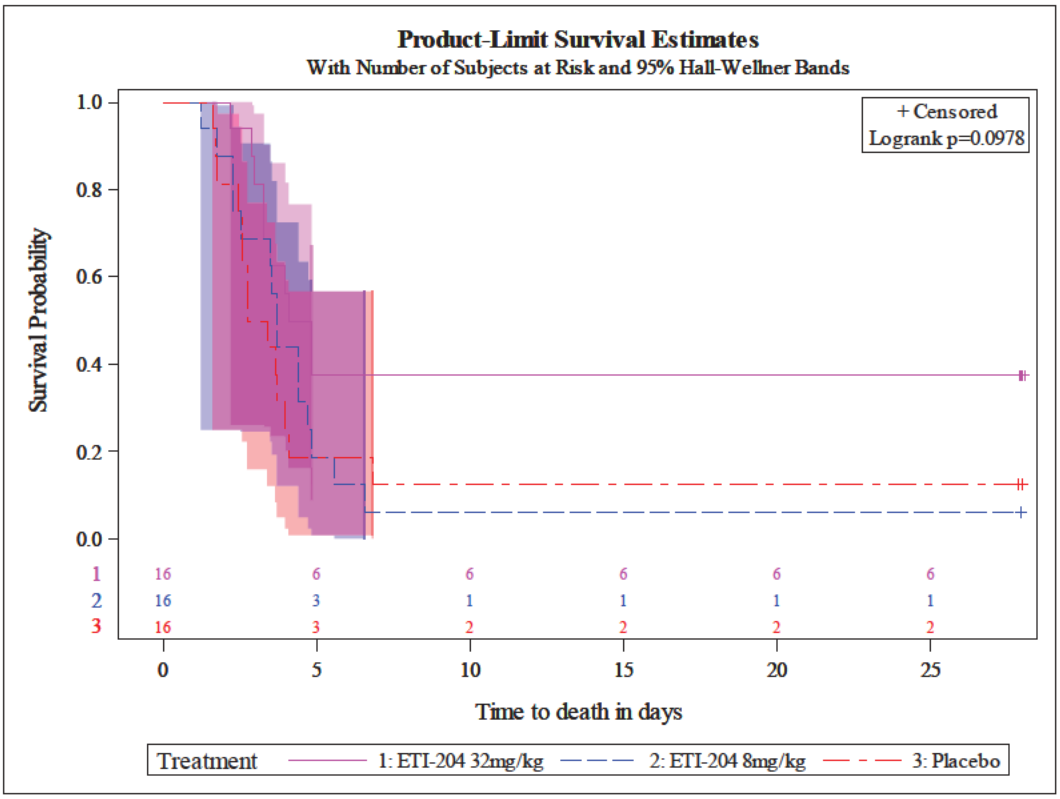
** Two-sided 95% confidence interval and one-sided p-values from Boschloo's test were calculated by the reviewer*

Source: Table 7 page 35 of study report AP203 and the biostatistics review by Xianbin Li, Ph.D.

Kaplan-Meier Graph

Kaplan-Meier estimates of survival for each treatment group from the time of challenge with *B. anthracis* to death are shown in Figure 6.10. There were no significant differences in survival among or between treatment groups. The placebo group had a shorter time to death compared to the group that received 32 mg/kg of obiltoxaximab.

Figure 6.10. Study AP203: Time to Death by Treatment Arm up to 28 Days Post-Challenge



Data Quality and Integrity - Reviewers' Assessment

The review of the study report did not reveal any issues of concern related to the integrity of the study data. This reviewer, in collaboration with the biostatistics reviewer, was able to replicate the reported survival results of the study using raw data in the study datasets.

Efficacy Results - Secondary and other relevant endpoints

A number of parameters were evaluated in an effort to explain the low survival rates in the obiltoxaximab treatment groups. Challenge doses were similar among dose groups, Table 6.11. The mean time from challenge to a positive protective antigen (trigger), time from trigger to treatment, and time to bacteremia were evaluated for the placebo, 8 mg/kg, and 32 mg/k dose groups and the results were similar for all the parameters tested. The mean bacteremia levels prior to treatment were slightly higher (bacterial load, 1.19×10^5cfu/mL) in the obiltoxaximab 8mg/kg group.

Table 6.13. Study AP203: Time from Challenge to Trigger (positive PA-ECL) and Treatment with Obiltoxaximab

Study AP203	Placebo (normal saline) (N=16)	Lonza ETI-204 8mg/kg IV (N=16)	ETI-204 32mg/kg IV (N=16)	All (N=48)
Time to bacteremia in hours Mean(SD) [Range]	29.98 (4.92) [22.65, 39.22]	28.34 (4.95) [22.2, 37.32]	30.56(5.32) [22.37, 40.97]	29.63(5.05) [22.2, 40.97]
Time to trigger (hours) Mean (SD) [Range]	33.3(4.7) [27.9, 45.1]	33.4 (4.2) [28.5, 42.7]	32.5 (5.5) [22.8, 45.5]	33.1 (4.7) [22.8, 45.5]
Time (hours)to randomized ETI-204 treatment Mean (SD) [Range]	37.1(4.2) [32.4, 47.4]	37.5(4.0) [32.6, 46.5]	36.2(5.2) [26.3, 47.5]	37(4.4) [26.3, 47.5]
Time from trigger to treatment (hours) Mean (SD) [Range]	3.8(0.6) [2.3, 4.7]	4.1(0.4) [3.4, 4.8]	3.8(0.7) [1.9, 5.0]	3.9(0.6) [1.9, 5.0]

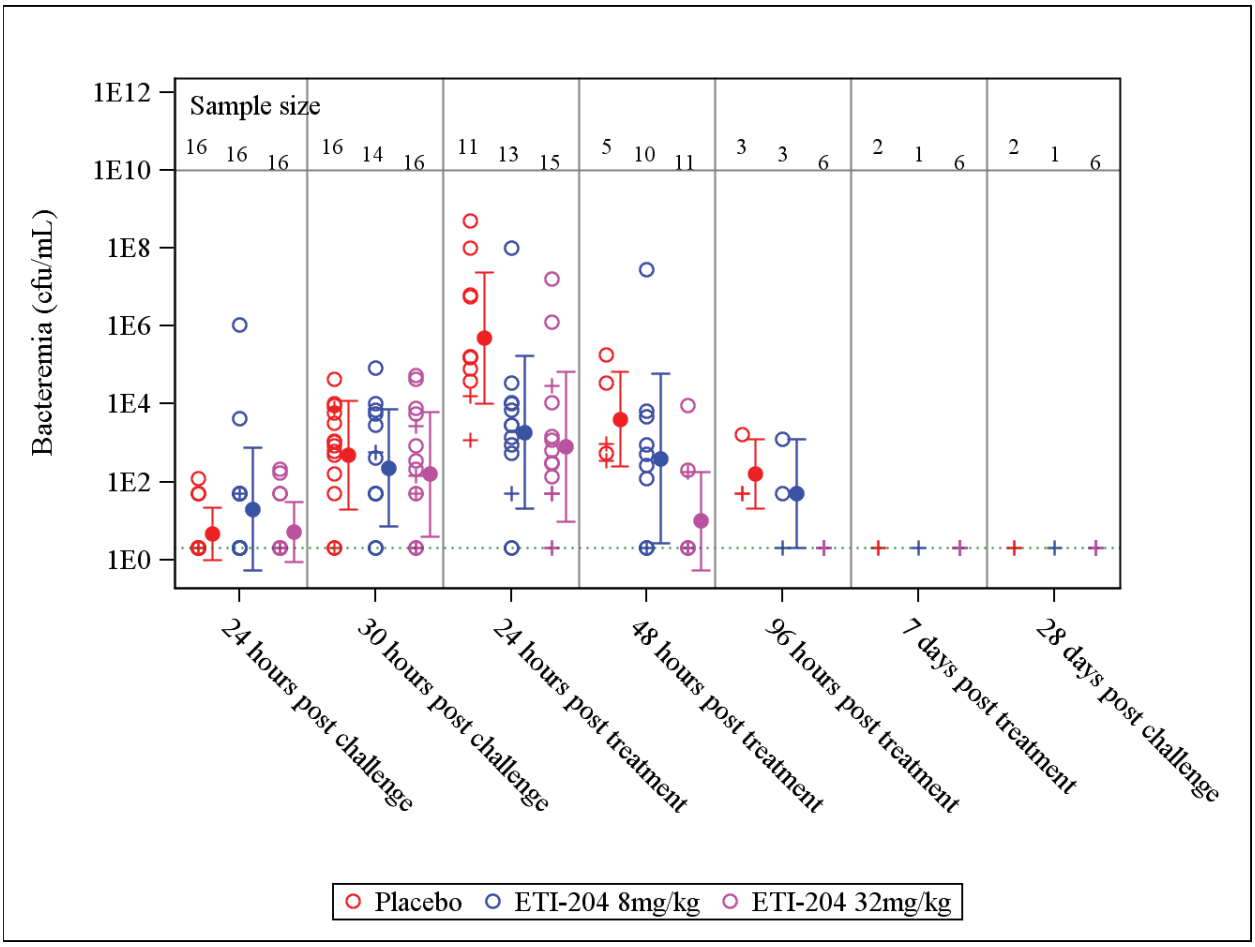
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Bacteremia

Mean bacteremia levels peaked at 24 to 36 hours post treatment and began to decline at 48 to 96 hours post treatment. However, the majority of animals died (open circles in graph, Fig. 14) between 24 to 96 hours post-treatment.

Five animals had positive blood cultures for *B. anthracis* at 96 hours post treatment, two in the placebo group (1 survivor), and three (1 survivor) in the obiltoxaximab 8 mg/kg group. The nine surviving animals (included two placebo animals) had negative blood cultures after Day 7 post-treatment and remained negative through Day 28. Mean bacteremia levels (geometric mean ± standard deviation) in animals post-challenge are plotted for each of the treatment arms and by survival status.

Figure 6.11. Study AP203: Bacteremia Levels* Post challenge by Treatment Arm and Survival



**Geometric mean ± standard deviation; + = survivor; o = dead animal; Bacteremia: limit of detection (LOD) = 3cfu/mL B. anthracis.*

Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Comparison of time from challenge to death between treatment groups

The p-values from pairwise log-rank tests comparing time from challenge to death between treatment groups are shown in

Table 6.14. The p-value for the comparison of 32 mg/kg group and the placebo group was statistically significant at the significance level of two-sided 0.05 with no multiple comparison adjustment. However, with a Bonferroni adjustment for multiple comparisons (using a two-sided significance level of 0.05/2=0.025), none of the observed differences were statistically significant.

Table 6.14. Study AP203: Two-sided p-values of pairwise log-rank tests comparing time from challenge to death between groups

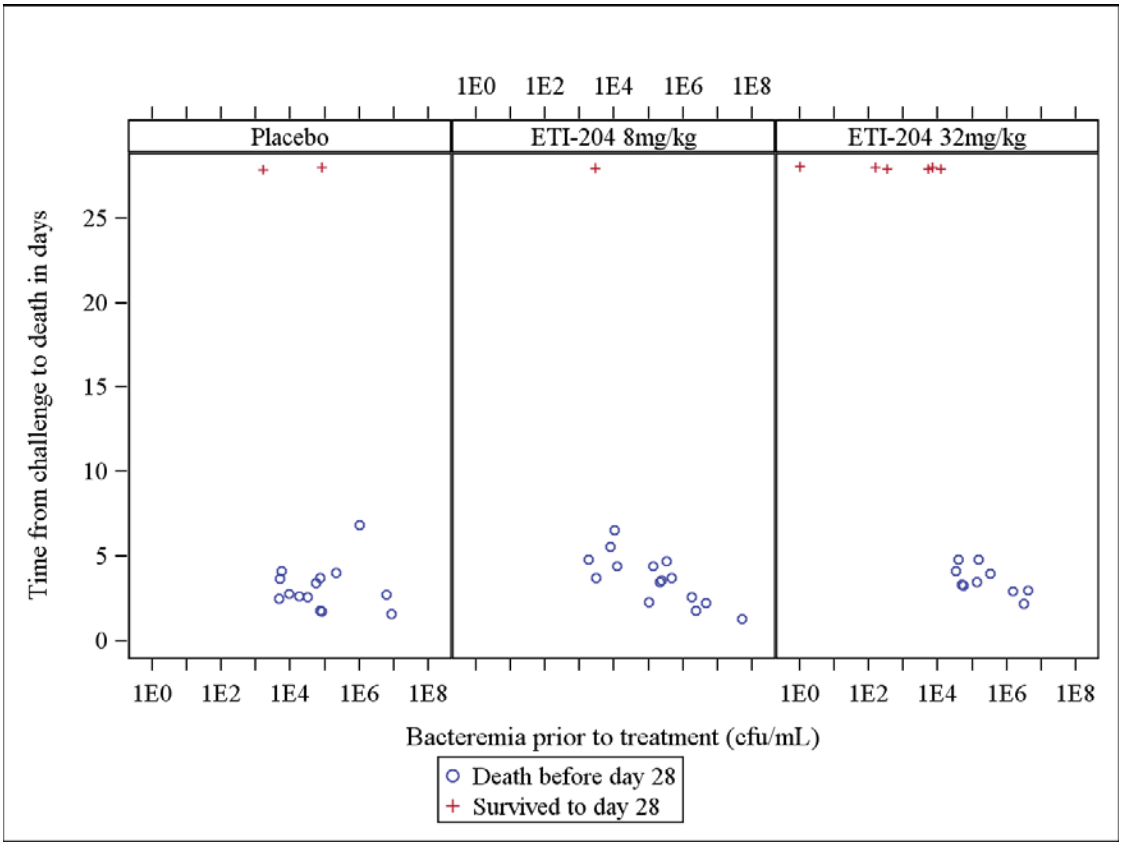
	ETI-204 8 mg/kg IV (N=16)	ETI-204 32 mg/kg IV (N=16)
Placebo	0.817	0.044
ETI-204 8mg/kg	-	0.083

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Time to death

Time to death for each animal that was bacteremic at baseline is plotted in Figure 6.12. Macaques that died (open circles) had higher bacteremia levels prior to treatment compared to bacteremia levels in survivors (+ sign). The analysis showed that a higher bacteremia level was associated with a lower survival probability. Animals with low bacteremia levels prior to treatment were more likely to survive to Day 28.

Figure 6.12. Study AP203: Time to Death versus Bacteremia prior to Treatment by Survival Status at Day 28

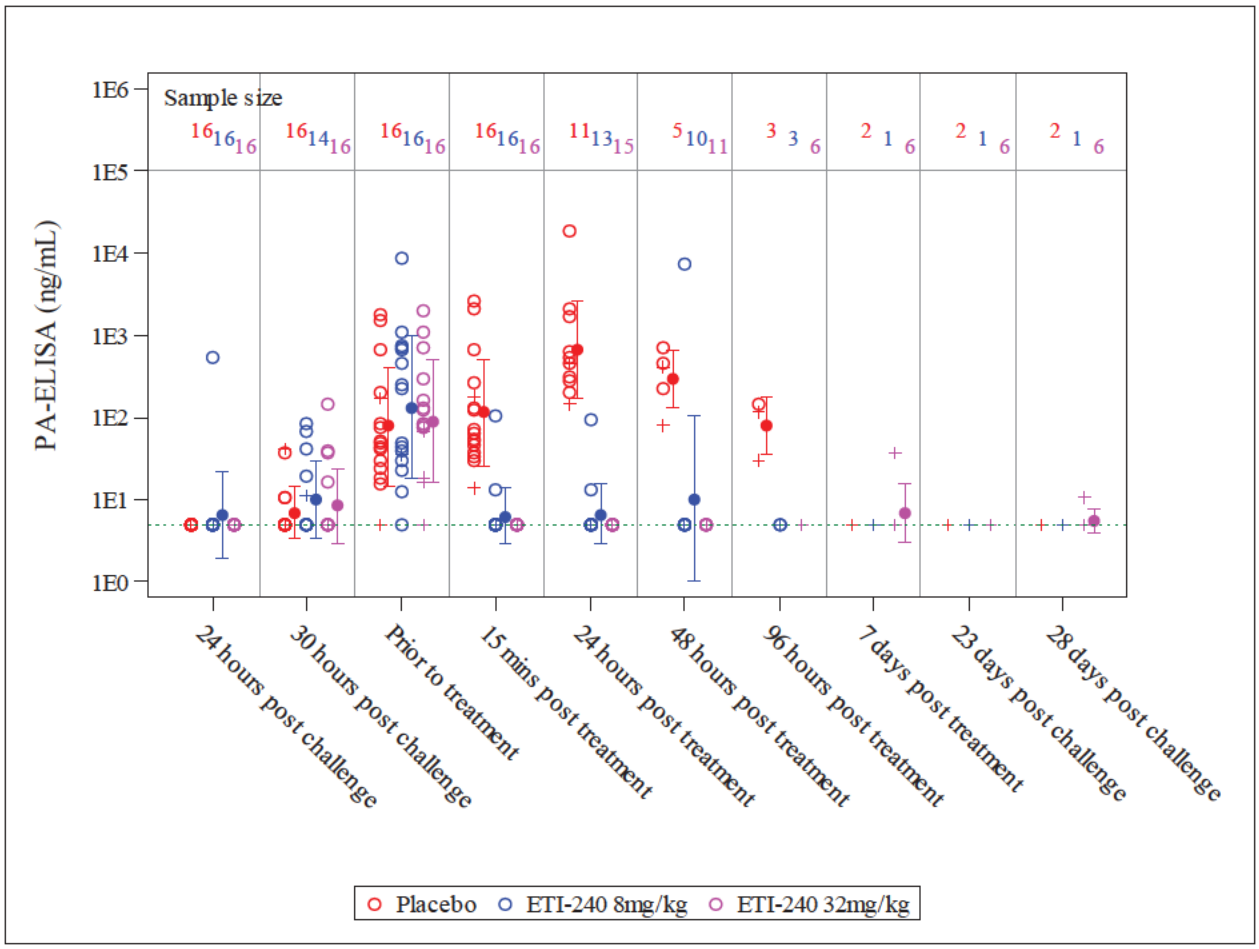


Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Protective Antigen

Mean PA-ELISA levels (ng /mL) by treatment arm during the study are shown in **Figure 6.13**. Protective antigen levels peaked as 15 minutes post treatment and then declined over time to below the LOD for all animals by Day 7. There was one exception, Animal C48922, in Group 3 had a PA level of 72 ng/mL, and levels declined below the LLOQ until Day 7 post-treatment; however, a subsequent blood sample was positive with a PA 305 ng/mL, followed by PA of 37 ng/mL at Day 16 and a PA below the LLOQ at Day 23. The animal (survivor) had positive blood cultures at 36 hours and remained negative for bacteremia from 48 hours through Day 28 post challenge, therefore the PA-ELISA levels may be false positive.

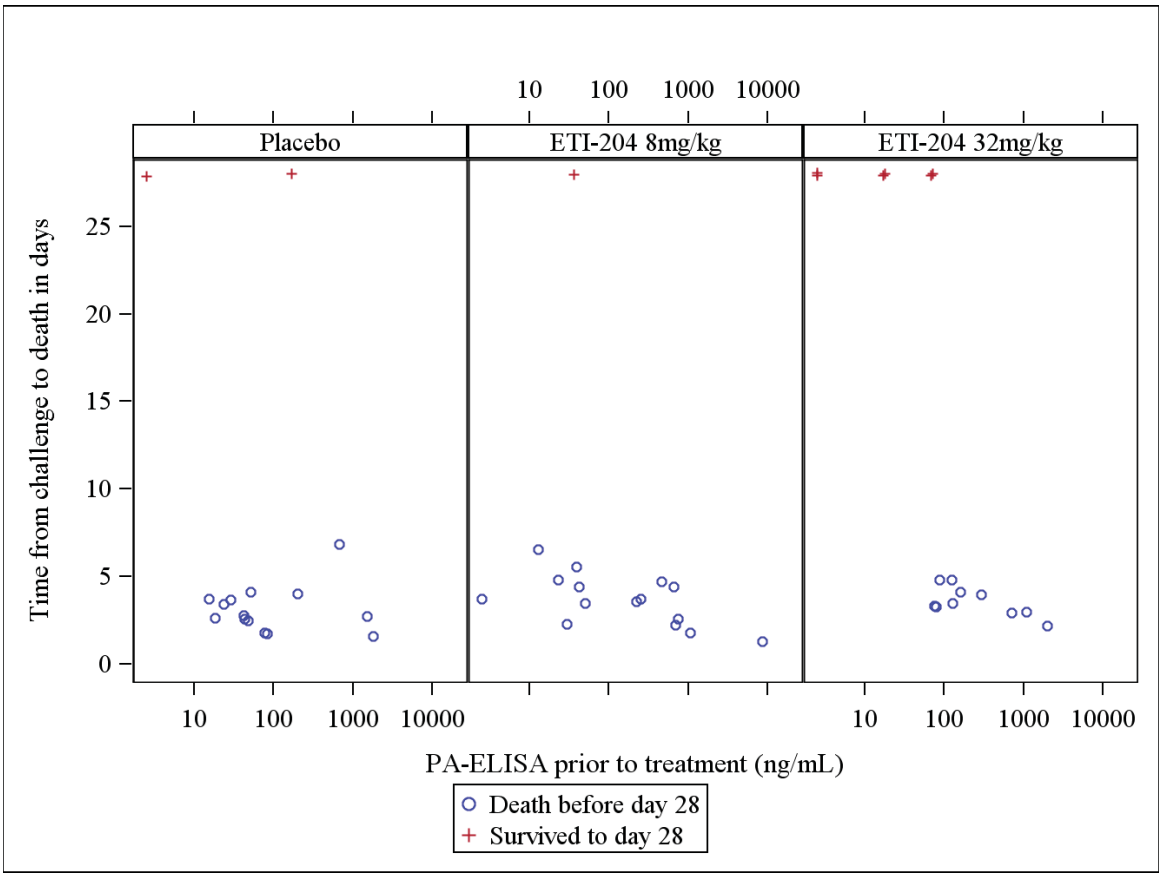
Figure 6.13. Study AP203: PA ELISA Levels Post challenge by Treatment Arm over 28 days



Source: Graph constructed by statistical reviewer, Xianbin Li, Ph.D.

Animals that died during the study had higher mean PA levels prior to treatment compared to survivors, **Figure 6.14**. Animals with lower PA-ELISA levels were more likely to survive.

Figure 6.14. Study AP203: Time to death versus PA-ELISA PTT by Survival Status at Day 28



PTT: prior to treatment; Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

The odds ratio of survival at Day 28 associated with treatment and bacteremia PA-ELISA prior to treatment are shown in **Table 6.15**. The high correlation coefficient between $\log_{10}$ PA-ELISA and $\log_{10}$ bacteremia did not allow inclusion of both variables in the same model. The analysis demonstrated that bacteremia and PA- ELISA were associated with a lower survival probability.

Table 6.15. Study AP203: Estimated odds ratio of survival at Day 28 associated with treatment and bacteremia or PA-ELISA PTT from logistic regression on survival

Covariate	Odds ratio	95% confidence interval	p-value
Model 1			
ETI-204 8 mg/kg	0.323	0.02, 5.98	0.1360
ETI-204 32 mg/kg	8.276	0.51, 133.20	0.4478
Log_{10} bacteremia prior to treatment	0.055	0.005, 0.621	0.0189
Model 2			

ETI-204 8 mg/kg	0.436	0.025, 7.744	0.5717
ETI-204 32 mg/kg	8.642	0.876 85.229	0.0648
Log_{10} PA-ELISA prior to treatment	0.094	0.016, 0.571	0.0101

PTT: prior to treatment. Significant p-values in red text. Source: Table constructed by the biostatistics reviewer, Xianbin Li, Ph.D.

Dose Response

There was no observed dose response in the study.

Persistence of Effect

Obiltoxaximab provided persistent inhibition of PA and with no recurrence of bacteremia or clinical signs in the nine survivors up to the end of the study, Day 28.

Additional Analyses Conducted on the Individual Trial

There were 39 (81%) deaths and 9 (19%) survivors in the study and 25/32 (78%) deaths occurred in the 8mg/kg and 32mg/kg groups Deaths included animals that were found dead or were sacrificed moribund. Twenty-two (46%) of the animals in this study were found dead during the study even though animals were being monitored every six hours for clinical signs of anthrax from Day 1 through Day 8.

Table 6.16. Study AP203: Survival Outcomes in Treatment and Placebo Arms

OUTCOMES	Placebo (Saline) N=16	8mg/kg ETI-204 N=16	32 mg/kg ETI-204 N=16	All Subjects N=48
DEATHS	**12 (29%)**	**15 (31%)**	**10 (21%)**	**39 (81%)**
Found Dead	10 (21%)	5 (10%)	7 (15%)	22 (46%)
Moribund Sacrifice	4 (8%)	10 (21%)	3 (6%)	17 (35%)
SURVIVORS	**2 (4%)**	**1 (2%)**	**6 (13%)**	**9 (19%)**

Source: Table constructed by clinical reviewer using JReview 9.2

Reviewer Comment: The proportion of animals found dead (46%) appears high when animals had scheduled monitoring every six hours. A similar proportion of animals were found dead (50%) in Study AP202. The interval of monitoring in future studies should be decreased to avoid unnecessary suffering in animals.

Survival status by gender, challenge dose, bacteremia, and PA level are summarized in **Table 6.17**. Because of small sample sizes, the effect of each grouping variable on survival was inconclusive.

Table 6.17. Study AP203: Survival at Day 28 by Gender, Challenge Dose, log_{10} Bacteremia, PA Prior to Treatment

	Placebo (N=16)	ETI-204 16 mg/kg IV (N=16)	ETI-204 32 mg/kg IV (N=16)	All (N=48)
Gender				
Female	0/8	2/8 (25.0)	1/8 (12.5)	3/24 (12.5)
Male	2/8 (25.0)	4/8 (50.0)	0/8	6/24 (25.0)
Challenge dose (LD_{50})				
<250	1/5 (20)	0/5	2/6 (33.3)	3/16 (18.8)
250 or higher	1/11 (9.1)	1/11 (9.1)	4/10 (40.0)	6/32 (18.8)
Log_{10} bacteremia prior to treatment				
$< 10^4$	1/5 (20)	1/4 (25.0)	5/5 (100)	7/14 (50.0)
10^4 - $<10^6$	1/9 (11.1)	0/8	1/8 (12.5)	2/25 (8.0)
10^6 or higher	0/2	0/4	0/3	0/9
PA prior to treatment (ng/mL)				
0 - < 10	1/1 (100.0)	0/1	2/2 (100)	3/4 (75.0)
10 - < 50	0/7 (0)	1/7 (14.3)	2/2 (100)	3/16 (18.8)
50 or higher	1/8 (12.5)	0/8	2/12 (16.7)	3/28 (10.7)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Survivors in Study AP203

The challenge doses, bacteremia levels, and PA levels prior to treatment in the nine survivors in Study AP203 are summarized in Table 6.18 . All the survivors were bacteremic prior to treatment and six had positive PA levels prior to treatment. Both of the surviving animals in the placebo group received greater than 200 LD_{50} of *B. anthracis* spores. Animal C49041 (placebo) had a negative blood culture at 24 hours post-challenge. The scheduled blood culture at 30 hours post-challenge grew 7.8 x 10^3 CFU/mL of *B. anthracis* and there were no subsequent positive blood cultures. Maximum PA level was 466ng/mL, (LOD = 9.68ng/mL), on Day 2 post-challenge. Animal C49058 (placebo) had negative blood culture at 24, 30, and 36 hours post-challenge. Blood cultures grew *B. anthracis*: 1.1 x 10^2 CFU/mL at 42 hours and 1.4 x 10^3 CFU/mL at 48 hours post-challenge. Maximum PA level was 142ng/mL, (LOD = 9.68ng/mL), on Day 1 post-challenge. Both of the animals underwent terminal sacrifice at Day 28. Blood cultures in both animals became negative at Day 7 through the end of the study. Post mortem tissue cultures (brain, spleen, lung, liver, kidney, and bronchial lymph node) were negative except for a brain tissue sample from Animal C49041 grew 1 to 5 colonies of *B. anthracis*.

Reviewer Comment: All animals in the study were naïve. As in all the nonhuman primate and rabbit studies, animals did not receive any supportive care such as supplemental oxygen or IV fluids. Anti-PA IgG levels were not measured in the study so it is not known if the survivors in the placebo group had protective antibodies against B. anthracis.

Table 6.18. Study AP203: Bacteremia and PA levels Prior to Treatment in Survivors

Unique Subject ID	*B. anthracis* Inoculum LD_{50}	Bacteremia (CFU/mL) PTT	PA (ng/mL) PTT
C40067	269	1.53×10^2	17.9
C40915*	220	(positive by enrichment)	< LLOQ
C44168	359	2.87×10^3	35.8
C47894	430	5.23×10^3	< LLOQ
C47896	285	1.20×10^4	68.1
C48903	280	3.33×10^2	16.8
C48922	226	6.90×10^3	72.0
C49041 (placebo)	205	8.13×10^4	168
C49058 (placebo)	315	1.64×10^3	< LLOQ

PTT: Prior to Treatment. Lower Limit of Detection, (<9.98ng/mL); *C40915 had no bacteremia count cfu/mL prior to treatment, however, enriched bacteremia prior to treatment was positive.

Summary of Key Findings

Study AP203 failed to show a survival benefit over placebo of the obiltoxaximab 8mg/kg and 32mg/kg doses. The 8mg/kg dose in this study had a lower survival rate than placebo. There was no statistically significance difference in survival rates between any obiltoxaximab group and the control group, in all randomized animals or in bacteremic animals. The high mean levels of bacteremia and PA toxin prior to treatment were related to the low survival rate in the obiltoxaximab groups.

6.3 Study AP204

6.3.1 Study Design

Overview and Objective

Study AP204 was a randomized, blinded to group, placebo-controlled, parallel-group, trigger to treat, dose-ranging study in *B. anthracis*-challenged cynomolgus macaques. The study was conducted at the (b) (4) in 2010.
The primary objective of this study was to evaluate the efficacy of a single IV bolus dose of obiltoxaximab 4 or 16 mg/kg IV compared to placebo to prevent lethality in cynomolgus macaques with inhalational anthrax..
The secondary objective was to perform expanded microscopic evaluations of brain and meningeal tissues for non-surviving and surviving nonhuman primates as well as neurological examinations pre-study, at Day 28, and Day 56 post-challenge.

Trial Design

The trial design was similar to studies AP202 and AP203. The animals were challenged on study Day 0 with a target dose of 200 LD_{50} *Bacillus anthracis* (Ames strain) spores. Animals were randomized (prior to challenge) by body weight into one of the three groups of 16 animals (with each group containing 8 males and 8 females), then randomized to one of three aerosol challenge days (16 animals per day), and finally randomized to a challenge order per day, Table 6.19. A positive PA-ECL was the trigger for treatment. Animals that did not have a positive serum PA-ECL screening assay result after obtaining results at the 54 hours post challenge time point, were treated.

Table 6.19. Study AP204: Study Design

Group	ETI-204 Dose	No. of cynomolgus macaques	Description
X	0 mg/kg IV	16	Placebo/Saline
Y	4 mg/kg IV	16	ETI-204
Z	16 mg/kg IV	16	ETI-204

Study Endpoints

The primary endpoint was survival of the treatment groups (4mg/kg or 16 mg/kg) versus the control group (saline) at Day 28 or at Day 56.

Statistical Analysis Plan

Analysis Populations

There were three populations in the primary analysis:

- Excluding animals that were not positive for bacteremia by culture prior to treatment and including animals that died prior to treatment as treatment failures. This population was for the primary analysis.
- Including all challenged animals. This was for a secondary analysis.
- Including only those animals that received treatment. However since all challenged animals survived to receive treatment, this population was the same as all challenged animals.

Primary Analysis
The survival data from each treatment group was compared to the control group using a one-sided Fisher's exact test (0.025 level). In the primary analysis, the sponsor excluded animals that were not bacteremic by culture prior to treatment.

Protocol Amendments

Protocol amendment #1 referred to the blood samples for blood cultures; this change clarified that for the two blood samples, one is plated as a neat sample and the other one should be diluted and then plated. Amendment # 2 clarified how the right brain hemisphere tissue samples should be prepared and stored for current and future histopathological and immunohistochemistry examinations. It also clarified that the stability testing of ETI-204 bulk drug substance was to be performed at (b) (4) Amendment #3 added additional information on the stability studies. Amendment #4 clarified that spinal cords would undergo microscopic evaluation because the comprehensive microscopic evaluation of the cynomolgus macaque brains performed in the study provided enough data justifying spinal cord evaluations. In protocol amendment #5, the sponsor identified an alternative facility for doing ETI-204 for pharmacokinetics, at (b) (4). The Applicant requested additional analysis to determine the relationship between quantitative bacteremia and PA ELISA assay results. Protocol amendments #6 and #7 referred to the saving of blood samples for potential future use to detect circulating PA in the "total" PA-ELISA when this assay becomes available and brain tissue for potential future use in the event the specialized staining /immunohistochemistry is required. The statistical analysis used to analyze survival results was changed from the two-sided Fisher's exact test at the 0.05 level to a one-sided Fisher's exact test at the 0.025 level.
Protocol amendments #8 and #9 referred to personnel management changes at the (b) (4) and minor changes to the laboratory analyses. In amendment #10, the Applicant noted that anti-drug antibody results are not currently available for the samples collected in Study AP204; therefore, the Applicant plans to report the result when it is available in an amendment to the final study report.

Reviewer Comment: The amendments did not make substantial changes to the original protocol.

6.3.2 Study Results

Compliance with Good Laboratory Practices

The Applicant submitted a statement that Study AP204 was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21CFR Part 58).

Patient Disposition

See demographics, Table 6.20.

Protocol Violations/Deviations

Protocol deviations reported by the Applicant were evaluated by the clinical reviewer for significant impact on the conduct of the study. The majority of the deviations that occurred were related to occasional failures of verification of documentation by technicians at (b) (4). Technicians where required to review the standard operating procedures SOPs for each part of the study in which deviations occurred.

Reviewer Comment: These violations did not appear to impact the integrity of the study.

Table of Demographic and Baseline Characteristics

Demographic and baseline characteristics characteristics of the macaques in the three dose groups are described in Table 6.20. Animals (50% males, 50% females) of similar age and body weight were distributed evenly among each of the dose groups. The mean challenge dose was 212 LD_{50}. A total of 47 (98%) macaques were bacteremic prior to treatment, PA was positive in 46 (96%) monkeys by PA-ECL and 41 (71%) animals by PA-ELISA prior to treatment. Animal C43303, in the 16 mg/kg dose group, had negative blood cultures and PA levels below the LLOQ, at all study time points.

Table 6.20. Study AP204: Demographic Variables and Baseline Characteristics by Treatment

	Placebo (N=16)	**ETI-204 4 mg/kg IV (N=16)**	**ETI-204 16 mg/kg IV (N=16)**	**All (N=48)**
Age (years)				
Mean (SD)	3.1 (0.2)	3.0 (0.2)	3.1 (0.2)	3.0 (0.2)
Range	2.6, 3.3	2.7, 3.3	2.8, 3.3	2.6, 3.3
Gender [n (%)]				
Male	8 (50.0)	8 (50.0)	8 (50.0)	24 (50.0)
Female	8 (50.0)	8 (50.0)	8 (50.0)	24 (50.0)
Body weight (kg)				
Mean (SD)	2.8 (0.3)	2.8 (0.2)	2.8 (0.2)	2.8 (0.2)
Range	2.3, 3.5	2.5, 3.3	2.5, 3.3	2.3, 3.5
Challenge dose (LD_{50})				
Mean (SD)	220.1 (49.2)	207.4 (34.7)	209.2 (47.0)	212.2 (43.5)
Range	136.0, 327.0	155.0, 279.0	136.0, 325.0	136.0, 327.0
Challenge dose (LD_{50}), n(%)				
<200	6 (37.5)	7 (43.8)	7 (43.8)	20 (41.7)
200 or higher	10 (62.5)	9 (56.3)	9 (56.3)	28 (58.3)
BACTEREMIA				
Bacteremia enriched prior to treatment (n(%))	16 (100.0)	16 (100.0)	15 (93.8)	47 (97.9)
Bacteremia - prior to treatment (cfu/mL)				
N	16	16	16*	48
Geometric mean	12287	14649	3139	9082
95% confidence interval	3344, 45140	4954, 43320	606, 16271	4276,19290
Mean (SD) of $\log_{10}$ bacteremia	4.09 (1.06)	4.17 (0.88)	3.50 (1.34)	3.92 (1.13)
PROTECTIVE ANTIGEN				
PA-ECL at Trigger (n(%))	16 (100.0)	16 (100.0)	14 (87.5)	46 (95.8)
PA-ELISA (ng/mL) -prior to Treatment				
Geometric mean	38.1	60.7	31.0	41.6
95% confidence interval	18.6, 78.2	36.5, 101	15.8, 60.9	29.3, 59.1
Mean (SD) of $\log_{10}$ PA-ELISA	1.58 (0.59)	1.78 (0.41)	1.49 (0.55)	1.62 (0.53)

PTT: prior to treatment;
*Excluded one animal C43303 with no evidence of bacteremia.

Efficacy Results - Primary Endpoint

Survival results for the placebo, 4 mg/kg and 16 mg/ kg dose groups are summarized in **Table 6.21**. The survival rate was 6% (1/16) in the placebo group, 25% (4/16) in the 4 mg/kg group, and 50% (8/16) in 16 mg/kg group. There was no significant difference in survival between the obiltoxaximab 4 mg/kg group and the placebo group. There was a significant difference in

survival rate between the obiltoxaximab 16 mg/kg group and placebo in all animals and in bacteremic animals. In this study, all randomized animals received treatment, so the mITT population includes all animals.

Table 6.21. Study AP204: Survival at Day 28 by Treatment Group

	Placebo (N=16)	ETI-204 4 mg/kg IV (N=16)	ETI-204 16 mg/kg IV (N=16)	All (N=48)
Includes all animals				
N (%)	1 (6.3)	4 (25.0)	8 (50.0)	13 (27.1)
Difference in survival proportion [exact 95% CI] one-sided p-value compared to placebo		0.188 [-0.090, 0.473] 0.1077	0.438 [0.113, 0.703] 0.0036	
Excludes one animal without bacteremia prior to treatment				
N (%)		Same as above	7 (0.467)	
Difference in survival proportion [exact 95% CI] one-sided p-value compared to placebo		Same as above	0.404 [0.089, 0.681] 0.0058	

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

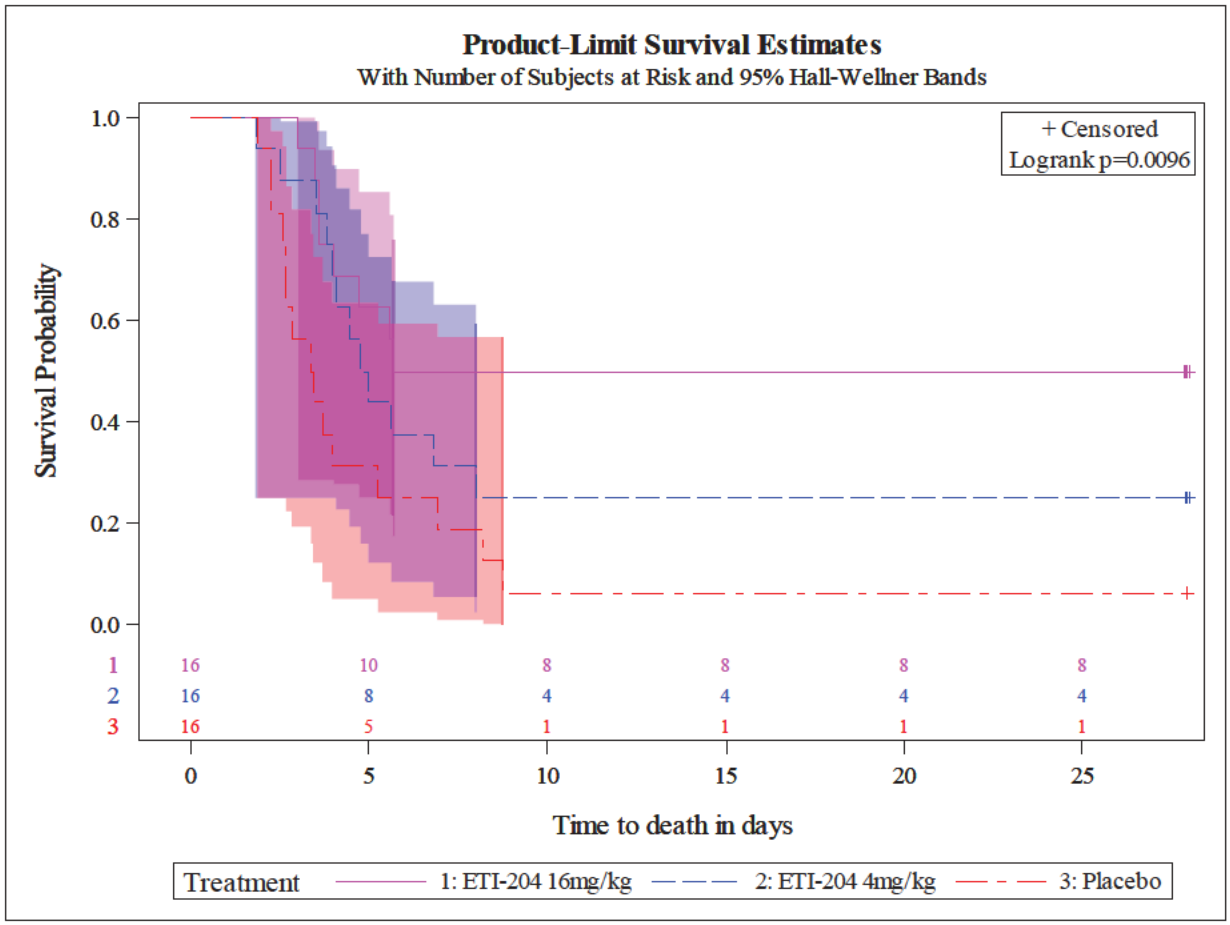
The survivor in the placebo group, Animal C42861, had anthrax disease and it survived to Day 28. It had a positive blood culture for *B. anthracis* and PA levels prior to treatment which resolved and became negative without treatment in four days. Survival was probably related to the animal's innate immunity to *B. anthracis*. Blood cultures were negative at 24 hours post-challenge and the cultures initially grew *B. anthracis* 1 to 5 colonies in the primary streak at 30 hours. At 36 hours post-challenge, quantitative bacteremia was 6.27 x 10^2 cfu/mL and was 1.34 x 10^2 cfu/mL *B. anthracis* at 48 hours post challenge. Blood cultures were < 10 CFU/mL at 96 hours post treatment. Blood cultures became negative on Day 4, and remained negative through Day 28. Maximum C-reactive protein (CRP) was 2.21 mg/dL at 16 days post-challenge and CRP dropped to 0.82 mg/dL at Day 28. Serum PA-ECL was positive prior to treatment. PA-ELISA, was positive at 6 and 24, 48 hours post-treatment and then became negative through Day 28.

Kaplan-Meier Graph

Kaplan-Meier estimates of survival for each treatment group from the time of challenge with *B. anthracis* to death are displayed in Figure 6.15. The survival rate in the obiltoxaximab4mg/kg group vs. the placebo was not statistically significant, p-value 0.096 from a log-rank test. The

comparison of survival rates in the 16 mg/kg group vs. the placebo group was statistically significant, p-value = 0.003.

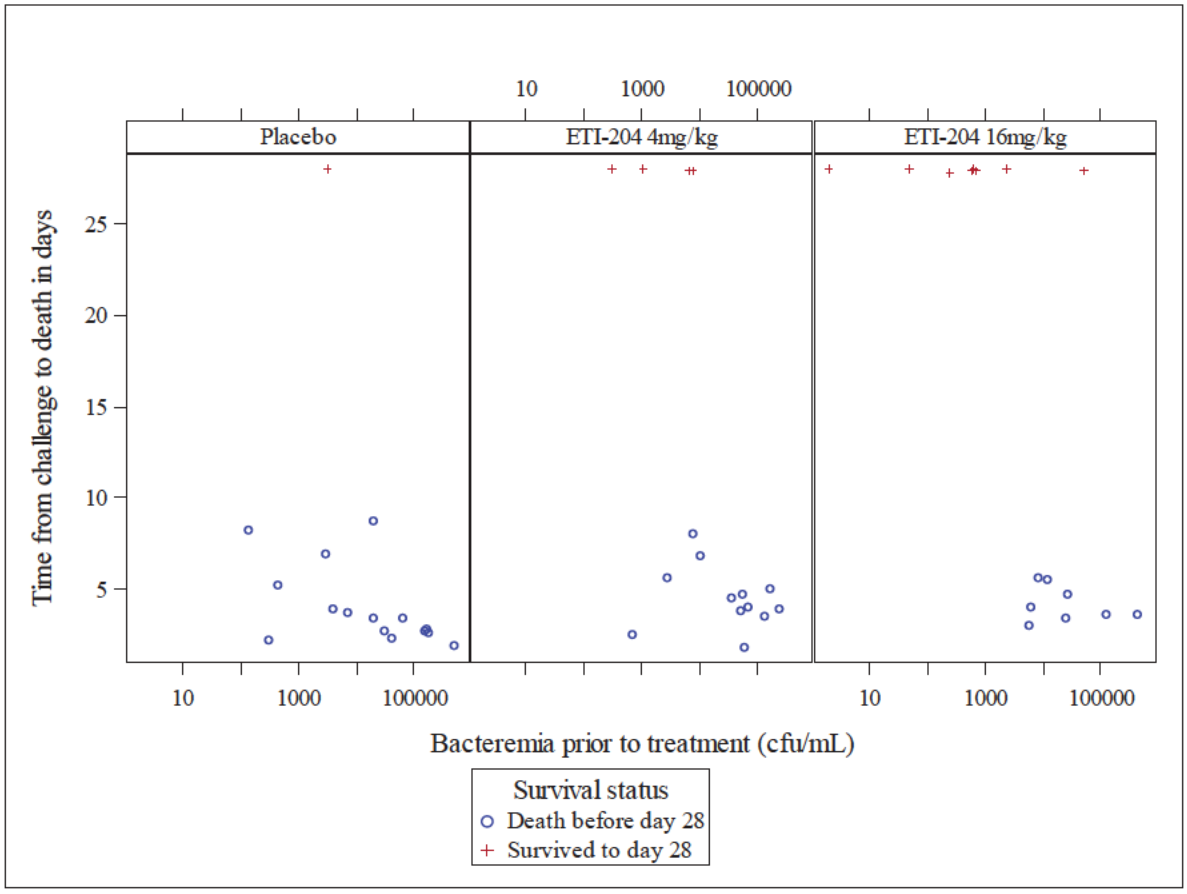
Figure 6.15. Study 204: Kaplan Meier Survival Curve of ETI-204 versus Placebo



This graph includes one surviving animal without bacteremia prior to treatment in the ETI-204 16mg/kg group. P-values calculated using (two-sided significance level of 0.025, using the Bonferroni adjustment method for multiple comparisons). *Source: K-M curve constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

High levels of bacteremia prior to treatment were associated with a shorter time to death post challenge. Animals with bacteremia > 10^4 cfu/mL died within five days post-challenge in all treatment groups, **Figure 6.16**. Some animals in the 16mg/kg dose group survived with bacterial loads at higher concentrations ≥ 10^5 CFU/mL prior to treatment.

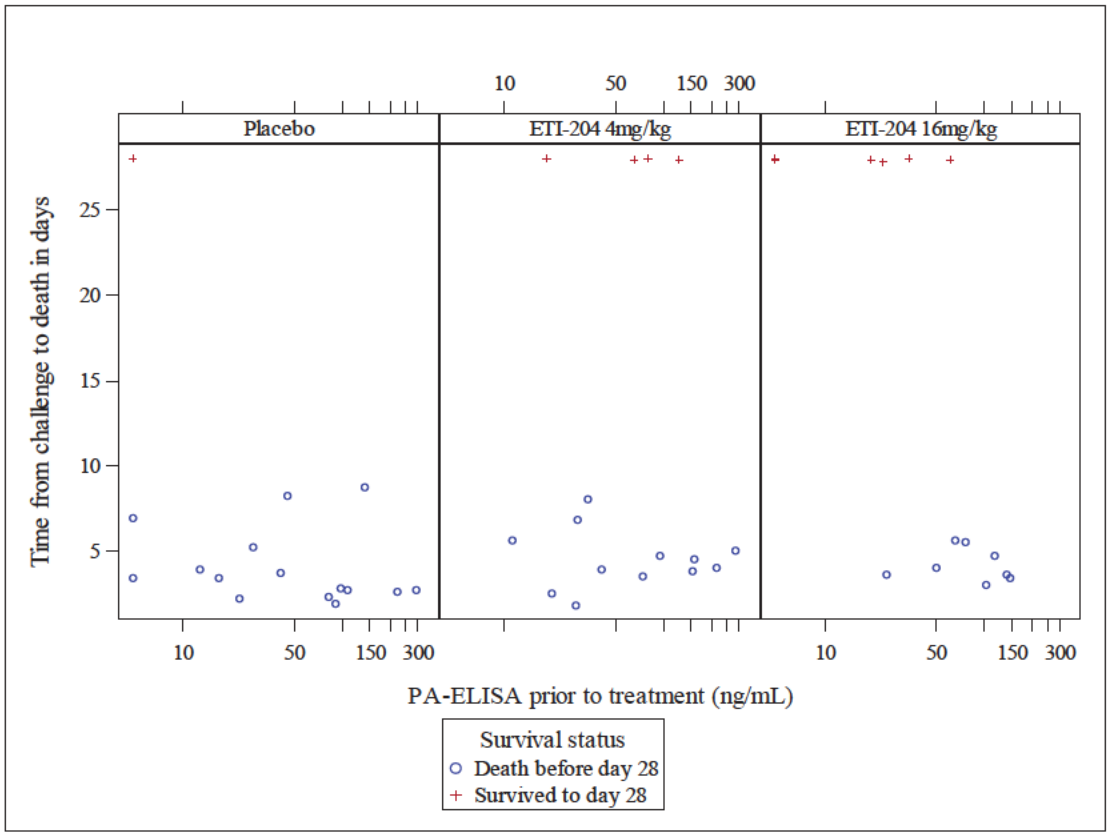
Figure 6.16. Study AP204: Time to Death by Bacteremia and Treatment Group



Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Animals with a lower PA-ELISA level prior to treatment were more likely to survive as shown in **Figure 6.17**.

Figure 6.17. Study AP204: Time to Death by PA-ELISA level and Treatment Group

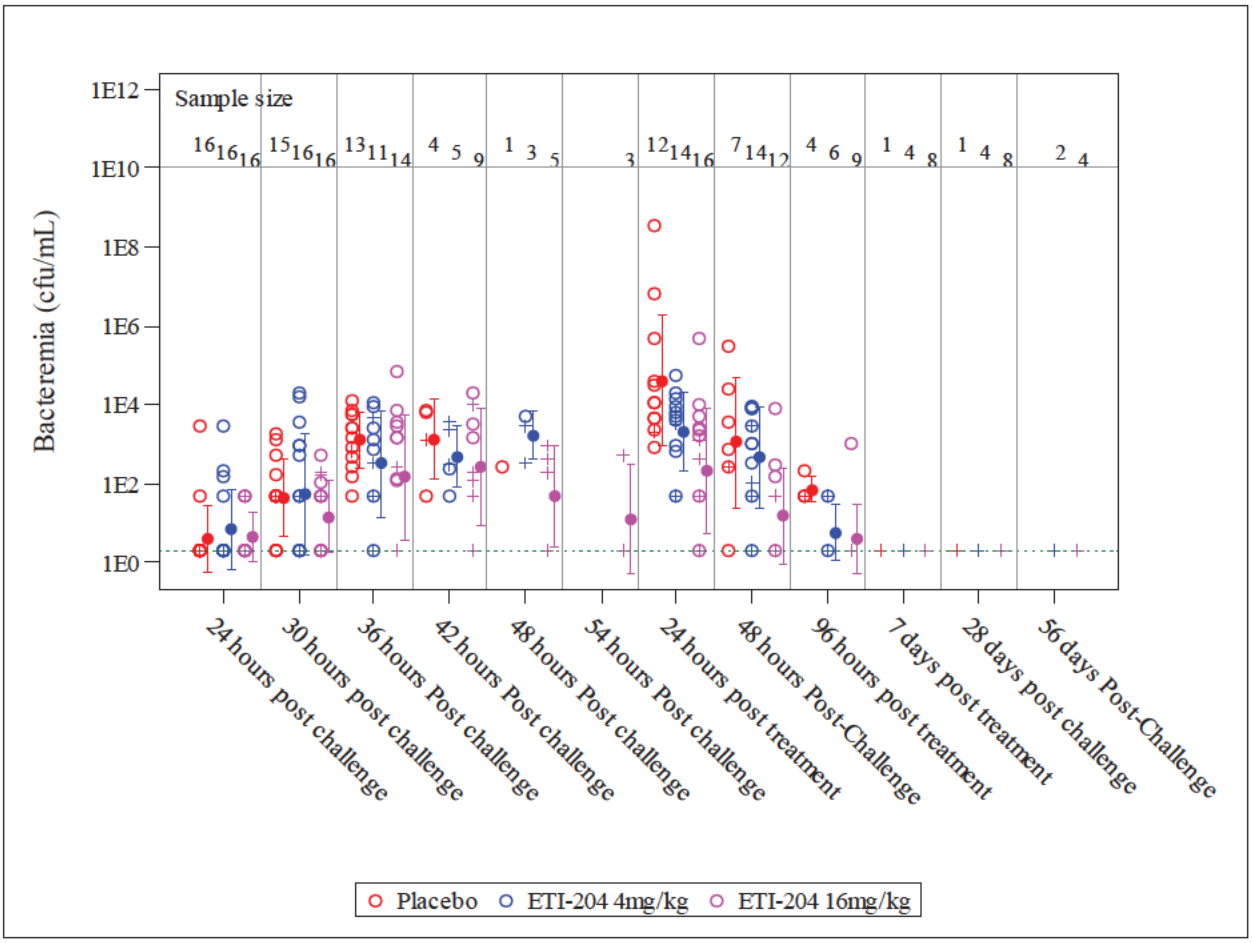


Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Bacteremia levels in animals over time by treatment arm are depicted in **Figure 6.18**. Geometric mean and standard deviation for each treatment group are depicted for each study time point. Animals who died or were sacrificed moribund are depicted as "o" (circles) and animals who survived are depicted as "+" (plus sign).

After administration of study treatment, the bacteremia levels began to decrease in the three study groups between 48 and 96 hours post treatment. Deaths occurred between 24 hours and 96 hours post-treatment in all treatment groups. All survivors cleared their bacteremia by Day 7.

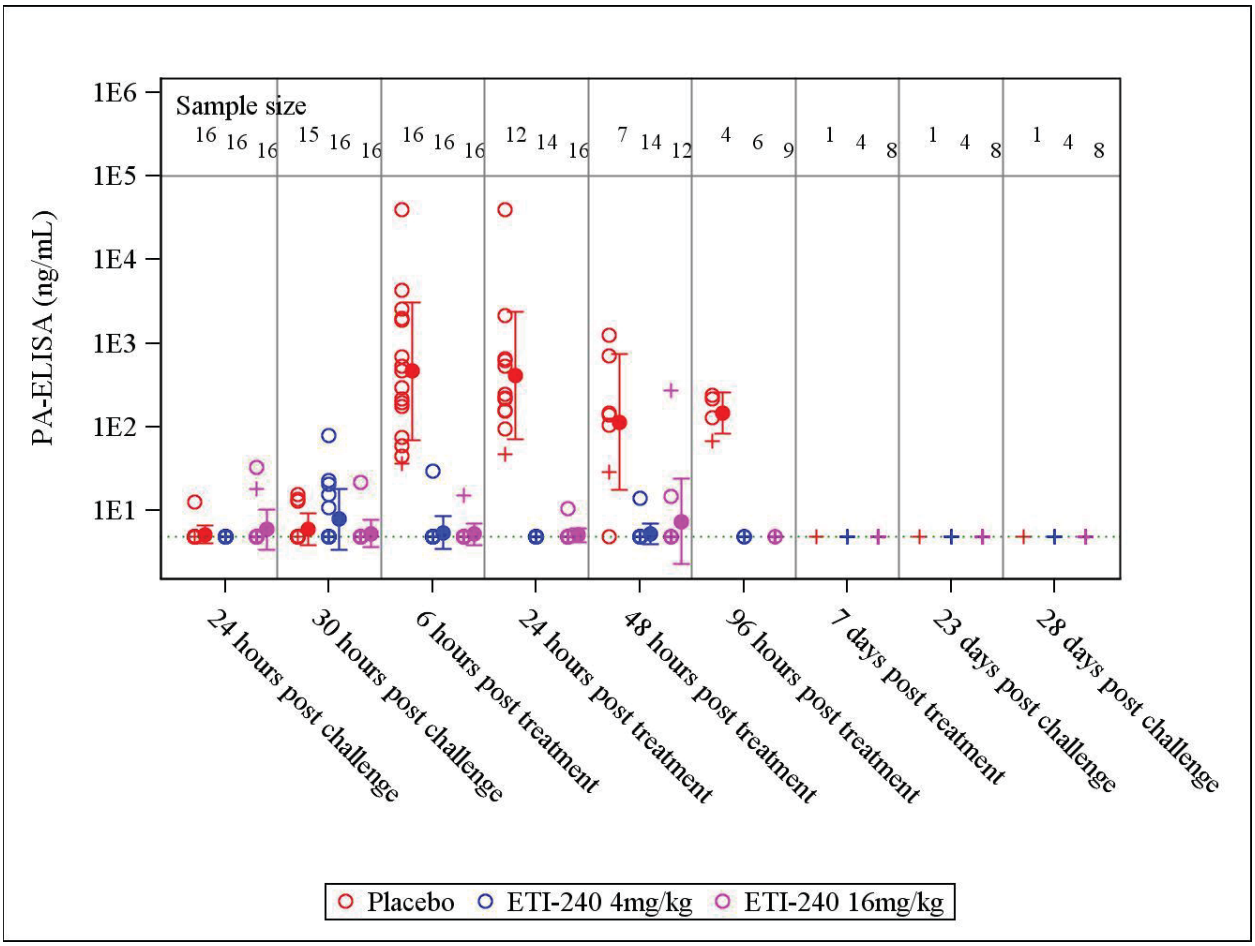
Figure 6.18. Study AP204: Bacteremia level by visit and survival



"+"= survived to Day 28; "o" = died before Day 28. *Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

PA-ELISA levels in animals over time are plotted in **Figure 6.19**. There was a significant decrease in PA levels starting at six hours post treatment i.e., on study Day 3, in animals that received obiltoxaximab 4mg/kg IV or 16mg/kg IV.

Figure 6.19. Study AP204: PA-ELISA Level by Visit and Survival Status



"+"= survived to Day 28; "o" = died before Day 28
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Efficacy Results - Secondary and other relevant endpoints

The mean time to a positive PA-ECL (trigger-to-treat) was 38 hours (range: 25-56 hours) for macaques in the study and it was slightly longer in the obiltoxaximab-treatment groups compared to placebo. These differences in time-to-trigger may be a function of sampling times and the overall mean times to trigger were similar among the treatment groups.
The mean time from trigger to treatment was approximately three hours in all study groups.

Table 6.22. Study AP204: Time to challenge, trigger, and treatment by Treatment Group

	Placebo (N=16)	ETI-204 4 mg/kg IV (N=16)	ETI-204 16 mg/kg IV (N=16)	All (N=48)
Time to bacteremia (hours)				
Mean (SD)	29.89 (3.58)	31.7 (5.64)	33.18 (9.96)	31.56 (6.82)
Range	21.93, 34.8	23.62, 42.25	21.62, 58.73	21.62, 58.73
Time to trigger (hours)				
Mean (SD)	35.68 (5.32)	37.12 (6.24)	41.37 (8.97)	38.05 (7.29)
Range	25.10, 46.52	29.67, 48.10	27.13, 55.90	25.10, 55.90
Time to randomized treatment (hours)				
Mean (SD)	39.18 (4.96)	40.42 (5.97)	44.41 (8.70)	41.34 (6.96)
Range	28.47, 49.65	33.32, 51.22	30.18, 58.78	28.47, 58.78
Time from trigger to treatment (hours)				
Mean (SD)	3.50 (0.97)	3.31 (0.92)	3.05 (1.26)	3.28 (1.05)
Range	0.12, 4.22	0.03, 3.98	0.05, 4.20	0.03, 4.22

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Dose Response

A dose response was observed in the two doses tested.

Durability of Response

A single dose of obiltoxaximab was effective in preventing death in 8/16 (50%) of the macaques up to Day 28 (end of study) at which time these animals were terminally sacrificed per protocol.

Persistence of Effect

Obiltoxaximab provided persistent inhibition of PA and with no recurrence of bacteremia or clinical signs of anthrax up to the end of the study, Day 28, Figure 23.

Additional Analyses Conducted on the Individual Trial

A total of 35 (73%) macaques died during the study and 19(40%) were found dead in their cages. High numbers of animals found dead in their cages was consistent observation in the three studies, study AP202, AP203, and AP204 indicating that clinical observations at six hour intervals may not be sufficient to monitor infected animals.

Table 6.23. Study AP204: Survival Outcomes in Treatment and Placebo Arms

OUTCOMES	Placebo (Saline) N=16	4mg/kg ETI-204 N=16	16 mg/kg ETI-204 N=16	All Subjects N=48
ALL DEATHS	**15 (32%)**	**12 (25%)**	**8 (16%)**	**35 (73%)**
Found Dead	9 (19%)	7 (15%)	3 (6%)	19 (40%)
Moribund Sacrifice	6 (13%)	5 (10%)	5 (10%)	16 (33%)
SURVIVORS	**1 (2%)**	**4 (8%)**	**8 (17%)**	**13 (27%)**

Source: Table constructed by clinical reviewer using JReview 9.2

Survival of animals by gender, challenge dose, bacteremia, and PA-ELISA level

Survival of animals by gender, challenge dose, bacteremia, and PA-ELISA level prior to treatment at Day 28 is summarized in **Table 6.24**. There was considerable variability in survival rates by gender and challenge dose across the study arms. Low levels of bacteremia were associated with a higher survival proportion.

A higher PA level in the 4 mg/kg group was associated with a higher survival proportion when compared with a lower PA level in the same treatment group, however the sample size was small and it was not possible to reach reliable conclusions from these subgroup analyses. In the placebo group, one female macaque with a challenge dose of 163 LD_{50}, bacteremia (3,130 CFU/mL), and a PA-level less than the LLOQ, survived which suggests that this animal may have had natural immunity to *B. anthracis*.

Table 6.24. Study AP204: Survival by Gender, Challenge Dose, Bacteremia, and PA prior to treatment with Obiltoxaximab

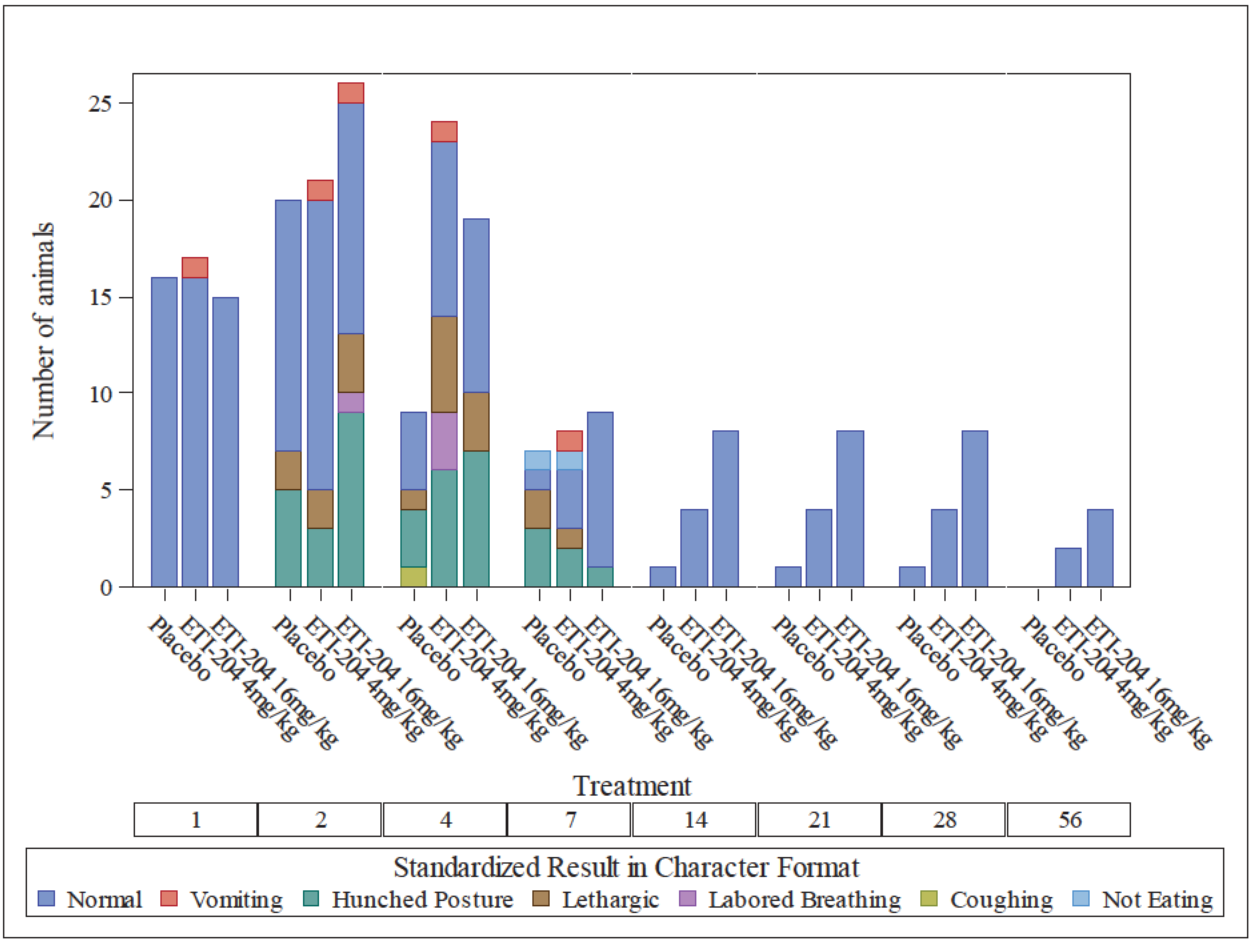
	Placebo (N=16)	ETI-204 4 mg/kg IV (N=16)	ETI-204 16 mg/kg IV (N=16)	All (N=48)
Gender				
Female	1/8 (12.5)	2/8 (25.0)	3/8 (37.5)	6/24 (25.0)
Male	0/8	2/8 (25.0)	5/8 (62.5)	7/24 (29.2)
Challenge dose (LD_{50}) (n(%))				
<250	1/13 (7.7)	2/14 (14.3)	8/15 (53.3)	11/42 (26.2)
250 or higher	0/3	2/2 (100)	0/1	2/6 (33.3)
Bacteremia prior to treatment (cfu/mL)				
$<10^2$	0	0	2/2 (100%)	2/2 (100%)
10^2 - 10^4	1/7 (14.3%)	4/8 (50%)	5/8 (62.5%)	10/23 (43.5%)
10^4 - $<10^6$	0/9	0/8	1/6 (16.7%)	1/23 (4.3%)
PA prior to treatment (ng/mL)				
0 - < 10	1/3 (33.3%)	0	4/4 (100.0%)	5/7 (71.4%)
10 - < 50	0/6	1/7 (14.3%)	3/5 (60.0%)	4/18 (22.2%)
50 or higher	0/7	3/9 (33.3%)	1/7 (14.3%)	4/23 (17.4%)

Source: Graph constructed by biostatistics Xianbin Li, Ph.D.

CLINICAL OBSERVATIONS

Stool abnormalities, respiratory abnormalities, lethargy, anorexia, and hunched posture were noted in all challenged animals. In obiltoxaximab-treated animals that survived to the end of the study, abnormal observations were no longer noted after Day 14 post-challenge, **Figure 6.20**. The Applicant noted that some animas had sporadic stool abnormalities which are not uncommon in laboratory-housed nonhuman primates.

Figure 6.20. Study AP204: Clinical Observations in Animals Exposed to *B. anthracis*



Source: Graph constructed by biostatistics Xianbin Li, Ph.D.

Neurological Examinations

Neurological examinations were performed by a veterinarian with expertise in performing these evaluations in nonhuman primates. Neurological examinations were performed on all animals on study Day -6 and in all survivors on Day 28 and Day 56 with the exception of those survivors euthanized on study Day 28. All animals had a normal neurological exam at Day -6. No significant neurological abnormalities were noted in the follow-up neurological examinations. A small number of animals had decreased motion of their thoracic limbs and one animal had a head tilt but none of these findings were considered to be of clinical significance associated with disease.

HISTOPATHOLOGY

The secondary endpoint for Study AP204 was to include an expanded microscopic evaluation of brains and meninges of surviving and non-surviving macaques as well as neurological examinations pre-study, at Day 28, and Day 56 post-challenge. The histopathological findings in the animals that died were consistent with inhalational anthrax and anthrax meningitis. All macaques that were found dead or euthanized in a moribund condition prior to Days 28 or 56 (unscheduled-death monkeys) had gross and or microscopic findings consistent with anthrax. Animals that survived to Days 28 or 56 did not have lesions consistent with anthrax. Obiltoxaximab-treated animals that died or were sacrificed in a moribund condition more commonly developed a more appreciable morphologic/immune response compared to morphologic/immune response in the brains of controls/placebo. It is reasonable to assume that the affected obiltoxaximab -treated animals were able to mount a response whereas the saline-treated animals lacked this ability due to overwhelming infection.

According to the veterinary pathology report, there were no obiltoxaximab-related pathologies identified in the tissues examined from the macaques that survived until Day 28 or 56 in this study. Please see the pharmacology/toxicology review by Dr. Amy Nostrandt, DVM for a more detailed analysis of the neuropathology results for this study.

Summary of Key Findings

Study AP204 was conducted after study AP201. Unlike study AP201, the survival rate in macaques treated with 4mg/kg dose in Study AP204 was not significantly better than placebo. The mean bacteremia and PA levels in animals prior to treatment in study AP204 were higher than in study AP201 which is the likely reason that the 4mg /kg dose of obiltoxaximab was less effective in study AP204.

Obiltoxaximab 16 mg/kg demonstrated a significant improvement in survival compared to placebo; 50% of animals survived in AP204 which is higher than the 31% survival rate with the 16mg/kg IV dose in study AP202. The difference in survival rates between the AP204 and AP202 could be attributed to a higher mean bacteremia level and PA prior to treatment in study AP202. PA and bacteremia levels became undetectable in all the animals that survived. Clinical signs in survivors resolved by Day 14 post-challenge.

6.4 Study AP201

6.4.1 Study Design

Overview and Objective

Study AP201 was the initial GLP monotherapy study conducted in cynomolgus macaques. The primary objective was to evaluate the efficacy of a single-dose of obiltoxaximab to prevent death in cynomolgus macaques with systemic anthrax due to inhalational exposure *to B. anthracis* spores. The study was conducted at the (b) (4) in 2009.

Trial Design

This was a randomized, blinded-to-group, placebo-controlled, parallel-group, trigger-to-treat, dose-ranging, study of anthrax-challenged cynomolgus macaques. The study design was similar to the other nonhuman primate monotherapy studies, AP202, AP203, and AP204 and only pertinent aspects of the protocol are discussed. The target challenge dose was 200 LD_{50} of *B. anthracis* (Ames strain). The trigger-to-treat was a positive serum protective antigen by ECL assay. Animals that had a positive PA-ECL on or before the 54 hour post-challenge time point were treated with obiltoxaximab or placebo. Animals that had a negative serum PA-ECL on or at the 54 hour post-challenge time point were treated empirically. The study staff was blinded to treatment assignment.
Forty-four (54) healthy cynomolgus macaques were randomized to challenge day and challenge order per day and to one of three dose groups, placebo, or obiltoxaximab 4 mg/kg or 8 mg/kg. As in the other nonhuman primate monotherapy studies, macaques were observed every six hours between 24 hours and eight days post-median-challenge-time for clinical signs of anthrax. Observations were conducted twice daily between study Day 9 and study Day 30 (end of the in life animal phase). The original protocol stated that 45 nonhuman primates were available for use in the study however one animal, C39111, died prior to telemetry implant surgery; the cause of death was reported as an allergic reaction to anesthesia. The study design is outlined in Table 6.25.

Table 6.25. Study AP201: Study Design

Blinded Group	ETI-204 Dose mg/kg	Number of Animals planned	Treatment Arm
Y	0	14**	Placebo
X	4	14*	ETI-204
Z	8	15	ETI-204

*Animal C39111, died prior to telemetry implant surgery; **Animal C39076 was removed from study prior to challenge because it had an elevated WBC and CRP on Day -7 and it was not included in the analysis.

Collection of blood samples for blood culture and PA levels were at similar time points as in the other nonhuman monotherapy studies. Histopathologic examinations of the brain were performed to characterize potential monoclonal antibody-related changes and these examinations were performed blinded by a veterinary pathologist.

Study Endpoints

The primary endpoint was survival to 30 days post-challenge with *Bacillus anthracis* spores.

Statistical Analysis Plan

Analysis Populations
The protocol planned to analyze all challenged animals, all challenged animals that had positive bacteremia prior to treatment, and all challenged and treated animals. All challenged animals were included in the analysis, since 100% of the monkeys were treated and were bacteremic prior to treatment.

Primary Analysis
For treatment efficacy, the survival data from each treatment group was compared to the control group using a one-sided Fisher's exact test. Survival analysis was performed for all challenged animals. The analysis was adjusted for multiple comparisons using a Bonferroni adjustment.

Secondary analysis
Time to death was calculated by Kaplan-Meier survival estimates. The Log Rank test was used to test for a significant difference in protection from death between groups. Geometric means with 95% confidence intervals were calculated for bacteremia (quantitative) and protective antigen levels by PA- ELISA by study group at each study time point.

Protocol Amendments

Protocol amendment #1 clarified the time points at which quantitative bacteremia would be performed and the time points for collection of blood samples for PA-ELISA. Protocol amendment #2 clarified that on Day 30 (end of in-life portion of study) blood samples would be collected from animals while they were anesthetized (prior to euthanasia).
Of the survivors euthanized on study Day 30, approximately 50% from each treatment group were to undergo histopathology evaluations. A sample of spleen and mediastinal or bronchial lymph nodes were to be collected during gross necropsy from all animals found dead or euthanized including those survivors euthanized on study Day 30.

Reviewer Comment: The FDA reviewed the protocol and requested that all the surviving animals be euthanized at the end of the study, necropsied, and tissues collected for histopathological evaluation.

Protocol amendment #3 sponsor clarified that histopathologic evaluations will be performed on all surviving animals euthanized at the end of study rather than 50% survivors as originally planned. Protocol amendment #4 indicated that additional testing facilities would conduct dose formulation analysis and microscopic evaluations of tissues. Additional microscopic analysis of

the brain was included in the protocol. The Applicant noted that only a proportion of pre-challenge and pre-treatment samples would be tested for obiltoxaximab levels as these results would be expected to be below the LOD. Protocol amendment #5 listed the types of brain tissue samples (wet brain tissue in formalin) to be sent for additional microscopic evaluations to (b) (4). Protocol amendment #6 noted that the remaining brain tissues, blocks, and slides from all surviving animals would be shipped to (b) (4) to support the expanded histopathologic evaluations. Protocol amendment #7 included additional statistical analyses to support efficacy of the study treatment in addition to the protocol-directed analyses. Other changes included details regarding the new location of archived histopathology specimens.

Reviewer Comment: The protocol amendments were acceptable.

6.4.2 Study Results

Compliance with Good Laboratory Practices

The Applicant submitted a statement that Study AP201 was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21CFR Part 58). The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

Patient Disposition

See Demographics, **Table 6.26.**

Protocol Violations/Deviations

Protocol violations and deviations are discussed. Two plasma samples from two animals destined for CRP analysis could not be located. There were some errors in recording with regard to the draw date of blood samples and the GLP corrections for these hours were verified using other study records. They were several deviations with regard to the dating / initialing of recorded data on study forms by study technicians. Corrective action was taken by the study director to increase supervision and mentoring of junior technicians. Results documented as "not applicable" were actually zero and these counts were reported as such in the study report. According to the standard operating procedure, the plates for quantitative bacteremia were to be incubated for approximately 16 to 24 hours. In some instances, plates (19 samples) for quantitative bacteremia were not removed from the incubator within the designated time frame. [The study director noted that the majority of the blood culture plates provided countable colonies and reported the deviation as minimal impact on the study]. Clinical observations were not recorded every six hours ± one hour on a particular day for a few macaques, however, clinical observations were in most cases recorded four times daily throughout the early post-challenge observation period. The acceptance criteria for the PA-ECL

assay at the 30hr, 42hr and 48hr post-challenge time points for animals on challenge Day C all failed, however these failures impacted the treatment decision for only one animal.

Reviewer Comment: The reported protocol deviations appear to have had minimal impact on the integrity of the study.

Table of Demographic Characteristics

Animals were evenly distributed by age, gender, and body weight among the placebo, 4 mg, and 16 mg/kg dose groups. Approximately 60% of macaques received a less than 200 LD_{50} dose, however, all animals (n=43) were bacteremic prior to therapy. One animal, C36423, in the 4 mg/kg dose group had a missing value for qualitative bacteremia but had a positive quantitative blood culture for *B. anthracis* prior to therapy. Demographic variables and baseline characteristics are summarized in Table 6.26.

Table 6.26. Study AP201: Demographic Variables and Baseline Characteristics

	Placebo (N=14)	ETI-204 4 mg/kg IV (N=14)	ETI-204 8 mg/kg IV (N=15)	All (N=43)
Age (years)				
Mean (SD)	3.6 (0.6)	3.6 (0.6)	3.7 (0.6)	3.7 (0.6)
Range	2.9, 5.1	2.6, 4.9	2.9, 5.1	2.6, 5.1
Gender [n (%)]				
Male	8 (57.1)	7 (50.0)	7 (46.7)	22 (51.2)
Female	6 (42.9)	7 (50.0)	8 (53.3)	21 (48.8)
Body weight (kg)				
Mean (SD)	3.4 (0.8)	3.3 (0.6)	3.3 (0.5)	3.4 (0.6)
Range	2.5, 5.3	2.6, 4.6	2.6, 4.7	2.5, 5.3
CHALLENGE DOSE				
Challenge dose (LD_{50})				
Mean (SD)	198.7 (65.8)	200.7 (51.9)	198.8 (64.9)	199.4 (59.8)
Range	96.0, 305.0	140.0, 280.0	109.0, 356.0	96.0, 356.0
Challenge dose (LD_{50}) [n(%)]	8 (57.1)	8 (57.1)	10 (66.7)	26 (60.5)
<200				
200 or higher	6 (42.9)	6(42.9)	5 (33.3)	17 (39.5)
Challenge dose (x 10^7 cfu)				
Mean (SD)	1.227 (0.406)	1.240 (0.321)	1.229 (0.401)	1.232 (0.369)
Range	0.591, 1.880	0.865, 1.730	0.676, 2.200	0.591, 2.200
BACTEREMIA				
No. of subjects bacteremic (qualitative) prior to treatment – [n (%)]	14 (100)	13 (92.9)	15 (100.0)	42 (97.7)
No. of Subjects with	13(92.9)	13(92.9)	15(100)	41(95.3)

bacteremia (quantitative) prior to treatment				
Log_{10} bacteremia positive prior to treatment, CFU per mill geometric mean 95% confidence interval	3.29 (0.89) 2.7, 5.8	3.27 (0.91) 2.7, 5.5	3.39 (1.00) 2.7, 6.4	3.32 (0.91) 2.7, 6.4
Bacteremia (quantitative) prior to treatment (cfu/mL x 10^4) Geometric mean 95% confidence interval Range	 0.19 0.06, 0.67 0.05, 70	 0.19 0.05, 0.65 0.05, 33.3	 0.25 0.07, 0.88 0.05, 240	 0.21 0.11, 0.41 0.05, 240
PROTECTIVE ANTIGEN				
PA-ECL positivity at trigger [n(%)]	13 (92.9)	12 (85.7)	15 (100.0)	40 (93.0)
PA-ELISA ng/mL prior to treatment Geometric Mean 95% Confidence interval Log_{10} PA-ELISA	10.0 3.8, 26.4 1.00 (0.73)	12.1 3.8, 37.9 1.08 (0.86)	11.7 3.8, 36.4 1.07 (0.89)	11.2 6.3, 20 1.05 (0.81)
PA-ELISA (ng/mL) prior to treatment Mean (SD) Range	36.5 (71.0) 1.2, 266.4	55.4 (83.2) 1.2, 228.2	78.3 (181.6) 1.2, 695.3	57.2 (122.5) 1.2, 695.3

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Reviewer Comment: The limit of detection (LOD) for bacteremia was 33 CFU/mL of B. anthracis in this study which was higher than in other nonhuman primate monotherapy studies, for example, the LOD was 3 CFU/mL B. anthracis in study AP202.

Efficacy Results - Primary Endpoint

Survival rates were 14%, 79%, and 74% for monkeys in the saline placebo, 4 mg/kg, and 8 mg/kg obiltoxaximab treatment groups, respectively. The obiltoxaximab 4mg/kg IV and 8 mg/kg IV treatment groups had statistically significant greater survival rates compared to the placebo control group with p-values of 0.00046 and 0.00075, respectively. Survival rates for the 4 mg/kg and 8mg/kg groups were similar and there was no statistical difference in survival between these two dose groups. There were two (14%) survivors in the placebo group and both of them were bacteremic prior to treatment.

Table 6.27. Study AP201: Survival at Day 28 by Treatment Group

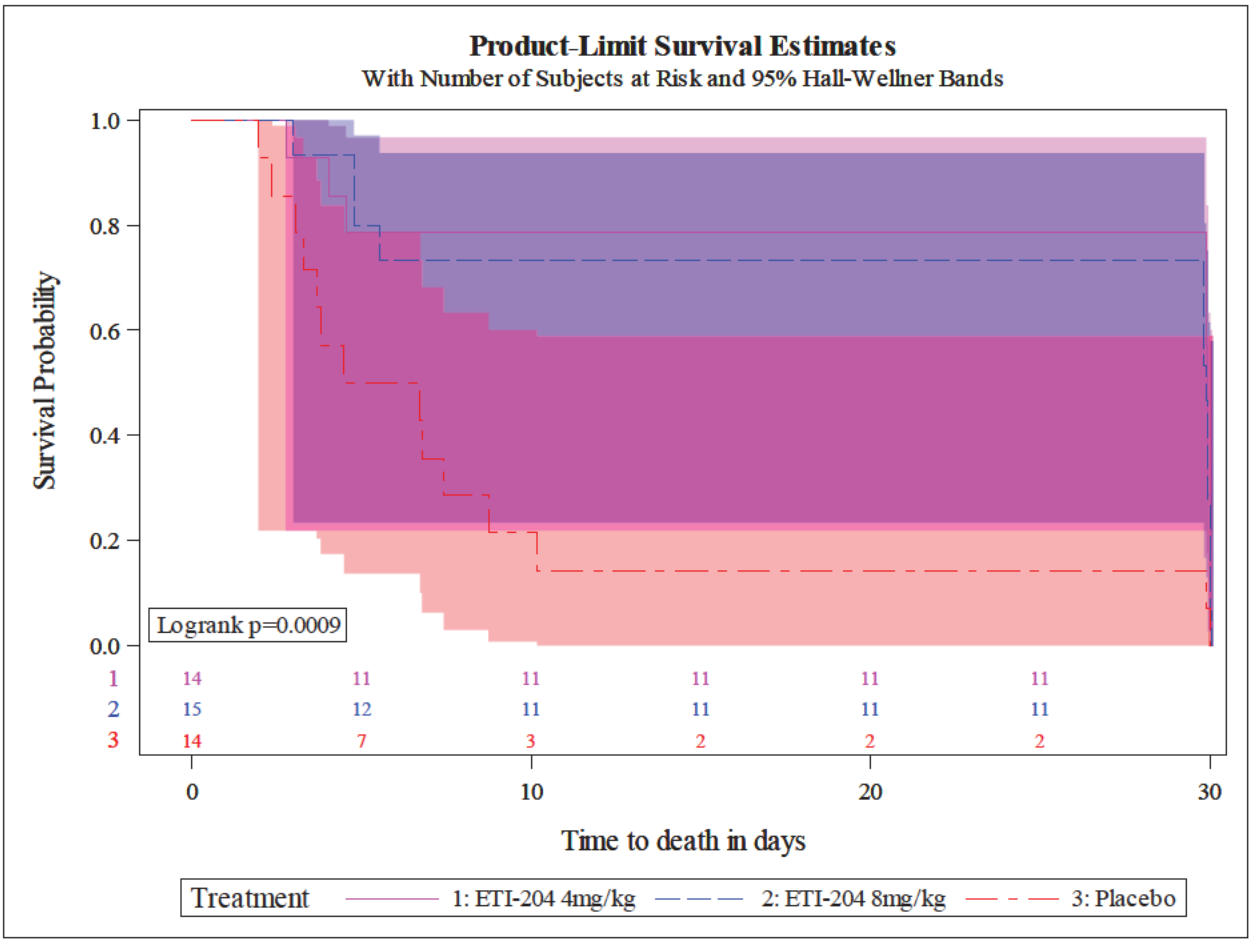
	Placebo (N=14)	ETI-204 4 mg/kg IV (N=14)	ETI-204 8 mg/kg IV (N=15)
Including all animals			
n (%)	2 (14.3)	11 (78.6)	11 (73.3)
Difference in survival proportion [exact 95% confidence interval] one-sided p-value compared with control		0.643 [0.260, 0.879] 0.00046	0.590 [0.207, 0.841] 0.00075
Adjusted exact 95% confidence interval		0.206, 0.898	0.162, 0.864
Excluding one animal without qualitative bacteremia			
n (%)	Same as	10/13 (76.9)	Same as above
Difference in survival proportion [exact 95% confidence interval] one-sided p-value compared with control	above	0.644 [0.271, 0.871] 0.00032	Same as above
Adjusted exact 95% confidence interval		0.179, 0.888	Same as above

LOD for bacteremia was 33 cfu/mL *B. anthracis.*
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Reviewer Comment: In study AP201, survival to Day 30 was the same as to Day 28. Therefore, survival to Day 28 was used to compare survival across the nonhuman primate, monotherapy, efficacy studies.

Kaplan-Meier estimates of survival for each treatment group from the time of challenge with *B. anthracis* to death are displayed in **Figure 6.21**. The survival results demonstrate a significant treatment effect of obiltoxaximab 4mg/kg and 8mg/kg compared to placebo. **Figure 6.21** and **Table 6.28** show that there was a statistically significant difference in survival rates between any obiltoxaximab group and the placebo group even with a Bonferroni adjustment for multiple comparisons using a two-sided significance level of 0.05/2=0.025).

Figure 6.21. Study AP201: Time to Death 28 by Treatment Group – Kaplan-Meier



Color bands indicate 95% confidence interval bands.

Source: K-M graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

A two-sided p-value of pairwise log-rank tests comparing time from challenge to death among treatment groups was conducted by the biostatistics reviewer, Dr. Li. Survival in the 4mg/kg IV and 8mg/kg IV doses groups were statistically significantly different from the placebo group, **Table 6.28**.

Table 6.28. Study AP201: Comparison of time from challenge to death among groups using two-sided p-values of pairwise log-rank tests

	ETI-204 4 mg/kg IV (N=14)	ETI-204 8 mg/kg IV (N=15)
Placebo (N=14)	0.0011*	0.0068*
Obiltoxaximab 4 mg/kg		0. 84

*Statistically significant at the significance level of 0.025. Source: AP201 Study Report, Table 11.

Among the 19 (43%) macaques that died post-challenge, 10 animals were found dead and 9 animals were sacrificed moribund, Table 6.29. The 24 (55%) animals that survived to Day 30 underwent terminal sacrifice. One animal in the placebo group was removed from study alive and this animal was counted among the survivors.

Table 6.29. Study AP201: Survival Outcomes in Treatment and Placebo Arms

Outcomes	Disposition Term	Placebo (Saline IV)	ETI-204 mg/kg	ETI-204 8 mg/kg	Animals
DEATHS	Found Dead	7 (16%)	2 (5%)	1 (2%)	10 (23%)
	Moribund Sacrifice	5 (11%)	1 (2%)	3 (7%)	9 (20%)
SURVIVORS	Removed from Study Alive	1 (2%)	0	0	1 (2%)
	Terminal Sacrifice	2 (5%)	11 (25%)	11 (25%)	24 (55%)
Total Subjects		15 (34%)	14 (32%)	15 (34%)	44 (100%)

Source: Table constructed by clinical reviewer using JReview 9.2.

Efficacy Results - Secondary and other Relevant Endpoints

The time to bacteremia and time to trigger and were similar among placebo and obiltoxaximab 4mg/kg and 8mg/kg IV dose groups. The mean time to bacteremia was 36 hours. The time from trigger to treatment in each of the treatment arms was within four hours as pre-specified in the protocol.

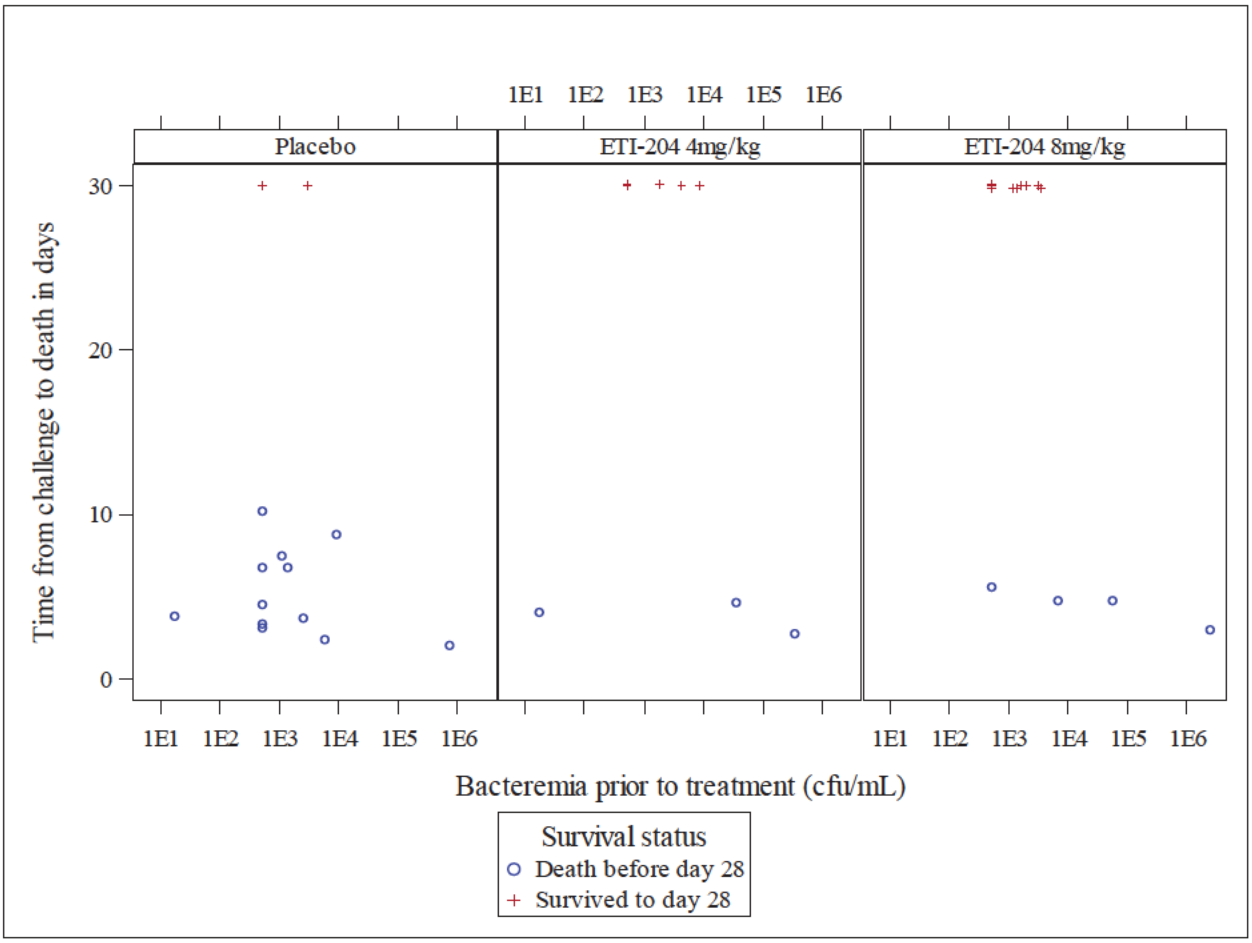
Table 6.30. Study AP201: Time from Challenge to Bacteremia, PA Trigger, and Treatment

	Placebo (N=14)	ETI-204 4 mg/kg IV (N=14)	ETI-204 8 mg/kg IV (N=15)	All (N=43)
Time to bacteremia (hours)				
Mean (SD)	37.7 (7.8)	34.4 (7.7)	35.6 (4.4)	35.9 (6.7)
Range	28.6, 55.4	25.5, 52.1	25.4, 41.8	25.4, 55.4
Time to trigger (hours)				
N	13*	13*	15	41
Mean (SD)	39.49 (8.05)	37.96 (10.12)	38.65 (8.00)	38.70 (8.54)
Range	28.58, 52.57	25.53, 55.92	25.43, 54.83	25.43, 55.92
Time to randomized treatment (hours)				
Mean (SD)	44.49 (8.49)	41.35 (9.54)	42.54 (7.22)	42.78 (8.34)
Range	31.80, 58.73	29.10, 59.07	29.35, 57.98	29.10, 59.07
Time from trigger to treatment (hours)				
N	13*	13*	15	41
Mean (SD)	3.90 (1.00)	3.14 (1.47)	3.89 (1.41)	3.65 (1.33)
Range	2.87, 5.62	0.07, 4.80	0.07, 5.93	0.07, 5.93

**One animal in the placebo group (C38277) and one in the obiltoxaximab 4 mg/kg group (C37686) were triggered for treatment based on time and had missing values in trigger time so they were not included in this calculation.*
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

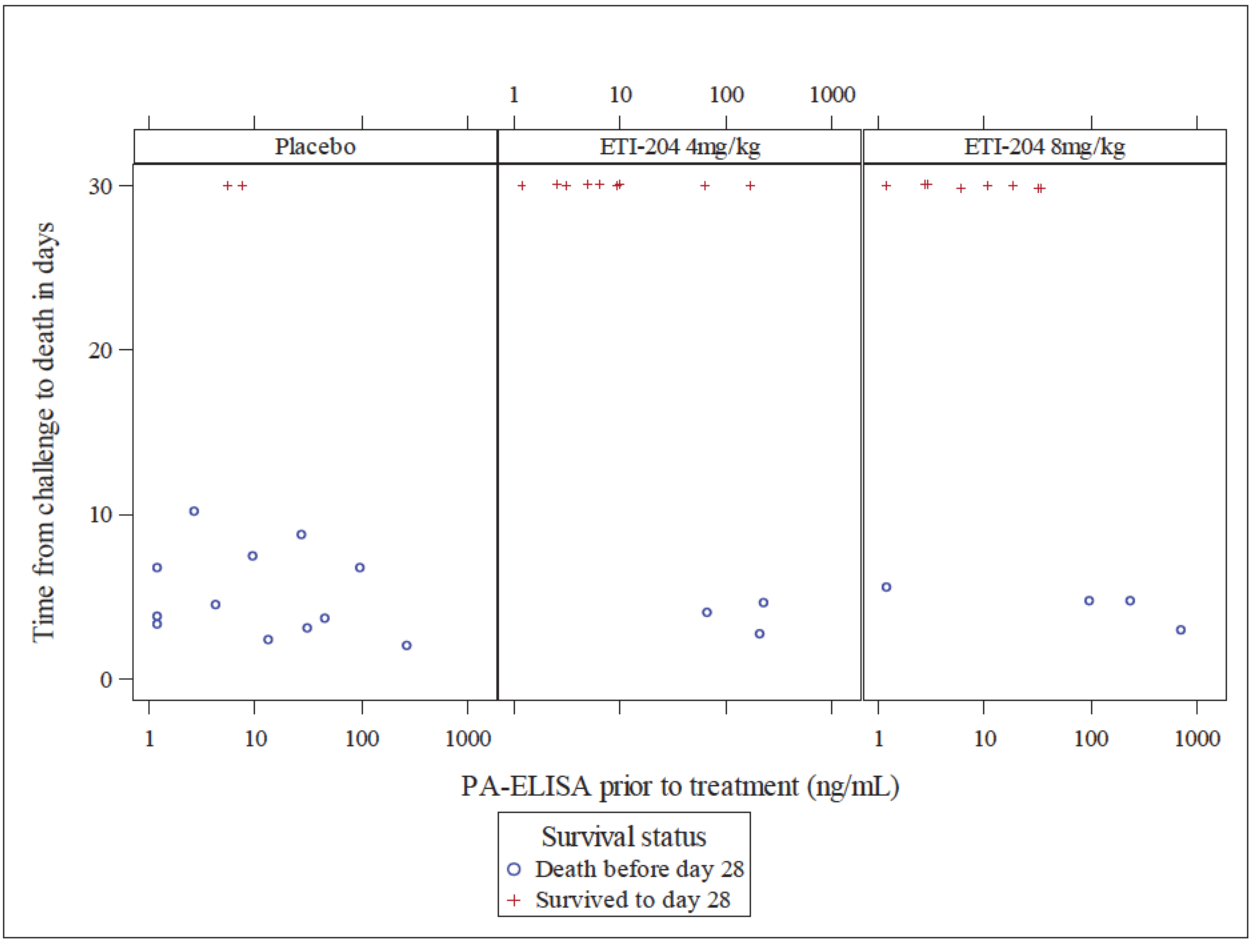
Figure 6.22 and **Figure 6.23** show that animals with a low bacteremia level or PA level prior to treatment were more likely to survive. All survivors had a bacteremia levels < $1x10^4$ (1E4) cfu/mL *B. anthracis* prior to treatment with study drug. The majority of survivors had a PA-ELISA level ≤ 10ng/mL prior to treatment with study drug, Figure 26.

Figure 6.22. Study AP201: Time to Death versus Bacteremia PTT by Survival Status at Day 30



PTT: prior to treatment; *Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Figure 6.23. Study AP 201: Time to death versus PA-ELISA PTT by Survival Status at Day 30

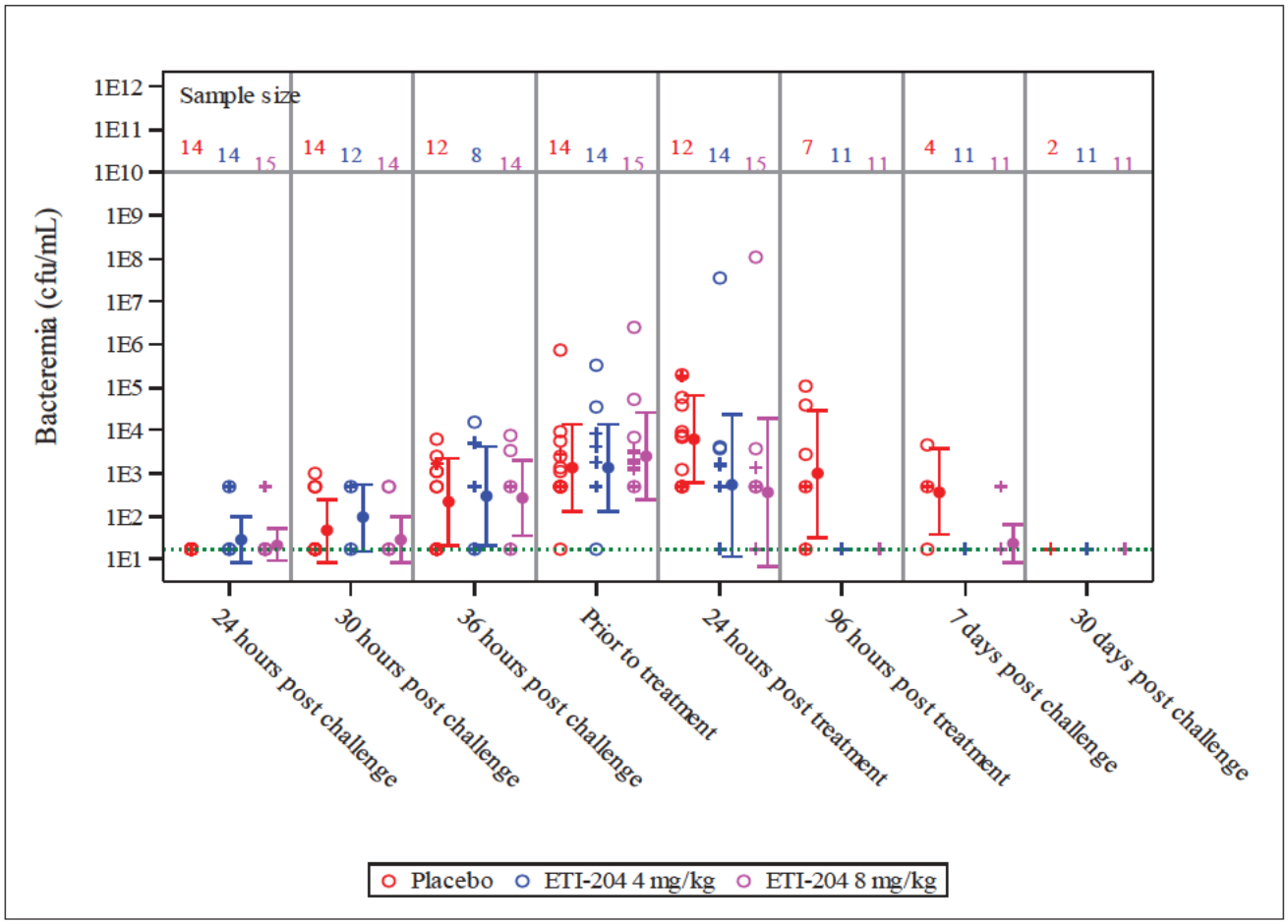


PTT: prior to treatment; *Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Bacteremia over Time

At 24 hours post-treatment (~study Day 3), the bacteremia levels were reduced in the two obiltoxaximab (4mg/kg IV and 8mg/kg IV) treatment groups. At 96 hours post-treatment, all surviving animals reached a level below the LOD = 33 CFU/mL.

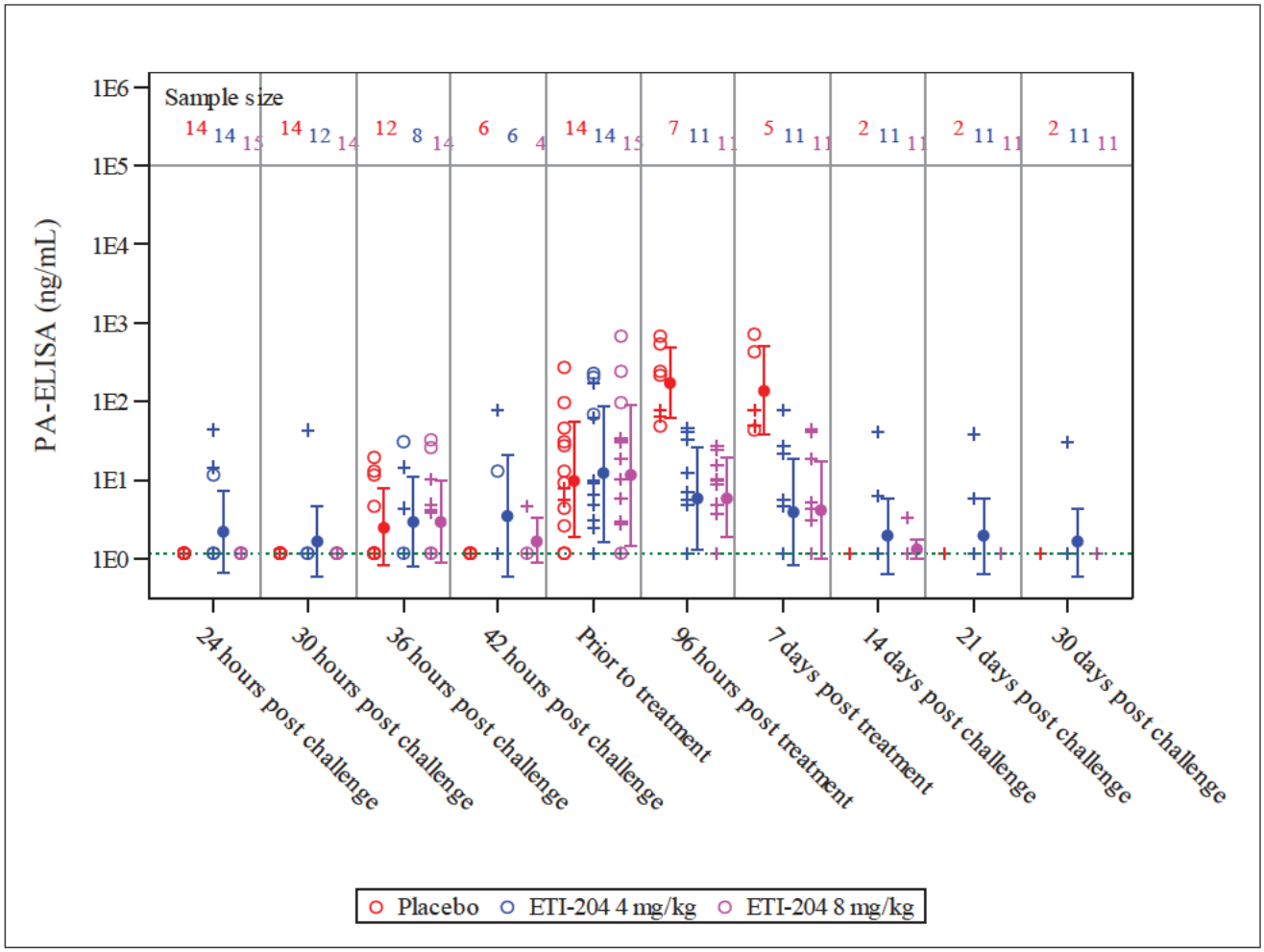
Figure 6.24. Study AP201: Bacteremia levels over Time by Survival status



+ "plus" =survived to Day 28; o "circle"=death before Day 28; Bacteremia CFU/mL - geometric mean and standard deviation are shown.

PA-ELISA levels over time by animal and by treatment group are plotted in the following graph, **Figure 6.25**. Prior to treatment the PA level in each treatment group increased and at approximately 96 hours post-treatment the PA levels became undetectable in the obiltoxaximab 4mg/kg and 8mg/kg IV dose groups in the animals that survived. However, one animal, C36338, had a positive PA-ELISA on Day -7 (test repeated), and on day 30 post-challenge this animal had PA of 30 ng/mL while all other surviving animals did not have detectable levels of protective antigen. In this animal, the anti-PA IgG (ELISA) were < LOQ at Day -7 and the Day 30-sample anti-PA IgG was 241.5 µg/mL. The results from the TNA and anti-PA IgG ELISA assay suggest that Day -7 sample had little to no neutralizing capacity. The elevated PA levels pre-challenge were likely a false positive result.

Figure 6.25. Study AP201: PA-ELISA levels prior to Treatment by Survival Status



"+ "=survived to day 30; "o"=death before Day 30; PA-ELISA levels, ng/mL: geometric mean and standard deviation are shown); *Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Microbiological and Histopathological Findings in the Brain and other Tissues of Non-Human Primates

No surviving animals had a positive bacterial load in bronchial lymph node and spleen. No data were available for bacterial load in other tissues. Two non-survivors in each group (i.e., 16.7%, 66.7%, and 50.0% in the 0, 4, 8 mg/kg groups, respectively) had positive pathological findings (discolorations) in the brain. No surviving animals (euthanized at Day 30) had pathological findings in the brain. For further details, see pharmacology/toxicology review of histopathologyy results by Amy Nostrandt, DVM.

Dose/Dose Response

There was no obvious dose response for survival with the 4mg/kg and 8mg/kg doses.

Durability of Response

A single dose of obiltoxaximab was effective in preventing death in 11(79%), and 11(74%) monkeys in the 4 mg/kg IV and 8 mg/ kg IV dose groups up to Day 30 at which time these animals were terminally sacrificed per protocol.

Persistence of Effect

There was no relapse of anthrax pneumonia, bacteremia, or PA toxemia in treated macaques during the 30-day study period.

Additional Analyses Conducted on the Individual Trial

The survival proportions, 57% and 55%, were similar between male and female macaques, respectively. For other parameters such as challenge dose, the sample sizes were too small to make any definite conclusions. The two survivors in the placebo group were bacteremic prior to treatment: One female animal received a challenge dose of 187 LD_{50}, and and blood cultures were positive for 500 CFU/mL of *B. anthracis* and PA-ELISA level was 7.7 ng/mL prior to treatment. One male animal received a challenge dose of 145 LD_{50}, and was bacteremic with B. anthracis 2,830 cfu/mL with a PA-ELISA of 5.54 ng/mL, prior to treatment.
Animals with the lowest levels of bacteremia and PA prior to treatment were more likely to survive, Table 6.31.

Table 6.31. Study AP201: Survival at Day 30 by Challenge dose, Bacteremia, PA prior to Treatment

	Placebo (N=14)	**ETI-204 4 mg/kg IV (N=14)**	**ETI-204 8 mg/kg IV (N=15)**	**All (N=43)**
Gender				
Female	1/8 (12.50)	6/7 (85.7)	5/7 (71.4)	12/22 (54.6)
Male	1/6 (16.67)	5/7 (71.4)	6/8 (75.0)	12/21 (57.1)
Challenge dose (LD_{50})				
<250	2/10 (20%)	8/11 (72.7%)	9/13 (69.2%)	19/34 (55.9%)
250 or higher	0/4	3/3 (100%)	2/2 (100%)	5/9 (55.6%)
Bacteremia prior to treatment (cfu/mL)				
$<10^2$	0/1	0/1	0	0/2
10^2 - 10^4	2/12 (16.7%)	11/11 (100%)	11/13 (84.6%)	24/36 (66.7%)
10^4 - $<10^6$	0/1	0/2	0/1	0/4
10^6 or higher	0	0	0/1	0/1
PA-ELISA prior to treatment (ng/mL)				
0 - < 10	2/8 (25%)	8/8 (100%)	6/7 (85.7%)	16/23 (69.6%)
10 - < 50	0/4	1/1 (100%)	5/5 (100%)	6/10 (60.0%)
50 or higher	0/2	2/5 (40.0%)	0/3	2/10 (20.0%)

Summary of Key Findings

Significant improvements in survival were observed with obiltoxaximab 4 mg/kg IV and 8 mg/kg IV doses compared to placebo. The 28-day survival rate was 79% for the 4 mg/kg dose and 73% for the 8mg/kg dose compared to 14% for the placebo group. Survivors in the placebo group were bacteremic with *B. anthracis* and must have had natural immunity to anthrax. The survival rates were the highest observed in the nonhuman primate monotherapy efficacy studies and were most likely related to the fact that animals in this study had the lowest mean levels of bacteremia and PA prior to treatment compared to the other monotherapy efficacy studies in cynomolgus macaques, discussed above.

6.5 **Study AR021**

6.5.1 Study Design

Overview and Objective

This study evaluated the efficacy of obiltoxaximab when administered therapeutically in NZW rabbits infected with *B. anthracis*. The goal of this dose-ranging study was to identify a target dose for obiltoxaximab, which when administered therapeutically, protected rabbits from lethality due to inhalational anthrax exposure. The primary objective was to evaluate the efficacy of a single-dose of obiltoxaximab to prevent death in animals with systemic anthrax due to inhalational exposure *to B. anthracis* spores. The study was conducted at the (b) (4) in 2008.

Trial Design

The study was a randomized, placebo-controlled, parallel group, , dose-ranging study in *B. anthracis*- challenged New Zealand White (NZW) rabbits. Sixty-four rabbits (32 males and 32 females) were randomized by body weight into three groups of 10 animals, i.e., groups 1,2, and 5, and two groups of 17 animals (groups 3 and 4) and they were randomized to one of three challenge days and to a challenge order per day. On Day 0, animals were challenged with a target dose of 200 LD_{50} of aerosolized *B. anthracis* (Ames) spores. The trigger for treatment intervention was either the first positive PA (via ECL assay) or three consecutive critical body temperature readings or when an animal had exhibited two consecutive critical body temperature readings twice.
Animals were monitored for significant increase in body temperature (SIBT), with hourly temperatures, from 18 through 72 hours post-challenge and for a positive PA-ECL, every six hours from 18 hours through 48 hours post-challenge. Animals were treated with obiltoxaximab IV or saline IV and oral levofloxacin or water for injection (control) via oral gavage. Levofloxacin or water were given as a three oral doses with the first dose given upon meeting treatment intervention criteria and the second and third doses were given at 24 hours and 48 hours after the initial treatment. Following challenge, each animal was monitored for clinical signs of disease, abnormal CRP, bacteremia, and circulating levels of PA by the ECL screening assay.

Table 6.32. Study AR021: Study Design

Group No.	Number of Animals	ETI-204 mg/kg	Levofloxacin [x]
1	10	Saline^	Control*
2	10	1.0	Control*
3	17	4.0	Control*
4	17	16.0	Control*
5	10	Saline^	50 mg/kg (via oral gavage)

Source: Adapted from BLA 225509, AR021 study report, Table 1, page 12
** Water For Injection (WFI) was administered as a control (at 2 ml/kg) for levofloxacin.*
^ Saline was administered as a control (at 0.5ml/kg) for ETI-204 (See Appendix B, DR-7243)
x Levofloxacin or control material was administered in three doses: upon meeting treatment intervention criteria and at 24 (±1) and 48 (±3) hours after the initial treatment.

Criteria for Euthanasia
The following criteria were pre-established for euthanasia: Presence of any seizure (denoting meningitis or encephalitis), respiratory distress, dyspnea, or forced abdominal respirations, unresponsive to touch or external stimuli, and moribundity. Animals judged to be moribund by a trained life sciences technician, (b) (4) veterinarian, or by the Study Director, were immediately euthanized.

Significant Increase in Body Temperature and Protective Antigen

The trigger-to-treatment in this NZW rabbit study was a significant increase in body temperature or a positive protective antigen by electro chemiluminescence (ECL).

Each rabbit received at least two transponder implants. Body temperatures readings were taken from transponders implanted in the rabbits' shoulders in this study because there was less variability in temperatures from the shoulder implant than from the rump implant. Baseline body temperatures were taken starting on Day -5 up to the morning of Day 0 prior to challenge. A baseline average body temperature was calculated from pre-challenge measurements for each rabbit. The hourly monitoring period for all rabbits commenced relative to the challenge end time of the first rabbit challenged (±10 minutes), and continued every hour through 72 hours post-challenge end time for the last rabbit. One rabbit, K99423, had a malfunctioning shoulder implant and its temperature readings were taken from the rump implant.

If an animal has not been treated with study drug by 72 hours (negative PA and did not meet body temperature criteria), the animal was treated after its last hourly body temperature reading.

Blood Cultures

Blood samples for culture were collected in EDTA tubes and were cultured at time points indicated in the following table to determine the presence or absence of *B. anthracis.* A full blood count, CRP, PA levels, ETI-204 levels in serum and levofloxacin levels in plasma were

performed at the time points shown in the following table.

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Table 2 Blood Draw Schedule[a]

Approximate Time Point	Blood Tube type/ Approximate Blood volume	Bacteremia (Culture)	CBC/ CRP	Serum PA level (via ECL assay)	Serum for ETI-204 assay	Plasma for Levofloxacin Assay
Day -7	EDTA ~1.5 ml *EDTA ~1.0ml SST ~2.0ml	X	X	X	X	X
^18hr PC	EDTA ~1.5 ml SST ~1.0 ml	X	X	X		
^24hr PC	EDTA ~1.5 ml SST ~1.0 ml	X	X	X		
^30hr PC	EDTA ~1.5 ml SST ~1.0 ml	X	X	X		
^36hr PC	EDTA ~1.5 ml SST ~1.0 ml	X	X	X		
^42hr PC	EDTA ~1.5 ml SST ~1.0 ml	X	X	X		
^48hr PC	EDTA ~1.5 ml SST ~1.0 ml	X	X	X		
PTT	EDTA ~1.5 ml SST ~1.0ml *EDTA ~1.0ml SPS ~1.0 ml	X[#]	X	X[f]		X
1hr PT	*EDTA ~1.0ml					X
24hr PT (prior to Trt2)	EDTA ~1.5 ml *EDTA ~1.0ml SST ~1.0ml	X	X		X	X
49hr PT (1hr PTrt3)	*EDTA ~1.0ml					X
72hr PT (24hr PTrt3)	EDTA ~1.5 ml *EDTA ~1.0ml	X	X			X
7 days PC [b]	EDTA ~2.0 ml	X	X			
14 days PC [b]	EDTA ~2.0 ml	X	X			
21 days PC [b]	EDTA ~2.0 ml	X	X			
28 days PC [b]	EDTA ~2.0 ml	X	X			
Terminal [c,d]	EDTA ~2.0 ml *EDTA ~1.0ml	X	CRP only			X[e]

PC = Post-Challenge
PTT = Prior to Treatment
PT = Post-Treatment
Trt2 = Treatment 2
Trt3 = Treatment 3

[a] Post-challenge pre-treatment bleed time points were relative to a median challenge time for a challenge cohort. Post-treatment bleed times were calculated from the time each animal's IV treatment ended. Blood samples occurred within ±60 minutes of the calculated time, except for the 1hr PT and 49hr PT samples which occurred within 15 minutes of the calculated time. The Day -7, Day 7, Day 14, Day 21 and Day 28 post-challenge bloods were relative to the day of challenge.
[b] Blood samples 7, 14, 21 and 28 days post-challenge were not collected from the VAP.
[c] The terminal sample, if occurring >7 days post-challenge, was not collected from the VAP.
[d] If collection was possible.
[e] Plasma for Levofloxacin analysis was only collected from terminal samples occurring ≤48 hours post treatment #3.
[f] This sample for Serum PA level (via ECL assay) was not be run immediately onsite (relative to collection time).
* Chilled EDTA for Levofloxacin Analysis
^ Post-Challenge, pre-treatment sampling stopped once decision to treat was made.
# PTT Bacteremia performed on sample collected in SPS tube

Source: Study AR021 study report, Table 2 page 26.

Study Endpoints

The primary endpoint was the survival rate in the obiltoxaximab group versus the placebo group at Day 28 post-exposure to *B. anthracis* spores.

Statistical Analysis Plan

Sample Size Calculation

The Applicant assumed that the true probability of survival in the control group (group 1) was less than 5% and the true probability of survival in either of the two highest dose treatment groups (group 3 or 4) was greater than 55%, then 10 control animals and 17 treated animals provided 81.3% power to detect a difference in survival probabilities between these two groups. If the probability of survival in the levofloxacin treatment group (group 5) was assumed to be greater than 65%, then 10 control animals and 10 treated animals provided 86.1% power to detect a difference in survival probabilities between the levofloxacin treated group and the control group. These calculations were for a one-sided, 0.05 level Fisher exact test.

Analysis Populations

There were no analysis populations defined in the protocol. Survival analyses was performed:

- in all animals
- in all the animals excluding two that were inadvertently dosed with levofloxacin (Animal K99373 from the placebo group and Animal K99383 from the ETI-204, 1mg/kg group)
- excluding animals that were not bacteremic at any study time point prior to and including treatment time removed
- in all animals that were not bacteremic through treatment with Animals K99373 and K99383 removed.

Statistical Methods

One-sided Fisher's exact tests were utilized to perform all pairwise comparison of survival rates between the groups. A Bonferroni-Holm adjustment was used to maintain an overall 0.05 significance level.

The time-to-death data were analyzed to determine if there were differences in protection for the obiltoxaximabtreatment groups based on a time-to-death. When the log-rank test was significant, pairwise log-rank tests were computed to determine which groups were significantly different. Since there were five groups, this involved ten comparisons. The Bonferroni-Holm adjustment method was used to maintain an overall 0.05 level of significance.

Reviewer Comment: The statistical plan was acceptable, however, the biostatistics reviewer commented that the study may be underpowered based on the sponsor assumptions of survival rates for placebo and levofloxacin.

6.5.2 Study Results

Compliance with Good Laboratory Practices

The Applicant submitted a statement that Study AR021 was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21CFR Part 58).

Patient Disposition

See Demographics, Table 6.33.

Protocol Violations/Deviations

The protocol stated that on study Day 3 and thereafter, monitoring of body temperatures would occur twice-daily until Study Day 28.They were a number of instances of failure of technicians to correctly record the dates of raw data entry. Evening temperatures were not taken from animals on one day. Some blood samples were collected outside the timeframe allowed by the protocol. Technicians recorded the presence and description of contamination of blood cultures but omitted to record the result for *B. anthracis*. This was resolved by looking at photographs of the plates and it was determined that the plates did not contain *B. anthracis*.

Reviewer Comment: These deviations do not appear to have impacted the integrity of the study.

Demographic Characteristics

Demographic variables and baseline characteristics are summarized in Table 6.33. Variables such as age, gender, and body weight were equally distributed across different treatment groups.

All NZW rabbits were randomized and treated. Animal K99373 from the placebo group and Animal K99383 from obiltoxaximab, 1 mg/kg group, were inadvertently dosed with levofloxacin and are included in the randomized groups in this table. Fifty percent (31/62) of the animals were treated based on a positive PA-ECL and 50% were treated based on a SIBT. The defined times to SIBT from the Applicant's datasets were used in analyses in this review. PA-ECL positivity was slightly lower in the obiltoxaximab 4 mg/kg and 16 mg/kg groups;

Table 6.33. Study AR021: Demographic Variables and Baseline Characteristics

	Placebo (N=10)*	ETI-204 1 mg/kg (N=10)*	ETI-204 4 mg/kg (N=17)	ETI-204 16 mg/kg (N=17)	Levofloxacin 50 mg/kg (N=10)	Total (N=62)
Age (years) Mean (SD) Range	7,8	7,8	7,8	7,8	7,8	7,8
Gender [n (%)] Male Female	4 (44.4) 5 (55.6)	4 (44.4) 5 (55.6)	9 (52.9) 8 (47.1)	8 (47.1) 9 (52.9)	5 (50.0) 5 (50.0)	30 (48.4) 32 (51.6)
Body weight (kg) Mean (SD) Range	3.2 (0.1) 3.2	3.2 (0.2) 3.3	3.2 (0.1) 3.1	3.2 (0.2) 3.2	3.2 (0.2) 3.2	3.2 (0.2) 3.2
Challenge dose (LD_{50}) Mean (SD) Range	193.8(69.7) 85.0, 343.0	175.3 (35.6) 112.0, 217.0	200.0 (51.8) 89.0, 309.0	174.9 (61.2) 86.0, 300.0	164.8 (48.2) 79.0, 221.0	183.0 (54.9) 79.0, 343.0
Challenge dose (LD_{50}) [n(%)] <200 200 or higher	6 (66.7) 3 (33.3)	7 (77.8) 2 (22.2)	9 (52.9) 8 (47.1)	10 (58.8) 7 (41.2)	8 (80.0) 2 (20.0)	40 (64.5) 22 (35.5)
Challenge dose (x 10^7 cfu) Mean (SD) Range	193.8 (69.7) 85.0, 343.0	175.3 (35.6) 112.0, 217.0	200.0 (51.8) 89.0, 309.0	174.9 (61.2) 86.0, 300.0	164.8 (48.2) 79.0, 221.0	183.0 (54.9) 79.0, 343.0
BACTEREMIA						
Bacteremic rabbits (enriched) PTT [n (%)]	9 (100.0)	8 (88.9)	15 (88.2)	14 (82.4)	9 (90.0)	55 (88.7)
PA						
Rabbits with PA-ECL positivity at trigger [n(%)]	5 (55.6)	6 (66.7)	6 (35.3)	8 (47.1)	6 (60.0)	31 (50.0)

PA: protective antigen; PTT: prior to treatment

*Animal K99373 from the placebo group and Animal K99383 from obiltoxaximab 1 mg/kg group were inadvertently dosed with levofloxacin and were included in the randomized groups in this table.
Source: Table constructed by biostatistics reviewer, Xianbin Li, PhD.

Animals Replaced on Study

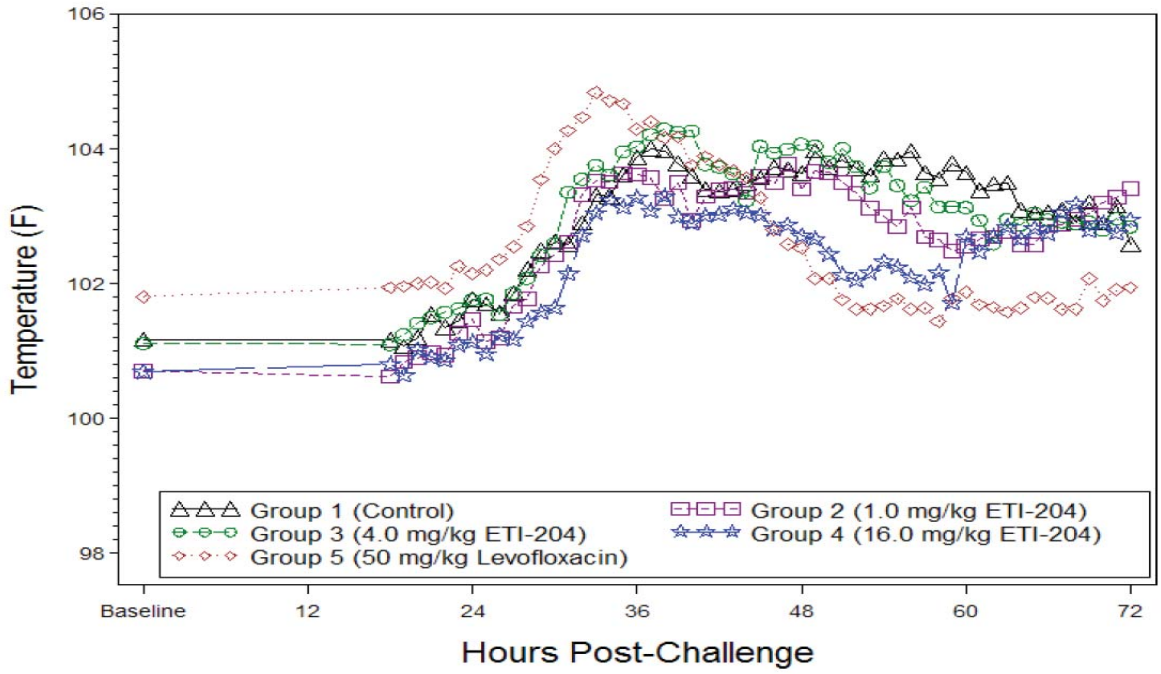
After the initial randomization, a total of three animals were replaced on study, Animal K99397 (female, Group 3) was replaced with Animal K99381 (female) as K99397 had a non-functioning IV catheter. Animal K99366 (female, Group 3) was replaced with Animal K99369 (female) because K99366 had a significantly contaminated Day-7 blood culture plate (plate had a lawn of bacteria which was not consistent with *B. anthracis*). Animal K99406 died accidentally from a non-study related injury and was replaced with Animal K99416 (found dead) randomized to placebo, group 1. Animal K99373 from Group 1 and Animal K99383 from Group 2 were excluded by the Applicant from the survival analyses because these animals were inadvertently dosed with levofloxacin; these two animals survived and were euthanized at the end of study

Reviewer Comment: The exclusion of the mis-dosed animals did alter the significance of the p-values when comparing survival rates between treatment groups. The p-values went from insignificant to significant when the mis-dosed Group 2 (1mg/kg) animal was excluded from the analysis.

Trigger to Treatment

The trigger for the initiation of treatment was SIBT. Body temperatures began to increase in all treatment groups from 24 to 36 hours post challenge. The average temperature for each group up to hour 72 post-challenge is plotted in **Figure 6.26**. The average time (for a group) from challenge to SIBT was between 27 hours and 32 hours. Prior to treatment 35 of 62 (56%) of the animals had reached a SIBT.

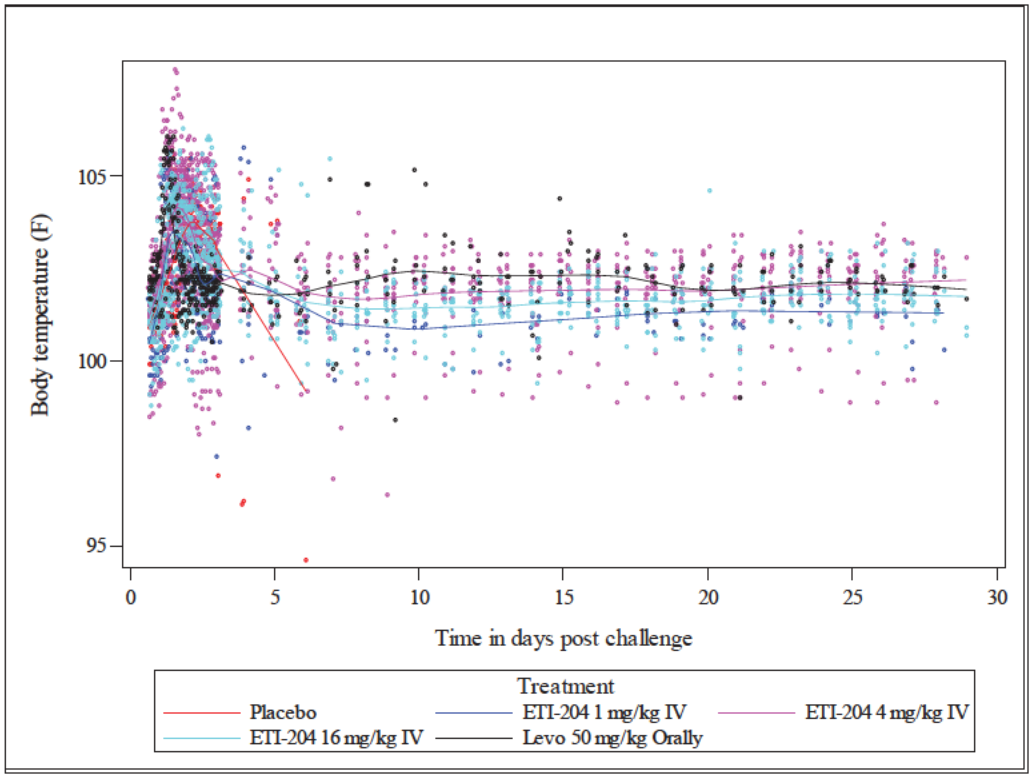
Figure 6.26. Study AR021: Body Temperatures (Mean) at Baseline and 18 to 72 Hours Post Challenge



Source: BLA 125509, SDN 1, AR021 Study Report, Fig 1, page 11

Average body temperatures from challenge through to Day 28 (end of study) are shown in **Figure 6.27**. At two days post-challenge, the mean temperature in the obiltoxaximab 4 mg/kg IV and 16 mg/kg IV groups and the levofloxacin group returned to baseline. The mean temperature in the placebo group dropped below 100°F, due to low body temperatures in the animals prior to death.

Figure 6.27. Study AR021: Mean Body Temperature over Time by Treatment



One temperature value for Animal K99421 at Day 8 in the obiltoxaximab 4 mg/kg group was not plotted, because it was too low. Animal K99373 (mis-dosed) in the control group was not included.
Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Protective Antigen by ECL

A positive PA level at some point prior to treatment was present in 81% (50/ 62) of the rabbits. The average time (for a dose-group) from challenge to a positive PA-ECL result was between 25 and 30 hours, (**Table 6.34**, **Table 6.35**).

Table 6.34. Study AR021: No. of Animals with Positive Protective Antigen by ECL in each Dose Group

	Group 1 Saline N=9	**Group 2 ETI -204 1mg/kg N=9**	**Group 3 ETI-204 4mg/kg N=17**	**Group 4 ETI-204 16mg/kg N=17**	**Group 5 Levo 50mg N=10**	**Total N=62**
No. of Animals with positive PA prior to treatment	8	7	14	13	8	50
Proportion Positive;	0.89	0.79	0.82	0.76	0.80	0.81
95% Confidence Intervals	0.52, 1.0	0.4, 0.97	0.57, 0.96	0.5, 0.93	0.44, 0.97	

ECL: Electrochemiluminescence

The proportion of abnormal PA-ECL values (by group) at the various study time points up to 48 hours post challenge are included in **Table 6.35**. PA levels were initially detected at 24 hours post-challenge in all dose groups.

Table 6.35. Study AR021: Serum Protective Antigen (PA-ECL) by Dose Groups

Study Time	Group 1		Group 2		Group 3		Group 4		Group 5	
	P	Proportion Abnormal (95% Confidence Interval)	P	Proportion Abnormal (95% Confidence Interval)	P	Proportion Abnormal (95% Confidence Interval)	P	Proportion Abnormal (95% Confidence Interval)	P	Proportion Abnormal (95% Confidence Interval)
Baseline	0/9	0.00 (0.00, 0.34)	0/9	0.00 (0.00, 0.34)	0/17	0.00 (0.00, 0.20)	0/17	0.00 (0.00, 0.20)	0/10	0.00 (0.00, 0.31)
Hour 18 PC	0/9	0.00 (0.00, 0.34)	0/9	0.00 (0.00, 0.34)	0/17	0.00 (0.00, 0.20)	0/17	0.00 (0.00, 0.20)	0/9	0.00 (0.00, 0.34)
Hour 24 PC	2/8	0.25 (0.03, 0.65)	4/8	0.50 (0.16, 0.84)	6/15	0.40 (0.16, 0.68)	6/16	0.38 (0.15, 0.65)	5/8	0.63 (0.24, 0.91)
Hour 30 PC	4/6	0.67 (0.22, 0.96)	1/3	0.33 (0.01, 0.91)	3/6	0.50 (0.12, 0.88)	5/8	0.63 (0.24, 0.91)	1/2	0.50 (0.01, 0.99)
Hour 36 PC	0/2	0.00 (0.00, 0.84)	1/1	1.00 (0.03, 1.00)	0/0	NA	2/3	0.67 (0.09, 0.99)	0/0	NA
Hour 42 PC	2/2	1.00 (0.16, 1.00)	0/0	NA	0/0	NA	0/0	NA	0/0	NA
Hour 48 PC	0/0	NA	0/0	NA	0/0	NA	0/0	NA	0/0	NA
PTT	8/9	0.89 (0.52, 1.00)	7/9	0.78 (0.40, 0.97)	14/17	0.82 (0.57, 0.96)	13/17	0.76 (0.50, 0.93)	8/10	0.80 (0.44, 0.97)

P Number of animals with positive PA-ECL/number of animals alive in the group.
NA No blood was drawn from these animals at this study time due to animal already being abnormal.

Source: Table 4, page 12, AR021 Study Report - BLA 125509, SDN 1.

Efficacy Results - Primary Endpoint

Survival status at Day 28 in each of the treatment groups is summarized in Table 6.36. The first panel in the table includes all randomized animals, including two animals which were inadvertently treated with levofloxacin and survived to Day 28. Because the two animals survived, including one survivor in the control group is a conservative approach to the analysis of survival. In all randomized animals and in those animals that were bacteremic prior to treatment, there were statistically significant difference in survival rates between obiltoxaximab-treated groups and the placebo group, except for the 1 mg/kg group.
The obiltoxaximab 4mg/kg IV and 16mg/kg IV treatment groups had statistically significant survival rates of 76% and 94%, respectively, compared to placebo (10%). A dose response was observed as the dose increased from 4 to 16mg/kg IV, the survival rate increased from 76% to 94%.
The obiltoxaximab 16 mg/kg IV group had a similar survival rate to the oral levofloxacin 50mg/kg group, i.e., 94% vs. 90%, respectively in all animals and survival rates of 93% vs. 89%, respectively, in animals that were bacteremic prior to treatment.

Table 6.36. Study AR021: Survival at Day 28 by Treatment Group

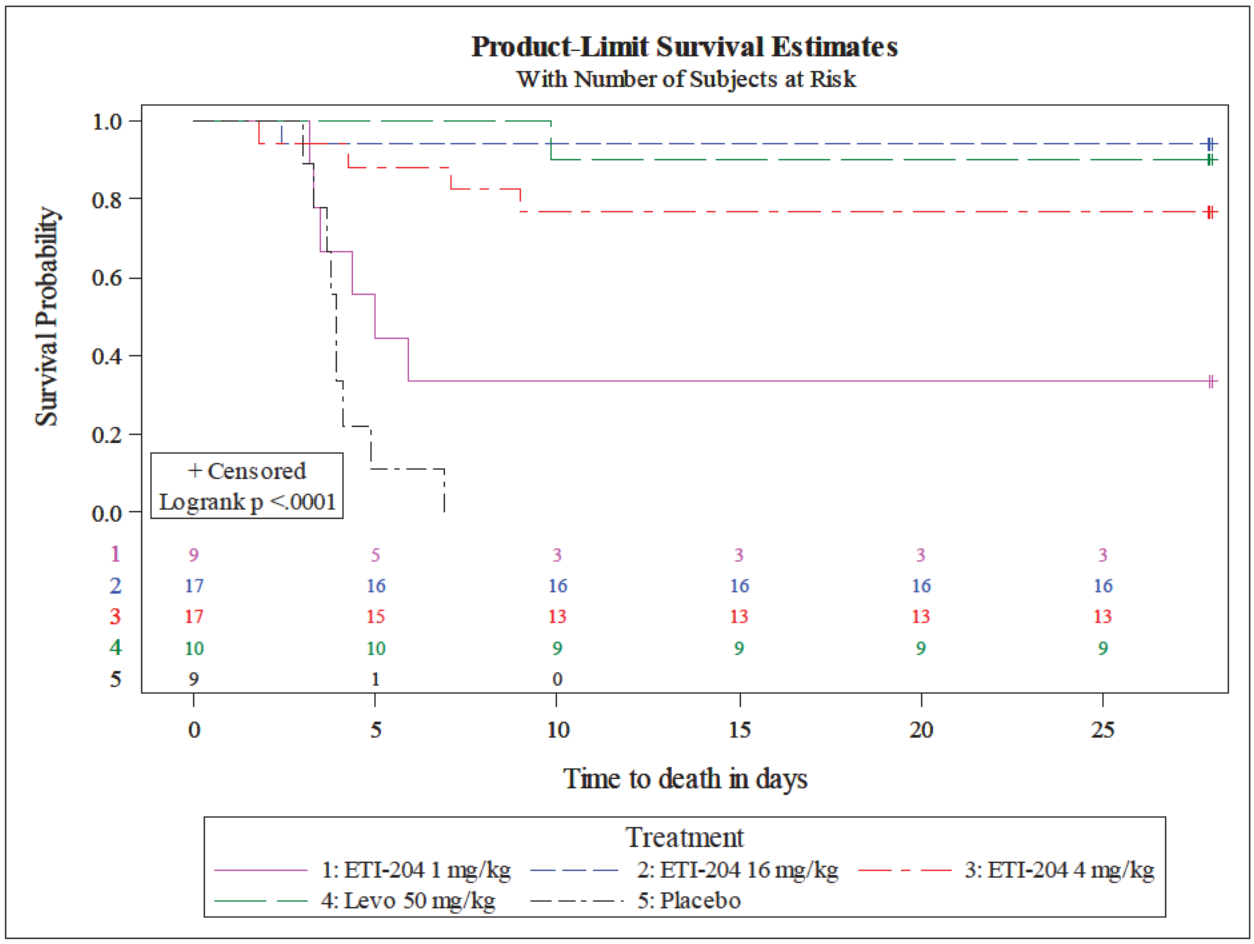
	Placebo (N=10)	ETI-204 1 mg/kg (N=10)	ETI-204 4 mg/kg (N=17)	ETI-204 16 mg/kg (N=17)	Levofloxacin 50 mg/kg (N=10)
N (%) of Survivors	1 (10)	4 (40)	13 (76.5)	16 (94.1)	9 (90.0)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.3 [-0.107, 0.659] 0.0755	0.665 [0.249, 0.878] 0.0005	0.841 [0.443, 0.978] <0.0001	0.80 [0.366, 0.975] 0.0002
Adjusted exact 95% confidence interval		-0.219, 0.732	0.155, 0.918	0.352, 0.989	0.244, 0.988
Calculations only including animals that were bacteremic at some time prior to treatment					
n/N (%)	1/10 (10)	4/9 (44.4)	11/15 (73.3)	13/14 (92.9)	8/9 (88.9)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.344 [-0.078, 0.709] 0.059	0.633 [0.232, 0.878] 0.0011	0.829 [0.431, 0.976] <0.0001	0.789 [0.335, 0.972] 0.0004
Adjusted exact 95% confidence interval		-0.192, 0.779	0.120, 0.905	0.326, 0.989	0.209, 0.987
Calculations not including Animals K99373 and K99383 in the first two groups					
n/N (%)	0/9 (0)	3/9 (33.3)	13/17 (76.5)	16/17 (94.1)	9/10 (90.0)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.333 [0.071, 0.701] 0.0488	0.765 [0.400, 0.932] <0.0001	0.941 [0.619, 0.999] <0.0001	0.900 [0.477, 0.998] <0.0001
Adjusted exact 95% confidence interval		-0.1952, 0.7714	0.219, 0.955	0.426, 1.000	0.354, 0.999
Calculation includes animals that were bacteremic at some time prior to treatment (enriched bacteremia), excluding animal K99373 and K99383 in the first two groups					
n/N (%)	0/9 (0)	3/8 (37.5)	11/15 (73.3)	13/14 (92.9)	8/9 (89)
Difference in survival proportion compared with placebo [exact 95% confidence] one-sided p-value		0.375 [-0.022, 0.755] 0.032	0.733 [0.298, 0.9251] 0.0002	0.929 [0.593, 0.998] <0.0001	0.889 [0.454, 0.997] <0.0001
Adjusted exact 95% confidence interval		-0.142, 0.822	0.208, 0.955	0.413, 1.000	0.326, 0.999

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Reviewer Comment: These results demonstrate that obiltoxaximab is efficacious in preventing death due to anthrax when administered therapeutically to NZW rabbits with inhalational anthrax.

The following Kaplan-Meier survival curve shows the results of the time to death for each dose group and the placebo. The difference in time to death between any treatment group and the placebo group was statistically significant, except for the 1 mg/kg obiltoxaximab group. All placebo (saline) animals were dead by study Day 7.

Figure 6.28. Study AR021: Kaplan-Meier Survival Curve by Treatment Group



ETI-204: obiltoxaximab.

Note: The placebo group does not include two animals (K99373 and K99383) inadvertently dosed with levofloxacin. Including these two surviving animals did not change the overall p-value shown in the graph.

Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

The differences in survival rates between the obiltoxaximab 4and 16mg/kg IV , and levofloxacin 50mg /kg (oral) group compared to the placebo group were statistically significant, Table 6.37.

Table 6.37. Study AR021: Comparison of time from challenge to death among groups, two-sided p-values of pairwise log-rank

	ETI-204 1 mg/kg IV	ETI-204 4 mg/kg IV	ETI-204 16 mg/kg IV	Levofloxacin 50 mg/kg
Placebo	0.0878	<0.0001	<0.0001	<0.0001

Not including animals inadvertently doses with levofloxacin (K99373 and K99383). Including these two surviving animals in the intended groups changed the first p-value for the 1mg/kg dose group from 0.0878 to 0.147.
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Efficacy Results - Secondary and other relevant endpoints

The time between challenge, trigger, and treatment are summarized in Table 6.38.

Bacteremia
The time to qualitative bacteremia was longer in the first three treatment groups, compared with that in the 16 mg/kg group and the levofloxacin group. Fifty-four (87%) animals were bacteremic prior to treatment (this excludes the two mis-dosed rabbits). Of the 20 rabbits that died, 20 (100%) were bacteremic at the time of death. All rabbits that survived to the end of the study had negative blood cultures by Day 7 and remained negative for the duration of the 28-day study.

Table 6.38. Study AR021: Time from Challenge to Bacteremia, Trigger, and Treatment in NZW Rabbits

	Placebo (N=10)	ETI-204 1 mg/kg IV (N=10)	ETI-204 4 mg/kg IV (N=17)	ETI-204 16 mg/kg IV (N=17)	Levofloxacin 50 mg/kg PO (N=10)	Total (N=64)
Time to qualitative bacteremia (hours)						
N	9*	9*	15	14	7	54
Mean(SD)	37.7 (21.8)	43.3 (25.5)	38.2 (15.2)	27.5 (3.7)	25.0 (2.3)	34.5 (16.7)
Range	23.8, 94.1	23.7, 104.3	23.6, 60.7	23.8, 35.7	23.7, 30.1	23.6, 104.3
Time to trigger (hours)						
Mean (SD)	29.95 (7.61)	26.49 (4.70)	27.65 (4.13)	28.77 (5.25)	24.85 (3.38)	27.69 (5.20)
Range	20.88, 43.82	21.80, 35.57	22.20, 35.58	21.62, 40.30	18.48, 30.43	18.48, 43.82
Time to significant increase in body temperature (hours)						
N	5	4	11	9	4	33
Mean (SD)	32.3 (10.4)	25.9 (5.1)	28.5 (4.5)	30.2 (5.8)	24.4 (4.9)	28.7 (6.2)
Range	20.9, 43.8	21.8, 32.9	22.2, 35.6	21.6, 40.3	18.5, 30.4	18.5, 43.8
Time from trigger to treatment (hours)						
Mean (SD)	1.73 (1.19)	1.73 (1.19)	1.40 (1.21)	1.61 (1.34)	2.09 (1.38)	1.69 (1.27)
Range	0.27, 3.45	0.27, 3.45	0.23, 3.45	0.23, 3.50	0.20, 3.88	0.18, 3.88

*Two animals (K99373 and K99383) were negative for *B. anthracis* in the laboratory (LB) data set

Dose Response

A dose response was observed; as the dose increased from 4mg to 16mg/kg IV, the survival rate increased from 76% to 94%.

Durability of Response

Single doses of obiltoxaximab 4mg/kg or 16mg/kg IV were effective in preventing death in 13 (79%) and 16 (94%) NZW rabbits, respectively, up to Day 28 (end of study) at which time these animals were terminally sacrificed per protocol.

Persistence of Effect

There was no recurrence of bacteremia to the end of the study, Day 28.

Additional Analyses Conducted on the Individual Trial

Results of subgroup analyses by gender or challenge dose at Day 28 are shown in Table 6.39. Survival proportions were higher in the female animals than in the male animals across dose groups. The sample sizes for challenge dose categories were too small to draw conclusion about survival rates.

Table 6.39. Study AR021: Survival Outcomes in NZW Rabbits by Gender and Challenge Dose at Day 28

	Placebo (N= 10)	ETI-204 1 mg/kg IV (N= 10)	ETI-204 4 mg/kg IV (N= 17)	ETI-204 16 mg/kg IV (N= 17)	Levo 50 mg/kg PO (N= 10)	Total (N= 64)
Gender						
Female	1/5 (20%)	3/5 (60%)	9/9 (100%)	8/8 (100%)	5/5 (100%)	26/32 (81.3%)
Male	0/5	1/5 (20%)	4/8 (50%)	8/9 (88.9%)	4/5 (80%)	17/32 (53.1%)
Challenge Dose (LD_{50}) (n(%))						
<250	1/9 (11.1%)	4/10 (40%)	11/14 (78.6%)	15/16 (93.8%)	9/10 (90.0%)	40/59 (67.8%)
≥ 250	0/1		2/3 (66.7%)	1/1 (100.0%)		3/5 (60.0%)

levo: levofloxacin;

Reviewer Comment: There were no obvious differences in the manifestations of inhalational anthrax in male and female animals. The differences in survival rates between females and males may be related to the relatively low numbers of animals in the study. Significant differences in survival rates for male and female animals were not evident in the NZW rabbit monotherapy efficacy study, AR033.

In this study, 41(66%) of rabbits survived to Day 28, 7(11%) were euthanized before Day 28 and 14(23%) were found dead. The perecentage of rabbits found dead was lower than the 50% of animals found dead in the monotherapy efficacy studies in the cynomolgus macaques, Table 6.40.

Table 6.40. Study AR021: Survival Outcomes in NZW Rabbits Post-treatment with Obiltoxaximab

Group No.	Description of Planned Arm	FOUND DEAD, N = 14	MORIBUND SACRIFICE, N = 7	TERMINAL SACRIFICE i.e., SURVIVORS TO DAY 28, N = 41
1	Placebo (saline-IV bolus or water for injection via oral gavage) N=9*	8	1	0
2	1 mg/kg IV ETI-204 N=9*	4	2	3 (5%)
3	4 mg/kg IV ETI-204 N=17	1	3	13(21%)
4	16 mg/kg IV ETI-204 N=17	0	1	16(26%)
5	50 mg/kg Levofloxacin N=10	1	0	9 (14%)
Total no. Animals N=62		14(23%)	7 (11%)	41(66%)

*Two animals mis-dosed with levofloxacin (one each from group 1 and group 2, respectively) are excluded.

Clinical Observations

The most common clinical observations made post-challenge were a decrease in food consumption, lethargy, soft stool or absent stool, and respiratory abnormalities. Generally, surviving animals returned to normal baseline between 5 to 8 days post-challenge other than occasional inappetence.

Clinical signs of anthrax disease were not generally observed until within 24 hours of death at which time the rabbits became progressively lethargic and weak. Fulminating disease was described as an all-or-none response; no protracted illness was observed regardless of the challenge dose. Several rabbits exhibited brief periods of excitation and hyperactivity within hours or minutes before death.

Necropsy and Histopathology
Gross lesions in multiple organs including lung and brain were typical of anthrax in NZW rabbits and correlated histologically with hemorrhage, necrosis, edema and acute inflammation. No gross lesions were evident among the surviving animals that were terminated at study completion. Microscopic findings considered consistent with anthrax were present in all rabbits that died or became moribund during the study. Lesions typical of anthrax had microscopic evidence of acute fibrinous to heterophilic inflammation, necrosis, hemorrhage, edema, and the presence of large rod-shaped bacteria in the brain (meninges), heart, kidney, liver, lung, and spleen. *See pharmacology/toxicology review by Dr. Amy Nostrandt DVM, for further details on the histopathological findings.*

Summary of Key Findings

In this study in NZW rabbits, the 16 mg/kg IV dose of obiltoxaximab was statistically superior to placebo for rate of survival at Day 28. This study also supports the efficacy of the 4 mg/kg IV dose for treatment. Surviving animals returned to normal baseline between 5 to 8 days post-challenge with *B. anthracis*.

6.6 Study AR033

6.6.1 Study Design

Overview and Objective

Study AR033 evaluated the efficacy of obiltoxaximab when administered therapeutically in NZW rabbits infected with *B. anthracis*. The objective was to explore a range of therapeutic doses of obiltoxaximab in *B. anthracis*-challenged rabbits and collect data for pharmacokinetic (obiltoxaximab serum levels), quantitative free PA, and quantitative bacteremia to support selection of the human dose.

Trial Design

This was a randomized, blinded, placebo-controlled, parallel group, trigger-to-treat, dose-ranging study in *B. anthracis* challenged NZW rabbits. Healthy rabbits weighing between 3 to 4 kg were included in the study. The age of the rabbits was not a criterion for study entry. The target inhaled dose was 200 LD_{50} of aerosolized *B. anthracis (*Ames strain*)* spores. In the first step, 70 rabbits were randomized (prior to challenge) by weight into one of five groups of 14 animals (with each group containing 7 males, 7 females).
The animals were then randomized to one of three challenge days (second step) and a challenge order per day (third step). There were three challenge days because all animals on study could not be challenged in a single day, there were 23 rabbits each on

Challenge Days A and B and 24 rabbits on Challenge Day C. The remaining eight animals served as replacements. The study design of Study AR033 is summarized in Table 6.41.

Table 6.41. Study AR033: Overview of Study Design

Blinded Group Assignment	Obiltoxaximab mg/kg IV bolus	Number of Animals N = 70
4	0 (IV Saline, Placebo)	14
3	1	14
1	4	14
5	8	14
2	16	14

Initiation of intravenous (IV) obiltoxaximab or saline (control) treatment for each rabbit was based on a positive result in a qualitative, ECL assay to detect PA (PA-ECL) in blood or a significant increase in body temperature (SIBT). Animals received single IV bolus doses of obiltoxaximab 1, 4, 8, or 16 mg/kg. Animals were monitored for up to 28 days post-challenge for clinical signs of anthrax, hematological abnormalities, abnormal C-reactive protein (CRP) levels, quantitative bacteremia, and circulating levels of free PA as assessed quantitatively by an ELISA (PA-ELISA).
All surviving rabbits were euthanized at the end of the in-life phase on study Day 28.
Complete gross necropsies and histopathology evaluations of the lungs, liver, spleen, kidney, mediastinal or bronchial lymph nodes, spinal cord, and any gross lesions were conducted on all rabbits found dead or euthanized due to illness (found moribund) to confirm *B. anthracis* infection as well as all rabbits that survived to the end of the study.

Study Endpoints

The primary endpoint was survival to Day 28 post-challenge with *B. anthracis* spores.

Statistical Analysis Plan

The survival data from each treatment group was compared to the control (saline IV) group using a one-sided Fisher's exact test (0.025 level).

Sample Size Calculation

With an assumption that the true probabilities of survival were 5% and 70% in the control group and a treated group, respectively, 14 animals per group would provide 83.4% statistical power, using a two-sided, 0.05 level, Fisher's exact taking into account a Bonferroni adjustment

to control for multiple comparisons across four tests. Reviewer Comment: Using a two-sided type I error of 0.0125 the biostatistics reviewer, Dr. Li, replicated this sample size calculation.

Analysis Populations

The primary analysis excluded animals that were not positive for bacteremia by culture (qualitative, quantitative, or enriched) at some time point prior to treatment, but included animals that died prior to treatment as treatment failures regardless of the presence or absence of bacteremia.

A secondary analysis included all challenged animals regardless of bacteremia status and included those animals that received treatment.

Statistical Methods
The survival data from each treatment group were compared to the control group using a two-sided Fisher's exact test, using a Bonferroni adjustment for multiple comparisons.

Protocol Amendments

Amendment #1: The sponsor selected an alternative testing facility for the ETI-204 serum concentration and anti-ETI-204 antibody serum concentration analyses.
Amendment #2: Included a clarification of the microbiological assessments of tissues obtained at necropsy.
Amendment#3: Technicians analyzing the samples for quantitative PA were to remain blinded to group assignments until all samples have been analyzed. Pathology specialists were scheduled to assess eight sections of each rabbit brain.
Amendment #4: Administrative updates were added in the protocol
Amendment #5: Clarification of the name of the neuropathologist (b) (6) who evaluated brain pathology. Amendment #6: Based on FDA comments, the statistical analysis used to analyze survival results was changed from a two-sided Fisher's exact test at the 0.05 level to a one-sided Fisher's exact test at the 0.025 level. (Both statistical methods gave the same answer).
Amendment #7: This amendment included updates on management changes at the (b) (4).

Reviewer Comment: The protocol amendments were accceptable.

6.6.2 Study Results

Compliance with Good Laboratory Practices

The Applicant submitted a statement that Study AP202 was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21CFR Part 58).

Patient Disposition

See demographics Table 6.42.

Protocol Violations/Deviations

The protocol deviations did not significantly impact the conduct or integrity of the study.

Table of Demographic Characteristics

A total of 70 healthy NZW rabbits were included in the study. All animals survived to receive treatment and were included in the analyses. These variables were comparable across different groups except for the slightly lower challenge dose in the 8 mg/kg obiltoxaximab group. Twenty-four percent (17/70) and 76% (53/70) of the animals were treated based on a positive PA-ECL result or a SIBT, respectively. Demographic variables and baseline characteristics of the study animals are summarized in **Table 6.42**.

Table 6.42. Study AR033: Demographic Variables and Baseline Characteristics

	Placebo/ saline IV (N=14)	ETI-204 1 mg/kg IV (N=14)	ETI-204 4 mg/kg IV (N=14)	ETI-204 8 mg/kg IV (N=14)	ETI-204 16 mg/kg iV (N=14)	Total (N=70)
Age (month)						
Mean (SD)	8.9 (1.2)	9.3 (2.0)	9.8 (2.2)	8.9 (2.2)	9.9 (3.5)	9.4 (2.3)
Range	7.0, 12.0	7.0, 12.0	7.0, 15.0	7.0, 13.0	7.0, 19.0	7.0, 19.0
Gender [n (%)]						
Female	7 (50.0)	7 (50.0)	7 (50.0)	7 (50.0)	7 (50.0)	35 (50.0)
Male	7 (50.0)	7 (50.0)	7 (50.0)	7 (50.0)	7 (50.0)	35 (50.0)
Body weight (kg)						
Mean (SD)	3.6 (0.2)	3.5 (0.2)	3.6 (0.2)	3.5 (0.1)	3.6 (0.2)	3.5 (0.2)
Range	3.3, 3.8	3.2, 3.9	3.2, 3.8	3.2, 3.7	3.2, 4.0	3.2, 4.0
CHALLENGE DOSE						
Challenge dose (LD_{50})						
Mean (SD)	201.6 (33.8)	208.7 (27.8)	208.5 (45.4)	188.6 (38.0)	196.1 (30.2)	200.7 (35.4)

Range	132.0, 263.0	155.0, 255.0	102.0, 278.0	137.0, 290.0	129.0, 238.0	102.0, 290.0
Subjects that received Challenge dose (LD_{50}) (n(%))						
<200	6 (42.9)	3 (21.4)	6 (42.9)	12 (85.7)	5 (35.7)	32 (45.7)
200 or higher	8 (57.1)	11 (78.6)	8 (57.1)	2 (14.3)	9 (64.3)	38 (54.3)
Challenge dose (x 10^7 cfu)						
Mean (SD)	2.116 (0.354)	2.193 (0.291)	2.190 (0.477)	1.982 (0.401)	2.060 (0.316)	2.108 (0.372)
Range	2.110	2.250	2.155	1.920	2.160	2.110
BACTEREMIA						
Subjects with Qualitative direct bacteremia prior to treatment [n (%)]	13 (92.9)	12 (85.7)	11 (78.6)	13 (92.9)	13 (92.9)	62 (88.6)
Bacteremia prior to treatment (cfu/mL)						
Geometric mean	705.9	1310.1	1937.1	2050.0	1362.2	1379.9
95% confidence interval	81.7, 6098.6	131.2, 13085	248.4, 15108.3	280.8, 14966.8	193.7, 9581.3	593.2, 3209.9
PROTECTIVE ANTIGEN						
Subjects with PA-ECL positivity at trigger (n(%))	2 (14.3)	3 (21.4)	5 (35.7)	5 (35.7)	2 (14.3)	17 (24.3)
PA-ELISA prior to treatment (ng/mL)						
Geometric mean	5.3	5.5	5.7	5.7	5.8	5.6
95% confidence interval	4.3, 6.6	4.2, 7.2	4, 8.2	4.5, 7.3	3.9, 8.8	5, 6.4
SIBT						
Subjects with a SIBT as trigger (n(%))	12 (85.7)	11 (78.6)	9 (64.3)	9 (64.3)	12 (85.7)	53 (75.7)

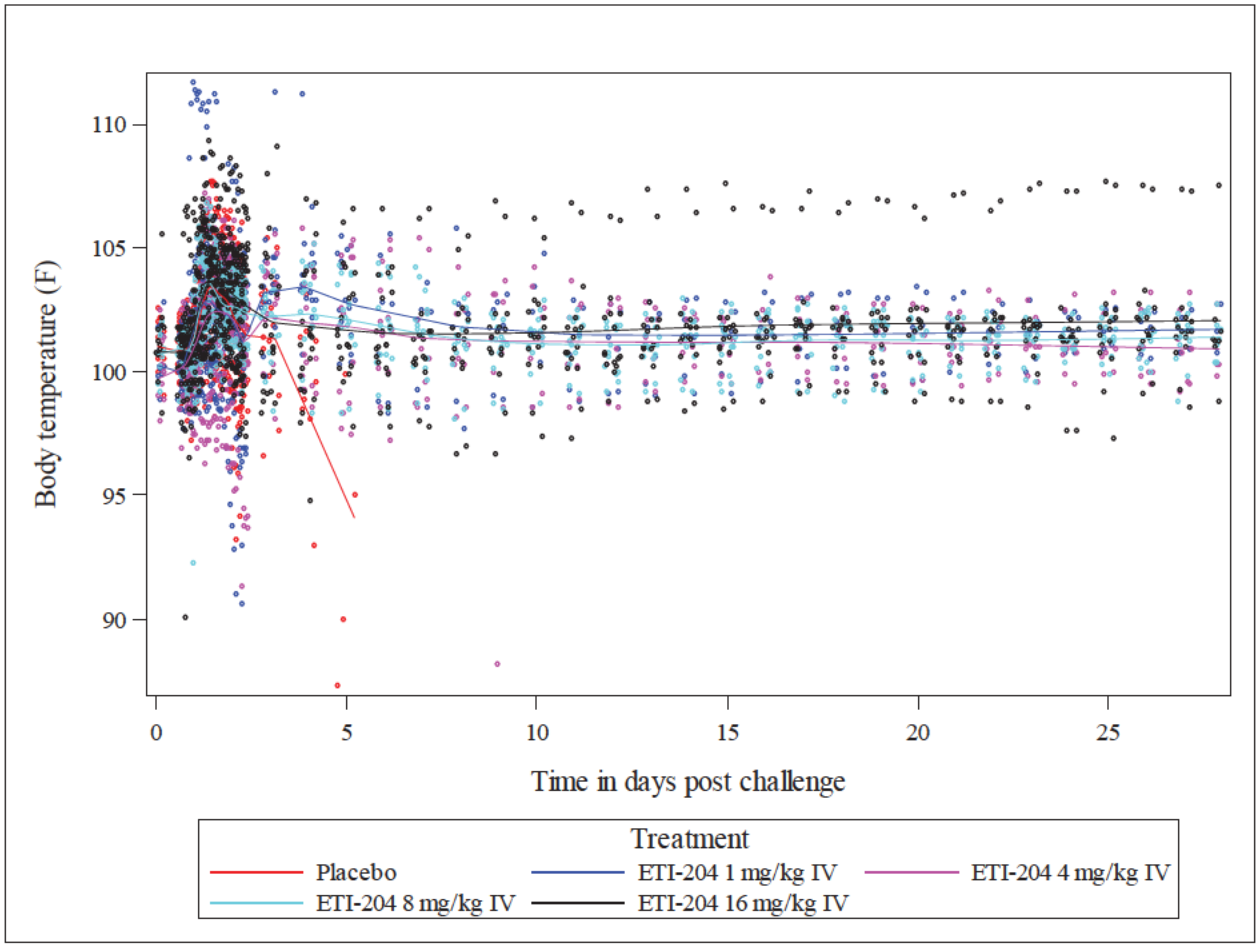
SIBT: Significant increase in body temperature. Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Trigger to Treat

Initiation of intravenous (IV) ETI-204 or saline (control) treatment for each rabbit was based on a positive result in a qualitative, PA-ECL assay for PA or a SIBT. Seventy-six percent (53/70) of the rabbits were treated based on body temperature. The mean time from challenge until a SIBT for the treatment groups was between 26 to 28 hours. Body temperatures in the placebo group dropped as they succumbed to anthrax.

At three to five days post-challenge, mean body temperatures of rabbits in the 4 mg/kg, 8mg/kg, and 16 mg/kg IV obiltoxaximab groups and the levofloxacin group returned to baseline. The average body temperature results from challenge through to Day 28 (end of study) are shown in Figure 6.29.

Figure 6.29. Study AR033: Mean Body Temperature over Time by Treatment



Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Efficacy Results - Primary Endpoint

All control/placebo animals died which indicates that the inoculum of inhaled *B. anthracis* was adequate to cause lethal disease. Twenty-nine (41%) animals survived to Day 28 and were euthanized. Thirty-six (51%) rabbits were found dead which indicates how quickly animals succumbed to anthrax between the 6-hourly observation time points. Five (7%) animals were found moribund and were euthanized.

Table 6.43. Study AR033: Survival Outcomes by Treatment Group in NZW Rabbits

GROUP No.	TREATMENT ARM	FOUND DEAD	MORIBUND SACRIFICE	TERMINAL SACRIFICE = SURVIVORS	SUBJECTS N=70
4	0 mg/kg (Saline,	14 (20%)	0	0	14 (20%)
3	1 mg/kg ETI-204	9 (13%)	1 (1%)	4 (6%)	14 (20%)
2	16 mg/kg ETI-204	4 (6%)	1 (1%)	9 (13%)	14 (20%)
1	4 mg/kg ETI-204	6 (9%)	2 (3%)	6 (9%)	14 (20%)
5	8 mg/kg ETI-204	3 (4%)	1 (1%)	10 (14%)	14 (20%)
All Groups		36 (51%)	5 (7%)	29 (41%)	70 (100%)

NZW = New Zealand white; Source: Table constructed by reviewer using JReview v.9.2

Animals treated with obiltoxaximab at 4, 8, and 16 mg/kg IV were statistically significantly different from the placebo group in the analysis of survival outcomes which included all animals regardless of bacteremia status prior to treatment. In the qualitatively bacteremic animals, only the 8 and 16 mg/kg treatment groups had a significant treatment effect with a 69% and 62% survival rate, respectively.

Table 6.44. Study AR033: Survival at Day 28 by Treatment Group in all Animals

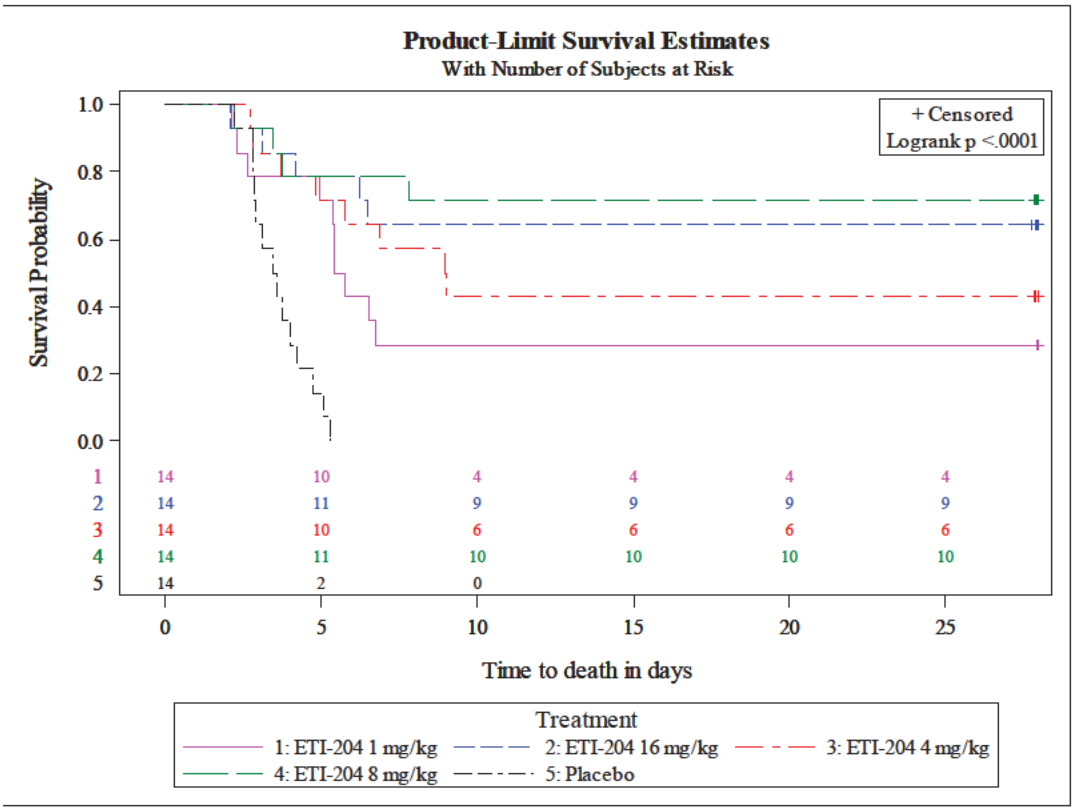
	Placebo (N=14)	ETI-204 1 mg/kg IV (N=14)	ETI-204 4 mg/kg IV (N=14)	ETI-204 8 mg/kg IV (N=14)	ETI-204 16 mg/kg IV (N=14)
n/N (%)	0/14	4/14 (28.6)	6/14 (42.9)	10/14 (71.4)	9/14 (64.3)
Difference in survival proportion compared with placebo [95% CI] p-value*		0.286 [0.012, 0.581] 0.02081	0.429 [0.135, 0.711] 0.003	0.714 [0.406,0.916] <0.001	0.643 [0.334,0.872] 0.001
Exact 95% confidence interval		-0.077, 0.649	0.044, 0.769	0.312, 0.944	0.237, 0.909
Including only qualitatively bacteremic animals					
n/N (%)	0/13	2/12 (16.7)	3/11 (27.3)†	9/13 (69.2)	8/13 (61.5)
Difference in survival proportion compared with placebo [95% CI] one-sided p-value*		0.167 [-0.098, 0.484] 0.118	0.273 [-0.031, 0.610] 0.036	0.692 [0.367, 0.909] <0.001	0.615 [0.290, 0.861] <0.001
Exact 95% confidence interval		0.208, 0.563	-0.138, 0.683	0.268, 0.939	0.189, 0.901

[Differences in survival calculated by the biostatistics reviewer using a Bonferroni adjustment (one-sided significance level of 0.00625)].Two-sided 95% confidence interval and one-sided p-values were calculated by the biostatistics reviewer, Xianbin Li, Ph.D.
†Animal L48722 had negative qualitative blood cultures, but had positive quantitative blood cultures bacteremia (mean *B. anthracis count* < 10 cfu/mL) prior to treatment and at 4 hours post treatment, and it was included in the Applicants's analysis, but was excluded in this analysis. If this rabbit was included, the survival proportion was 0.333 (4/12), which would be less conservative in the comparison with the placebo group.

Kaplan-Meier Survival Curve

The following Kaplan-Meier survival curve shows the results of the time to death for each treatment group and placebo. The difference in time to death between any treatment group and the placebo group was statistically significant [Bonferroni adjustment (two-sided significance level of 0.0125)]. All placebo (IV saline) animals were dead by Day 5 or Day 6.

Figure 6.30. Study AR033: Kaplan-Meier Survival Curve by Treatment Group



Source: Graph constructed by biostatistics reviewer, Xianbin Li, PhD.

Log Rank Test

The following table compares time from challenge to death among groups using two-sided p-values of pairwise log-rank tests. The differences in time to death between all the treatment groups and the placebo group were statistically significant.

Table 6.45. Study AR033: Comparison of Time from Challenge to Death among Dose Groups (two-sided p-values of pairwise log-rank tests)

	ETI-204 1 mg/kg (N=14)	ETI-204 4 mg/kg (N=14)	ETI-204 8 mg/kg (N=14)	ETI-204 16 mg/kg (N=14)
Placebo	0.0003	0.0001	<0.0001	<0.0001

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

The time from challenge to bacteremia, time to trigger, and the time from trigger to treatment was comparable across all treatment groups, Table 6.46. The SIBT (trigger) in the study report was verified by deriving the time from the Applicant's temperature dataset.

Table 6.46. Study AR033: Time between Challenge, Trigger, Bacteremia, and Treatment

	Placebo (N=14)	ETI-204 1 mg/kg (N=14)	ETI-204 4 mg/kg (N=14)	ETI-204 8 mg/kg (N=14)	ETI-204 16 mg/kg (N=14)	Total (N=70)
Time to bacteremia (quantitative) (hours)						
N	14	12	13	14	12	65
Mean (SD)	36.7 (20.8)	31.3 (13.6)	28.2 (6.5)	30.1 (12.2)	34.8 (18.9)	32.2 (15.2)
Range	22.1, 103.7	22.9, 73.7	23, 44.8	22.4, 69	23.7, 92.6	22.1, 103.7
Time to trigger (hours)						
Mean (SD)	25.78 (5.30)	26.83 (3.61)	27.40 (5.87)	25.94 (4.75)	27.73 (5.34)	26.74 (4.95)
Range	18.42, 36.92	20.43, 33.35	19.78, 42.82	19.88, 36.32	17.83, 37.07	17.83, 42.82
Time from trigger to treatment (hours)						
Range	0.95 (1.23)	0.95 (1.05)	1.60(1.35)	1.45 (1.55)	0.71 (0.75)	1.13 (1.23)
Mean (SD)	0.30, 4.48	0.28, 3.22	0.37, 4.25	0.23, 4.22	0.27, 2.82	0.23, 4.48

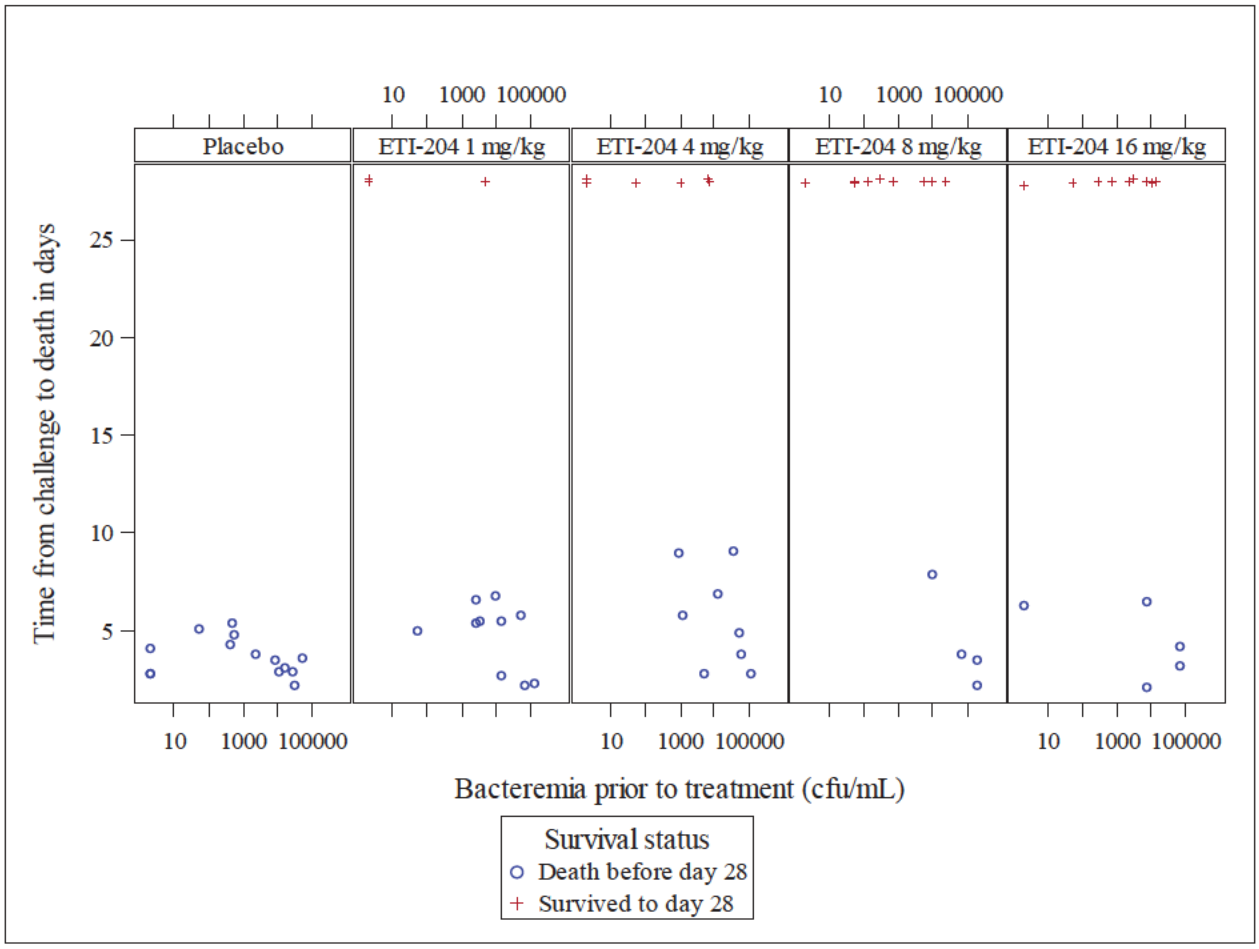
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Efficacy Results - Secondary and other relevant endpoints

Time to Death by Bacteremia and PA Levels

The time to death versus the level of bacteremia prior to treatment is summarized in Figure 6.31. Deaths occurred at all bacteremia levels and there was no cut-off point prior to treatment to predict surviving and non-survivors.

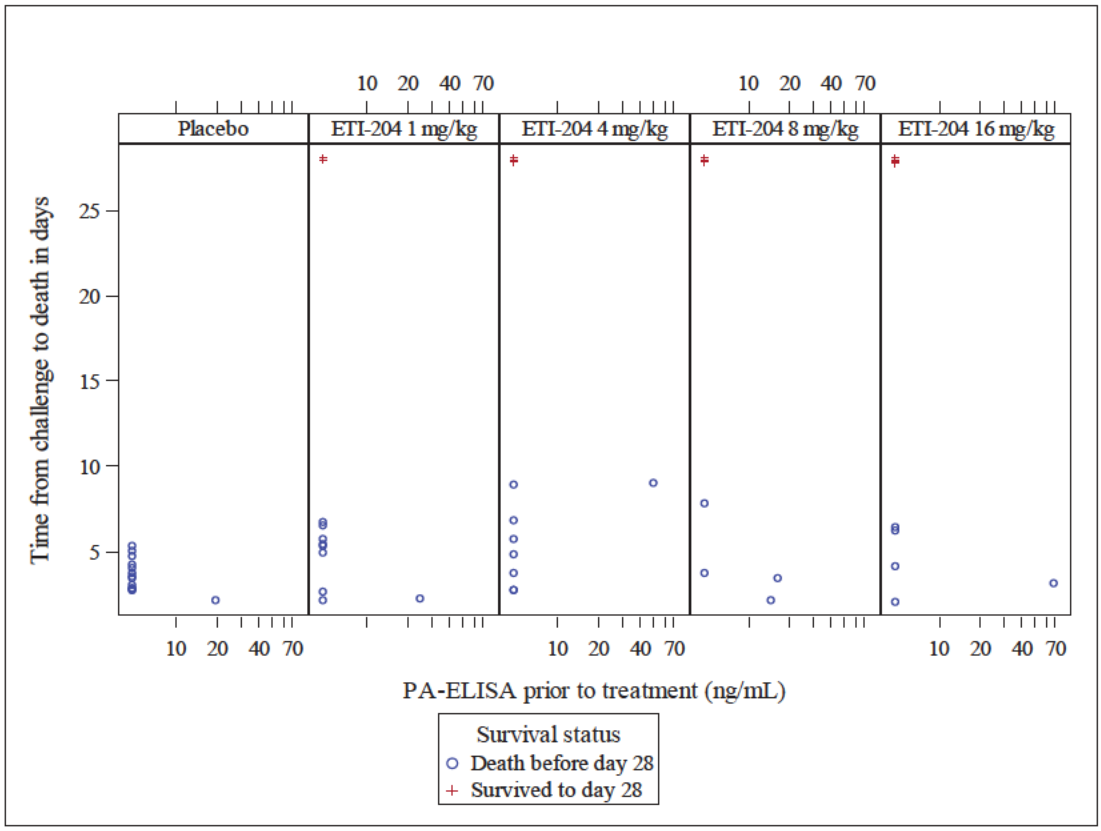
Figure 6.31. Study AR033: Time to Death vs. Bacteremia PTT by Survival Status at Day 28



PTT: prior to treatment
Source: Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

All animals in the control group died regardless of the level of PA. Animals in the treatment groups with a PA less than the lower limit of quantification (LLOQ) were more likely to survive, Figure 6.32.

Figure 6.32. Study AR033: Time to death versus PA-ELISA prior to treatment by survival status at Day 28

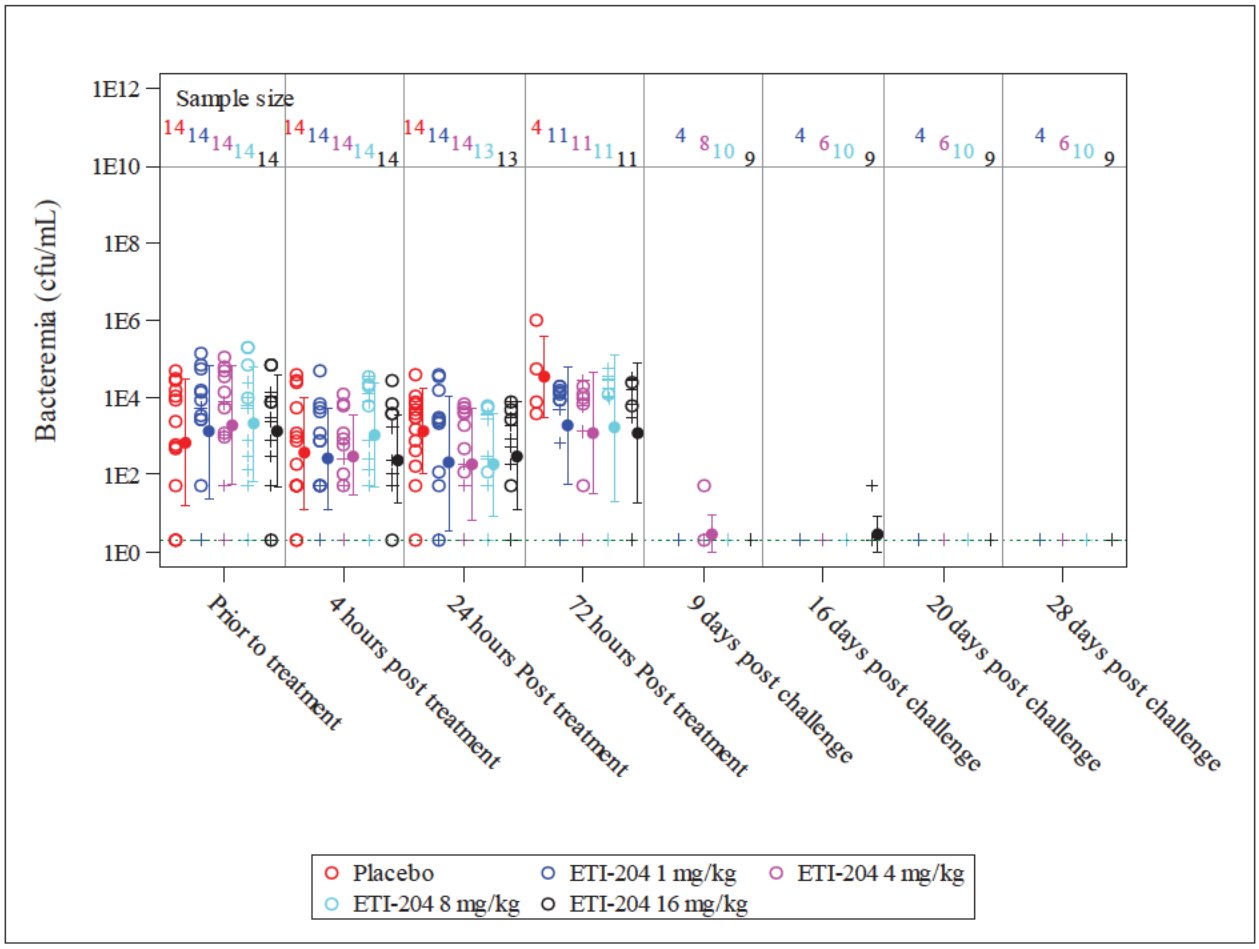


Reviewer Comment: Rabbits that died had lower PA levels prior to treatment than the PA levels observed prior to treatment in the cynomolgus macaque monotherapy studies.

Bacteremia

There were no significant differences among the study groups with regard to the proportion of animals with bacteremia at any time point post-challenge, **Figure 6.33**. The majority of the non-survivors were dead by 72 hours post challenge. Blood cultures (bacteremia cfu/mL, geometric mean and standard deviation are shown) became negative after Day 8 or 9 post-challenge in the majority of rabbits that survived. One survivor, L48757, in the 16mg/kg IV group had a transient low level of bacteremia (1 to 5 colonies in the qualitative/enriched cultures) at Day 16 post-challenge however the quantitative blood cultures for *B. anthracis* were negative. Bacteremia was not detected in this animal L48757after Day 16 through the end of the study. The PA-ELISA levels in Animal L48757 were below the LLOQ at Day 16, and all the time points throughout the study.

Figure 6.33. Study AR033: Bacteremia Levels (geometric mean ± SD) over Time by Survival Status



+: survived to Day 28; o: death before Day 28. Bacteremia, LOD: 3 cfu/mL; SD: standard deviation

Protective Antigen

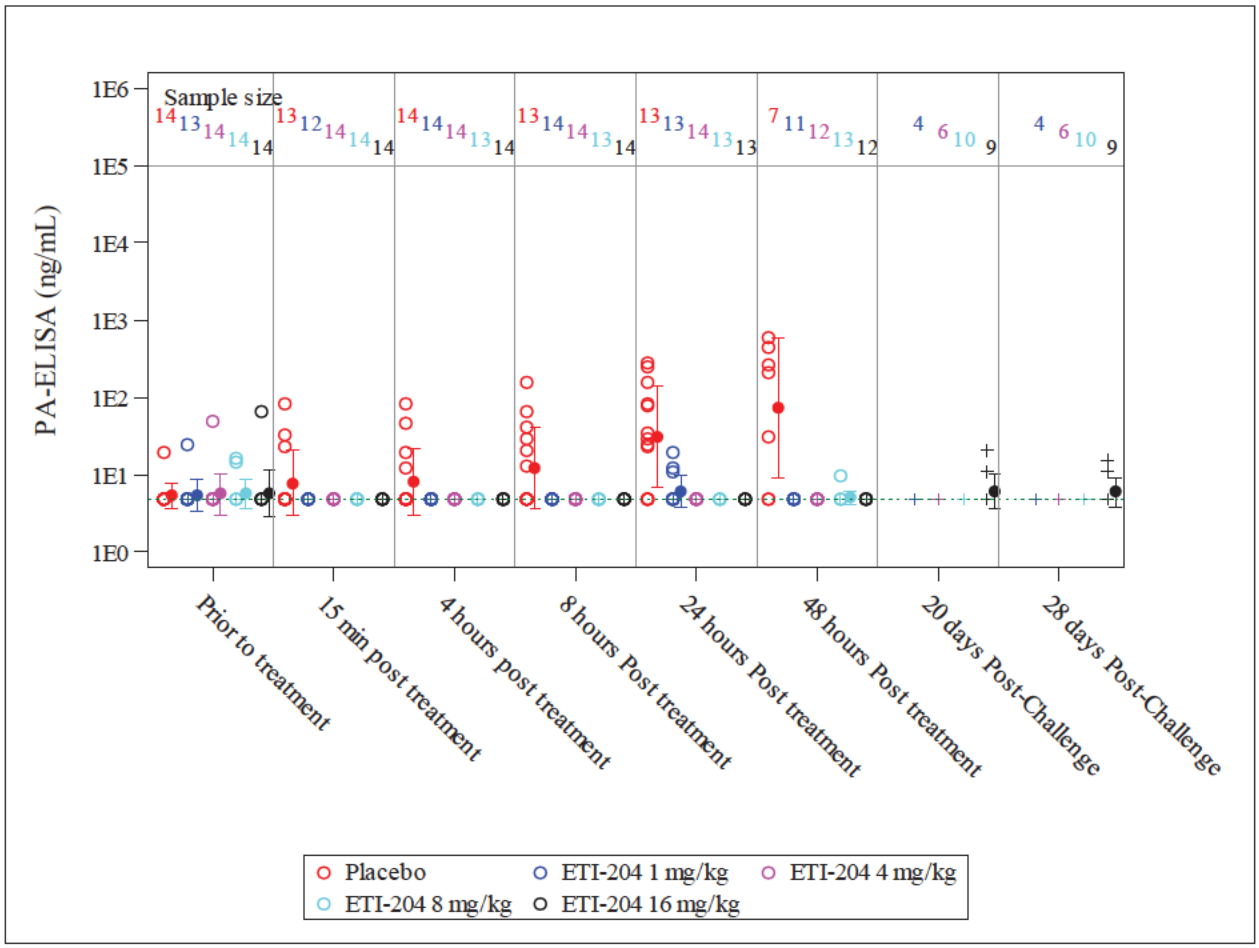
Animals with a positive PA prior to treatment in each of the treatment group are summarized in **Figure 6.34**. A positive PA-ELISA was present in 6/70 (8.5%) of the rabbits at some point prior to treatment. In the placebo group, PA-ELISA levels increased until death. In the other groups, except for the 1 mg/kg group, the PA-ELISA levels did not increase, indicating a treatment effect of obiltoxaximab. At the 8 hour, 24 hour, and 48 hour post-treatment time points, the saline control group had significantly more animals with free PA above the LLOQ (9.68 ng/mL) as compared to all of the obiltoxaximab -treated groups ($p < 0.0001$, Fisher's Exact Test).

None of the obiltoxaximab-treated survivors had a free PA value above the LLOQ at any time point prior to treatment. However, in the 16 mg/kg group, three surviving animals had detectable levels of PA level above the LLOQ post-treatment; these results may have been false positives as the levels were close to the LLOQ. For example, Animal L48770 had values of

ranging from 10 to 12 ng/mL on Days 8 and Day 28 post-challengerespectively. Animal L48758 had a PA values that decreased from 37ng/mL on Day 8 to 15 ng/mL on Day 28 (scheduled sacrifice time point).

Reviewer Comment: Animals with PA levels below the LLOQ prior to treatment were more likely to survive. A total of 29 (41%) animals survived to Day 28 and were euthanized. Twenty (69%) of the terminal blood samples (blood collected prior to euthanasia or after animal was found dead) had free PA levels above the LLOQ. The high percentage of blood samples from survivors with detectable PA suggests a lack of specificity of the PA- ELISA assay and/or the specified cut-off value for a positive result.

Figure 6.34. Study AR033: PA-ELISA (Geometric Mean ± SD) over Time by Survival Status



+: survived to Day 28; o: death before Day 28; PTT: prior to treatment; dotted line: LLOQ of PA (9.68ng/mL); SD: standard deviation

CNS and Cerebrospinal fluid (CSF)
Eighty-five percent 22/26 (85%) rabbits that died on study had evidence of anthrax meningitis with positive CSF for presence of bacteria indicating disseminated disease. All animals that survived had negative CSF bacterial cultures. There were no positive pathological findings in the brains of survivors. *For further detail, see review of histopathological findings by clinical pharmacology reviewer, Amy Nostrandt, DVM.*

Tissue Bacterial Cultures and Pathological Findings in the Brain
Almost all of the animals that succumbed to anthrax had a positive *B. anthracis* culture from the tissues tested i.e., bronchial lymph node, brain, liver and spleen. One (11.1%) animal, L48752, out of the nine surviving animals in the 16 mg/kg group had a positive *B. anthracis* culture in a bronchial lymph node among all of the tissues (brain, kidney, lung, liver and spleen) tested. Among non-survivors, 2(14.3%), 1(10%), 1(25%), and 2(40%) animals had brain discoloration(s) in the 0, 1, 8, 16 mg/kg groups, respectively. There were no positive pathological findings in the brains of survivors.

Clinical Observations
The most common clinical observations in the rabbits within the first few days post-challenge were lethargy, respiratory abnormalities, and reduced food consumption. In the animals that succumbed to anthrax, there was a characteristic rapid progression of signs of disease from unremarkable to lethargy, respiratory abnormalities, and moribundity. Survivors returned to their baseline between 7 to 11 days post-challenge.

Dose/Dose Response

Animals treated with obiltoxaximab 8mg and 16 mg/kg IV had higher survival rates of 71%, 64% respectively than the survival rate (43%) in the obiltoxaximab at 4mg/kg dose. The trend was similar in bacteremic animals.

Durability of Response

A single dose of obiltoxaximab 8mg or 16mg/kg was effective in preventing death in 10/14 (71%) and 9/14 (64%) animals up to Day 28 (end of study)..

Persistence of Effect

There was no recurrence of *B. anthracis* bacteremia or clinical symptoms up to the end of the study, Day 28.

Additional Analyses Conducted on the Individual Trial

Survival results for subgroup analyses by gender, challenge dose, log_{10} bacteremia, and PA level are summarized in **Table 6.47**. The sample sizes were too small to observe a reliable trend for each of the variables.

Table 6.47. Study AR033: Survival at Day 28 by Gender, Challenge dose, Log_{10} Bacteremia, PA prior to Treatment

	Placebo (N= 14)	ETI-204 1 mg/kg IV (N= 14)	ETI-204 4 mg/kg IV (N= 14)	ETI-204 8 mg/kg IV (N= 14)	ETI-204 16 mg/kg IV (N= 14)	Total (N= 70)
Gender Female	0/7	1/7 (14.3%)	4/7 (57.1%)	5/7 (71.4%)	5/7 (71.4%)	15/35 (42.9%)
Male	0/7	3/7 (42.9%)	2/7 (28.6%)	5/7 (71.4%)	4/7 (57.1%)	14/35 (40.0%)
Challenge dose (LD_{50})						
<250	0/1	1/1 (100%)	2/2 (100%)	0/1	0	3/5 (60%)
250 or higher	0/13	4/12 (33.3%)	6/13 (46.2%)	10/12 (83.3%)	9/13 (69.2%)	29/63 (46.0%)
PA prior to treatment (ng/mL)						
0 - < 10	0/13	4/12 (33.3%)	6/13 (46.2%)	10/12 (83.3%)	9/13 (69.2%)	29/63 (46.0%)
10 - < 50	0/1	0/1	0/1	0/2	0	0/5
50 or higher	0	0	0	0	0/1	0/1
Bacteremia prior to treatment (cfu/mL)						
$<10^2$	0/4	3/4 (75%)	3/3 (100%)	3/3 (100%)	2/3 (66.7%)	11/17 (64.7%)
10^2 - 10^4	0/5	1/5 (20%)	3/6 (50%)	6/7 (85.7%)	5/7 (71.4%)	15/30 (50%)
10^4 - $<10^6$	0/5	0/5	0/5	1/4 (25%)	2/4 (50%)	3/23 (13.0%)

Summary of Key Findings

As in study AR021, the 16 mg/kg IV dose of obiltoxaximab was statistically superior to placebo with regard to rate of survival at Day 28. In this study, the 8 mg/kg dose was statistically superior to placebo for all analyses, while the 4 mg/kg dose was only significant in the analysis of all randomized animals. Survivors returned to their normal baseline observations between 7 to 11 days post-challenge. It is not clear why the survival rates were lower in this study compared to AR021; PA-ELISA levels were not measured systematically in AR021.

6.7 Study AP301 – Post Exposure Prophylaxis

6.7.1 Study Design

Overview and Objective

Study AP301 investigated the pharmacokinetics (PK) of obiltoxaximab administered via intramuscular (IM) route for post-exposure prophylaxis in a cynomolgus macaque model of the anthrax infection. The study was conducted under 21 CFR Part 58, Good Laboratory Practice (GLP) Regulations.
The primary objective was to examine the PK of obiltoxaximab when administered IM to cynomolgus macaques at increasing time intervals following exposure to *Bacillus anthracis* spores. The secondary objective was to evaluate the impact of the time of treatment on the PK of obiltoxaximab following IM administration.

Trial Design

The study was a randomized, blinded, placebo-controlled, parallel group, dose-ranging study of obiltoxaximab IM in naïve cynomolgus macaques challenged with aerosolized *B. anthracis.* Delayed treatment occurred at 18, 24, and 36 hours post-challenge. A total of 42 healthy macaques were included in the study. Animals were stratified by weight and were randomized to seven study groups, Table 6.48.

Table 6.48. Study AP301: Study Design

Group	ETI-204 mg/kg intramuscular (IM)	Treatment/hours (h) post challenge	No. of Animals	Last Day of Clinical Observations
1	0	Placebo / 18h	6	28
2	8 mg/kg	ETI 204 / 18h	6	28
3	16 mg/kg	ETI 204 / 18h	6	56
4	8 mg/kg	ETI 204 / 24h	6	28
5	16 mg/kg	ETI 204 / 24h	6	56
6	8 mg/kg	ETI 204 / 36h	6	28
7	16 mg/kg	ETI 204 / 36h	6	56

Animals were then randomized to three challenge days and then assigned to a random challenge order. Assignment was only known to the statistician preforming the randomizations, product preparation technicians, (b) (4) Quality Assurance Unit, and the study subject matter expert.

On the day of challenge, animals were exposed to a target inoculum of 200 LD_{50} of *B. anthracis* (Ames) spores. They were treated with placebo, 8mg or 16 mg/kg of obiltoxaximab single-dose IM injection based on pre-specified times. Clinical observations were performed twice daily. Blood samples were collected for bacterial culture, PA levels, anti-obiltoxaximab antibodies, and anti-PA IgG. The last day of observation for the placebo and 8 mg/kg groups was Day 28 and Day 56 for the 16 mg/kg IM groups. Gross necropsies were performed on all macaques that are found dead or were euthanized. Sections of tissues from brain/meninges, lungs, liver, spleen, spinal cord, kidney, and mediastinal and bronchial lymph nodes and injection site(s) were examined. Tissue samples were cultured prior to fixation for qualitative bacterial culture.

Study Endpoints

The objective of the study is to collect pharmacokinetic (PK) data of two doses of obiltoxaximab, dosed IM, in challenged animals and to determine the impact of time of treatment on the PK profile. The efficacy of the different treatment doses and time points was also analyzed. Survival was not the primary endpoint, but survival at Day 28 post *B. anthracis* spore challenge was considered the primary analysis for this review.

Statistical Analysis Plan

Sample Size Calculation
In the protocol, it was stated that the number of animals (6 in each group) used in this study was expected to be sufficient and to generate the necessary PK results while demonstrating survival trends between treatment and control groups.

Analysis Populations
All animals that survived to treatment were included in the study population. Animals were included regardless of bacteremia status.

Statistical Methods
For treatment group comparison, the survival data from each treatment group was compared to the control group using a one-sided, 0.025 level Fisher's exact test with and without adjustment for multiple comparisons. Although statistical comparisons were made between all group pairs, it should be noted that this study was not powered to determine statistical differences between groups.

6.7.2 Study Results

Compliance with Good Laboratory Practices

The study was conducted under 21 CFR Part 58, Good Laboratory Practice (GLP) Regulations.

Patient Disposition

See demographic variables and baseline characteristics, Table 6.49.

Table of Demographic Characteristics

Demographic variables were comparable across the obiltoxaximab IM treatment groups, Table 6.49. As time to initiation of treatment increased from 18 to 36 hours post-challenge, the bacteremia levels and the proportions of bacteremic (quantitative) animals increased.

Table 6.49. Study AP301: Demographic Variables and Baseline Characteristics by Treatment

	Placebo (N=6)	ETI-204 8 mg/kg IM 18 hrs PC (N=6)	ETI-204 8 mg/kg IM 24 hrs PC (N=6)	ETI-204 8 mg/kg IM 36 hrs PC (N=6)	ETI-204 16 mg/kg IM 18 hrs PC (N=6)	ETI-204 16 mg/kg IM 24 hrs PC (N=6)	ETI-204 16 mg/kg IM 36 hrs PC (N=6)	Total (N=42)
Age (years)								
Mean(SD)	2.9 (0.5)	2.8 (0.1)	2.8 (0.2)	2.8 (0.1)	3.0 (0.6)	3.1 (0.7)	2.8 (0.1)	2.9 (0.4)
Range	2.6, 4.0	2.6, 2.9	2.7, 3.1	2.7, 3.0	2.6, 4.2	2.6, 4.6	2.7, 2.9	2.6, 4.6
Gender, n (%)								
Female	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	21 (50)
Male	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	21 (50)
Body weight (kg)								
Mean (SD)	2.77 (0.21)	2.68 (0.18)	2.78 (0.15)	2.75 (0.22)	2.78 (0.26)	2.88 (0.19)	2.78 (0.16)	2.78 (0.19)
Range	2.50, 3.10	2.50, 2.90	2.60, 3.00	2.50, 3.10	2.60, 3.30	2.60, 3.10	2.60, 3.00	2.50, 3.30
Challenge dose (LD_{50})								
Mean	395.67	461.67	385.50	409.50	422.83	305.17	431.83	401.74
(SD)	(166.85)	(151.57)	(133.39)	(131.11)	(157.82)	(130.22)	(215.41)	(152.87)
Range	257, 725	278, 673	250, 602	266, 584	290, 700	152, 501	216, 810	152, 810
Challenge dose (LD_{50}) (n(%))								
<200	0	0	0	0	0	1 (16.7)	0	1 (2.4)
200 or higher	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (83.3)	6 (100)	41 (97.6)
Challenge dose (x 10^7 cfu)								
Mean (SD)	2.445 (1.031)	2.853 (0.939)	2.382 (0.824)	2.532 (0.811)	2.612 (0.973)	1.885 (0.808)	2.667 (1.331)	2.482 (0.945)

Range	1.590, 4.480	1.720, 4.160	1.550, 3.720	1.640, 3.610	1.790, 4.320	0.938, 3.100	1.330, 5.000	0.938, 5.000
Positive quantitative bacteremia prior to treatment (n(%))	0	0	2(33.3)	6 (100)	0	2(33.3)	6 (100)	16 (38.1)
Log_{10} bacteremia prior to treatment (cfu/mL)								
Mean (SD)	0.30 (0)	0.30 (0)	1.11 (1.40)	4.78 (0.46)	0.30 (0.00)	1.13 (1.45)	4.51 (2.00)	1.77 (2.12)
Range	0.30, 0.30	0.30, 0.30	0.30, 3.73	4.21, 5.40	0.30, 0.30	0.30, 3.85	1.70, 7.79	0.30, 7.79
Bacteremia prior to treatment (cfu/mL)								
Geometric mean	2.0	2.0	12.8	60287.8	2.0	13.4	32327.4	59.6
95% confidence interval	NA	NA	0.4, 378.6	19996, 181766	NA	0.4, 442.5	255.4, 4091563	13, 273.3

NA: Not available for one value. Source: Table constructed by Xianbin Li, Ph.D.

Efficacy Results

Forty-two cynomolgus macaques were challenged with a mean inoculum of 402 ± 153 LD_{50} *B. anthracis* spores via aerosol exposure. Animals received obiltoxaximab 8 mg/kg or 16 mg/kg IM of at 18 hours, 24 hours, or 36 hours post-challenge or they received placebo at 18 hours post-challenge. Survival proportions for each dose group are presented in Table 6.50.

Survival – Primary Analysis
None of the macaques in the control group survived. The survival rate was 100% when 8mg/kg or 16mg/kg IM dose was administered at 18 hours post challenge. Animals in the 8 mg/kg and 16 mg/kg dose groups had the same survival rates (83%) when treatment was delayed until 24 hours post-challenge. As the time to the initiation of obiltoxaximab increased, the survival proportion decreased in animals treated with 8 mg/kg or 16 mg/kg. A higher proportion of animals survived in the 16 mg/kg group at 36 hours compared to the animals that received 8 mg/kg at 36 hours, (50% vs. 0%). There were statistically significant differences between the 8

mg/kg and 16 mg/kg groups and the placebo group if treatment was initiated 18 or 24 hours post challenge, using a one-sided significance level of 0.025/6=0.00417. Overall, a treatment delay was associated with a lower survival rate.

Table 6.50. Study AP301: Survival at Day 28 by Treatment Group

		Obiltoxaximab Intramuscular (IM)					
	Placebo	**8mg/kg**	**8 mg/kg**	**8 mg/kg**	**16 mg/kg**	**16 mg/kg**	**16 mg/kg**
Post challenge (PC) hours	18h	18 h	24 h	36 h	18 h	24 h	36 h
No. of Animals, N (%)	0	6 (100)	5 (83.3)	0	6 (100)	5 (83.3)	3 (50.0)
Difference in survival proportion compared with placebo [95% CI], one-sided p-value*		1 [0.47,1] 0.0002	0.833 (0.230, 0.996) 0.0032	0 (-0.493, 0.493) 0.5	1 (0.47,1) 0.0002	0.833 (0.230, 0.996) 0.0032	0.5 [-0.037, 0.882] 0.034

Two-sided 95% confidence interval and one-sided p-values were calculated by the biostatistics reviewer, Xianbin Li, Ph. D.
*Significant at the one-sided significance level of 0.025/6

Reviewer Comment: These results indicate that the 16 mg/kg IM dose may have an advantage over the 8 mg/kg IM dose with regard to survival when treatment is initiated beyond 24 hours post exposure to B. anthracis.

Kaplan-Meier Survival Curve

There were statistically significant differences in survival outcomes between the 8 mg/kg and 16 mg/kg groups and the placebo group if treatment was initiated 18 hours post challenge, using a two-sided significance level of 0.05/6=0.00833, Figure 6.35 and Table 6.51. There was no significant treatment effect observed with any dose of obiltoxaximab that was started 36 hours post-challenge. There was a trend that treatment delay within the same dose group was associated with a lower survival rate.

Figure 6.35. Study AP301: Kaplan-Meier Survival Curve by Treatment Group

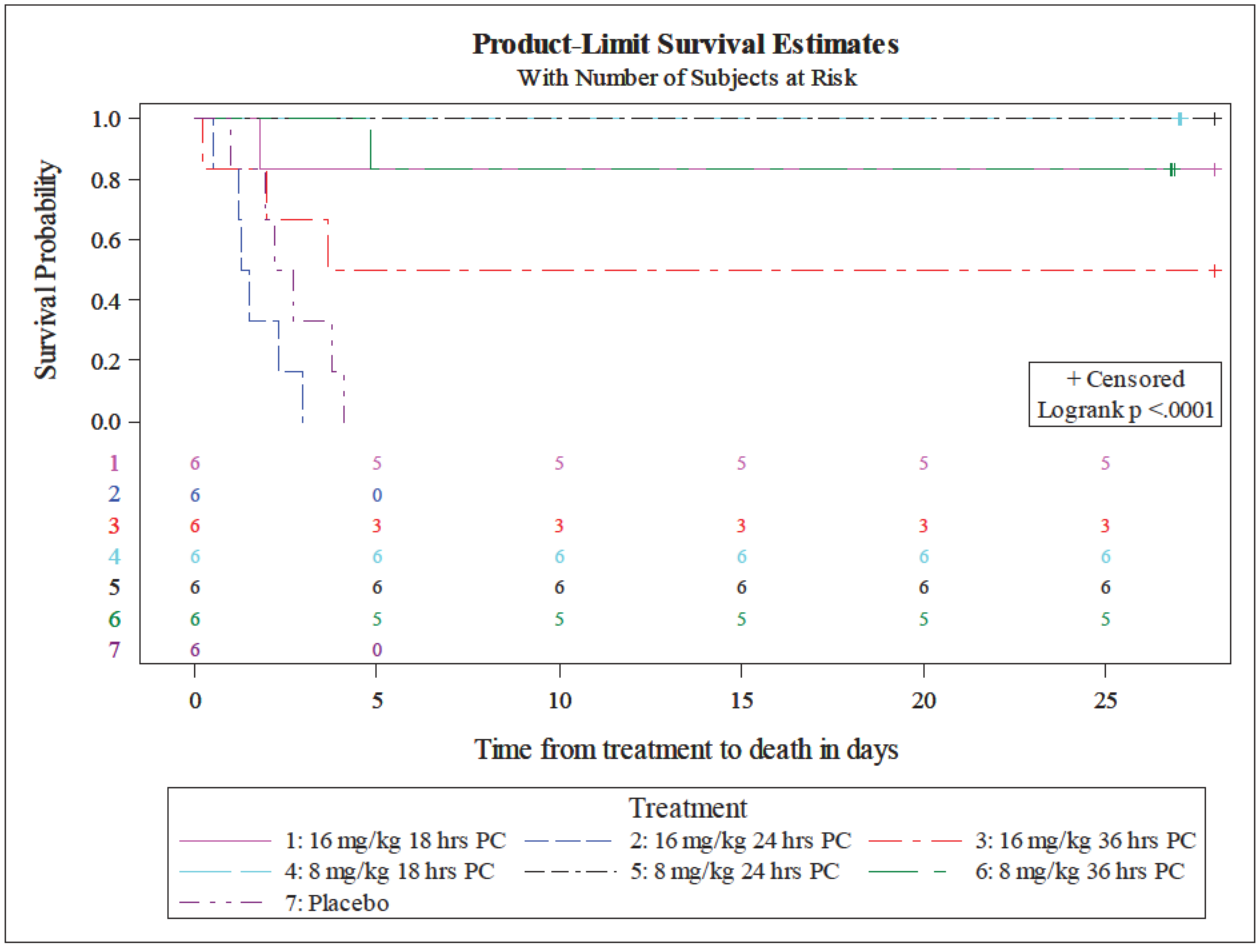


Table 6.51. Study AP301: Two-sided p-values of pairwise log-rank tests comparing time from treatment to death between a treatment group and the placebo group

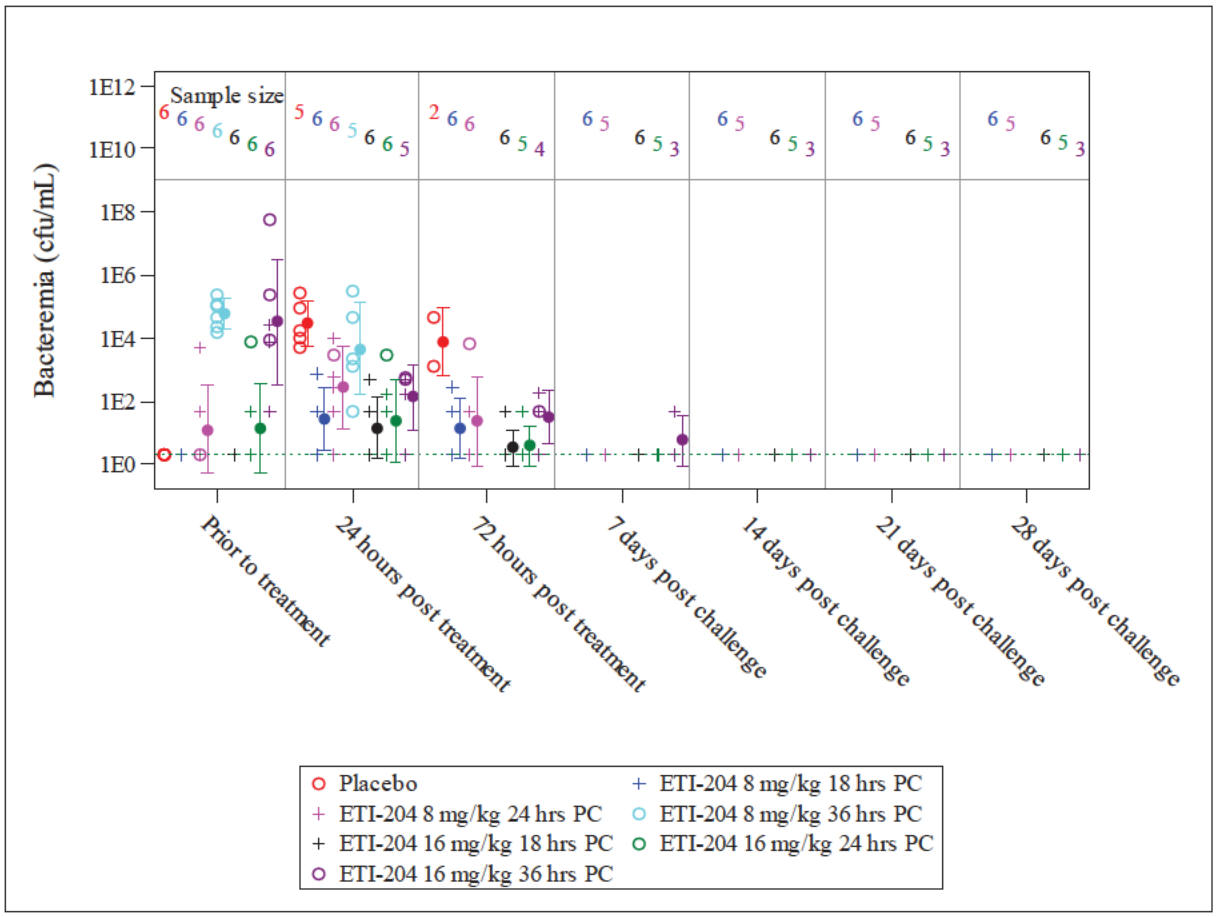
ETI-204 8 mg/kg 18 hrs PC	ETI-204 8 mg/kg 24 hrs PC	ETI-204 8 mg/kg 36 hrs PC	ETI-204 16 mg/kg 18 hrs PC	ETI-204 16 mg/kg 24 hrs PC	ETI-204 16 mg/kg 36 hrs PC
0.0005	0.0005	0.162	0.005	0.009	0.151

PC = post challenge; Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Bacteremia and Survival

Changes in bacteremia levels (cfu/mL) over time by survival status for the dose groups are shown in **Figure 6.36**. The bacteremia levels prior to treatment reflect the timing of the measurements. At 24 hours post-treatment with obiltoxaximab, the mean bacteremia level increased except for the two groups that initiated treatment at 36 hours post-challenge. At 72 hours post treatment, all mean bacteremia levels had decreased slightly in the treatment groups. All survivors cleared their bacteremia by Day 7 except for one animal, C54169, in the 16mg/kg 36h post -challenge group; *B. anthracis* (< 10 colonies) grew from its blood culture at Day 7. At Day 14 post treatment, all surviving animals had a bacteremia level below the LOD.

Figure 6.36. Study AP301: Bacteremia Levels (Geometric Mean ± SD) by Survival Status

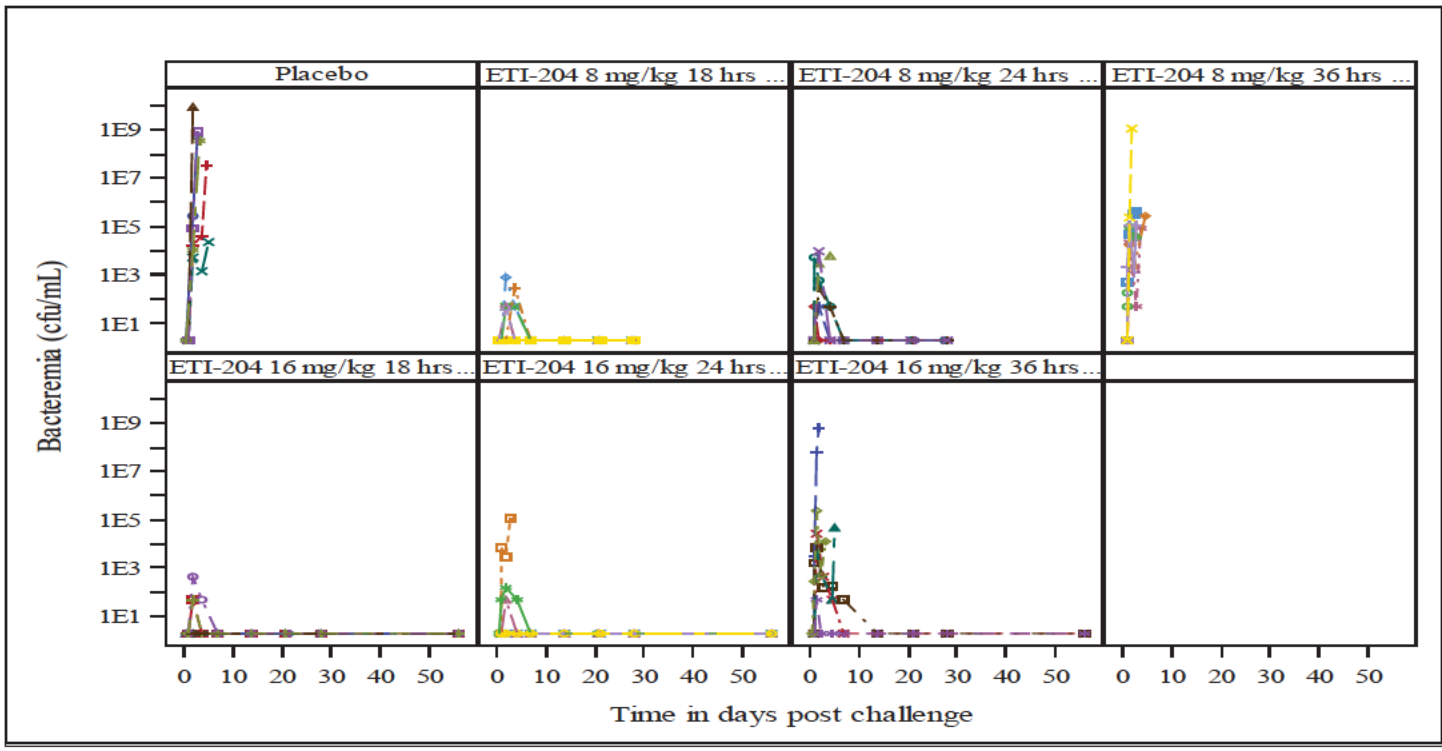


+: Survived to Day 28; O: Died before day 28; Limit of detection (LOD): 3cfu/mL; Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Reviewer Comment: Animals that died on placebo or on treatment prior to the end of the study were bacteremic and had elevated PA levels.

Bacteremia levels for individual animals over time are shown , **Figure 6.37**. The bacteremia levels prior to treatment reflected the timing of measurement. If treatment was initiated earlier the peaks for bacteremia levels were lower and all surviving animals had a bacteremia level of below the LOD at Day 14.

Figure 6.37. Study AP301: Bacteremia Levels Over time by Treatment Group and Animal



Graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Durability of Response

A single dose of obiltoxaximab 8mg/kg or 16mg/kg IM administered post-exposure to *B. anthracis* was effective in preventing death in animals up to Day 28 at the end of study.

Additional Analyses Conducted on the Individual Trial

Time to Bacteremia

The mean time to bacteremia was between 30 to 51 hours post-challenge. It appears that in the treatment groups, for the same dose, animals became bacteremic (quantitative) earlier as treatment was further delayed.

Table 6.52. Study AP301: Time to Quantitative Bacteremia Post Challenge by Dose Group

	Placebo	ETI-204 8 mg/kg 18 hrs	ETI-204 8 mg/kg 24 hrs	ETI-204 8 mg/kg 36 hrs	ETI-204 16 mg/kg 18 hrs	ETI-204 16 mg/kg 24 hrs	ETI-204 16 mg/kg 36 hrs	Total
No. of subjects	6	5	6	6	3	3	6	35
Time to bacteremia (quantitative) (hours)								
Mean (SD)	41.7 (1.0)	51.0 (21.6)	40.5 (12.9)	28.9 (8.2)	42.3 (1.3)	31.8 (13.8)	30.2 (7.1)	37.9 (12.9)
Range	40.8, 43.2	40.5, 89.6	23.1, 49.7	17.7, 36.8	41.3, 43.7	23, 47.7	23.4, 36.8	17.7, 89.6

ETI-204: obiltoxaximab

Table 6.53. Study AP301: Survival at Day 28 Post Challenge by Challenge Dose and Log_{10} Bacteremia

	Placebo (N= 6)	ETI-204 8 mg/kg 18 hrs (N= 6)	ETI-204 8 mg/kg 24 hrs (N= 6)	ETI-204 8 mg/kg 36 hrs (N= 6)	1 ETI-204 6 mg/kg 18 hrs (N= 6)	ETI-204 16 mg/kg 24 hrs (N= 6)	ETI-204 16 mg/kg 36 hrs (N= 6)	Total (N= 4
Gender								
Female	0/3	3/3 (100%)	2/3 (66.7%)	0/3	3/3 (100%)	3/3 (100%)	1/3 (33.3%)	12/21 (57.1
Male	0/3	3/3 (100%)	3/3 (100%)	0/3	3/3 (100%)	2/3 (66.7%)	2/3 (66.7%)	13/21 (61.9
Challenge dose (LD_{50})								
<250	0	0	0	0	0	3/3 (100%)	1/2 (50%)	4/5 (8
250 or higher	0/6	6/6 (100%)	5/6 (83.3%)	0/6	6/6 (100%)	2/3 (66.7%)	2/4 (50%)	21/37 (56.8
Bacteremia prior to treatment (cfu/mL)								
$<10^2$	0/6	6/6 (100%)	4/5 (80%)	0	6/6 (100%)	5/5 (100%)	1/1 (100%)	22/29 (75.9
10^2 - 10^4	0	0	1/1 (100%)	0	0	0/1	1/2 (50%)	2/4 (5
10^4 - $<10^6$	0	0	0	0/6	0	0	1/2 (50%)	1/8 (12.5
10^6 or higher	0	0	0	0	0	0	0/1	0/1

ETI-204: obiltoxaximab

Clinical Observations

Animals that survived until scheduled sacrifice (obiltoxaximab dosed animals) had hunched posture or stool abnormalities within the first few days post-challenge but returned to normal by 11 days post-challenge with an occasional diarrhea/soft stool noted which is not uncommon with laboratory housed nonhuman primates. There was one exception, Animal C54136 (a survivor) [Group 4; obiltoxaximab (8 mg/kg) at 24 hours post-challenge]. Animal C54136 continued to have a hunched posture and stool abnormalities at nearly all time points until Day 27 post-challenge. The animal had a positive blood culture for *B. anthracis* at 24 hours post-

challenge and blood cultures remained negative from 24 hours post treatment through Day 28. It had a positive lymph node culture for *B. anthracis* and all other tissue cultures were negative. Animal C54107 (Group 1; Control) had inappetence in the afternoon of Day 4 post-challenge and this animal was found dead at the next time point (morning of Day 5 post-challenge). Inappetence was also noted for animal C53908 (Group 5; ETI-204 16 mg/kg IM) at 24 hours post-challenge) in the morning of Day 4 post-challenge and the animal was observed as normal during subsequent observations and survived to the end of the study.

Tissue Bacterial Cultures and Pathological Findings in the Brain
The veterinary pathologist who conducted the necropsies considered gross lesions observed in the macaques to be typical of anthrax.
Histopathologic findings were typical of anthrax disease. Survivors had no evidence of pathologic findings in the brain. Some animals that died on placebo or on treatment had changes consistent with anthrax meningitis. Please refer to the pharmacology/toxicology review by Dr. Amy Nostrandt, DVM for a full discussion of the histopathological findings across studies.

6.8 Study AP307 - Post Exposure Prophylaxis

6.8.1 Study Design

Overview and Objective

Study AP307 evaluated the post-exposure efficacy of obiltoxaximab via intramuscular administration in the cynomolgus macaque inhalation model of anthrax. The primary objective was to determine the protective efficacy of obiltoxaximab against lethality when administered intramuscularly to cynomolgus macaques at increasing times following exposure to *B. anthracis* spores. The secondary objective was to determine the pharmacokinetics of obiltoxaximab when administered via the IM route; to evaluate the impact of the time of obiltoxaximab administration on PA levels; to evaluate quantitative bacteremia.

Trial Design

This was a randomized, open-label, placebo-controlled, parallel-group, intramuscular obiltoxaximab study with dosing at 24, 36, and 48 hours following exposure to *B. anthracis* spores. Only the veterinary pathologist who performed the analyses of the histopathology was blinded to study results.
A total of 54 healthy cynomolgus macaques, 27 males and 27 females were randomized into one group of 10, two groups of 14, and one group of 16 animals.

Table 6.54. Study AP307: Overview of Study Design

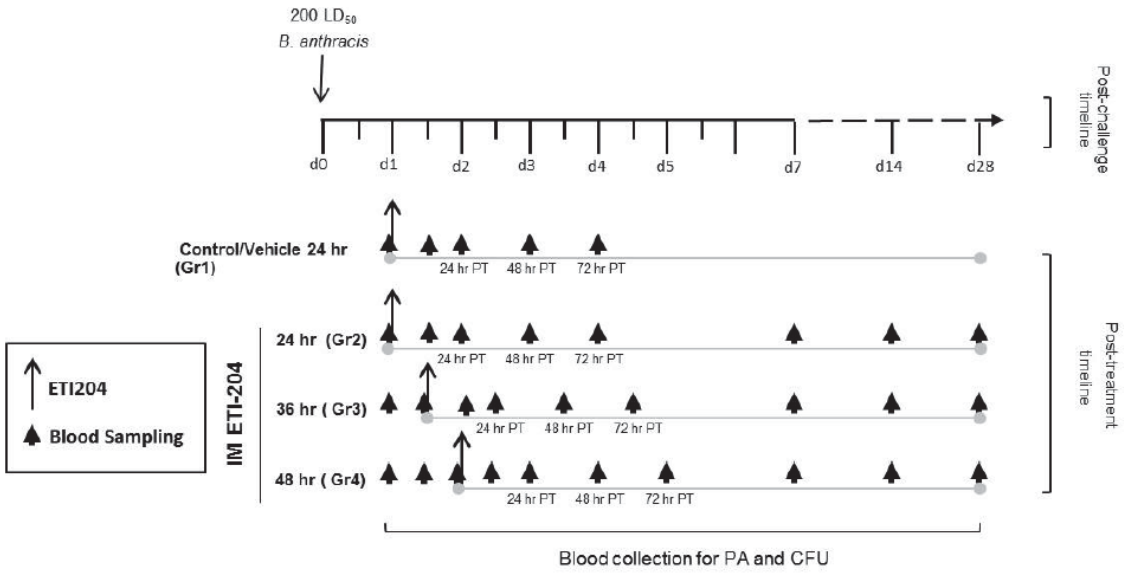
Group	No. of cynomolgus macaques	ETI-204 mg/kg, IM (thigh)	Hours post challenge
1	10	0 (vehicle)	24h
2	14	16	24h
3	14	16	36h
4	16	16	48h

ETI-204: obiltoxaximab; IM: Intramuscular;

Animals were challenged with a target dose of 200 LD_{50} of *B. anthracis* spores. Obiltoxaximab was administered at 24, 36, and 48 ± 1 hours following exposure to *B. anthracis* post mean challenge time. The mean challenge time was calculated for each challenge day from the end of the first and last animals challenged. The maximum volume per IM injection into the thigh did not exceed 0.5 mL per standard operating procedure. The two IM injections for each macaque were split and given in the left and right thigh.
Animals were observed twice-daily for clinical signs of infection for example anorexia, lethargy, respiratory distress, moribundity, seizures, or other abnormal clinical observations.

The collections of blood samples were scheduled based on either post-challenge or post-treatment times.
Blood was collected for serum PA-ELISA, quantitative bacteremia, obiltoxaximab levels and serum for retention for evaluation of anti-obiltoxaximab IgG. Blood cultures were obtained at Day -7, 24, 36, 48 hours post-challenge and at 24 hours, 48 hours, 72 hours, and at 7 days, 14 days, 21 days, and 28 days post-treatment.
Gross necropsy was performed on all macaques that were found dead or euthanized including the survivors euthanized on Day 28. See Figure 6.38 for a summary of the study design.

Figure 6.38. Study AP307: Schematic of Study Design



Source: Study AP307, Study Report, figure 2, page 17.

Study Endpoints

The primary efficacy endpoint was the survival rate of macaques in the obiltoxaximab- treated groups compared to placebo in the ITT population.

Statistical Analysis Plan

Statistical analysis was performed based on the treatment animals received, including all the animals that survived to treatment and all challenged animals based on their assigned group. The primary efficacy endpoint, survival proportion, was summarized by group using descriptive statistics with 95% confidence intervals. The survival data from each treatment group was compared to the control group using a one-sided, 0.025 level Fisher's exact test with and without adjustment for multiple comparisons.

Sample Size Calculation

The Applicant assumed that the true probabilities of survival in control and treatment groups were 10% and 65% respectively, there was 80% power to detect a difference in survival rates between each treated group (n=14) and the control group (n=10). Power calculation was for a one-sided, 0.05 level, Fisher's exact test with no adjustment for multiple comparisons across the three tests.

Analysis Populations
The two analysis populations were defined:
1) Animals that survived to treatment, regardless of the bacteremia status,
2) All-inclusive population that included all challenged animals based on assigned group.

Statistical Methods
The survival data from each treatment group was compared to the control group using a one-sided, 0.025 level Fisher's exact test with and without adjustment from multiple comparisons. For each of these tests, only control animals that survived to the matching time of treatment for the treated group in the comparison were included in the test.

Protocol Amendments

Pertinent aspects of the protocol amendments are outlined below.
Protocol Amendment #1: An additional analysis was added to the protocol that pools only animals that were positive for bacteremia before treatment across obiltoxaximab-treated groups.
Protocol Amendments #2 and #3: Updated points of contact at (b) (4) and at (b) (4) were included.
Protocol Amendment #4: Minor changes to the methodology for neuropathology (each brain was to be cut into hemispheres and the left hemisphere placed in 10% formalin for potential future neuropathology examination). Exploratory survival analyses were included for subsets of animals based on whether they were positive or negative for bacteremia. The two-sided Fisher's Exact Test at the 0.05 level was changed to a one-sided Fisher's Exact Test at the 0.025 level based on FDA recommendations. (Note: The conclusions will likely be the same for both tests for most of the expected survival outcomes).
Protocol Amendment #5: The statistical methods were updated to include a statement that all statistical analyses of the primary efficacy endpoint, survival proportion, were to be performed based on the ITT dataset unless otherwise specified. This resulted in an additional population for analysis of mortality.

Reviewer Comment: The protocol amendments were acceptable.

6.8.2 Study Results

Compliance with Good Laboratory Practices

The study was not conducted under 21 CFR Part 58, Good Laboratory Practice (GLP) Regulations; however, it was conducted in accordance to the protocol as amended and SOPs at the (b) (4).

Patient Disposition

See Table 6.55.

Table of Demographic Characteristics

Demographics and baseline characteristics of all macaques in the study are summarized for each treatment group in Table 6.55. Two animals (C49209 and C51315 in Group 4) did not survive to their group-specified treatment time at 48 hours post mean challenge and were not included in the analyses. Gender, age, and body weights were well balanced across treatment groups. The mean challenge dose of *B. anthracis* was 205 LD_{50} of *B. anthracis* (Ames) spores. Approximately, 50% of the animals in the study received the target dose or higher. Thirty-two (59%) animals of the animals were positive for quantitative bacteremic prior to treatment.

Table 6.55. Study AP307: Demographic Variables and Baseline Characteristics by Treatment Group

	Group 1 Placebo (N=10)	Group 2 ETI-204 16 mg/kg 24 hrs PC IM (N=14)	Group 3 ETI-204 16 mg/kg 36 hrs PC IM (N=14)	Group 4 ETI-204 16 mg/kg 48 hrs PC IM (N=16)	Total (N=54)
Age (years)					
Mean(SD)	3.8 (0.4)	3.7 (0.5)	3.8 (0.4)	4.0 (0.0)	3.8 (0.4)
Range	3.0, 4.0	3.0, 4.0	3.0, 4.0	3.0, 4.0	3.0, 4.0
Gender [n (%)]					
Female	5 (50.0)	7 (50.0)	7 (50.0)	7 (57.1)	28 (51.9)
Male	5 (50.0)	7 (50.0)	7 (50.0)	9 (42.9)	26 (48.1)
Body weight (kg)					
Mean (SD)	3.21 (0.31)	3.16 (0.35)	3.12 (0.24)	3.35 (0.78)	3.21 (0.47)
Range	2.70, 3.80	2.60, 3.90	2.90, 3.60	2.60, 5.60	2.60, 5.60
CHALLENGE DOSE					
Challenge dose (LD_{50})					
Mean	200.70	209.00	197.64 (92.43)	211.57 (70.14)	204.50 (67.62)
(SD)	(45.98)	(56.83)			
Range	131, 265	112, 310	84, 346	131, 329	84, 346
Challenge dose (LD_{50}) [n(%)]					
<200	4 (40.0)	6 (42.9)	8 (57.1)	8 (57.1)	27 (50.0)
200 or higher	6 (60.0)	8 (57.1)	6 (42.9)	6 (42.9)	27 (50.0)
BACTEREMIA					
Positive	5 (50.0)	1 (7.1)	12 (85.7)	14 (100.0)	32 (59.3)

quantitative bacteremia prior to treatment (n(%))					
Log_{10} bacteremia prior to treatment (cfu/mL) N Mean (SD) Range	 1.14 (0.93) 0.30, 2.57	 0.48 (0.66) 0.30, 2.78	 3.73 (2.21) 0.30, 6.86	 4.79 (1.75) 2.26, 7.94	 2.64 (2.37) 0.30, 7.94
Bacteremia prior to treatment (cfu/mL) Geometric mean 95% confidence interval	 13.8 3, 63.5	 3.0 1.2, 7.2	 5380.0 286.8, 100921.9	 61537.9 6036.6, 627322.5	 438.4 96.2, 1998
PROTECTIVE ANTIGEN					
PA-ELISA Positivity prior to treatment	0	0	7 (50)	14 (100)	23 (42.6)
Log_{10} PA-ELISA prior to treatment N Mean (SD) Range	 0.70 (0.00) 0.70, 0.70	 0.70 (0.00) 0.70, 0.70	 1.30 (0.77) 0.70, 3.15	 2.36 (0.86) 1.20, 4.20	 1.31 (0.91) 0.70, 4.20
PA-ELISA prior to treatment (ng/mL) Geometric mean 95% confidence interval	 5.0 NA	 5.0 NA	 19.8 7.1, 55.5	 228.5 72.5, 720.3	 20.3 11.3, 36.2

Efficacy Results - Primary Endpoint

Survival at Day 28 Post-Challenge

The proportion of animals that survived in the obiltoxaximab 16 mg/kg IM administered 24 hours post-challenge was significantly improved compared to the placebo group, (93% versus 10%). Survival rates decreased as the time to treatment was delayed from 24 hours to 36 and 48 hours. There was no significant difference in survival proportions between drug and placebo

at the 36 and 48 hours post-challenge. Survival rates for each dose group are presented in Table 6.56.

Table 6.56. Study AP307: Survival at Day 28 Post-Challenge by Treatment Group

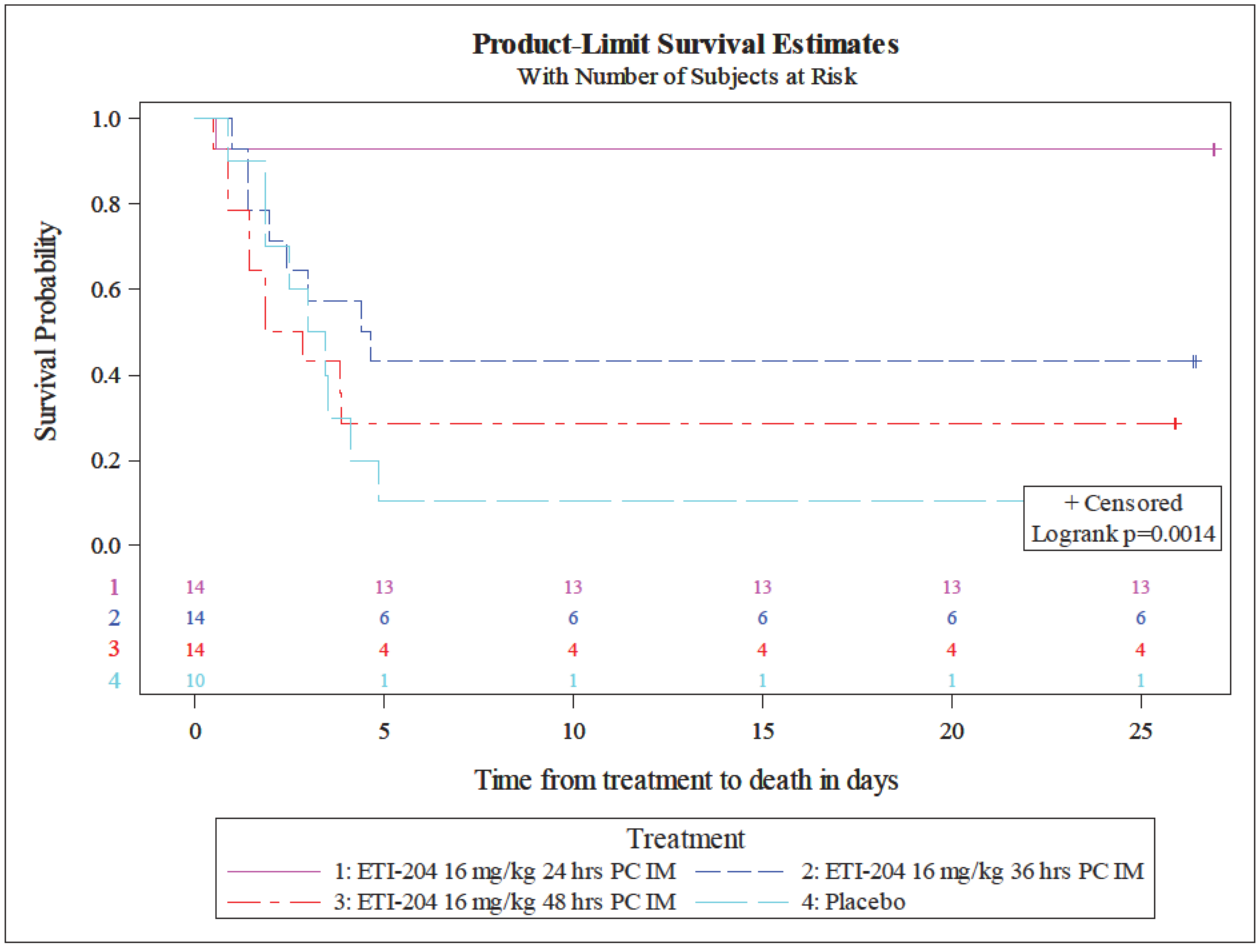
	Placebo	ETI-204 16 mg/kg IM	ETI-204 16 mg/kg IM	ETI-204 16 mg/kg IM
Hours Post-challenge	**18h**	**24h**	**36h**	**48h**
	(N=10)	**(N=14)**	**(N=14)**	**(N=14)**
N (%)	1 (10.0)	13 (92.9)	6 (42.9)	4 (28.6)
Difference in survival proportion compared with placebo [95% CI] one-sided p-value*		0.829 [0.431,0.976] <0.0001	0.329 [-0.068, 0.643] 0.053	0.186 [-0.201, 0.517] 0.165

* 95% CI and p-values from exact method and Boschloo's one-sided test calculated by the biostatistics reviewer, Xianbin Li, PhD.

Survival (time-to-death) analyses demonstrated that only the obiltoxaximab 16 mg/kg IM group administered 24 hours post-challenge was statistically significant from the placebo group (at the significance level of 0.05/3=0.0167 to adjust for multiple comparisons), as shown in Figure 6.39 and

.

Figure 6.39. Study AP307: Kaplan-Meier Survival Curve by Treatment Group



Source: Kaplan-Meier curve constructed by biostatistics reviewer, Xianbin Li, Ph.D.

The time from treatment to death post-challenge between a treatment group and the placebo group is compared in Table 64. Analyses demonstrated that the obiltoxaximab 16 mg/kg IM group administered 24 hours post-challenge had statistically significant improvement in survival compared to the placebo group.

Table 6.57. Study AP307: Comparison of time from treatment to death between a treatment group and the placebo group (two-sided p-values of pairwise log-rank tests)

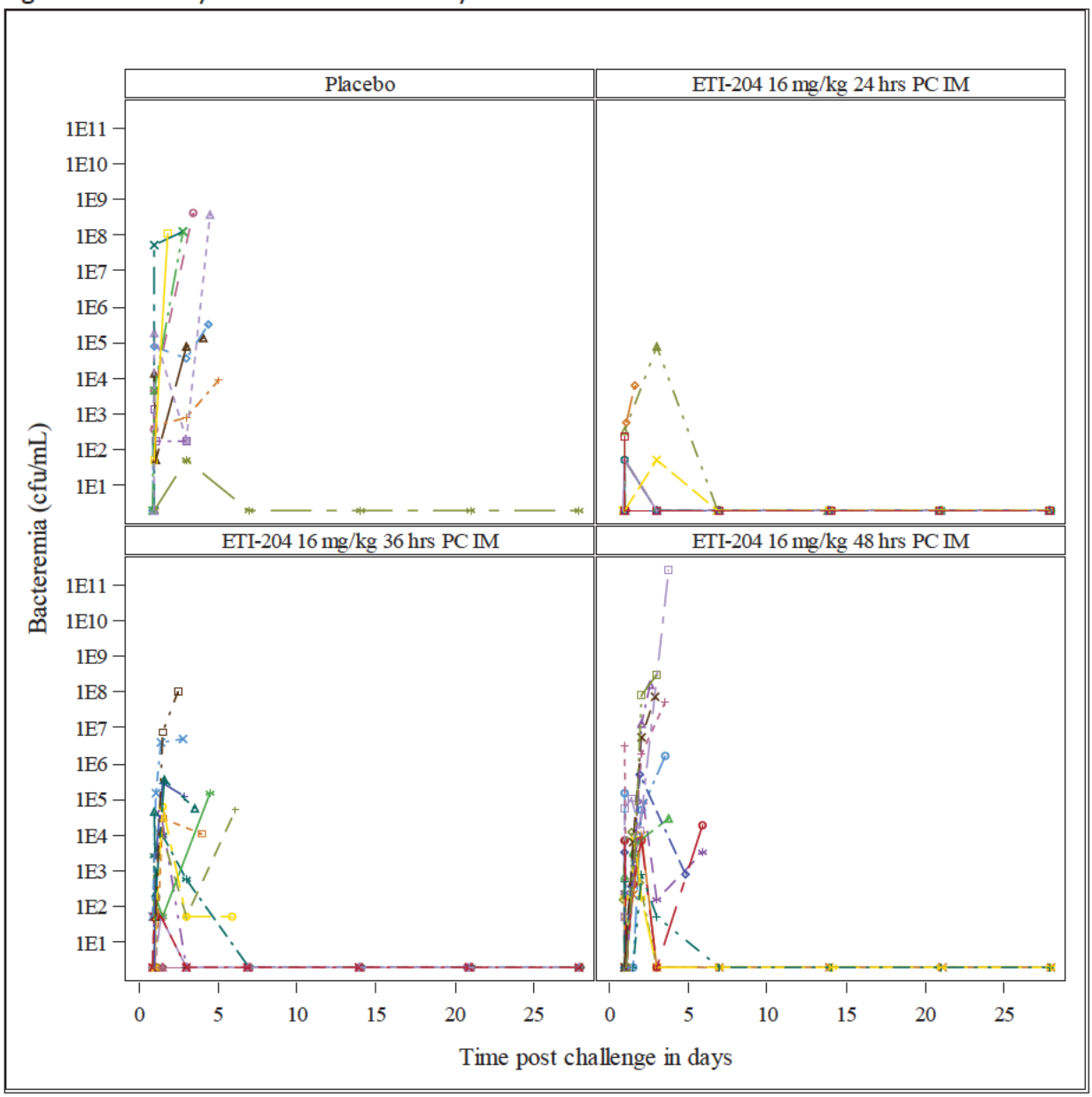
ETI-204 16 mg/kg 24 hrs PC IM (N= 14)	ETI-204 16 mg/kg 36 hrs PC IM (N= 14)	ETI-204 16 mg/kg 48 hrs PC IM (N= 14)
<0.0001	0.149	0.836

Bacteremia and Survival

The two groups that were treated with at 36 and 48 hour post-challenge treatment had a higher mean bacteremia level than the placebo and the group treated at 24 hours,

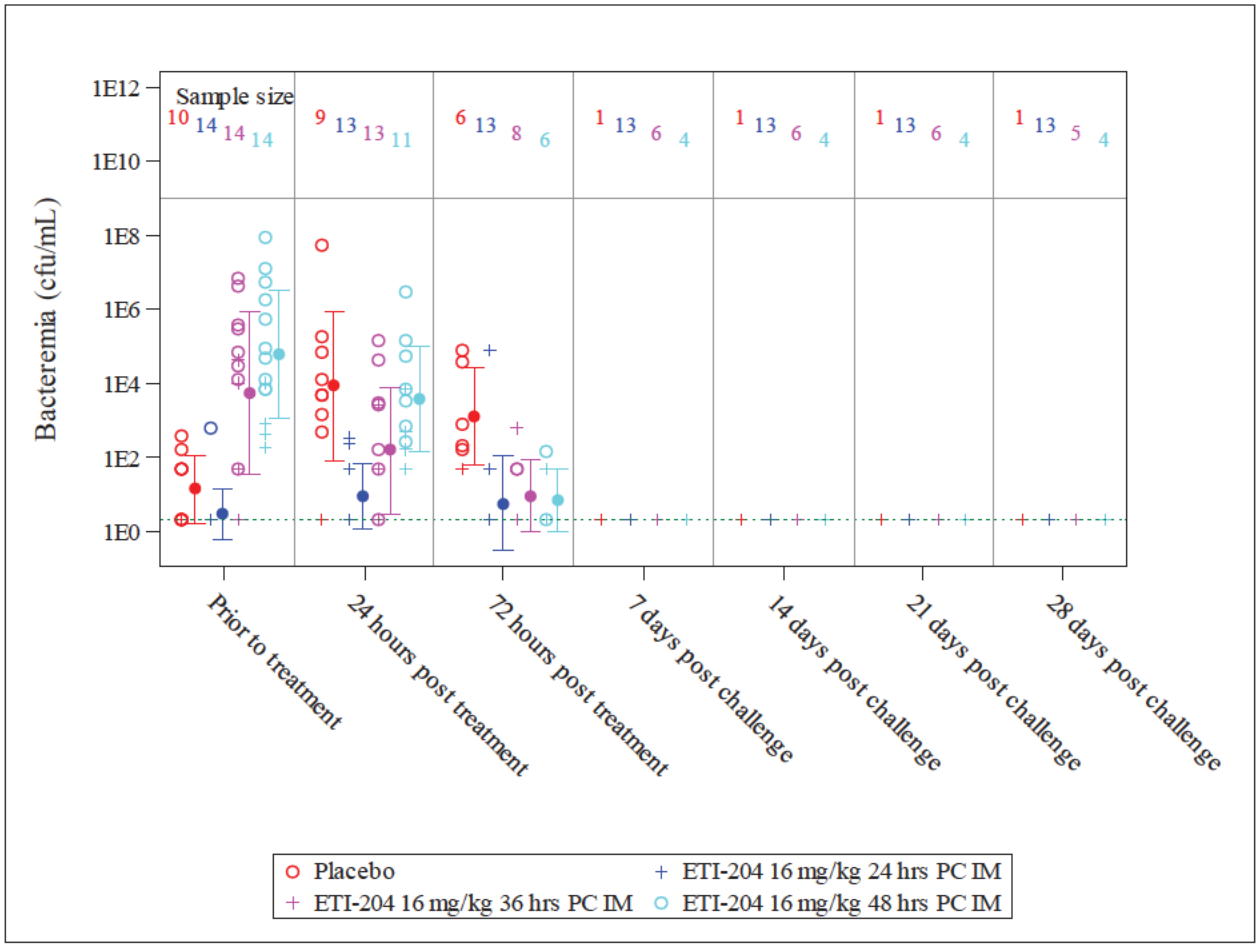
Figure 6.40. The geometric mean bacteremia levels prior to treatment steadily increased as the time from challenge to treatment increased and bacteremia levels decreased in all groups following treatment (even in the survivor, C50738, in the placebo group).

Figure 6.40. Study AP307: Bacteremia by treatment and animals



At 72 hours post challenge, the bacteremia levels in all treatment groups had decreased compared to the previous time point. All animals that survived including one placebo animal, (C50738) cleared their bacteremia by Day 7 post-challenge and remained culture negative until the end of the study, Figure 6.41.

Figure 6.41. Study AP307: Bacteremia (Geometric Mean ± SD) by Survival Status

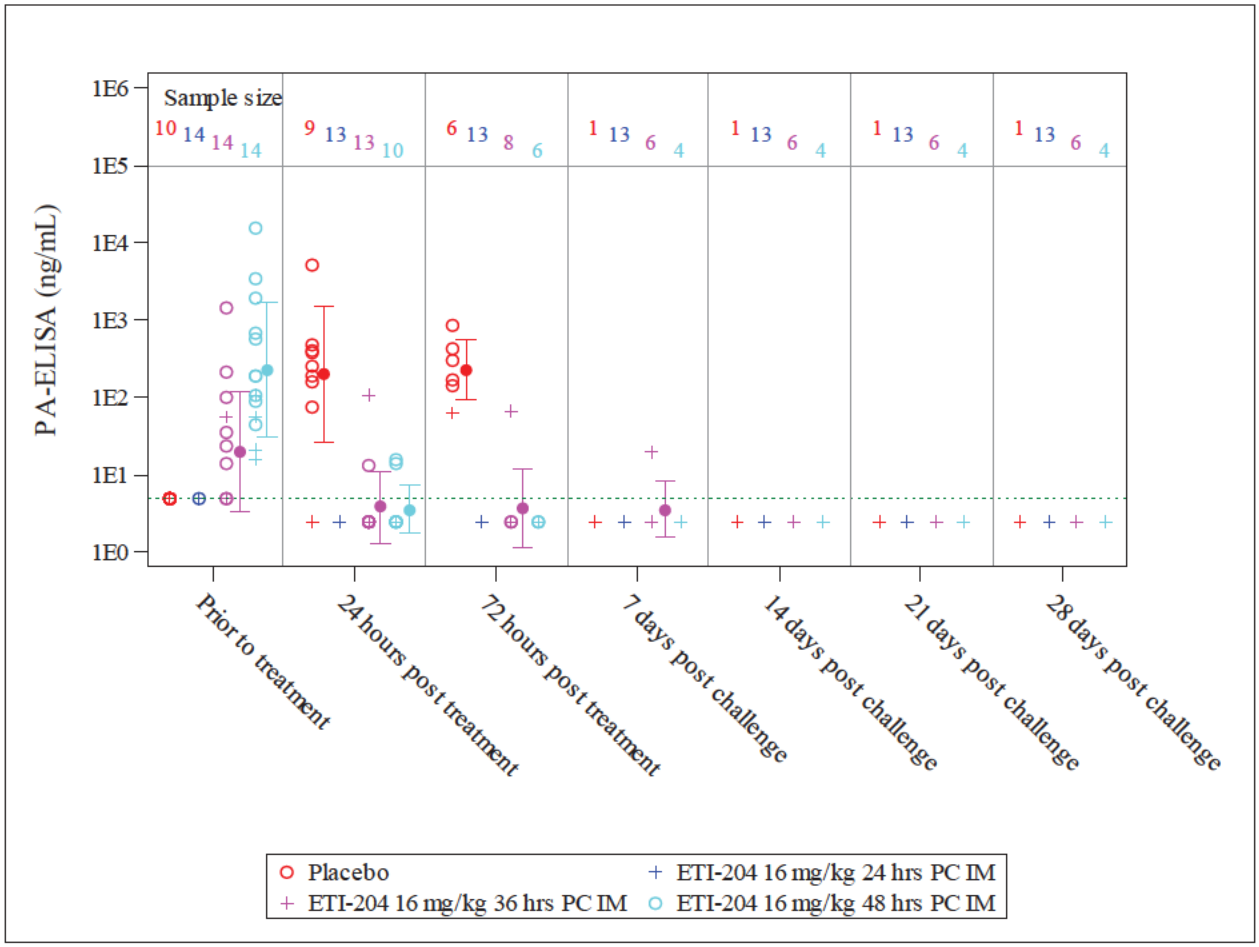


"+"=survived to day 28; "o"= died before day 28; LOD: 3cfu/mL; SD: standard deviation.

Protective Antigen and Survival

The placebo and the groups administered obiltoxaximab at 24 hours post-challenge did not have PA levels above the LOD prior to treatment. The PA levels increased in the treatment groups administered at 36 hours and 48 hours post challenge. After administration of obiltoxaximab, the PA levels decreased in all groups except the placebo. PA-ELISA was negative in all survivors by Day 7 except for one survivor, C51386, who had a positive PA level (19.9ng/mL) at Day 7.

Figure 6.42. Study AP307: PA-ELISA (geometric mean and standard deviation) Prior to Treatment by Survival Status



"+"=survived to Day 28; "o"= died before Day 28; LOD (dotted line) = 9.48ng/mL. Source: Graph constructed by Xianbin Li, Ph. D.

Efficacy Results - Secondary and other Relevant Endpoints

Time between Challenge and Bacteremia

The time between challenge with *B. anthracis* and bacteremia is shown in Table 6.58. The obiltoxaximab 16 mg/kg IM group administered 24 hours post-challenge had the longest time (50 hours) to bacteremia post-challenge compared to the other two treatment groups; and 7/14 (50%) animals in this group had positive quantitative bacteremia.

Table 6.58. Study AP307: Time between Challenge and Bacteremia

	Placebo (N=10)	ETI-204 16 mg/kg 24 hrs PC IM (N=14)	ETI-204 16 mg/kg 36 hrs PC IM (N=14)	ETI-204 16 mg/kg 48 hrs PC IM (N=14)	Total (N=52)
Time to quantitative bacteremia (hours)					
N	10	7	12	14	43
Mean (SD)	39.8 (22.7)	50.1 (20.8)	31.2 (5.3)	36.6 (7.5)	38.0 (15.4)
Range	22.2, 95.9	25.2, 93.5	21.9, 36.3	21.9, 49.8	21.9, 95.9

Durability of Response

A single dose of obiltoxaximab 16mg/kg IM was effective in preventing death in animals up to Day 28 (end of study) in animals that received treatment at 24 hours post challenge with *B. anthracis* spores.

Persistence of Effect

The persistence of effect of obiltoxaximab, i.e., prevention of death, could not be assessed beyond 28 days (end of study). There were no relapses of bacteremia in surviving animals once animals had cleared their bacteremia.

Additional Analysis of the Clinical Trial

Pathological Findings and Tissue Bacterial Assessments

Microscopic findings consistent with anthrax were present in all macaques. Animals surviving to scheduled termination typically had lesions consistent with previous inflammation for example, hyperplasia (bronchial and/or mediastinal lymph nodes and/or lymphoid follicles in the spleen. Among animals that died, 4 (44%), 5(63%), and 2 (20%) from the placebo group, 16 mg/kg/ 36 hours and 16 mg/kg /48 hours post challenge groups, respectively, had microscopic histopathological findings in the brain. No survivors had significant histopathological findings. See the pharmacology /toxicology review by Amy Nostrandt, DVM for a full discussion of the histopathologic findings.

Subgroup Analyses
The following table shows the survival results of subgroup analyses by gender, challenge dose, $\log_{10}$ bacteremia, PA. The sample sizes were too small to see a reliable trend by each grouping variable.

Table 6.59. Study AP307: Survival at Day 28 by Gender, Challenge Dose, Log_{10} Bacteremia, PA Prior To Treatment

	Placebo (N= 10)	ETI-204 16 mg/kg 24 hrs PC IM (N= 14)	ETI-204 16 mg/kg 36 hrs PC IM (N= 14)	ETI-204 16 mg/kg 48 hrs PC IM (N= 14)	Total (N= 54)
Gender	0/5	6/7 (85.7%)	2/7 (28.6%)	2/8 (25.0%)	10/28 (35.7%)
Female	1/5 (20%)	7/7 (100%)	4/7 (57.1%)	2/6 (33.3%)	14/26 (53.8%)
Male	0/5	6/7 (85.7%)	2/7 (28.6%)	2/8 (25%)	10/28 (35.7%)
Challenge dose (LD_{50})					
<250	0/8	10/11 (90.9%)	2/9 (22.2%)	3/10 (30%)	15/40 (37.5%)
250 or higher	1/2 (50%)	3/3 (100%)	4/5 (80%)	1/4 (25%)	9/14 (64.3%)
Bacteremia prior to treatment (cfu/mL)					
$<10^2$	1/8 (12.5%)	13/13 (100%)	4/5 (80%)	0	18/26 (69.2%)
10^2 - 10^4	0/2	0/1	1/1 (100%)	3/5 (60%)	4/9 (44.4%)
10^4 - $<10^6$	0	0	1/6 (16.7%)	1/5 (20%)	2/11 (18.2%)
10^6 or higher	0	0	0/2	0/4	0/6
PA prior to treatment (ng/mL)					
0 - < 10	1/10 (10%)	13/14 (92.9%)	5/7 (71.4%)	0	19/31 (61.3%)
10 - < 50	0	0	0/3	2/3 (66.7%)	2/6 (33.3%)
50 or higher	0	0	1/4 (25.0%)	2/11 (18.2%)	3/15 (20.0%)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

6.9 Study AP107 - Post-exposure Prophylaxis

6.9.1 Study Design

Overview and Objective

Study AP107 is a post-exposure prophylaxis, dose-ranging, study in cynomolgus macaques exposed to *Bacillus anthracis* spores followed by treatment with intravenous (IV) or intramuscular (IM) obiltoxaximab.
The primary objective was to evaluate efficacy of obiltoxaximab against lethality when administered IV or IM to cynomolgus macaques at 24 hours post- exposure to aerosolized *B. anthracis* spores. It was conducted at the (b) (4) in 2009.

Trial Design

A total of 42 cynomolgus macaques were planned but one animal (A03266) died during quarantine and Group 5 was reduced from nine to eight animals. Forty-one (20 males, 21

females) cynomolgus macaquesweighing between 2.1-3.5 kg (2-5 years of age) at randomization were included in the study. On study Day 0, all animals were challenged with a targeted dose of aerosolized 200 LD_{50} *B. anthracis* (Ames strain) spores. Obiltoxaximab or placebo control was administered IV or IM at 24 hours ± 30 minutes post-challenge to each animal relative to the end of their challenge time.

Table 6.60. Study AP107: Study Design

Group	Obiltoxaximab	No. of cynomolgus macaques	Route (IV or IM)
1	Saline Control 0.5 mg/mL	6	IV
2	8 mg/kg	9	IV
3	2 mg/kg	9	IV
4	8 mg/kg	9	IM
5	4 mg/kg	8	IM

Post-challenge, animals were observed for 30 days for clinical signs of anthrax infection including anorexia, lethargy, respiratory distress, activity (recumbent, weak, or unresponsive), seizures, moribundity, and other abnormal clinical observations. Blood sample collections from pre challenge and Day -5 to Day 30 (terminal sacrifice) are outlined in Table 6.61.

Table 6.61. Study AP107: Blood Collection and Assay Schedule

Approximate Collection Time Point	Blood Tube type/ Approximate Blood volume	Bacteremia (Culture)	Serum ETI-204 Concentration (serum shipped to Elusys)	CBC
Study day -5	EDTA ~1.5 ml + SST ~2.0 ml	X	X	X
24 hours PC (prior to treatment)	EDTA ~1.5 ml	X		X
32 hours PC	EDTA ~1.5 ml	X		X
40 hours PC	EDTA ~1.5 ml	X		X
48 hours PC	EDTA ~1.5 ml + SST ~2.0 ml	X	X	X
14 days PC	EDTA ~1.5 ml	X		X
Terminal [a]	EDTA ~0.5 ml + SST ~2.0 ml	X	X	

Study Endpoints

The primary endpoint was survival to Day 30 post *B. anthracis* spore challenge.

Statistical Analysis Plan

Sample Size Calculation
The protocol states that the sample sizes of nine animals per treatment group and six animals in the control group were sufficient to test treatment efficacy in comparison to untreated controls with 83% power, when the probability of survival in the treated group was 85% and the probability of survival in the control group was 15%. This was based on a one-sided, Fisher's exact test.

Reviewer Comment: Using a one-sided 0.05 type I error the biostatistics reviewer could replicate this calculation. However, using a two-sided type I error of 0.05 only provides a 76.9% statistical power per the biostatistics reviewer's calculations.

Analysis Population
There was no analysis population defined in the protocol, but the analysis included all randomized animals.

Statistical Methods
Fisher's exact tests were used to establish efficacy of individual treatments relative to the control group. A procedure was used to maintain an overall 0.05 significance level using the Bonferroni-Holm adjustment. A time-to-death analysis was also performed on these data to determine where there were differences in protection for the different groups.

6.9.2 Study Results

Compliance with Good Laboratory Practices

The Applicant states that all in-life aspects of this protocol was conducted in accordance with 21 CFR Part *58,* Good Laboratory Practice (GLP) Regulations and (b) (4) procedures and practices.

Table of Demographic Characteristics

The demographic variables and baseline characteristics of the randomized animals by treatment group are presented in Table **6.62**. Animals were balanced across treatment groups with regard to gender, age, and body weight. The mean challenge dose was 315 LD_{50} of *B.*

anthracis and one animal received a dose below the target dose of 200 LD_{50}. The challenge dose in the obiltoxaximab 4 mg/kg IM group was slightly higher than in other groups. At 24 hours post-challenge, the proportion of animals with qualitative positive bacteremia in any treatment group was less than 23%, and the differences in these proportions among different treatment groups were large due to the small sample sizes.

Table 6.62. Study AP107: Demographic Variables and Baseline Characteristics by Obiltoxaximab Treatment Group

	Group 1 Saline IV (N=6)	**Group 3 ETI-204 2 mg/kg IV (N=9)**	**Group 5 ETI-204 4 mg/kg IM (N=8)**	**Group 4 ETI-204 8 mg/kg IM (N=9)**	**Group 2 ETI-204 8 mg/kg IV (N=8)**	**Total (N=41)**
Age (years)						
Range	2-5	2-5	2-5	2-5	2-5	2-5
Gender [n (%)]						
Female	3 (50.0)	5 (55.6)	4 (50.0)	4 (44.4)	4 (50.0)	21 (51.2)
Male	3 (50.0)	4 (44.4)	4 (50.0)	5 (55.6)	4 (50.0)	20 (48.8)
Body weight (kg)						
Mean (SD)	2.4 (0.2)	2.4 (0.2)	2.4 (0.2)	2.5 (0.3)	2.6 (0.4)	2.5 (0.3)
Range	2.2, 2.6	2.2, 2.7	2.1, 2.6	2.1, 3.1	2.2, 3.5	2.1, 3.5
CHALLENGE DOSE						
Challenge dose (LD_{50})						
Mean (SD)	324.2 (70.6)	315.6 (83.4)	366.0 (113.6)	289.0 (51.8)	293.8 (49.9)	314.9 (78.3)
Range	254.0, 458.0	213.0, 451.0	198.0, 551.0	222.0, 351.0	225.0, 370.0	198.0, 551.0
Challenge dose (LD_{50}) [n(%)]						
<200	0	0	1 (12.5)	0	0	1 (2.4)
200 or higher	6 (100)	9 (100)	7 (87.5)	9 (100)	8 (100)	40 (97.6)
BACTEREMIA*						
Positive qualitative bacteremia 24	1 (16.7)	2 (22.2)	1 (12.5)	2 (22.2)	1 (12.5)	7 (17.1)

hours after challenge* (n(%))						

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

Efficacy Results Primary Endpoint

Obiltoxaximab was administered to macaques at 24 hours post-exposure to *B. anthracis*. One (17%) of six control animals treated with sterile saline/placebo survived, whereas 6/8 (75%) animals that received 8mg/kg IV and 4/9 (44%) macaques treated with obiltoxaximab 2.0mg/kg IV, survived. An increase in survival over placebo was observed in macaques treated with obiltoxaximab, 5/9 (56%) and 6/8 (75%) in the 8 mg/kg IM and 4mg/kg IM treatment groups, respectively, survived.
There were no significant differences in survival rates between any treatment group and the placebo group using a Bonferroni adjustment method (a one-sided significance level of 0.025/4=0.0125), as shown in Table 6.63.

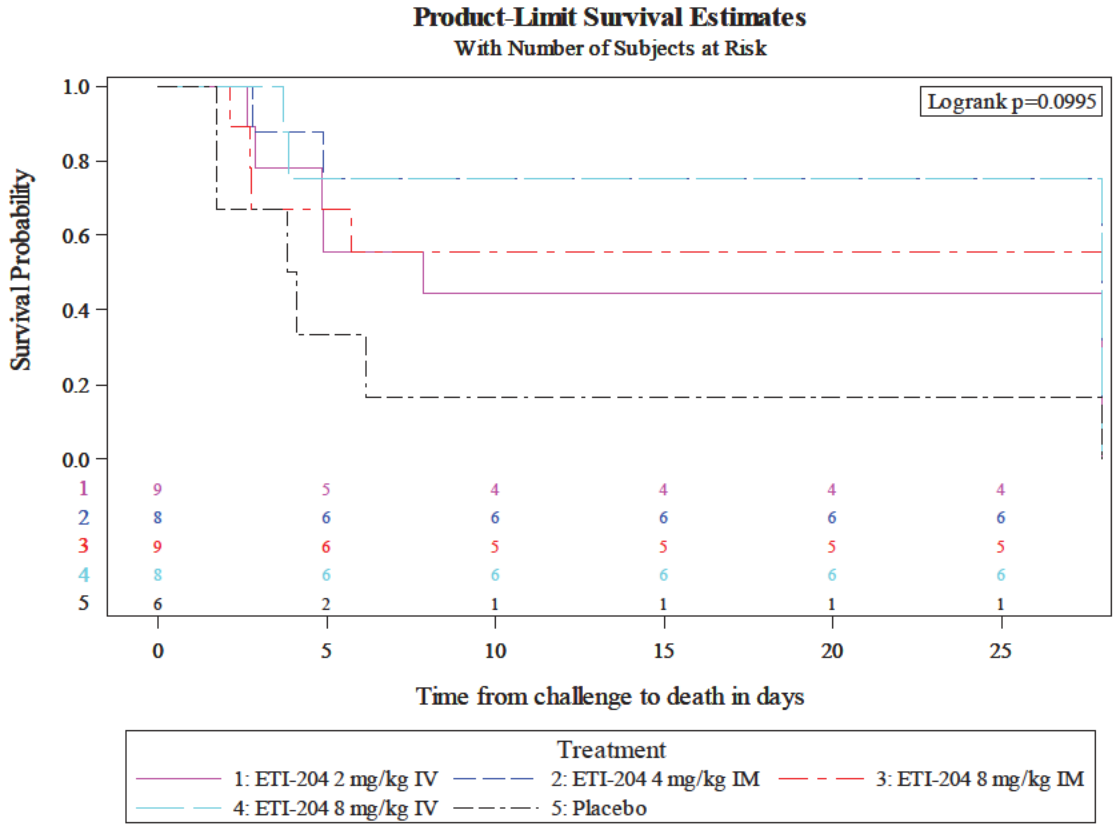
Table 6.63. Study AP107: Survival at Day 28 by Treatment Group

	Group 1 Saline IV Placebo (N=6)	**Group 3 ETI-204 2 mg/kg IV (N=9)**	**Group 5 ETI-204 4 mg/kg IM (N=8)**	**Group 4 ETI-204 8 mg/kg IM (N=9)**	**Group 2 ETI-204 8 mg/kg IV (N=8)**
N (%)	1 (16.7)	4 (44.4)	6 (75.0)	5 (55.6)	6 (75.0)
Difference in survival proportion compared with placebo [95% CI] one-sided p-value*		0.233 [-0.295, 0.641] 0.210	0.583 [0.018, 0.902] 0.020	0.389 [-0.158, 0.777] 0.087	0.583 [0.018, 0.902] 0.020

* 95% CI and p-values from exact method and Boschloo's one-sided test calculated by the reviewer. *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D*

There were no statistically significant differences in time to death between any treatment group and the placebo group using a Bonferroni method for multiple comparison adjustment (0.05/4=0.0125), as shown in the in Kaplan-Meier survival analysis, **Figure 6.43** and Table **6.64**.

Figure 6.43. Study AP107: Kaplan-Meier Curve: Survival by Treatment Group



Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

The time from challenge to death was not significantly different between the obiltoxaximab treatment groups and the placebo group, **Table 6.64**.

Table 6.64. Study AP107: Two sided p-values of pairwise log-rank tests comparing time from challenge to death compared with the placebo group

ETI-204 2 mg/kg IV (N=9)	ETI-204 4 mg/kg IM (N=8)	ETI-204 8 mg/kg IM (N=9)	ETI-204 8 mg/kg IV (N=8)
0.1662	0.0278	0.1695	0.0380

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

Data Quality and Integrity - Reviewers' Assessment

In general the submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. The clinical and biostatistics reviewer could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

The following table shows the results of subgroup analyses. The sample sizes were too small to observe a reliable trend by each grouping variable.

Table 6.65. Study AP107: Survival status by Gender and Challenge Dose

	Placebo (N= 6)	**ETI-204 2 mg/kg IV 24 hrs PC (N= 9)**	**ETI-204 4 mg/kg IM 24 hrs PC (N= 8)**	**ETI-204 8 mg/kg IM 24 hrs PC (N= 9)**	**ETI-204 8 mg/kg IV 24 hrs PC (N= 9)**	**Total (N= 41)**
Gender						
Female	0/3	2/5 (40%)	4/4 (100%)	3/4 (75%)	4/5 (80%)	13/21(61.9%)
Male	1/3 (33.3%)	2/4 (50%)	2/4 (50%)	2/5 (40%)	2/4 (50%)	9/20 (45%)
Challenge dose (LD_{50})						
<250	0	1/2 (50%)	0/1	2/3 (66.7%)	1/3 (33.3%)	4/9 (44.4%)
250 or higher	1/6 (16.7%)	3/7 (42.9%)	6/7 (85.7%)	3/6 (50.0%)	5/6 (83.3%)	18/32 (56.3%)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

Clinical Observations

The majority of NZW rabbits exhibited abnormal clinical signs consistent with anthrax following challenge. Lethargy, inappetence, and respiratory abnormalities were most commonly noted. Animals that succumbed to anthrax demonstrated a progression of signs that generally followed the usual progression in rabbits from being found normal to documented lethargy and not eating, followed by respiratory abnormalities and finally to the occasional seizure and/or moribundity. All the treatment groups showed a significant increase in neutrophils from baseline at 40 and 48 hours post-challenge. Lymphocytes demonstrated significant increases for all groups at 32 hours post-challenge and a significant decrease at 48 hours post-challenge Surviving animals returned to normal but still had the occasional not eating and/or diarrhea/soft stool which is not uncommon with laboratory housed non-human primates.

Necropsy and Histopathology
Gross lesions at necropsy were consistent with anthrax. Microscopic findings considered consistent with anthrax were present in the two *B. anthracis*- exposed animals examined histologically.
A definitive cause of death could not be established for Animal A03226, which died during quarantine, prior to placement on study. Tissue samples from two anthrax spore-challenged animals evaluated microscopically were confirmed to have anthrax, and gross lesions and bacteremia data in all other animals were consistent with anthrax. *See pharmacology/ toxicology review by Amy Nostrandt, DVM for a full discussion of necropsy and histopathological findings.*

6.10 **Study AR004 - Post-exposure Prophylaxis**

6.10.1 Study Design

Overview and Objective

Study AR004 evaluated the therapeutic efficacy of the (b) (4) monoclonal anti-PA antibody (from the (b) (4) cell line) against aerosolized anthrax when administered post-challenge in the NZW rabbit model. The primary objective was to examine the efficacy of the (b) (4) ETI-204 in delaying or preventing death in NZW rabbits from anthrax when administered as a therapeutic treatment at various time points following an inhalational exposure to *Bacillus anthracis.*

Reviewer Comment: (b) (4) monoclonal anti-PA antibody was an earlier formulation of ETI-204. Subsequently, a new cell line, (b) (4), was used for production of the monoclonal antibody. Though very similar to the (b) (4) Mab, there were small difference in (b) (4) which were thought to perhaps affect the safety profile; thus an additional human safety/PK study, AH102, was conducted using doses of 120mg (~1.5 mg/kg), 240mg (~3 mg/kg) and 360mg (~4.5 mg/kg) and no clinically significant adverse reactions were noted.

Trial Design

Study AR004 was a randomized, placebo-controlled, parallel group, with treatment administered as a fixed 10mg single-dose and at varying time points post-challenge, conducted at (b) (4) in 2004. Obiltoxaximab 10mg IV was administered between 24 and 48 hours post challenge.

- ETI-204 10 mg/animal IV, 24 hrs post-challenge
- ETI-204 10 mg/animal IV, 36 hrs post-challenge
- ETI-204 10 mg/animal IV, 48 hrs post-challenge

- Placebo (PBS) IV, 48 hrs post-challenge

NZW rabbits were randomized by sex and weight to a treatment group and then randomized into two challenge days and then a challenge order within a challenge day. Animals were challenged with a targeted dose of approximately 200 LD_{50} *B. anthracis* (Ames).

Study Endpoints

The primary endpoint was survival to 28 days post-challenge with *B. anthracis* spores.

Statistical Analysis Plan

Sample Size Calculation
Sample sizes of 10 control and 10 treated animals were considered in the protocol sufficient to provide greater than 80% power to detect a difference when the survival probabilities were 10% in the control group and 70% in the treated group, using a one-sided Fisher's exact test.

Reviewer Comment: The biostatistics reviewer noted that a Type I error was not specified. Using a one-sided and two-sided level of 0.05, the statistical power was 82.4%, and 66.7%.

Analysis Populations

The analysis population included randomized animals that survived to treatment. Three animals in Group 3 and one animal in Group 4 died prior to the treatment time point. These animals were not included in the statistical analysis.

Statistical Methods

A one-sided Fisher's exact test, at a 0.05 level, was used to compare the survival rates between each individual obiltoxaximab group and the control group.

6.10.2 Study Results

Compliance with Good Laboratory Practices

This is a non GLP study. The study was conducted as per the protocol and SOPs at the (b) (4)

Demographic Characteristics

Demographic variables and baseline characteristics are shown in Table 6.66 and these variables were generally well balanced across treatment groups. A total of 58% of rabbits received a challenge dose < 200 LD_{50} and the 24- and 48-hour groups included a higher proportion of animals that received (~70%) of less than 200 LD_{50}. The higher mortality rate in the 48-hour group suggested that the lower challenge dose was not a major obstacle to evaluating the efficacy in the 24-hour group. No animals were bacteremic (qualitative) at 24 hours post-challenge. One animal from the placebo group and three animals from the group starting treatment at 48 hour post challenge died prior to the post-challenge treatment time and are not included in the analysis.

Table 6.66. Study AR004: Demographic Variables and Baseline Characteristics by Treatment Group

	Placebo (N=9)	ETI-204 10 mg/kg 24 hrs PC (N=10)	ETI-204 10 mg/kg 36 hrs PC (N=10)	ETI-204 10 mg/kg 48 hrs PC (N=7)	Total (N=36)
Age (weeks) Range	13-17	13-17	13-17	13-17	13-17
Gender [n (%)]					
Female	4 (44.4)	5 (50.0)	5 (50.0)	3 (42.9)	17 (47.2)
Male	5 (55.6)	5 (50.0)	5 (50.0)	4 (57.1)	19 (52.8)
Challenge dose (LD_{50}) [n(%)]					
<200	5 (55.6)	7 (70.0)	4 (40.0)	5 (71.4)	21 (58.3)
200 or higher	4 (44.4)	3 (30.0)	6 (60.0)	2 (28.6)	15 (41.7)

PC= post challenge; ETI-204: obiltoxaximab; Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

Bacteremia and Survival

Blood cultures for *B. anthracis* bacteremia were performed on all surviving rabbits at Day 1, 2, 7, 10, 14, 21, and 28. All of the surviving monoclonal antibody-treated animals had a negative blood culture for every time point analyzed during the course of the study. Three out of 10 control rabbits demonstrated positive *B. anthracis* cultures on study Day 2 with 8 of 10 animals having a positive culture at the time of morbidity or death.

Efficacy Results - Primary Endpoint

The fixed dose of obiltoxaximab 10mg IV administered at 24 hours had a significant effect on survival. The Applicant's derived p-values for the three comparisons using a one-sided Fisher's exact test were 0.0006, 0.0217, and 0.0625; they concluded that the 24- and 36-hour obiltoxaximab treatment groups demonstrated a significant increase in survival proportions. However, the FDA analysis demonstrated that only the survival rates in the 24-hour treatment group was statistically significantly different from the placebo group, using a one-sided significance level of 0.025/3=0.0083.

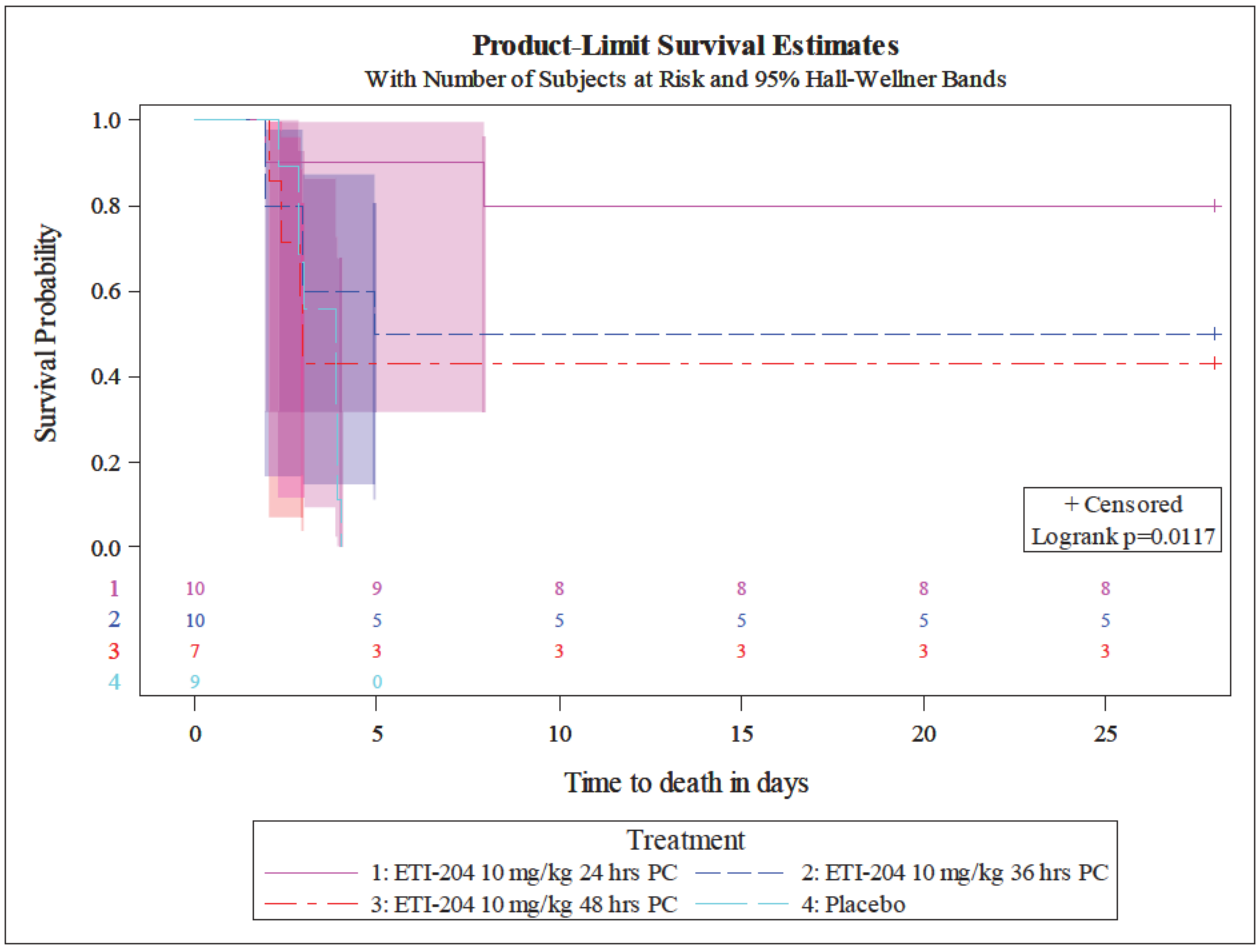
Table 6.67. Study AR004: Survival at Day 28 by Treatment Group

	Placebo (N=9)	ETI-204 10 mg IV 24 hrs PC (N=10)	ETI-204 10 mg IV 36 hrs PC (N=10)	ETI-204 10 mg IV 48 hrs PC (N=7)
N (%)	0	8 (80.0)	5 (50.0)	3 (42.9)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.8 [0.402, 0.975] 0.0001	0.5 [0.084, 0.813] 0.010	0.429 [0.012, 0.816] 0.0226
Adjusted 95% confidence interval		0.303, 0.986	-0.017, 0.856	-0.084, 0.865

* 95% CI and p-values from exact method and Boschloo's one-sided test; Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

There was a statistically significant difference in time to death for the monoclonal antibody, obiltoxaximab 10mg dose, administered at 24 but not at 36 and 48 hours, Figure 6.44.

Figure 6.44. Study AR004: Kaplan-Meier curve and 95% confidence band by Treatment Group



Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

The p-values from the pairwise log-rank tests in the following table also demonstrated that only the 24-hour treatment group had the statistically significant treatment effect for survival (using a two-sided significance level of 0.05/3=0.0167), Table 6.68.

Table 6.68. Study AR004: Two-sided p-values of pairwise log-rank tests comparing time from challenge to death compared with the placebo group

ETI-204 10 mg/ 24 hrs PC (N=10)	ETI-204 10 mg 36 hrs PC (N=10)	ETI-204 10 mg 48 hrs PC (N=7)
0.0001	0.040	0.277

PC= post-challenge; *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D*

Data Quality and Integrity - Reviewers' Assessment

In general the submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. In general, the reviewers could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

Subgroup analysis results for gender and challenge dose are shown in Table 6.69. The 24- and 36-hour treatment groups had a higher LD_{50} challenge dose and a lower survival rate.

Table 6.69. Study AR004: Survival at Day 28 by Gender and Challenge Dose

	Placebo (N= 9)	**ETI-204 10 mg IV 24 hrs PC (N= 10)**	**ETI-204 10 mg IV 36 hrs PC (N= 10)**	**ETI-204 10 mg IV 48 hrs PC (N= 7)**	**Total (N= 36)**
Gender					
Female	0/4	4/5 (80%)	1/5 (20%)	1/3 (33.3%)	6/17 (35.3%)
Male	0/5	4/5 (80%)	4/5 (80%)	2/4 (50%)	10/19 (52.6%)
Challenge dose *B. anthracis* (LD_{50})					
<250	0/8	10/11 (90.9%)	2/9 (22.2%)	3/10 (30%)	15/40 (37.5%)
250 or higher	1/2 (50%)	3/3 (100%)	4/5 (80%)	1/4 (25%)	9/14 (64.3%)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

6.11 Study AR012 - Post-exposure Prophylaxis

6.11.1 Study Design

Overview and Objective

The primary objective was to determine the maximally-effective dose, optimally-effective dose, and lowest effective dose of obiltoxaximab when given by the IV and IM routes at 24 hours post-exposure to *B. anthracis* spores.

Trial Design

This was a randomized, placebo-controlled, parallel group, open-label, dose ranging study with treatment administered at fixed time point, conducted at (b) (4) in 2007. The study was considered as an open-label study because no blinding information was found.

Eighty-four animals were randomized to one of the following treatment groups:

- Placebo IV (phosphate buffered saline, PBS)
- ETI-204 2.5 mg/animal IV
- ETI-204 5 mg/animal IM
- ETI-204 10 mg/animal IV
- ETI-204 10 mg/animal IM
- ETI-204 20 mg/animal IV
- ETI-204 20 mg/animal IM
- ETI-204 40 mg/animal IM

All animals were challenged with a targeted 200 LD_{50} dose on study Day 0. ETI-204 or placebo was administered 24 hour post- challenge *with B. anthracis* spores.

Study Endpoints

The primary endpoint was survival to 14 days post-challenge of *B. anthracis* spores.

Statistical Analysis Plan

Sample Size Calculation
It was stated in the protocol that sample sizes of 9 control and 9 treated animals were sufficient to provide greater than 82.4% power to detect a difference when the survival probabilities were 10% in the control group and 75% in the treated groups using a one-sided Fisher's exact test. With 12 treated animals there was 82.2% power for the sample comparison when the probability of survival was 70% in the treated group.

Reviewer Comment: A one-sided type I error of 0.05 was used in the power calculations.

Analysis Populations
The analysis population included all randomized animals.

Statistical Methods
One-sided Fisher's exact tests were utilized to compare the survival rates between the treatment groups and the control group.

6.11.2 Study Results

Compliance with Good Clinical Practices

The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58).

Table of Demographic Characteristics

Demographic variables and baseline characteristics are summarized in **Table 6.70**. Animals were evenly distributed by age, gender, and weight across dose groups. The mean challenge dose was 201 LD_{50} *B. anthracis*. The proportion of qualitative bacteremia at 24 hours post-challenge varied across different groups and there was no clear relationship with challenge dose due to the small sample sizes.

Table 6.70. Study AR012: Demographic Variables and Baseline Characteristics by Treatment Group

	Placebo (N=9)	ETI-204 2.5 mg IV (N=9)	ETI-204 5 mg IM (N=9)	ETI-204 10 mg IV (N=12)	ETI-204 10 mg IM (N=9)	ETI-204 20 mg IV (N=12)	ETI-204 20 mg IM (N=12)	ETI-204 40 mg IM (N=12)	Total (N=84)
Age (months)	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
Gender [n (%)]									
Female	4 (44)	5 (55)	5 (56)	6 (50)	4 (44)	6 (50)	6 (50)	6 (50)	42 (50)
Male	5 (56)	4 (44)	4 (44)	6 (50)	5 (56)	6 (50)	6 (50)	6 (50)	42 (50)
Weight kg (SD)	2.63	2.62	2.61	2.56	2.61	2.59	2.59	2.62	2.60
Range	(0.11) 2.49, 2.80	(0.13) 2.46, 2.79	(0.11) 2.49, 2.75	(0.15) 2.26, 2.81	(0.11) 2.43, 2.74	(0.12) 2.40, 2.81	(0.14) 2.36, 2.76	(0.12) 2.38, 2.84	(0.12) 2.26, 2.84
CHALLENGE DOSE									
Challenge dose (LD_{50})									
Mean	205.7	193.2	187.2	189.8	230.7	218.5	180.7	201.9	200.5
(SD)	(47.4)	(34.3)	(32.3)	(27.3)	(87.5)	(117.2)	(46.4)	(62.6)	(64.3)
Range	111, 258	126, 239	149, 248	151, 243	167, 432	136, 567	111.0, 269.0	131.0, 357.0	111.0, 567.0
Challenge dose (LD_{50}) [n(%)]									
<200	3 (33.3)	4 (44.4)	5 (55.6)	9 (75.0)	5 (55.6)	8 (66.7)	10 (83.3)	7 (58.3)	51 (60.7)
200 or higher	6 (66.7)	5 (55.6)	4 (44.4)	3 (25.0)	4 (44.4)	4 (33.3)	2 (16.7)	5 (41.7)	33 (39.3)
BACTEREMIA									
Positive qualitative bacteremia prior to treatment (n(%))	4 (44.4)	7 (77.8)	6 (66.7)	6 (50.0)	2 (22.2)	4 (33.3)	5 (41.7)	8 (66.7)	42 (50.0)
Positive qualitative bacteremia 27 hours after challenge (n(%))	6 (66.7)	7 (77.8)	6 (66.7)	7 (58.3)	4 (44.4)	5 (41.7)	8 (66.7)	9 (75.0)	52 (61.9)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D

Efficacy Results - Primary Endpoint

None of the placebo animals survived indicating that the challenge inoculum of *B. anthracis* spores was sufficient to cause lethal disease. The highest survival rates were observed with the 20mg IV and 20 mg IM doses, 58% and 50% respectively, (using a one-sided significance level of 0.025/7=0.0036).

Table 6.71. Study AR012: Survival at Day 28 by Treatment Group

	Placebo (N=9)	ETI-204 2.5 mg IV (N=9)	ETI-204 5 mg IM (N=9)	ETI-204 10 mg IV (N=12)	ETI-204 10 mg IM (N=9)	ETI-204 20 mg IV (N=12)	ETI-204 20 mg IM (N=12)	ETI-204 40 mg IM (N=12)
All animals								
N (%)	0	1 (11.1)	1 (11.1)	6 (50)	3 (33.3)	7 (58.3)	5 (41.7)	4 (33.3)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.111 [-0.224, 0.483] 0.4073	0.111 [-0.224, 0.483] 0.4073	0.5 [0.094, 0.789] 0.0074	0.333 [-0.071, 0.701] 0.049	0.583 [0.187, 0.848] 0.0026	0.417 [0.034,0.725] 0.0186	0.333 [-0.066, 0.655] 0.051
Adjusted exact 95% confidence interval		-0.436, 0.610	-0.436, 0.610	-0.057, 0.859	-0.238, 0.794	-0.018, 0.904	-0.134, 0.806	-0.217, 0.749
Only qualitatively bacteremic animals								
N (%)	0/4	1/7 (14.3)	0/6	2/6 (33.3)	0/2	0/4	1/5 (20%)	1/8 (12.5)

Two-sided 95% confidence interval and one-sided p-values were calculated by the reviewer. Confidence intervals were not reported for the bacteremic population because no significant differences were observed. *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D*

Reviewer Comment: The Applicant concluded that the three treatment groups (10 mg IV, 20 mg IM and IV) had significantly higher survival rates than the placebo group using a one-sided Fisher's Exact Tests to compare the survival rates between each individual antibody group and the control group.

Data Quality and Integrity - Reviewers' Assessment

In general the submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. The clinical and biostatistics reviewers could replicate the primary efficacy analysis results and main study results.

Efficacy Results - Secondary and other relevant endpoints

Time to bacteremia
Qualitative bacteremia data were available at 24, 27 hours and Day 14 post-challenge. Therefore, no time to bacteremia was included in this review, because it was not an accurate assessment of the actual time to bacteremia, given these infrequent measurements.

Additional Analyses Conducted on the Individual Trial

The following table shows the results of subgroup analyses by gender and challenge dose are shown in Table 6.72. The sample sizes were too small to see a reliable trend by each grouping variable.

Table 6.72. Study AR012: Survival at Day 28 by Gender and Challenge Dose

	Placebo (N= 9)	**ETI-204 2.5 mg IV (N= 9)**	**ETI-204 5 mg IM (N= 9)**	**ETI-204 10 mg IV (N= 12)**	**ETI-204 10 mg IM (N= 9)**	**ETI-204 20 mg IV (N= 12)**	**ETI-204 20 mg IM (N= 12)**	**ETI-204 40 mg IM (N= 12)**	**Total no. Animals (N= 84)**
Gender									
Female	0/4	1/5 (20%)	0/5	4/6 (66.7%)	1/4 (25%)	3/6 (50%)	2/6 (33.3%)	3/6 (50.0%)	14/42 (33.3%)
Male	0/5	0/4	1/4 (25%)	2/6 (33.3%)	2/5 (40%)	4/6 (66.7%)	3/6 (50%)	1/6 (16.7%)	13/42 (31.0%)
Challenge dose (LD_{50})									
<250	0/8	1/9 (11.1%)	1/9 (11.1%)	6/12 (50%)	3/6 (50%)	7/10 (70.0%)	5/10 (50%)	3/10 (30%)	26/74 (35.1%)
250 or higher	0/1				0/3	0/2	0/2	1/2 (50%)	1/10 (10%)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

6.12 **Study AR0315 Post-exposure Prophylaxis**

6.12.1 Study Design

Overview and Objective

The primary objective was to evaluate the survival rate of NZW rabbits when the monoclonal antibody, obiltoxaximab, was administered IM at either 18 or 24 hours post-challenge with aerosolized *B. anthracis* spores.

Trial Design

This was a randomized, placebo-controlled, parallel group, dose ranging with obiltoxaximab treatment administered at a fixed time points post-challenge with *B. anthracis*. All NZW rabbits were challenged on study Day 0 with aerosolized 200 LD_{50} dose of *B. anthracis* spores (Ames).

Animals were randomized into four groups of 12 and one group (placebo) of 10 animals post-challenge with aerosolized *B. anthracis* spores.

- Placebo, saline IM 24 hrs
- obiltoxaximab 4 mg/kg ETI-204 IM, 18 hrs
- obiltoxaximab 16 mg/kg ETI-204 IM, 18 hrs
- obiltoxaximab 4 mg/kg ETI-204 IM, 24 hrs
- obiltoxaximab 16 mg/kg ETI-204 IM, 24 hrs

Study Endpoints

The primary endpoint was survival to 28 days post-challenge *with B. anthracis* spores.

Statistical Analysis Plan

Sample Size Calculation

Sample sizes of 12 animals per treated group and 10 in the control group provided 80.8% power to compare the survival rates of 5% and 60%, with a two-sided 0.05 level Fisher's exact test, with no adjustment for multiple comparisons.

Analysis Population
The analysis population included all randomized animals.

Statistical Methods
Two-sided Fisher's exact tests were utilized to compare the survival rates between the treated groups and the control group.

6.12.2 Study Results

Compliance with Good Clinical Practices

This is a non GLP study. The study was conducted per the protocol and SOPs at the (b) (4)

Table of Demographic Characteristics

Demographic variables and challenge dose were comparable across obiltoxaximab treatment groups. The mean challenge dose was 236 LD_{50} of *B. anthracis.* Bacteremia levels were higher when treatment was administered at 24 hours post-challenge than at 18 hours post challenge.

Table 6.73. Study AR0315: Demographic Variables and Baseline Characteristics by Treatment Group

	Placebo 24 h PC (N=10)	ETI-204 4 mg/kg 18 hrs PC IM (N=12)	ETI-204 4 mg/kg 24 hrs PC IM (N=12)	ETI-204 16 mg/kg 18 hrs PC IM (N=12)	ETI-204 16 mg/kg 24 hrs PC IM (N=12)	Total (N=58)
Age (years) Range	6 to 7	6 to 7	6 to 7	6 to 7	6 to 7	6 to 7
Gender [n (%)] Female Male	5 (50.0) 5 (50.0)	6 (50.0) 6 (50.0)	6 (50.0) 6 (50.0)	6 (50.0) 6 (50.0)	6 (50.0) 6 (50.0)	29 (50.0) 29 (50.0)
Body weight (kg) Mean (SD) Range	2.9 (0.2) 2.4, 3.2	3.0 (0.1) 2.8, 3.2	3.0 (0.2) 2.7, 3.2	2.9 (0.3) 2.0, 3.3	2.9 (0.3) 2.1, 3.2	2.9 (0.2) 2.0, 3.3
CHALLENGE DOSE						
Challenge dose (LD_{50}) Mean (SD) Range	245.5 (16.2) 218.0, 270.0	235.3 (27.6) 197.0, 278.0	221.6 (15.7) 197.0, 253.0	223.5 (31.0) 141.0, 261.0	255.7 (53.0) 150.0, 337.0	236.0 (33.7) 141.0, 337.0
Challenge dose (LD_{50}) [n(%)] <200 200 or higher	0 10 (100)	1 (8.3) 11 (91.7)	1 (8.3) 11 (91.7)	1 (8.3) 11 (91.7)	2 (16.7) 10 (83.3)	5 (8.6) 53 (91.4)
BACTEREMIA						
Positive quantitative bacteremia prior	5 (50.0)	5 (41.7)	11 (91.7)	5 (41.7)	11 (91.7)	37 (63.8)

to treatment (n(%))						
Log_{10} bacteremia PTT (cfu/mL)						
Mean (SD)	1.39 (1.17)	0.88 (0.72)	2.87 (1.17)	0.97 (0.87)	2.75 (1.25)	1.78 (1.34)
Range	0.30, 2.98	0.30, 1.70	0.30, 5.01	0.30, 2.74	0.30, 5.01	0.30, 5.01
Bacteremia PTT (cfu/mL)						
Geometric mean	24.4	7.6	735.5	9.3	556.3	60.8
95% confidence interval	3.5, 167.4	2.7, 21.9	133.1, 4063.8	2.6, 33.6	89.7, 3449.4	26.9, 137.1

PTT: prior to treatment; *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Efficacy Results - Primary Endpoint

The two obiltoxaximab 16 mg/kg groups administered at 18 to 24 hours post challenge had significantly improved survival as did the obiltoxaximab 4 mg/kg administered at 18 hours post-challenge.

Table 6.74. Study AR0315: Survival at Day 28 by ETI-204 Treatment Group

	Placebo (N=10)	ETI-204 4 mg/kg IM 18 hrs PC (N=12)	ETI-204 4 mg/kg IM 24 hrs PC (N=12)	ETI-204 16 mg/kg IM 18 hrs PC (N=12)	ETI-204 16 mg/kg IM 24 hrs PC (N=12)
N (%)	0	11 (91.7)	5 (41.7)	11 (91.7)	8 (66.7)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.917 [0.535, 0.998] <0.0001	0.417 [0.065, 0.723] 0.0131	0.9167 [0.535, 0.998] <0.0001	0.667 [0.290, 0.901] 0.0005
Adjusted exact 95% confidence interval		0.425, 1	-0.058, 0.786	0.425, 1	0.172, 0.934

* 95% CI and p-values calculated using a one-sided significance level of 0.025/4=0.00625 (Bonferroni method);
Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Data Quality and Integrity - Reviewers' Assessment
The submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. The clinical and biostatistics reviewers could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

The following table shows the results of subgroup analyses by gender, challenge dose, and bacteremia prior to treatment. The sample sizes were too small to see a reliable trend by each grouping variable.

Table 6.75. AR0315: Subgroup Analyses by Gender, Challenge Dose, and Bacteremia Prior to Treatment

	Placebo (N= 10)	ETI-204 4 mg/kg 18 hrs PC IM (N= 12)	ETI-204 4 mg/kg 24 hrs PC IM (N= 12)	ETI-204 16 mg/kg 18 hrs PC IM (N= 12)	ETI-204 16 mg/kg 24 hrs PC IM (N= 12)	Total (N= 58)
Gender						
Female	0/5	5/6 (83.3%)	4/6 (66.7%)	5/6 (83.3%)	4/6 (66.7%)	18/29 (62.1%)
Male	0/5	6/6 (100.0%)	1/6 (16.7%)	6/6 (100.0%)	4/6 (66.7%)	17/29 (58.6%)
Challenge dose (LD_{50})						
<250	0/5	7/8 (87.5%)	4/11 (36.4%)	9/10 (90%)	2/4 (50%)	22/38 (57.9%)
250 or higher	0/5	4/4 (100%)	1/1 (100%)	2/2 (100%)	6/8 (75%)	13/20 (65%)
Bacteremia prior to treatment (cfu/mL)						
$<10^2$	0/5	11/12 (91.7%)	1/2 (50%)	11/11 (100%)	3/3 (100%)	26/33 (78.8%)
10^2 - 10^4	0/5	0	3/9 (33.3%)	0/1	5/8 (62.5%)	8/23 (34.8%)
10^4 - $<10^6$	0	0	1/1 (100%)	0	0/1	1/2 (50%)

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Key Findings

This study demonstrated that obiltoxaximab 4 mg/kg IM administered at 18 hours post-challenge and 16 mg/kg IM administered at 18 or 24 hours improved survival significantly compared to placebo. Obiltoxaximab 4 mg/kg IM administered 24 hours did not improve survival significantly indicating that obiltoxaximab 4 mg/kg is too low a dose for prophylaxis.

6.13 **Study AR035 Post –exposure Prophylaxis**

6.13.1 Study Design

Overview and Objective

The primary objective was to assess the pharmacokinetics (PK) of obiltoxaximab following a single IM dose in NZW rabbit infected via inhalation with *B. anthracis* spores and to identify the optimal window of protection when obiltoxaximab, administered IM, could effectively reduce the mortality rate in anthrax-infected NZW rabbits.

Trial Design

This was a randomized, open-label, placebo-controlled, dose-ranging study of obiltoxaximab IM administered to NZW rabbits at 18, 24, and 30 hours post exposure to *B. anthracis* spores. The study was, conducted at (b) (4) in 2012.

Animals were randomized into the following four treatment groups.

- Placebo (vehicle)
- obiltoxaximab 16 mg/kg 18 hrs PC, IM
- obiltoxaximab 16 mg/kg 24 hrs PC, IM
- obiltoxaximab 16 mg/kg 30 hrs PC, IM

NZW rabbits were randomized by body weight into four treatment groups of 12 animals and a control group of 10 animals. Animals were also randomized to one of two challenge days and challenge order. The target challenge dose was 200 ± 50 LD_{50} *B. anthracis* (Ames) spores.

Group	No. NZW Rabbits	Obiltoxaximab mg/kg IM	Time (hours) of Dosing
1	10	0	18h
2	12	16	18h
3	12	16	24h
4	12	16	30h

Study Endpoints

The primary endpoint was survival to 28 days post challenge to *B. anthracis* spores.

Statistical Analysis Plan

Excerpt from biostatistics review by Xianbin Li, Ph.D.

Sample Size Calculation
The sample size of the study (10 per group) was considered in the protocol to be adequate to demonstrate data trending to support the utility of the rabbit model of anthrax.

Analysis Populations
All animals received treatment.
All animals were confirmed infected either by blood bacteremia or by the detection of circulating endogenous anti-PA antibodies.

Statistical Methods
One-sided 0.025 level Fisher's exact test used to compare survival rate in ETI-204 treated group to that in the control group, with and without multiple comparison adjustment.

6.13.2 Study Results

Compliance with Good Laboratory Practices

The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58).

Protocol Violations/Deviations

Protocol deviations did not have a significant impact on the conduct or integrity of the study.

Table of Demographic Characteristics

Forty NZW rabbits were randomized and challenged. Two animals assigned to the 30-hour post-challenge group died or were sacrificed moribund prior to drug administration, therefore these two animals were not included in the analyses. Animals were evenly distributed across treatment groups by gender, age, and body weight. Only in Group 3 and Group 4 were some animals bacteremic prior to treatment.

Table 6.76. Study AR035: Demographic variables and baseline characteristics by treatment group

	Group1 Placebo 24 hrs PC (N=10)	Group 2 ETI-204 16 mg/kg IM 18 hrs PC (N=10)	Group 3 ETI-204 16 mg/kg IM 24 hrs PC (N=10)	Group 4 ETI-204 16 mg/kg IM 30 hrs PC (N=8)	Total (N=38)
Age (months)					
Range	6-7	6-7	6-7	6-7	6-7
Gender [n (%)]					
Male	10 (100)	10 (100)	10 (100)	8 (100)	38 (100)
Body weight (kg)					
Mean (SD)	3.3 (0.2)	3.3 (0.2)	3.3 (0.2)	3.2 (0.2)	3.3 (0.2)
Range	3.1, 3.6	3.1, 3.7	3.0, 3.7	3.0, 3.5	3.0, 3.7
CHALLENGE DOSE					
Challenge dose (LD_{50})					
Mean (SD)	283.1 (84.9)	281.7 (84.2)	281.7 (84.4)	297.9 (89.4)	285.5 (82.2)
Range	151.0,427.0	151.0, 424.0	151.0, 423.0	150.0, 424.0	150.0, 427.0
Challenge dose (LD_{50}) [n(%)]					
<200	1 (10.0)	1 (10.0)	1 (10.0)	1 (12.5)	4 (10.5)
200 or higher	9 (90.0)	9 (90.0)	9 (90.0)	7 (87.5)	34 (89.5)
BACTEREMIA					
Positive quantitative bacteremia prior to treatment (n(%))	0	0	4 (40.0)	7 (87.5)	11 (28.9)
Log_{10} bacteremia prior to treatment (cfu/mL)					
Mean (SD)	0.30 (0.00)	0.30 (0.00)	0.93 (1.19)	4.51 (2.65)	1.35 (2.12)
Range	0.30, 0.30	0.30, 0.30	0.30, 4.02	0.30, 7.70	0.30, 7.70
Bacteremia prior to treatment (cfu/mL)					
Geometric mean	2.0	2.0	8.5	32574.7*	22.5
95% confidence interval	NA	NA	1.2, 59.7	197.2, 5382200.8	4.5, 111.8

*One animal's bacteremia was truncated at 3E7 because the value was >3E7. NA: not available because all animals had the same value. Source: Table constructed by biostatistics reviewer, Xianbin Li PhD.

Efficacy Results - Primary Endpoint

Survival rates for all obiltoxaximab treatment groups versus placebo are shown in Table 6.77. One animal in the 18-hour treatment group was euthanized on study Day 20 and the death was not considered to be attributed to anthrax. The Applicant considered this animal a survivor, but in the following conservative analysis, it was considered a death. In treatment group 4, the Applicant's analysis included two animals that died prior to treatment. The following analysis excludes these two animals because they died before receiving treatment. If they were included, the survival proportion was still equal to zero in Group 4.

The survival rates in the 18- and 24-hour obiltoxaximab treatment groups were statistically significantly different from the placebo group (using a one-sided significance level of 0.025/3=0.0083). However, administration of obiltoxaximab at 30 hours post-challenge was too long of a delay to be effective for prophylaxis against anthrax.

Table 6.77. Study AR035: Survival in NZW rabbits at Day 28 by Treatment Group

	Group 1 Placebo (N=10)	Group 2 ETI-204 16 mg/kg IM 18 hrs PC (N=10)	Group 3 ETI-204 16 mg/kg IM 24 hrs PC (N=10)	Group 4 ETI-204 16 mg/kg IM 30 hrs PC (N=8)
N (%)	0	6 (60.0)	6 (60.0)	0
Difference in survival proportion compared with placebo [95% CI] one-sided p-value*		0.60 [0.213, 0.878] 0.0018	0.60 [0.213, 0.878] 0.0018	0 [-0.309, 0.369]

* 95% CI and p-values from exact method and Boschloo's test; *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Data Quality and Integrity - Reviewers' Assessment

In general, the submitted data sets were of high quality. All datasets were submitted in AdaM and SEND standard format. The clinical and the biostatistics reviewers could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

Only male rabbits were included in this study. The sample sizes were too small to see a reliable trend by challenge inoculum of B. anthracis and bacteremia levels.

Table 6.78. Study AR035: Survival at Day 28 by Challenge inoculum of *B. anthracis* and bacteremia

	Placebo (N= 10)	ETI-204 16 mg/kg 18 hrs PC IM (N= 10)	ETI-204 16 mg/kg 24 hrs PC IM (N= 10)	ETI-204 16 mg/kg 30 hrs PC IM (N= 8)	Total (N= 38)
Challenge inoculum of *B. anthracis* (LD_{50})					
<250	0/5	2/5 (40%)	3/5 (60%)	0/3	5/18 (27.8%)
250 or higher	0/5	4/5 (80%)	3/5 (60%)	0/5	7/20 (35%)
<200	0/1	0/1	1/1 (100%)	0/1	1/4 (25%)
Bacteremia prior to treatment (CFU/mL)					
$<10^2$	0/10	6/10 (60%)	6/9 (66.7%)	0/1	12/30 (40%)
10^2 - 10^4	0	0	0	0/2	0/2
10^4 - $<10^6$	0	0	0/1	0/2	0/3

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Key Findings

This study demonstrated that obiltoxaximab 16 mg/kg administered IM at 18 or 24 hours post-challenge with *B. anthracis* significantly improved survival compared to placebo. A delay in administration of obiltoxaximab IM beyond 24 hours did not provide protection against anthrax.

6.14 Study AR037 – Post-exposure Prophylaxis

6.14.1 Study Design

Overview and Objective

The primary objective of study AR037 was to assess the effect of a single IM dose of obiltoxaximab administered at 24 hours post challenge with an aerosolized lethal dose of *B. anthracis* spores in NZW rabbits. The secondary objectives were to assess time to death and to

evaluate the dose response of obiltoxaximab on overall mortality rate, time to death, bacteremia, tissue bacteremia burden, and free circulating PA level.

Trial Design

This was a randomized, open-label, placebo-controlled dose-ranging study of obiltoxaximab IM, conducted at (b) (4) in 2012.

Animals were randomized into the following four treatment groups:

- Placebo (vehicle)
- obiltoxaximab 8 mg/kg, IM
- obiltoxaximab 16 mg/kg, IM
- obiltoxaximab 32 mg/kg, IM

NZW rabbits were randomized by sex and body weight and then assigned to four challenge days based on numerical order by group. Although a few animals were mis-dosed (four of the animals in group 3 were switched to Group 4), the imbalance of animals among the challenge cohorts had minimal impact on the study, because body weight, gender, and challenge dose were well balanced across groups.

Animals were challenged with approximately 200 ± 50 LD_{50} *B. anthracis* (Ames) spores via aerosol on Day 0. Clinical observations were performed twice daily (AM and PM).

Study Endpoints

The primary endpoint was survival to 28 days post-challenge with *B. anthracis* spores.

Statistical Analysis Plan

Sample Size Calculation

The sample size of the study (minimum of 10/group) animals was considered adequate in the protocol to demonstrate data trending to support the utility of the rabbit model of anthrax for application to a therapeutic setting. According to the protocol, data analysis would use a Fisher's exact test (one-sided, one sample) using a 0.05 level of significance.

Analysis Populations

Analysis Populations

The ITT datasets included all challenged animals that received treatment. This was the population defined in the protocol. Animals that were confirmed infected either by detection of

bacteremia or by the detection of circulating anti-PA antibodies was added in the primary analysis section of the study report.

Statistical Methods
According to the protocol, the primary analysis only included descriptive statistics for the primary endpoint and comparison of survival rates with control group was one secondary analysis. In the study report, it was stated that one-sided 0.025 level Fisher's exact test used to compare survival rate in ETI-204 treated group to that in the control group.

6.14.2 Study Results

Compliance with Good Laboratory Practices

The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58).

Table of Demographic Characteristics

Demographic variables and baseline characteristics by treatment group are shown in Table 6.79. Animals were evenly distributed by gender, age, and body weight across treatment groups. There were slightly higher proportions of animals with bacteremia and positive PA levels in the obiltoxaximab treatment groups.

Table 6.79. Study AR037: Demographic Variables and Baseline Characteristics by Treatment Group

	Placebo (N=10)	ETI-204 8 mg/kg 24 hrs PC IM (N=16)	ETI-204 16 mg/kg 24 hrs PC IM (N=16)	ETI-204 32 mg/kg 24 hrs PC IM (N=16)	Total (N=58)
Age (weeks)					
Mean (SD) Range	28.2 (1.2) 26.6, 29.6	28.1 (1.2) 26.6, 29.6	27.4 (0.9) 26.6, 28.7	28.9 (0.8) 27.6, 29.6	28.1 (1.1) 26.6, 29.6
Gender [n (%)]					
Female Male	5 (50.0) 5 (50.0)	8 (50.0) 8 (50.0)	8 (50.0) 8 (50.0)	8 (50.0) 8 (50.0)	29 (50.0) 29 (50.0)
Body weight (kg) Mean (SD) Range	3.5 (0.3) 3.0, 3.9	3.5 (0.3) 2.9, 4.0	3.5 (0.3) 2.9, 4.0	3.5 (0.3) 3.0, 3.9	3.5 (0.3) 2.9, 4.0
CHALLENGE DOSE					

B. anthracis (LD_{50})					
Mean (SD)	153.1 (50.5)	142.1 (44.7)	156.2 (54.0)	124.7 (123.5)	143.1 (138.0)
Range	101.0, 271.0	76.0, 268.0	76.0, 269.0	64.0, 151.0	64.0, 271.0
Challenge dose (LD_{50}) [n(%)]					
<200	8 (80.0)	15 (93.8)	13 (81.3)	16 (100)	52 (89.7)
200 or higher	2 (20.0)	1 (6.3)	3 (81.8)	0	6 (10.3)
BACTEREMIA					
No. of animals Positive quantitative bacteremia 24 hours post challenge (n(%))	2 (20.0)	5 (31.3)	5 (31.3)	6 (37.5)	18 (31.0)
Log_{10} bacteremia 24 hours post challenge (cfu/mL)					
Mean (SD)	0.70 (0.85)	1.10 (1.42)	1.33 (1.65)	1.16 (1.31)	1.11 (1.36)
Range	0.30, 2.44	0.30, 4.33	0.30, 5.00	0.30, 3.87	0.30, 5.00
Bacteremia 24 hours post challenge (cfu/mL)					
Geometric mean	5.1	12.7	21.3	14.4	13.0
95% confidence interval	1.2, 20.7	2.2, 72.2	2.8, 162.3	2.9, 71.6	5.7, 29.6
PROTECTIVE ANTIGEN					
PA-ELISA Positivity 24 hours post challenge	0	1 (6.3)	3 (18.8)	3 (18.8)	7 (12.1)
Log10 PA-ELISA 24 hours post challenge					
Mean (SD)	0.70 (0.00)	0.72 (0.09)	0.92 (0.53)	0.85 (0.32)	0.81 (0.33)
Range	0.70, 0.70	0.70, 1.07	0.70, 2.36	0.70, 1.59	0.70, 2.36
PA-ELISA 24 hours post challenge (ng/mL)					
Geometric mean	5.0	5.3	8.3	7.0	6.4
95% confidence interval	NA	4.7, 5.9	4.3, 16	4.7, 10.4	5.2, 7.9

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph. D.

Efficacy Results - Primary Endpoint

The survival rate for each obiltoxaximab treatment group was 31% at Day 28. There was not statistically significant difference between any treatment group and the placebo group, as shown in Table 6.80.
Three animals with anti-PA IgG at seven days prior to challenge (two in the 8 mg/kg group and one in the placebo group) succumbed to anthrax on Study Day 2 or Day 4.

Table 6.80. Study AR037: Survival in NZW rabbits at Day 28 by Treatment Group

	Placebo (N=10)	**ETI-204 8 mg/kg IM 24 hrs PC (N=16)**	**ETI-204 16 mg/kg IM 24 hrs PC (N=16)**	**ETI-204 32 mg/kg IM 24 hrs PC (N=16)**
N (%)	0	5 (31.3)	5 (31.3)	5 (31.3)
Difference in survival proportion compared with placebo [95% CI] one-sided p-value*		0.313 [-0.019, 0.587] 0.033	0.313 [-0.019, 0.587] 0.033	0.313 [-0.019, 0.587] 0.033

*Two-sided 95% confidence interval and one-sided p-values were calculated by the biostatistics reviewer, Xianbin Li, Ph.D.

Data Quality and Integrity - Reviewers' Assessment

The submitted data sets were generally of high quality. All datasets were submitted in AdaM and SEND standard format. The biostatistics and clinical reviewers could replicate the primary efficacy analysis results and main study results from the submitted data.

Bacteremia
From 24 to 36 hours post-challenge, bacteremia levels increased. Then, bacteremia levels declined in the treated groups but did not reach a level below the LOD until 7 days post challenge. All of the deaths occurred between 36 hours and 7 days post challenge.

Persistence of Effect

No recurrence of bacteremia or of signs of anthrax occurred up to the end of the study, Day 28.

Additional Analyses Conducted on the Individual Trial

The results of subgroup analyses by gender, challenge dose, and bacteremia prior to treatment in NZW rabbits are summarized in **Table 6.81**. The sample sizes were too small to see a reliable trend by gender and challenge dose. Surviving animals had the lowest levels of bacteremia and PA prior to treatment.

Table 6.81. Study AR037: Survival in NZW Rabbits at Day 28 by Challenge Dose

	Placebo (N= 10)	ETI-204 8 mg/kg 24 hrs PC IM (N= 16)	ETI-204 16 mg/kg 24 hrs PC IM (N= 16)	ETI-204 32 mg/kg 24 hrs PC IM (N= 16)	Total (N= 58)
Gender					
Female	0/5	2/8 (25.0%)	3/8 (37.5%)	0/8	5/29 (17.2%)
Male	0/5	3/8 (37.5%)	2/8 (25.0%)	5/8 (62.5%)	10/29 (34.5%)
Challenge dose (LD_{50})					
<250	0/6	2/9 (22.2%)	2/7 (28.6%)	3/11 (27.3%)	7/33 (21.2%)
250 or higher	0/4	3/7 (42.9%)	3/9 (33.3%)	2/5 (40.0%)	8/25 (32.0%)
<200	0/1	0/3	1/3 (33.3%)	0/3	1/10 (10.0%)
Bacteremia prior to treatment (cfu/mL)					
$<10^2$	0/8	5/13 (38.5%)	5/11 (45.5%)	5/11 (45.5%)	15/43 (34.9%)
10^2 - 10^4	0/2	0/2	0/4	0/5	0/13
10^4 - $<10^6$	0	0/1	0/1	0	0/2
PA prior to treatment (ng/mL)					
0 - < 10	0/10	5/15 (33.3%)	5/13 (38.5%)	5/13 (38.5%)	15/51 (29.4%)
10 - < 50	0	0/1	0/1	0/3	0/5
50 or higher	0	0	0/2	0	0/2

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Key Findings

There was no statistically significant differences between obiltoxaximab 8, 16, or 32 mg/kg administered IM 24 hours post challenge and the control group. Bacteremia and PA levels prior to treatment were not higher than in Study AR035.

6.15 Study AP305 Pre-exposure Prophylaxis

6.15.1 Study Design

Overview and Objective

The primary objective of study AP305 was to determine the duration of obiltoxaximab prophylactic efficacy when administrated IM to cynomolgus macaques at increasing times prior to exposure to *B. anthracis* spores. The secondary objective was to perform a kinetic analysis of obiltoxaximab when administered IM. The third objective was to evaluate the impact of time of IM obiltoxaximab administration on bacteremia levels in cynomolgus monkeys challenged with *B. anthracis* spores.

Reviewer Comment: The primary objective is discussed in this review.

Trial Design

This was a randomized, blinded, placebo-controlled, study of obiltoxaximab administered within 24, 48, and 72 hours before challenge *B. anthracis* spores. Study AP305 was conducted at the (b) (4) in 2013.

Cynomolgus macaques were randomized in three steps. They were stratified by sex and body weight into three groups for each gender and randomized to each treatment group. Animals were then randomized to four challenge days and assigned a challenge order in a challenge day. Macaques were challenged with a targeted 200 LD_{50} dose of aerosolized *B. anthracis* (Ames) spores.

Group assignments were blinded to the Sponsor, Study Director, QA study auditor, and staff who evaluated animals to make decision about animal care and euthanasia. In addition, group assignments were blinded to microbiologists and the study pathologist. Obiltoxaximab was manufactured at Lonza Biologics.

Table 6.82. Study AP305: Study Design

Group	No. of cynomolgus macaques	ETI-204 (Lonza) mg/kg	Time of dosing: Study Day ay pre-challenge
1	10	0 (vehicle)	Day -1, Day -2, Day-3
2	14	16	Day -1
3	14	16	Day -2
4	15*	16	Day -3

Source: Adapted from study synopsis page 3 of Study AP305, BLA 125509, SDN 1.

Animal C56627 was inadvertently dosed with treatment intended for a different animal on Day -1 (Challenge Day A cohort). A replacement animal (C56638)* was added to group 4 per protocol amendment 3 and it received the same dosing regimen as Animal C56627.

Study Endpoints

The primary endpoint was survival to 56 days post anthrax spore challenge.

Statistical Analysis Plan

(Excerpt from biostatistics review by Xianbin Li, Ph.D.)

Sample Size Calculation
Assuming that the true probabilities of survival in the control and a treatment groups are 10% and 70% respectively, there was 83.1 % power to detect a difference in survival rates between each treated group (n=14) and the control group (n=10). Power calculation was for a one-sided, 0.025 level, Fisher's exact test with no adjustment for multiple comparisons across the three tests.

Reviewer Comment: The biostatistics reviewer was able to replicate the calculations.

Analysis Populations
All animals were assigned to groups based on the dose the animals received.

Statistical Methods
The principal of closed testing was used to test three hypotheses sequentially using the following pre-specified order of testing.

1. Null hypothesis that the survival proportions in the placebo group and the treatment group IM at Day -2 are equal versus the one-sided alternative proportion in the treatment group IM at Day -2 is greater than the survival proportion in the placebo group.

2. Null hypothesis that the survival proportions in the placebo group and the treatment group IM at Day -1 are equal versus the one-sided alternative proportion in the treatment group IM at Day -1 is greater than the survival proportion in the placebo group.

3. Null hypothesis that the survival proportions in the placebo group and the treatment group IM at Day -3 are equal versus the one-sided alternative proportion in the treatment group IM at Day -3 is greater than the survival proportion in the placebo group.

The second hypothesis was only tested if the first was significant and the third hypothesis was only tested if the first two were significant. There was no additional adjustment for multiple comparisons required. Thus, the overall significance level of 0.025 is maintained.

6.15.2 Study Results

Compliance with Good Laboratory Practices

The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58).

Table of Demographic Characteristics

Demographic variables and baseline characteristics were comparable with regard to gender, age, and body weight. Three (30%) placebo animals and 1 (6.7%) animal in the 16 mg/kg IM PrEP-3 groups were bacteremic within 24 hours post challenge. All placebo animals were bacteremic at least once post-challenge.

Table 6.83. Study AP305: Demographic Variables and Baseline Characteristics by Treatment Group

	Placebo (N=10)	ETI-204 16 mg/kg IM PrEP-3 (N=15)	ETI-204 16 mg/kg IM PrEP-2 (N=14)	ETI-204 16 mg/kg IM PrEP-1 (N=14)	Total (N=53)
Age (years)					
Range	2.36-3.96	2.36-3.96	2.36-3.96	2.36-3.96	2.36-3.96
Gender [n (%)]					
Female	5 (50.0)	8 (53.3)	7 (50.0)	7 (50.0)	27 (50.9)
Male	5 (50.0)	7 (46.7)	7 (50.0)	7 (50.0)	26 (49.1)
Body weight (kg)					
Mean (SD)	2.7 (0.2)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)	2.6 (0.2)
Range	2.3, 3.0	2.3, 2.9	2.3, 2.9	2.2, 3.0	2.2, 3.0
Challenge dose (LD_{50})					
Mean (SD)	217.8 (65.2)	220.2 (86.7)	209.3 (61.6)	237.3 (96.1)	221.4 (78.3)
Range	144.0, 330.0	126.0, 490.0	103.0, 315.0	138.0, 440.0	103.0, 490.0
Challenge dose (LD_{50}) [n(%)]					
<200	5 (50.0)	7 (46.7)	7 (50.0)	6 (42.9)	25 (47.2)
200 or higher	5 (50.0)	8 (53.3)	7 (50.0)	8 (57.1)	28 (52.8)
BACTEREMIA					
Positive quantitative	3 (30.0)	1 (6.7)	0	0	4 (7.5)

bacteremia 24 hours post challenge (n(%))					
Log_{10} bacteremia 24 hours post challenge (cfu/mL) Mean (SD) Range	1.14 (1.38) 0.30, 3.53	0.39 (0.36) 0.30, 1.70	0.30 (0.00) 0.30, 0.30	0.30 (0.00) 0.30, 0.30	0.49 (0.68) 0.30, 3.53
Bacteremia 24 hours post challenge (cfu/mL) Geometric mean 95% confidence interval	13.7 1.4, 132.5	2.5 1.6, 3.9	2.0 NA	2.0 NA	3.1 2, 4.7

Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Efficacy Results - Primary Endpoint

The survival rate was 100% in each of the three treatment groups, p-value <0.0001. There one surviving animal in the control group received a challenge dose of 330 LD_{50} *B. anthracis* spores, was bacteremic(400 cfu/mL) at 24 hours post challenge, and had negative blood cultures on Days 7, 14, 28, and 56.

Table 6.84. Study AP305: Survival in Cynomolgus Macaques at Day 28 by Treatment Group

	Placebo (N=10)	**ETI-204 16 mg/kg IM PrEP-3 (N=15)**	**ETI-204 16 mg/kg IM PrEP-2 (N=14)**	**ETI-204 16 mg/kg IM PrEP-1 (N=14)**
N (%)	1 (10.0)	15 (100.0)	14 (100.0)	14 (100.0)
Difference in survival proportion compared with placebo, [95% CI], one-sided p-value*		0.90 [0.554, 0.998] <0.0001	0.90 [0.555, 0.998] <0.0001	0.90 [0.554, 0.998] <0.0001

*95% confidence interval and P values from exact method and Boschloo's test. *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Reviewer Comment: This study demonstrated that obiltoxaximab 16 mg/kg administered 1 to 3 days prior to challenge provided significant prophylactic protection against anthrax infection.

Data Quality and Integrity - Reviewers' Assessment

The submitted datasets were of high quality. All datasets were submitted in AdaM and SEND standard format. The clinical and biostatistics reviewers could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

The survival proportions were comparable across different subgroups, because the survival proportions in the treatment groups were 100%. The only surviving animal in the control group was a male, challenged with a 330 LD_{50} dose.

Table 6.85. Study AP305: Survival at Day 56 by Gender, Challenge Dose and Bacteremia PTT

	Placebo (N= 10)	ETI-204 16 mg/kg PrEP-3 (N= 15)	ETI-204 16 mg/kg PrEP-2 (N= 14)	ETI-204 16 mg/kg PrEP-1 (N= 14)	Total (N= 53)
Gender					
Female	0/5	8/8 (100%)	7/7 (100%)	7/7 (100%)	22/27 (81.5%)
Male	1/5 (20%)	7/7 (100%)	7/7 (100%)	7/7 (100%)	22/26 (84.6%)
Challenge dose (LD_{50})					
<250	0/6	11/11 (100%)	10/10 (100%)	9/9 (100.0%)	30/36 (83.3%)
250 or higher	1/4 (25%)	4/4 (100%)	4/4 (100%)	5/5 (100%)	14/17 (82.4%)
<200	0/5	7/7 (100%)	7/7 (100%)	6/6 (100%)	20/25 (80%)
Bacteremia prior to treatment (cfu/mL)					
$<10^2$	1/7 (14.3%)	15/15 (100%)	14/14 (100%)	14/14 (100%)	44/50 (88%)
10^2 - 10^4	0/3				0/3

PTT: prior to treatment; *Source: Table constructed by biostatistics reviewer, Xianbin Li, Ph.D.*

Key Findings

This study demonstrated that obiltoxaximab 16 mg/kg administered 1 to 3 days prior to challenge with *B. anthracis* provided significant protection against anthrax infection and could be effective for prophylaxis in humans (see safety concerns, section 8.4). Cynomolgus macaques were followed for two months post-challenge and there was no evidence of anthrax in any of the treated animals. The survivor (placebo), Animal C53558, was initially bacteremic but had negative blood cultures from Day 7 through 56 post-challenge and had normal clinical observations throughout the entire study (except for soft stool on study Day 22) which suggests that the animal probably had natural immunity against *B. anthracis*.

6.16 **Study AR001 – Pre-exposure Prophylaxis**

6.16.1 Study Design

Overview and Objective

The primary objective was to examine the efficacy of the (b) (4) anti-PA monoclonal antibody (ETI-204), when administered as a therapeutic treatment, against lethality due to inhalational exposure to *B. anthracis* spores in NZW rabbits.

Trial Design

This was a randomized, placebo-controlled, pre-exposure (dosing 30-45 minutes prior to exposure) study, with treatment administered at a fixed dose to cynomolgus macaques, conducted in 2003.

Animals were randomized by weight into the following treatment groups:

- Placebo (phosphate-buffered saline, PBS) IV
- ETI-204 10 mg/animal IV (one animal received 8.13 mg)

After receiving a single IV dose, all animals were challenged with a targeted aerosol dose of 100 LD_{50} on study Day 0. Clinical observations were performed twice daily.

Study Endpoints

The primary endpoint was survival to 28 days post challenge with *B. anthracis* spores.

Statistical Analysis Plan

Excerpted from biostatistics review, Xianbin Li, Ph.D.

Sample Size Calculation
Sample sizes of 5 control and 10 treated animals were considered in the protocol sufficient to provide greater than 80% power to detect a difference when the survival probabilities were 10% in the control group and 80% in the treated group, using a one-sided Fisher's exact test.

Reviewer Comment: The biostatistics reviewer replicated this calculation using a one-sided type I error of 0.05, however, Dr. Li noted that a type I rate of 0.025 should be used.

Analysis Populations
The analysis population included all randomized animals.

Statistical Methods

One-sided Fisher's exact test was used to compare the survival rates between the antibody group and the control group.

6.16.2 Study Results

Compliance with Good Laboratory Practices

The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58).

Table of Demographic Characteristics

Gender, body weight, and challenge doses of *B. anthracis* were comparable across obiltoxaximab ((b) (4) monoclonal anti-PA antibody) and placebo groups. Because the targeted challenge dose of *B. anthracis* was 100 LD_{50}, about 80% of animals received a dose less than 200 LD_{50}. No animals were bacteremic at 24 hours post challenge.

Reviewer Comment: The (b) (4) *cell line was replaced by the* (b) (4) *cell line early in clinical development.*

Table 6.86. Study AR001: Demographic variables and baseline characteristics by treatment group

	Placebo (N=5)	**ETI-204 8.13 or 10.16 mg 30-45 min IV PrEP (N=9)**	**Total (N=14)**
Age (weeks) Range	 13-17	 13-17	 13-17
Gender [n (%)] Female Male	 2 (40.0) 3 (60.0)	 4 (44.4) 5 (55.6)	 6 (42.9) 8 (57.1)
Body weight (kg) Mean (SD) Range	 2.4 (0.2) 2.2, 2.6	 2.3 (0.1) 2.2, 2.4	 2.3 (0.1) 2.2, 2.6
CHALLENGE			
Challenge dose (LD_{50}) Mean (SD) Range	 171.9 (55.2) 96.4, 244.0	 156.0 (43.9) 106.1, 217.5	 161.7 (46.7) 96.4, 244.0
Challenge dose (LD_{50}) (n(%)) <200 200 or higher	 4 (80.0) 1 (20.0)	 8 (88.9) 1 (11.1)	 12 (85.7) 2 (14.3)

Source: Table constructed by the biostatistics reviewer, Xianbin Li, Ph. D.

Efficacy Results - Primary Endpoint

There was a statistically significant difference in survival rates between the (b) (4) monoclonal antibody and placebo, 100% versus 10%, **Table 6.87**.

Table 6.87. Study AR001: Survival at Day 28 by Treatment Group

	Placebo (N=5)	**(b) (4) Monoclonal Antibody* 10.16 mg IV @ 30-45 min PrEP (N=9)**
No. of Animals, N (%)	0 (10.0)	9 (100.0)
Difference in survival proportion compared with placebo, [95% CI], one-sided p-value*		1.00 [0.474, 1] 0.0001*

PrEP: pre-exposure; Two-sided 95% confidence interval and one-sided p-values were calculated by the biostatistics reviewer, Xianbin Li, Ph. D. *Significant at a one-sided significance level of 0.025

Bacteremia

Three control animals developed qualitative bacteremia on Day 2 (48 hours post-challenge) and there were no available data after this time point. No animals in the treated group developed bacteremia on Days 1, 2, 7, 10, 14, 21, and 28.

Data Quality and Integrity - Reviewers' Assessment

In general the submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. The clinical and biostatistics reviewers could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

There was no gender-related survival difference. All animals had a challenge dose less than 250 $LD_{50,}$ so it was not possible to examine the trend using this cut-off point for challenge dose.

Table 6.88. Study AR001: Survival at Day 28 by gender and challenge dose

	Placebo (N=5)	**ETI-204* 10.16 mg @ 30-45 min PrEP (N=9)**	**Total (N=14)**
Gender			
Male			
Female	0/2	4/4 (100%)	4/6 (66.7%)
Challenge dose of *B. anthracis* (LD_{50})	0/3	5/5 (100%)	5/8 (62.5%)
<250	0/5	9/9 (100%)	9/14 (64.3%)
250 or higher	0	0	0

Source: From review by biostatistics reviewer, Xianbin Li, Ph. D.

Key Findings

This proof of concept study indicated that a single dose of obiltoxaximab 10.16 mg of the monoclonal antibody administered IV, 30-45 minutes prior to challenge, provided significant prophylactic protection from anthrax infection. This study used the Elusys product, an older

formulation of the monoclonal from a prior cell line (b) (4) and therefore is of limited value as a supportive study for the pre-exposure prophylaxis indication.

6.17 **Study AR003 – Pre-exposure Prophylaxis**

6.17.1 Study Design

Overview and Objective

The primary objective was to examine the efficacy of varying doses of the obiltoxaximab ((b) (4) cell line) delaying or preventing death in NZW rabbits from anthrax when administered as a therapeutic treatment at various dose concentrations and routes immediately (within 35 minutes) prior to an inhalational exposure to *B. anthracis* spores.

Trial Design

This was a randomized, placebo-controlled, parallel group, pre-exposure (dosing within 35 minutes prior to exposure), dose ranging study with treatment administered at fixed doses, conducted in 2004. Within 35 minutes of exposure to *B. anthracis*200 LD_{50}, all animals were treated with ETI-204.

Rabbits were randomized into the one of the following groups:

Group	ETI-204 Monoclonal Antibody Dose (mg/animal)	Number of NZW rabbits
Placebo (PBS)	0	8
ETI-204 IV	1.25	8
ETI-204 IV	2.5	8
ETI-204 IV	5	8
ETI-204 IV	10	8
ETI-204 IM	20	8

PBS: phosphate-buffered saline; Source: From review by biostatistics reviewer, Xianbin Li, Ph. D.

Study Endpoints

The primary endpoint was survival to 28 days post challenge with *B. anthracis* spores.

Statistical Analysis Plan

(Excerpt from biostatistics review by Xianbin Li, Ph.D.)

Sample Size Calculation
The sample size of 8 rabbits in each arm provided 80% power at 5% significant level to detect the difference in survival rates between the treatment arms and the vehicle control arm.

Analysis Population
All randomized animals

Statistical Methods
One-sided Fisher's exact test was used to compare the survival rates between each individual antibody group and the control group.

6.17.2 Study Results

Compliance with Good Laboratory Practices

This study was not in compliance with good laboratory practices (GLP) but standard operating procedures were followed.

Table of Demographic Characteristics

Demographic variables and baseline characteristics were comparable across different treatment groups, except for challenge dose in the placebo group, which had more variability and a higher proportion of animals received less than 200 LD_{50}. However, all control animals succumbed to anthrax.

Table 6.89. Study AR003: Demographic variables and baseline characteristics by treatment group

	Placebo (N=8)	Antibody 1.25 mg (b) (4) (N=8)	Antibody 2.5 mg (b) (4) (N=8)	Antibody 5 mg (b) (4) (N=8)	Antibody 10 mg (b) (4) (N=8)	Antibody 20 mg (b) (4) (N=8)	Total (N=48)
Gender [n (%)]							
Female	4 (50.0)	3 (37.5)	5 (62.5)	4 (50.0)	4 (50.0)	4 (50.0)	24 (50.0)
Male	4 (50.0)	5 (62.5)	3 (37.5)	4 (50.0)	4 (50.0)	4 (50.0)	24 (50.0)

Body weight (kg) Mean (SD) Range	2.5 (0.0) 2.4, 2.6	2.4 (0.2) 2.2, 2.6	2.4 (0.1) 2.2, 2.6	2.4 (0.1) 2.3, 2.5	2.5 (0.1) 2.3, 2.5	2.5 (0.1) 2.4, 2.6	2.5 (0.1) 2.2, 2.6
Challenge dose (LD_{50}) Mean (SD) Range	 301.0 (117.8) 163.2, 434.6	 282.1 (84.8) 91.8, 358.8	 296.6 (53.1) 228.1, 401.5	 303.8 (78.0) 180.3, 413.7	 269.8 (99.6) 106.2, 404.6	 268.1 (56.6) 187.1, 352.5	 286.9 (81.4) 91.8, 434.6
Challenge dose (LD_{50}) [n(%)] <200 200 or higher	 3 (37.5) 5 (62.5)	 1 (12.5) 7 (87.5)	 0 8 (100)	 1 (12.5) 7 (87.5)	 2 (25.0) 6 (75.0)	 2 (25.0) 6 (75.0)	 9 (18.8) 39 (81.3)
Positive quantitative bacteremia 24 hours post challenge (n(%))	2 (25.0)	0	1 (12.5)	1 (12.5)	0	0	4 (8.3)

Source: From review by biostatistics reviewer, Xianbin Li, Ph. D.

Efficacy Results - Primary Endpoint

All treatment groups except for the 1.25 mg IV group had a statistically significant difference in survival (63 to 100%) compared with the placebo group, (0%).

Table 6.90. Study AR003: Survival in NZW Rabbits at Day 28 by Treatment Group

	Placebo (N= 8)	(b) (4) mAb 1.25 mg IV (N= 8)	(b) (4) mAb 2.5 mg IV (N= 8)	(b) (4) mAb 5 mg IV (N= 8)	(b) (4) mAb 10 mg IV (N= 8)	(b) (4) mAb 20 mg IM (N= 8)
N (%)	0	1 (12.5)	5 (62.5)	5 (62.5)	7 (87.5)	8 (100.0)
Difference in survival proportion compared with placebo [95% CI] one-sided p-value*		0.125 [-0.292, 0.527] 0.402	0.625 [0.173,0.915] 0.004	0.625 [0.173,0.915] 0.004	0.875 [0.395,0.997] 0.0003	1 [0.588, 1] <0.0001
Adjusted exact 95% confidence interval		-0.427, 0.632	0.019, 0.953	0.019, 0.953	0.237, 0.999	0.436, 1

mAb: monoclonal antibody; Two-sided 95% confidence interval and one-sided p-values using a one-sided type I error of 0.025/5=0.005 were calculated by the biostatistics reviewer, Xianbin Li, Ph.D.

Additional Analyses Conducted on the Individual Trial

The following table shows the results of subgroup analyses. The sample sizes were too small to see a reliable trend by gender and challenge dose.

Table 6.91. Study AR003: Survival in NZW Rabbits at Day 28 by Gender and Challenge Dose of *B. anthracis*

	Placebo (N= 8)	**ETI-204 1.25 mg IV (N= 8)**	**ETI-204 2.5 mg IV (N= 8)**	**ETI-204 5 mg IV (N= 8)**	**ETI-204 10 mg IV (N= 8)**	**ETI-204 20 mg IM (N= 8)**	**Total (N= 48)**
Gender							
Female	0/4	0/3	4/5 (80%)	3/4 (75%)	4/4 (100%)	4/4 (100%)	15/24 (62.5%)
Male	0/4	1/5 (20%)	1/3 (33.3%)	2/4 (50%)	3/4 (75%)	4/4 (100%)	11/24 (45.8%)
Challenge dose of *B. anthracis* (LD_{50})							
<250	0/4	0/1	0/1	2/2 (100%)	2/2 (100%)	2/2 (100%)	6/12 (50%)
250 or higher	0/4	1/7 (14.3%)	5/7 (71.4%)	3/6 (50%)	5/6 (83.3%)	6/6 (100%)	20/36 (55.6%)

Source: From review by biostatistics reviewer, Xianbin Li, Ph. D.

Key Findings

This study demonstrated that obiltoxaximab administered IV at a dose of 2.5 to 10mg/animal or IM 20 mg/animal within 35 minutes prior to challenge significantly improved survival. Similar to study AR001, this study used the Elusys product which is an older formulation of the monoclonal made using the (b) (4) cell line. The (b) (4) cell line was subsequently changed to the (b) (4) cell line early in clinical development.

6.18 **Study 1056: Combination Study**

6.18.1 Study Design

Overview and Objective

The study is entitled, *Efficacy of a Monoclonal Antibody given in Combination with Ciprofloxacin in the Cynomolgus Macaque Therapeutic Model of Inhalational Anthrax*.
The primary objective was to assess the efficacy of intravenous obiltoxaximab at 8 mg /kg in combination with ciprofloxacin at a less than human equivalent dose (HED) compared to ciprofloxacin alone on survival, when administered at 24 ±12 hours after inhalation exposure to *B. anthracis*.

The secondary objectives were 1) to evaluate the efficacy of obiltoxaximab when used after detection of positive PA by ECL and 2) to evaluate untreated controls until death or euthanasia to provide data on disease progression in cynomolgus macaques.

Reviewer Comment: The primary objective is the focus of this review.

Trial Design

This was a randomized, controlled, open label, factorial design study of obiltoxaximab and ciprofloxacin for the treatment of cynomolgus macaques post-exposure to inhalational *B. anthracis*. Animals were randomized prechallenge by body weight into two groups of eight and two groups of sixteen and each group consisted of 50% males and 50% females. Animals in each group were then randomized to one of three challenge days with a challenge order per day. The study design is summarized in Table **6.92**.

Table 6.92. Study 1056: Study Design

Group	Treatment	ETI-204 Dose	Ciprofloxacin Dose	Treatment Initiation	Therapy Duration	No. of Animals (N=48)
1	ETI-204	8 mg/kg	N/A	ECL Positive	Single dose (IV)	8
2	Ciprofloxacin	N/A	10 mg/kg	ECL Positive + 24±12 hours	4 days (oral)	16
3	ETI-204+ Ciprofloxacin	8 mg/kg	10 mg/kg	ECL Positive + 24±12 hours	Single dose (ETI-204; IV) + 4 days (Cipro; oral)	16
4	Control	N/A	N/A	N/A		8

Cynomolgus macaques were challenged with aerosolized *B. anthracis* (Ames) spores at 200 LD_{50} via a head only inhalation exposure chamber. The trigger for treatment was a positive serum PA by the ECL assay.

In Group 1, animals received obiltoxaximab was administered at the first positive PA-ECL. In Groups 2 and 3, the treatment was initiated at 24±12 hours following the first positive PA-ECL results. Animals received a single dose of obiltoxaximab 8 mg/kg and four days of oral ciprofloxacin 10 mg/kg per day which is less than the human equivalent dose (~26mg/kg). Control animals in Group 4, did not receive any treatment.

Study Endpoints

The primary endpoint was the survival rate at Day 28 post-challenge with *B. anthracis* spores.

Statistical Analysis Plan

Excerpt from biostatistics review, by Lan Ling, Ph.D.

Sample Size
The Applicant proposed sample size of 16 animals in each group based on the assumptions that the probability of survival was 87% and 40% in the obiltoxaximab + ciprofloxacin group and ciprofloxacin group, respectively, using one-sided test with a 0.05 level using Fisher's exact test.

Biostatistics Comment from Dr. Lan: If one-sided Fisher's test was used for sample size calculation, an alpha level of 0.025 should be used instead. The corresponding power was 70% with 16 animals per group under the same assumptions.

Study Population
The Applicant analyzed the study using two populations, one including all animals and one including animals who survived to treatment. This review referred to these populations as the Intent to treat (ITT) and modified intent to treat (mITT) populations, respectively.

Primary Analysis
The Applicant conducted one sided Fisher's exact test for comparison of survival rates among four study groups with Bonferroni-Holm adjustment with overall alpha level of 0.05. Additional pairwise comparison between treatment groups were also performed using log-rank test.

Biostatistics Comment from Dr. Ling: Pairwise comparisons among four study groups are not appropriate due to the different treatment initiation time in obiltoxaximab & ciprofloxacin and ciprofloxacin groups as compared to the obiltoxaximab group by study design. Therefore the reviewer's primary analysis population includes mITT and ITT animals in obiltoxaximab plus ciprofloxacin and ciprofloxacin groups that were bacteremic prior to treatment (PTT) and received delayed treatment.

Clinical Reviewer Comment: Survival rates for animals treated with obiltoxaximab plus ciprofloxacin or ciprofloxacin alone are compared in this review. The survival rate in the obiltoxaximab monotherapy group (Group 1) versus placebo is discussed as part of the monotherapy efficacy studies. Please refer to the biostatistics review by Ling Lan, Ph.D. for a full discussion of the statistical analysis plan (SAP).

6.18.2 Study Results

Compliance with Good Laboratory Practices

Study 1056 is a non GLP study. The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

Patient Disposition

A total of 48 cynomolgus macaques were challenged with *B. anthracis*. Six macaques died before treatment could be initiated, three in the ciprofloxacin only group and three in the obiltoxaximab + ciprofloxacin group. A total of 40 animals in the treatment groups were bacteremic or toxemic prior to treatment initiation and 34 of these macaques survived to be treated with obiltoxaximab, ciprofloxacin, or both. Three out of the 16 macaques died before the treatment initiation in cipro group and obiltoxaximab + ciprofloxacin group. Details of the animals' disposition before treatment initiation are outlined in Table 6.93.

Table 6.93. Study 1056: Disposition of the Cynomolgus Macaques Prior to Treatment

	G1 ETI-204 8mg/kg	**G2 Cipro 10mg/kg**	**G3 ETI-204 & Cipro**	**G4 Control**	**Total**
Animals challenged	8	16	16	8	48
Animals who died before treatment					6/40 (15%)
A(2010-02-09)	0	1	0		1
B(2010-02-16)	0	1	1		2
C(2010-02-23)	0	1	2		3
Animals who survived to be treated	8	13	13		34/40 (85%)
Analysis population					
All animals	8	16	16		48
Toxemic at or before treatment initiation	8	16	16		40
Bacteremic at or before treatment initiation	8	16	16		40
Survived to be treated	8	13	13		34

G = Group; Cipro: ciprofloxacin; ETI-204: obiltoxaximab; Source: From review by biostatistics reviewer, Ling Lan, Ph. D.

Table of Demographic Characteristics

Demographic variables and baseline characteristics of the animals are summarized in

Table 6.94. Animals in all study groups were comparable with regard to age, sex, and body weight at baseline. All animals that survived to be treated at the 24 ± 12hours treatment time point were toxemic and bacteremic prior to treatment initiation. All control animals were bacteremic and toxemic.

Table 6.94. Study 1056: Demographics and Baseline Characteristics

	G1 ETI-204 8mg/kg n = 8	G2 Cipro 10mg/kg n = 16	G3 ETI-204&Cipro n = 16	G4 Control n = 8
Sex				
Male	4(50.0%)	8 (50.0%)	8 (50.0%)	4(50.0%)
Female	4(50.0%)	8 (50.0%)	8 (50.0%)	4(50.0%)
Body weight (kg) at challenge				
Mean ± SD	2.9±0.4	2.9±0.3	2.9±0.4	2.9±0.4
Median	2.8	2.8	2.9	2.9
(Min, Max)	(2.6, 3.7)	(2.2, 3.5)	(2.3, 4.1)	(2.3, 3.6)
Age (years)				
Mean ± SD	3.0±0	3.0±0.4	2.9±0.3	3.0±0.5
Median	3.0	3.0	3.0	3.0
(Min, Max)	(3.0, 3.0)	(2.0, 4.0)	(2.0, 3.0)	(2.0, 4.0)
Toxemic prior to treatment*	8(100%)	13(81.3%)	13(81.3%)	
Bacteremic prior to treatment	8(100%)	13(81.3%)	13(81.3%)	

G = Group;
*Animal A07179 in ETI-204 group was considered toxemic and included in the analysis because of positive PA-ECL and bacteremia results and negative PA-ELISA results prior to treatment. *Source: From review by biostatistics reviewer, Ling Lan, Ph. D.*

The proposed challenge dose was 200 LD_{50} *B. anthracis* spores. The median and mean challenge dose were similar across all study groups and including the six animals that died before treatment initiation; mean challenge dose was 185 ± 67 LD_{50} and median challenge dose was 161 LD_{50}. A total of 34 (71%) of the animals received a challenge dose slightly below the proposed challenge dose of 200 LD_{50} however all these animals were toxemic and bacteremic prior to treatment.

Table 6.95. Study 1056: Extent of Exposure to Aerosolized *B. anthracis in Cynomolgus Macaques*

	Group 1 ETI-204 8mg/kg n = 8	Group 2 Cipro 10mg/kg n = 16	Group 3 ETI-204 & Cipro n = 16	Group 4 Control n = 8	Died before Treatment n = 6	All Animals N=48
Challenge dose (LD_{50})						
Mean ± SD	202±84	178±82	182±58	187±28	179±98	185±67
Median	174	154	155	199	144	161
(Min, Max)	(83, 360)	(112, 377)	(127, 315)	(146, 218)	(115, 377)	(83, 377)
Challenge dose (LD_{50}) [N(%)]						
< 200	5(62.5)	14(87.5)	11(68.8)	4(50)	5(83.3)	34(70.8)
200 or higher	3(37.5)	2(12.5)	5(31.2)	4(50)	1(16.7)	14(29.2)
LD_{50} by Challenge day (N) Mean ± SD						
A	(3) 287±68	(5) 261±106	(5) 214±61	(3) 193±26	(1) 377	(16) 238±77
B	(3) 144±53	(5) 127±15	(5) 192±73	(3) 193±33	(2) 123±11	(16) 163±55
C	(2) 161±0	(6) 150±28	(6) 146±13	(2) 169±33	(3) 150±12	(16) 152±21

Source: From review by biostatistics reviewer, Ling Lan, Ph. D.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Bacteremia and Protective Antigen Levels prior to Treatment

Bacteremia and protective antigen levels for the 34 animals who survived to receive treatment and the eight control animals are summarized in,

Table 6.96. The mean bacteremia levels were comparable across the three treatment groups. Mean PA levels were higher in the ciprofloxacin and obiltoxaximab plus ciprofloxacin groups as compared to the obiltoxaximab only group due to the delayed initiation of treatment 24 ± 12 hours in these two groups.

Table 6.96. Study 1056: Toxemia and Bacteremia levels prior to Treatment in **Cynomolgus Macaques**

	G1 ETI-204 8mg/kg n = 8	G2 Cipro 10mg/kg n = 13	G3 ETI-204 & Cipro n = 13	G4 Control (48h) n = 8
Log_{10} bacteremia (cfu/mL) PTT				
Mean ± SD	4.5±0.7	4.8±1.3	4.3±1.4	5.7±1.9
Median	4.3	4.7	3.8	4.6
(Min, Max)	(3.8, 5.8)	(2.9, 8.1)	(3.2, 8.7)	(4.1, 8.5)
Bacteremia (cfu/mL) PTT				
Geometric Mean	3.3×10^4	5.7×10^4	1.8×10^4	48.3×10^4
95% CI	(1.1×10^4, 9.8×10^4)	(1.1×10^4, 29.7×10^4)	(0.3×10^4, 10.7×10^4)	(2.4×10^4, 964.5×10^4)
PA (ng/ml) PTT*				
Mean ± SD	78.6±122.7	734.1±1614	1002.9±2721.4	1798.4±3619.5
Median	39.4	258.4	188.8	311.9
(Min, Max)	(1.2, 371.1)	(113.4, 6083)	(31.5, 10000)	(224.5, 9974.1)
Log_{10} PA (ng/ml) PTT*				
Mean ± SD	1.4±0.8	2.5±0.4	2.4±0.6	2.8±0.6
Median	1.6	2.4	2.3	2.5
(Min, Max)	(0.1, 2.6)	(2.1, 3.8)	(1.5, 4)	(2.4, 4)

G=Group; PTT: prior to treatment
*PA PTT for Animal A07179 has a PA level was below the limit of detection (<LOD) of 2.4 ng/mL and replaced with 1.2 ng/mL for the analysis; Animal A07895 had PA level >10000 ng/mL and replaced with 10000ng/mL for the analysis. *Source: From review by biostatistics reviewer, Ling Lan, Ph. D.*

The time between challenge and first positive PA and bacteremia is summarized in Table 6.97. The times to development of bacteremia and a positive PA (PA-ECL or PA-ELISA) were similar across all study groups.

Table 6.97. Study 1056: Time from Challenge to Detectable Protective Antigen and Bacteremia in all Animals

	Group 1 ETI-204 8mg/kg n = 8	Group 2 Cipro 10mg/kg n = 16	Group 3 ETI-204 & Cipro n = 16	Group 4 Control n = 8
Time (hours) to first positive PA-ECL				
Mean ± SD	31.9±5	32.4±6.5	34.3±2	34.8±4.4
Median	31.9	32.7	34.3	35.9
(Min, Max)	(24.7, 37.5)	(21.2, 44)	(30.8, 37.9)	(24.2, 39)
Time (hours)to first positive PA-ELISA				
Mean ± SD	33.9±4.9	34.3±5.1	37.3±4.5	34.8±5.5
Median	34.6	34.8	37.2	35.9
(Min, Max)	(26.6, 40.8)	(21.2, 43.1)	(26.8, 46.9)	(24.2, 42.1)
Time (hours) to bacteremia				
Mean ± SD	30.4±5.1	30.1±4.5	33.6±3.5	33.2±4.8
Median	29.8	30	34.2	35.4
(Min, Max)	(24.7, 37.5)	(21.2, 36.8)	(26.8, 40.7)	(24.2, 39)

Source: From review by biostatistics reviewer, Ling Lan, Ph. D.

The time in hours from challenge to treatment initiation is summarized in **Table 6.98**. The median/mean time interval to treatment initiation for the obiltoxaximab group was shorter than that for the obiltoxaximab+ ciprofloxacin groups per the study design. There was a delay of 24 ± 12hours for initiation of treatment in Group 2 and Group 3.

Table 6.98. Study 1056: Time (hours) from Challenge to Treatment Initiation for Treated Animals

	Group 1 ETI-204 8mg/kg n = 8	Group 2 Cipro 10mg/kg n = 13	Group 3 ETI-204 & Cipro n = 13	Group 4 Control N=8
Time to treatment initiation				
Mean ± SD	35.81±5.0	48.71±1.6	49.26±3.3	Not applicable
Median	35.86	48.15	48.82	
(Min, Max)	(28.58, 41.4)	(46.63,51.67)	(45.4,56.28)	

Source: From reviews by biostatistics reviewers, Xianbin Li Ph. D.and Ling Lan, Ph. D.

Efficacy Results - Primary Endpoint

The primary analysis population includes macaques in the ciprofloxacin group (Group 2) and the obiltoxaximab + ciprofloxacin group (Group 3) that were bacteremic prior to treatment (PTT) and received delayed treatment.

Survival rates at study Day 28 for the ciprofloxacin- treated group and the obiltoxaximab plus ciprofloxacin groups are summarized in Table 6.99. Animals treated with the combination of obiltoxaximab plus ciprofloxacin had a significantly higher survival rate, 61.5% versus 15.4% (p-value 0.021) compared with the ciprofloxacin- treated group. None of the untreated controls (group 4) survived.

Table 6.99. Study 1056: Survival Rates in Cynomolgus Macaques at Day 28

	Group 2 Cipro 10mg/kg	Group 3 ETI-204 & Cipro	Difference (ETI-204 & Cipro – Cipro) 95% CI**	P-value*
ITT (All animals)	2/16 (12.5%)	8/16 (50%)	0.38(0.08, 0.67)	0.027
mITT (Survived to be treated)	2/13 (15.4%)	8/13 (61.5%)	0.46(0.13, 0.79)	0.021

*P-value based on a 1-sided Fisher's exact test compared to 0.025; **Difference in % survivors with 95% exact confidence interval (CI). *Source: From reviews by biostatistics reviewers, Xianbin Li Ph. D.and Ling Lan, Ph. D.*

Delayed treatment with the combination of obiltoxaximab+ ciprofloxacin resulted in a significantly higher survival rate compared to animals than received delayed treatment with ciprofloxacin alone. The primary analysis demonstrated that, macaques in the obiltoxaximab+ ciprofloxacin group had a significantly higher survival rate as compared to the ciprofloxacin group (61.5% versus 15.4%), with a difference of 46.1% (95% CI: 13%, 79%), p-value of 0.021 from one-sided Fisher's exact test.

Obiltoxaximab versus Placebo

The obiltoxaximab 8 mg/kg IV group demonstrated a statistically significant effect on survival, 4/8(50%), (95% CI 0.058, 0.843) p-value of 0.014, compared with the survival rate (0%) in the control group The survival rate associated with the 8 mg/kg IV dose was statistically significant (-p- value = 0.014)at the one-sided significance level of 0.025/3=0.0083.

Table 6.100. Study NIAID 1056: Survival in Cynomolgus Macaques at Day 28 by Treatment Group

	ETI-204 8 mg/kg IV (N=8)	Total (N=16)
n (%)	4 (50)	4 (25)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value	0.50 [0.058, 0.843] 0.014	
Adjusted exact 95% confidence interval	-0.048, 0.885	

Two-sided 95% confidence interval and one-sided p-values from Boschloo's test were calculated by the biostatistics reviewer, Xianbin Li, Ph.D.

Reviewer Comment: The survival rate of 50% in the obiltoxaximab-treated group (no treatment delay) was similar to survival rate 50% with the 16mg/kg IV single dose observed in cynomolgus macaques in study AP204.

Data Quality and Integrity - Reviewers' Assessment

The submitted datasets were of high quality. We could replicate the primary efficacy analysis results and main study results. Most of the submitted data followed FDA guidance and was ready to be reviewed. The Applicant corrected a challenge dose for Study NIAID 1056 in response to an information request.

Additional Analyses Conducted on the Individual Trial

PA-ELISA levels changed in a similar pattern over time in the obiltoxaximab + ciprofloxacin and ciprofloxacin groups and began to decrease at around 48 hours post-challenge to below the LOD after Day 7 in animals that survived to receive delayed treatment. PA-ELISA levels in untreated controls remained elevated and all animals were dead within 5 days post-challenge. PA levels (geometric mean and 95% CI) measured by ELISA for treated animals by treatment group are summarized in

Figure 6.45.

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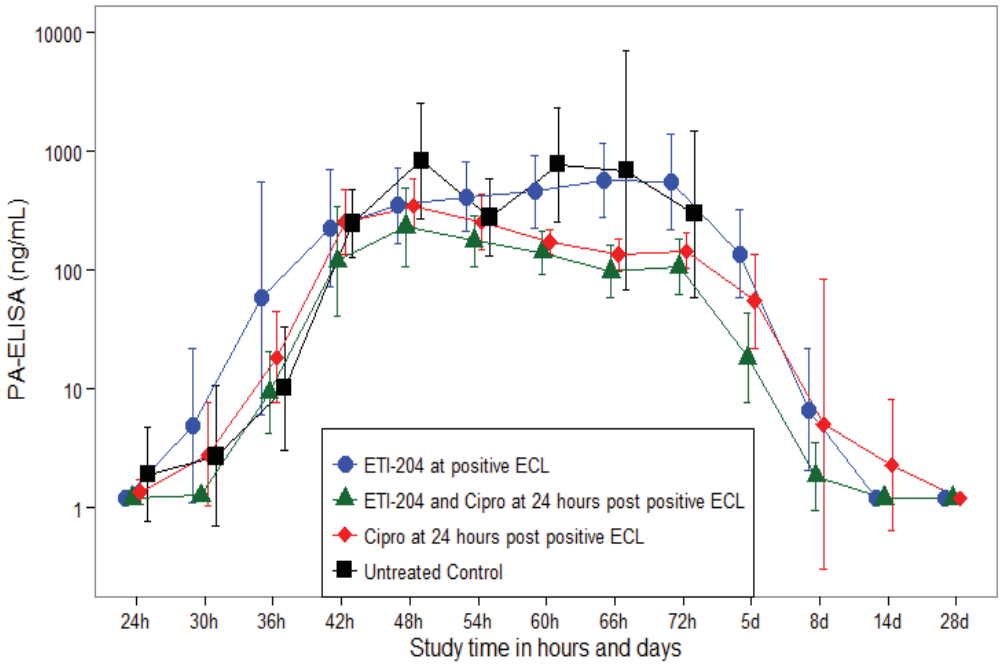
Figure 6.45. Study 1056: PA levels by ELISA over Time for Treated Animals by Treatment Group - Geometric Mean and 95% CI



Source: From review by biostatistics reviewers, Ling Lan, Ph. D.

6.19 NIAID 2469 - Combination Study

6.19.1 Study Design

Overview and Objective

Study 2469 was a randomized, controlled, open-label, factorial design study of obiltoxaximab with or without antibacterial therapy in cynomolgus macaques following inhalational exposure to *B. anthracis.* The primary objective was to assess the efficacy of obiltoxaximab 8 mg/kg administered alone and in combination with ciprofloxacin in preventing death when administered at 24 ± 12 hours after the first positive PA-ECL, following inhalational exposure to *B. anthracis* macaques.
The secondary objectives were to 1) evaluate the efficacy of delayed treatment with two doses of ciprofloxacin (10 mg per kilogram and 26 mg per kilogram) and 2) evaluate untreated controls to provide data on disease progression in cynomolgus macaques following challenge with aerosolized *B. anthracis*.

Reviewer Comment: This review will focus on analysis of the primary objective.

Trial Design

The study design includes four study groups, ciprofloxacin 10 mg/kg, ciprofloxacin 26 mg/kg, a combination of obiltoxaximab plus ciprofloxacin 10mg/kg, and an untreated control group. Obiltoxaximab was administered as a single dose intravenously and ciprofloxacin was administered orally for four days. The study was conducted at (b) (4) 2012.

Table 6.101. Study 2469: Study Design

Group	Treatment	ETI-204 Dose	Ciprofloxacin Dose	Treatment Initiation	Therapy Duration	No. of Animals
1	ETI-204+ Ciprofloxacin	8 mg/kg	10 mg/kg	ECL Positive + 24±12 hours	Single dose (ETI-204; IV) + 4 days (Cipro; oral)	16
2	Ciprofloxacin	N/A	10 mg/kg	ECL Positive + 24±12 hours	4 days (oral)	16
3	Ciprofloxacin	N/A	26 mg/kg	ECL Positive + 24±12 hours	4 days (oral)	16
4	Control	N/A	N/A	N/A	N/A	8

NA: not applicable; Cipro: ciprofloxacin. *Source: From review by biostatistics reviewers, Ling Lan, Ph. D.*
Note: Another sponsor's monoclonal antibody was also used in this NIAID -sponsored study but this will not be discussed in this review.

Cynomolgus macaques were randomized pre-challenge for each sex, by weight, *Klebsiella sp*. colonization status, and anti-PA IgG ELISA status into three treatment groups of 16 macaques and one group of eight macaques. Animals in each group were randomized to one of four challenge days with a challenge order per day. Study Day 0 for each group of macaques randomized to a challenge day was the day of the aerosol challenge. Macaques were challenged with aerosolized *B. anthracis* (Ames) spores 200 LD_{50} via a head-only inhalation exposure chamber. The trigger for treatment was a positive PA-ECL. Treatment with the monoclonal antibody and/or antibacterial drug was initiated 24 ± 12 hours following the first positive PA-ECL result. Group 1 animals were administered obiltoxaximab 8 mg/kg IV bolus and a first dose of ciprofloxacin (10 mg/kg; oral gavage) 24 hours (±12 h) following the first positive PA ECL result. Animals in Groups 2 and 3 received a first dose of ciprofloxacin (10 mg/kg or 26 mg/kg; oral gavage) 24 ±12 hours following the first positive PA-ECL result. The three subsequent ciprofloxacin doses were administered by oral gavage 24 hours (± 3h) following the previous dose. Control animals did not receive any treatment.

Reviewer Comment: Ciprofloxacin 26 mg per kilogram is the human equivalent dose, therefore the survival outcome for this combination may be more relevant to human disease.

Study Endpoints

The primary endpoint was the proportion of animals that survived to study Day 28 post-challenge.

Statistical Analysis Plan

(Excerpt from biostatistics review by Ling Lan, Ph.D.)
Sample Size
The Applicant proposed a sample size of 16 animals each in the combination treatment group and ciprofloxacin 10mg/kg group to ensure 81.6% power to detect a difference in survival rates between the two groups assuming that the probability of survival in the combination group is greater than 87% and less than 40% in the ciprofloxacin group, based one-sided, 0.05 level Fisher's exact test.

Biostatistics Comment from Dr. Lan: If one-sided Fisher's test was used for sample size calculation, an alpha level of 0.025 should be used instead. The corresponding power was 70% with 16 animals per group under the same assumptions.

Study Population
The sponsor analyzed the study using two populations, one including all animals and one including animals who survived to treatment. This review also refers to these populations as the Intent to treat (ITT) and modified intent to treat (mITT) populations, respectively.

Reviewer Comment: The primary analysis population was mITT animals in ETI-204 & obiltoxaximab & ciprofloxacin.

Primary Analysis
Survival analyses used animals that survived to receive at least one treatment. The Applicant conducted primary analysis to compare survival rates between obiltoxaximab & ciprofloxacin and ciprofloxacin groups using one-sided Fisher's exact test at alpha level of 0.05, and repeated this analyses using log-rank test. Additional comparison between each treatment group and the untreated controls were also performed analogously.

Biostatistics Comment from Dr. Lan: This review compared the survival proportion of animals in the obiltoxaximab & ciprofloxacin treatment group to that in the ciprofloxacin group using one-sided Fisher's exact test at alpha level 0.025 and log-rank test at alpha level 0.05.

Reviewer Comment: The statistical analysis plan was acceptable and for further commentary please refer to the biostatistics review by Ling Lan, Ph.D. This clinical reviewer's primary analysis population is the mITT i.e., animals in obiltoxaximab & ciprofloxacin versus ciprofloxacin groups. Survival rates for animals treated with obiltoxaximab 8mg/kg plus ciprofloxacin 10mg/kg and ciprofloxacin 10mg/kg alone are compared in this review.

6.19.2 Study Results

Compliance with Good Laboratory Practices

This is a non GLP study.

Animal Disposition

Fifty-six macaques were randomized to four study groups, 16 animals each to the obiltoxaximab + ciprofloxacin and ciprofloxacin only groups. Two animals in the obiltoxaximab +ciprofloxacin 10mg/kg group, three animals in the ciprofloxacin 10 mg/kg group, and one animal in the ciprofloxacin 26 mg per kilogram group died before treatment initiation. Forty-one (85%) of the 48 animals in the three treatment groups survived to be treated with the study drugs. All animals were bacteremic and toxemic (PA-ECL) prior to treatment initiation. Among the 32 macaques that were randomized to the obiltoxaximab +ciprofloxacin and Cipro 10 mg/kg treatment groups (groups 1 and 2) and challenged with *B. anthracis* spores, 27 (84%) macaques survived to 24±12 hours after the first positive PA-ECL result post exposure. There were 13 and 14 in Cipro 10 mg/kg group and obiltoxaximab +ciprofloxacin group, respectively, that received randomized treatment,

Table 6.102.

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Table 6.102. Study 2469: Disposition of Cynomolgus Macaques prior to Treatment Initiation

	ETI-204 & Cipro	Cipro (10 mg/kg)	Cipro 26mg/kg	Control	Total all study arms
Animals challenged	**16**	**16**	**16**	**8**	**56**
Animals who died before treatment	2	3	2		7/48 (15%)
Animals who survived to be treated	14	13	14		41/48 (85%)
Analysis populations					
Animals challenged and randomized	16	16	16		41
PA-ECL at or before treatment initiation	14	13	14		41
PA-ELISA at or before treatment initiation	14	11*	14		41
Bacteremic at or before treatment initiation	14	13	14		41

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Table of Demographic Characteristics

Cynomolgus macaques in the obiltoxaximab & ciprofloxacin and ciprofloxacin groups were comparable in sex, age, and body weight at baseline and were all toxemic and bacteremic before treatment. Seven animals were found to be colonized for *Klebsiella* species during prescreening prior to shipment to (b) (4) and four of them received antibacterial treatment. Eleven (24%) of 41 treated animals had a positive anti-PA IgG prescreen prior to randomization. Animals with a positive pre-challenge *Klebsiella sp*. screen and anti-PA IgG ELISA results were balanced across the study groups.

Table 6.103. Study 2469: Demographics and Baseline Characteristics

	ETI-204&Cipro n = 16	Cipro (10 mg/kg) n = 16	Cipro (26 mg/kg) n = 16	Control n = 8
Sex [n (%)]				
male	8 (50.0)	8 (50.0)	8 (50.0)	4 (50.0)
female	8 (50.0)	8 (50.0)	8 (50.0)	4 (50.0)
Body weight (kg) at challenge				
Mean ± SD	3.6±0.8	3.7±0.7	3.7±0.6	3.8±0.8
Median	3.5	3.5	3.7	3.7
(Min, Max)	(2.7, 5.4)	(2.8, 5.7)	(2.5, 4.9)	(2.8, 5.5)
Age (month)				
Mean ± SD	47.3±2.6	49.4±5.3	48.9±4.8	52.5±7.9
Median	47.5	48	49	49
(Min, Max)	(43, 51)	(45, 63)	(43, 60)	(44, 64)
***Klebsiella sp.* colonization pre-challenge [n (%)]**				
Positive	2 (12.5)	1 (6.2)	2 (12.5)	1 (12.5)
Anti-PA IgG pre-challenge [n (%)]				
Positive	4 (25.0)	3 (18.8)	4 (25.0)	1 (12.5)

Cipro= ciprofloxacin; *Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.*

Reviewer Comment: Four of the treated animals were colonized with Klebsiella species but were not infected and therefore this finding is unlikely to have impacted survival outcomes in the study.

The extent of exposure to *B. anthracis* is summarized in

Table 6.104. The majority (67%) of animals in the study received the target challenge dose of *B. anthracis* 200 LD_{50} or higher. The mean/median challenge LD_{50} dose of *B. anthracis* spores was similar among the three treatment groups and across the four challenge days.

Table 6.104. Study 2469: Extent of Exposure (LD_{50}) to *B. anthracis*

	ETI-204& Cipro (10 mg/kg) n = 16	**Cipro (10 mg/kg) n = 16**	**Cipro (26 mg/kg) n = 16**	**Control n = 8**	**Died before Treatment n = 7**	**All Animals N = 56**
Challenge dose *B. anthracis* (LD_{50})						
Mean ± SD	203.2±38.7	219.4±31.8	227.1±65.4	228.1±42.1	182.3±31.2	223.4±46.5
Median	197.5	231	217.5	210	166	216
(Min, Max)	(156, 298)	(163, 266)	(156, 374)	(187, 307)	(162, 240)	(156, 374)
Challenge dose (LD_{50}) [N(%)]						
< 200	9 (56.2)	4 (25.0)	7 (43.8)	1 (12.5)	5 (71.4)	16 (32.7)
200 or higher	7 (43.8)	12 (75.0)	9 (56.2)	7 (87.5)	2 (28.6)	33 (67.3)
***B. anthracis* LD_{50} by Challenge Day (N) Mean ± SD**						
A	(56) 235±36				(1) 213	(13) 236±37
B	(56) 197±38				(0)	(14) 197±38
C	(56) 209±45				(2) 165±2	(11) 220±44
D	(56) 233±58				(4) 189±44	(11) 244±57

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Bacteremia and Protective Antigen

The level of protective antigen (PA-ECL, PA-ELISA) and bacteremia prior to treatment for animals in the treatment groups and at 48 hours post-challenge for untreated controls are summarized in

Table 6.105. Animals that died prior to treatment are excluded from this analysis. Animals had similar levels of bacteremia and protective antigen across the treatment groups.

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Table 6.105. Study 2469: Protective Antigen and Bacteremia Levels Prior to Treatment in Treated and Control Animals

	ETI-204& Cipro (10 mg/kg) n = 14	Cipro (10 mg/kg) n = 13	Cipro (26 mg/kg) n = 14	Control n = 8 (@ 48h)
Log_{10} bacteremia (cfu/mL) PTT				
Mean ± SD	3.9±1.7	4.9±1.7	4.1±1.6	4±1.1
Median	3.4	5.1	4.1	3.8
(Min, Max)	(1.4, 7.7)	(1.9, 7.7)	(1.5, 8.1)	(2.9, 5.7)
Bacteremia (cfu/mL) PTT				
Geometric Mean	0.8×10^4	8.8×10^4	1.4×10^4	1.0×10^4
95% CI	(0.1×10^4, 5.7×10^4)	(1.0×10^4, 77.4×10^4)	(0.2×10^4, 9.9×10^4)	(0.2×10^4, 5.8×10^4)
PA (ng/ml) PTT*	n = 14	n = 11**	n = 14	
Mean ± SD	632.9±778.2	2611.4±7104.6	857.8±937.3	151.3±110.1
Median	251	368	365.5	161.5
(Min, Max)	(99.6, 2190)	(6.7, 24000)	(63.8, 2680)	(12.1, 365)
Log_{10} PA (ng/ml) PTT *	n = 14	n = 11**	n = 14	
Mean ± SD	2.5±0.5	2.6±0.9	2.6±0.5	2.0±0.5
Median	2.4	2.6	2.6	2.2
(Min, Max)	(2, 3.3)	(0.8, 4.4)	(1.8, 3.4)	(1.1, 2.6)

ULOD: upper limit of detection; PTT: prior to treatment;

** The Log $_{10}$ PA result for animal A11973 is greater than the ULOD (24000 ng/mL), replaced with 24000 ng/mL for the statistical analysis.*

*** Animal A12240 (Cipro 10mg/kg group) had no value due to either no sample or an insufficient volume of the sample was available for initial analysis. Animal A10768 (Cipro 10mg/kg group) titration curve was not within specifications- the test sample was not parallel to the reference standard.*

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

The time intervals between challenge dose and first positive protective antigen and bacteremia, are summarized in the following two tables. The mean and median time intervals from challenge to the first positive protective antigen were similar across study groups. The time intervals from challenge to development of bacteremia were also similar across the study groups.

Table 6.106. Study 2469: Time (Hours) to Detectable Protective Antigen and Bacteremia for All Animals

	ETI-204& Cipro (10 mg/kg) n = 16	Cipro (10 mg/kg) n = 16	Cipro (26 mg/kg) n = 16	Control n=8
Time (hours)to first positive PA-ECL				
Mean ± SD	35±4.4	37.4±7	36.6±4.7	37.9±7.4
Median	35	35.4	37.5	40.7
(Min, Max)	(24.5, 43.5)	(24.1, 54.4)	(28.5, 43)	(27.9, 45.9)
Time (hours) to first positive PA-ELISA				
Mean ± SD	32.5±4.6	35.9±8.5	35.1±4	35.8±3.6
Median	31.1	35	35.4	35.5
(Min, Max)	(24.5, 42.7)	(23.6, 60.6)	(28.5, 43)	(29.6, 40.8)
Time (hours) to bacteremia*				
Mean ± SD	29.8±5.7	34.7±11.2	33.6±5.8	34.3±7.6
Median	28.4	33.6	34.9	33.2
(Min, Max)	(22.7, 37.5)	(24.1, 72)	(22.4, 43)	(24.1, 45.6)

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

The time to positive PA-ECL or bacteremia and time to initiation of treatment were comparable among the treatment groups**.** There were no differences in the times (median= 49 hours) between the obiltoxaximab plus ciprofloxacin group and the ciprofloxacin 10 mg/kg only group**.**

Table 6.107. Study 2469: Time to treatment initiation

	ETI-204 8mg/kg & Cipro (10 mg/kg) n = 14	Cipro (10 mg/kg) n = 13	Cipro (26 mg/kg) n = 14
Time to treatment initiation			
Mean ± SD	50.4±6.7	53.4±10.4	56.4±11.7
Median	49.1	49	50.1
(Min, Max)	(46, 73.1)	(45.2, 72)	(46.1, 73)

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Efficacy Results - Primary Endpoint

The survival rate at Day 28 in animals that survived to receive to delayed treatment with obiltoxaximab (8 mg/kg) plus ciprofloxacin (10mg/kg) group and the ciprofloxacin 10 mg/kg

group are summarized in Table 6.108. The difference in survival rates for obiltoxaximab 8mg/kg plus ciprofloxacin 10mg/kg (57%) compared to ciprofloxacin 10mg/kg alone (31%) was numerically greater but not statistically significant, p-value of 0.16. Survival rates in animals with positive anti-PA antibodies pre-challenge was similar, i.e., obiltoxaximab plus ciprofloxacin group (50%) versus the ciprofloxacin (33%).

Table 6.108. Study 2469: Survival Rates in Cynomolgus Macaques at Study Day 28

	ETI-204 8mg/kg for and Cipro 10mg/kg	Cipro 10mg/kg	Difference (ETI-204 & Cipro – Cipro) 95% CI**	P-value*
ITT	8/16 (50%)	4/16 (25%)	0.25 ((-0.10, 0.56)	0.14
Treated animals	8/14 (57.1%)	4/13 (30.8%)	0.26 (-0.10, 0.62)	0.16
Treated and anti-PA IgG positive	6/12 (50%)	4/12 (33.3%)	0.17 (-0.26, 0.56)	0.34

Cipro: ciprofloxacin;
*P-value based on a 1-sided Fisher's exact test compared to 0.025.
**Difference in % survivors with 95% exact confidence interval (CI) based on normal approximation.
Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Biostatistics Comment from Dr. Lan: The 26% difference in survival rates between the 2 treated groups did not reach statistical significance (p = 0.16). However, this study was not adequately powered to detect a difference of 26%. It is difficult to adequately power added-benefit trials. Eighty percent power to detect a difference seen in the current study would require 65 animals per group to be treated (130 animals). With 84.4% of the animals estimated to be alive by treatment initiation, the total sample size of spore-challenged animals would need to be approximately 155. A trial of this size would not be feasible. An earlier study, NIAID 1056, had a similar study design to the current study.

An exploratory meta-analysis of these two studies was conducted to investigate the added benefit of ETI-204 in combination with Cipro (< HED) in macaques. Overall, the meta-analyses demonstrated that when animals received ETI-204 in combination with antibacterial, they had numerically greater probability of survival than those treated with antibacterial monotherapy regardless of the doses for antibacterial based on stratified exact fixed effect model. In addition, the added benefit of ETI-204 in survival for the treatment of inhalational anthrax in macaques was significant when co-administered with antibacterial below HED, compared to the antibacterial alone group. See Section 5.2.1 biostatistics review for the meta-analysis by Dr. Ling Lan.

Reviewer Comment: The dose of obiltoxaximab 8 mg/kg is half of the proposed therapeutic dose of obiltoxaximab and the dose of ciprofloxacin (10 mg/ kg) is less than half of the human equivalent dose of ciprofloxacin (~26 mg /kg). The efficacy of ciprofloxacin (at human equivalent doses) for treatment of inhalational anthrax in cynomolgus macaques is known to be

approximately 90% when initiated at the time of the first positive protective antigen. Delayed treatment with a less than HED of ciprofloxacin was utilized to demonstrate the added benefit of the monoclonal antibody when combined with an effective antibacterial drug. A delay of 24 ± 12 hours would allow for increase in bacterial load, toxemia, and disease progression in the animals. Serum PA levels are likely to increase significantly within the 24 ± 12 hours period following the first positive PA-ECL (see Fig. 67) and thus a survival rate of 50% with delayed treatment with a human equivalent dose (26 mg/kg) of ciprofloxacin and 31% with a less than human equivalent dose (10 mg/kg) appear reasonable. The results of Study 2469 indicate that the combination of obiltoxaximab with ciprofloxacin did not confer a statistically significant benefit in survival over treatment with ciprofloxacin alone but there was a numerical increase from 31% to 57% in the rate of survival with the combination ciprofloxacin and obiltoxaximab. I agree with the Applicant's assessment that the results of this study and study 1056 indicate that the cynomolgus macaque model of delayed treatment may be utilized when assessing added benefit of adjunctive anthrax therapies but the study design, timing of the intervention, and sample size should be carefully considered.

A total of 25% (2/8) animals in the untreated control group survived exposure to *B. anthracis.* One of these animals, A12335, had a positive anti-PA IgG titer pre-challenge, however the TNA result was negative suggesting that the antibodies detected were not functionally active in neutralizing PA. Animals, A07577 and A07712, also had positive anti-PA IgG titers at pre-screening but these animals died of anthrax.

Table 6.109. Study 2469: Summary of Survival Rates in Cynomolgus Macaques at Day 28

	ETI-204& Cipro (10 mg/kg)	Cipro (10 mg/kg)	Cipro (26 mg/kg)	Control
Survival Rates				
Challenged and Randomized	8/16 (50%)	4/16 (25%)	7/16 (43.8%)	2/8 (25%)
Treated Animals)	8/14 (57.1%)	4/13 (30.8%)	7/14 (50%)	N/A
Treated Group: Anti-PA IgG positive	6/12 (50%)	4/12 (33.3%)	6/13 (46.2%)	N/A

*Source: Table constructed by biostatistics reviewer, Ling Lan, Ph**.D.***

Data Quality and Integrity - Reviewers' Assessment

The submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. However, there are some minor issues. The clinical and biostatistics reviewers could replicate the primary efficacy analysis results and main study results.

Durability of Response

No relapse of bacteremia or clinical symptoms of anthrax up to the end of the study, Day 28.

6.20 Study AR007 - Combination Study

6.20.1 Study Design

Overview and Objective

Study AR007 evaluated the efficacy of obiltoxaximab with or without Levofloxacin in a NZW rabbit post-exposure, challenge model of anthrax.

The primary objective was to demonstrate that intravenous (IV) obiltoxaximab 10 mg (approximately 4 mg/kg) increased survival rate compared to oral levofloxacin at a human equivalent dose (50 mg/kg), when administered post-exposure (9 ± 3 hours post challenge) in New Zealand White (NZW) rabbits following aerosol exposure to *B. anthracis*.

The secondary objective was to demonstrate that intramuscular (IM) obiltoxaximab 20 mg (approximately 8 mg/kg) increased survival rate compared to levofloxacin at human equivalent dose when administered post-exposure (9 ± 3 hours post challenge) in NZW rabbits following aerosol exposure to *B. anthracis*.

Reviewer Comment: This review will focus on the comparison of survival rates in rabbits treated with obiltoxaximab (IV) versus obiltoxaximab (IV) combined with levofloxacin and obiltoxaximab (IM) versus obiltoxaximab (IM) combined with levofloxacin.

Trial Design

This study was a randomized, controlled, open-label, factorial design study of obiltoxaximab (IV and IM) with and without oral levofloxacin for post-exposure prophylaxis of inhalational anthrax. Combinations of obiltoxaximab 10 mg or 20 mg with a human equivalent dose of levofloxacin were tested in a post-exposure prophylaxis setting in the NZW rabbit model of inhaltional anthrax. Obiltoxaximab was administered as a single dose IV or IM and levofloxacin was administered by oral gavage for five days. The study design is summarized in Table 6.110.

Table 6.110. Study AR007: Study Design

Group	Treatment	ETI-204 Dose	Levo Dose	Treatment Initiation	Therapy Duration	No. of Animals
1	Control (PBS*)	N/A**	N/A	9±3 hours	Single dose (IV)	9
2	Levo +	N/A	50	9±3 hours	5 days (oral)	12

	PBS		mg/kg			
3	ETI-204 + Levo control	10 mg (4 mg/kg)	N/A	9±3 hours	Single dose (IV)	9
4	ETI-204 + Levo	10 mg (4 mg/kg)	50 mg/kg	9±3 hours	Single dose (ETI-204; IV) + 5 days (Levo; oral)	9
5	ETI-204 + Levo control	20 mg (8 mg/kg)	N/A	9±3 hours	(IM)	9
6	ETI-204 + Levo	20 mg (8 mg/kg)	50 mg/kg	9±3 hours	dose (ETI-204; IM) + 5 days (Levo; oral)	9

ETI-204: obiltoxaximab; Levo: levofloxacin; PBS: phosphate buffered saline; IV: intravenous.

* ETI-204 control used phosphate buffered saline (PBS) IV

** N/A – Not applicable

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Animals were aerosol-challenged with *B. anthracis* (Ames) strain spore dose of 200 LD_{50}. Rabbits were randomized into five groups of nine (group 1, 3, 4, 5 and 6) and one group of 12 (group 2) with each group consisting of 50% male and 50% females. Equal number of rabbits from each group was challenged on one of three challenge days (Challenge Day A, B and C). Treatment was initiated 9±3 hours post challenge for all study groups. Fixed doses were used for ETI-204 IV (10 mg) and IM (20 mg), equivalent to 4 mg/kg IV and 8 mg/kg IM, respectively.

Reviewer Comment: The rationale for co-administration of an antitoxin and antibacterial drug in the post-exposure prophylaxis setting (9 hours post challenge) is based on findings in experimental animal models indicating that antibacterial treatment early after B. anthracis challenge may lead to persistence of spores and disease development following antibacterial cessation.[19,20]

Study Endpoints

The primary endpoint was survival at Day 30 post-challenge with *B. anthracis.*

[19] Henderson DW, et al. Observations on the prophylaxis of experimental pulmonary anthrax in the monkey. *J Hyg 1956*; 54: 28-36.

[20] Vietri NJ, *et al.* A short course of antibiotic treatment is effective in preventing death from experimental inhalational anthrax after discontinuing antibiotics. J Infect Dis 2009;199: 336-341

Statistical Analysis Plan

(*Excerpt from biostatistics review by Ling Lan, Ph.D.)*

Study Population
The sponsor analyzed the study using all animals. This review referred to this population as the Intent to treat (ITT) population.

Primary analysis
The Applicant conducted one-sided Fisher's exact test for comparison of survival rates between treatment groups and the control, as well as each ETI-204 group and the levofloxacin-only group at an alpha level of 0.05. Additional time to death comparison between treatment groups were also performed using log-rank test.

There was no adjustment for multiple comparisons. This review compares the survival proportion of animals in the obiltoxaximab and levofloxacin group to that in the levofloxacin group using a one-sided 0.025 level Fisher's exact test.

6.20.2 Study Results

Compliance with Good Laboratory Practices

The Good Laboratory Practice (GLP) statement noted that the study was performed in compliance with the Food and Drug Administration's GLP regulations (21 CFR Part 58).

Animal Disposition

A total of 57 NZW rabbits were challenged and all survived to receive treatment/placebo in a post exposure setting. The primary efficacy analysis population for this review was 12 rabbits in the levofloxacin group, nine rabbits in obiltoxaximab (IV) plus levofloxacin group and nine rabbits in obiltoxaximab (IM) plus levofloxacin group.

Protocol Violations/Deviations

The protocol deviations did not significantly impact the conduct or integrity of the study.

Table of Demographic Characteristics

A total of 57 NZW rabbits in six treatment groups were challenged with a target inoculum *B. anthracis* 200 LD_{50} and all survived to receive treatment/placebo. Animals were evenly distributed by gender, sex, and body weight across the six treatment groups.

Table 6.111. Study AR007: Demographics and Baseline Characteristics

	ETI-204 (IV) & Levo n = 9	ETI-204 (IV) n = 9	ETI-204 (IM) & Levo n = 9	ETI-204 (IM) n = 9	Levo n = 12	Control n = 9
Sex [n(%)]						
male	4 (44.4)	5 (55.6)	5 (55.6)	4 (44.4)	6 (50.0)	5 (55.6)
female	5 (55.6)	4 (44.4)	4 (44.4)	5 (55.6)	6 (50.0)	4 (44.4)
Body weight (kg)						
Mean ± SD	2.5±0.2	2.5±0.1	2.5±0.1	2.5±0.1	2.5±0.1	2.5±0.1
Median	2.6	2.5	2.4	2.5	2.5	2.5
(Min, Max)	(2.2, 2.7)	(2.3, 2.6)	(2.3, 2.7)	(2.3, 2.7)	(2.4, 2.6)	(2.2, 2.6)
Age (months)						
Mean ± SD	4.0±0	4.0±0	4.0±0	4.0±0	4.0±0	4.0±0
Median	4.0	4.0	4.0	4.0	4.0	4.0
(Min, Max)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

The mean challenge doses of *B. anthracis* were comparable across the treatment groups and the mean challenge dose of *B. anthracis* in all exposed animals was 274 LD_{50} *B. anthracis.* There was no data on PA levels or bacteremia prior to treatment in this study.

Table 6.112. Study AR007: Extent of Exposure to *B. anthracis*

	ETI-204 (IV) & Levo n = 9	ETI-204 (IV) n = 9	ETI-204 (IM) & Levo n = 9	ETI-204 (IM) n = 9	Levo n = 12	Control n = 9	All Animals N = 57
Challenge dose (LD_{50})							
	262.3±40.8 271 (191, 320)	287.8±69.5 280 (158, 400)	252.6±41.7 262 (191, 299)	270.4±38.4 272 (201, 317)	297.3±55.2 284 (222, 396)	268.6±47.5 291 (153, 304)	274.4±50.6 275 (153, 400)
Challenge dose (LD_{50}) [N(%)]							
< 200	1 (11.1)	1 (11.1)	2 (22.2)	0 (0.0)	0 (0.0)	1 (11.1)	5 (8.8)
200 or higher	8 (88.9)	8 (88.9)	7 (77.8)	9 (100.0)	12 (100.0)	8 (88.9)	52 (91.2)
LD_{50} by Challenge day (N) Mean ± SD							
	A		B		C		
Mean ± SD	278.3±34.1		296.1±45.4		248.9±59.4		274.4±50.6
Median	279		296		252		275
(Min, Max)	(222, 379)		(201, 400)		(153, 396)		(153, 400)

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Time between challenge and treatment initiation was similar for all the treatment groups.

Table 6.113. Study AR007: Time to treatment initiation in hours for all animals

	ETI-204 (IV) & Levo	ETI-204 (IV)	ETI-204 (IM) & Levo	ETI-204 (IM)	Levo	Control
Time to treatment initiation	n = 9	n = 9	n = 9	n = 9	n = 12	n = 9
Mean ± SD	8.2±0.7	8.4±0.9	9.1±1.1	8.4±1.2	8.7±1	7.9±1
Median	8.6	8.5	9.2	8.3	8.9	7.5
(Min, Max)	(7.2, 9.1)	(6.8, 9.7)	(7, 10.3)	(6.6, 10.6)	(7.3, 10.2)	(6.9, 9.6)

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Efficacy Results - Primary Endpoint

The primary analysis demonstrated that, comparing with levofloxacin group with obiltoxaximab (IV) & Levo group had a significantly higher survival rate (88.9% versus 33.3%) with a difference of 55.6% (95% CI: 11%, 82%), p-value of 0.02. These results indicate that a single dose of

obiltoxaximab IV can provide lasting protection due to significantly longer presence in circulation as compared to levofloxacin alone.
Similarly, obiltoxaximab (IM) & levofloxacin group had a significantly higher survival rate (100% versus 33.3%) with a difference of 66.7% (95% CI: 27%, 90%), p-value of 0.002. All animals randomized and challenged survived to receive treatment so the analysis for the treated animals was the same as that for animals randomized and challenged.

Table 6.114. Study AR007: Survival Rates at Day 30 by Study Group

	Levo	ETI-204 (IV) & Levo	ETI-204 (IM) & Levo	Difference (ETI-204 & Levo – Levo) 95% CI**	P-value*
Challenged randomized and treated	4/12 (33%)	8/9 (89%)		0.56(0.11, 0.82)	0.02
	4/12 (33%)		9/9 (100%)	0.67(0.27, 0. 90)	0.002

*P-value based on a 1-sided Fisher's exact test compared to 0.025.
**Difference in % survivors with 95% exact confidence interval (CI) based on normal approximation.
ETI-204: obiltoxaximab. Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Reviewer Comment: In this study, rabbits received a HED dose of levofloxacin and were treated before signs of anthrax infection developed (post-exposure prophylaxis at 9±3 hours after challenge). The survival rate with levofloxacin alone was low at 33% however it is consistent with survival rates reported for antibacterial drugs in published prophylaxis studies in NZW rabbits.[21] Initiation of antibacterial drug treatment early after spore challenge was observed to lead to persistence of B. anthracis spores and disease development following discontinuation of the antibacterial drug. The increased survival seen in this study was associated with the long half-life (~21 days) of obiltoxaximab which continued to have activity against toxin in the bloodstream after levofloxacin was stopped.

The Applicant was asked to comment on the low survival rate in the NZW rabbits and they noted that all deaths in the levofloxacin-only group (8/12) occurred after withdrawal of the antibacterial drug, consistent with observations in published prophylaxis studies. Vietri et al., reported on a study of two groups of 10 rhesus macaques exposed to a lethal aerosol dose of B. anthracis spores.[22] Animals received ciprofloxacin prophylaxis beginning 1–2 h after exposure or after becoming bacteremic, and treatment was continued for 10 days. In the prophylactically treated group, no deaths occurred during antibacterial drug treatment, but only 20% of animals survived after antibiotics were discontinued. In the group treated after establishment of

[21] Ionin B. *et al.* Evaluation of immunogenicity and efficacy of anthrax vaccine adsorbed for post- exposure prophylaxis clinical and vaccine immunology 2013;20(7):1016-1026.

bacteremia, 3 deaths occurred during antibacterial treatment, but all 7 animals (100%) that were alive after 10 days of therapy survived when antibacterials were discontinued. Similarly, Ionin et al., reported a survival rate of 23% in the NZW rabbit model of inhalational anthrax following discontinuation of levofloxacin. In this study a human equivalent dose of levofloxacin was administered once daily for 7 days, starting 6-12 hours post challenge with 200 LD_{50} of B. anthracis spores. Animals were dosed once a day for 7 days with levofloxacin at 50 mg/kg via oral gavage, with the first dose administered within 6 to 12 h post-challenge with B. anthracis spores. These studies demonstrate that antibacterial drugs administered post-exposure can reduce the incidence or progression of anthrax disease, but they do not protect against the disease resulting from the germination of spores that may remain in the body after stopping the antibacterial drug.

Survival rates of 90 to 100% have been reported for levofloxacin alone in the treatment of inhalational anthrax in the NZW rabbit model in studies where the antibacterial drugs were administered using the trigger to treat i.e., a significant increase in body temperature or a positive protective antigen levels. In a treatment study of the anti-PA monoclonal antibody, raxibacumab, in NZW rabbits, levofloxacin (at 50 mg/kg x 3 doses) alone was administered at the development of signs of anthrax (approximately 27 hours post challenge) and the survival rate was 95%. In study AR034 in this submission, rabbits received levofloxacin at 30 hours post challenge with B. anthracis and the survival rate in infected NZW rabbits treated with levofloxacin alone was 100%.

Table 6.115. Study AR007: Summary of Survival Rates and Time to Death

	ETI-204 (IV) & Levo n = 9	**ETI-204 (IV) n = 9**	**ETI-204 (IM) & Levo n = 9**	**ETI-204 (IM) n = 9**	**Levo n = 12**	**Control n = 9**
Survival rates [n(%)]	8 (88.9)	9 (100.0)	9 (100.0)	9 (100.0)	4 (33.3)	0
Time to death (hour)						
Mean ± SD	28.5±4.4	30±0	30±0	30±0	19.6±8.1	3.7±1
Median	30	30	30	30	15.5	3.3
(Min, Max)	(16.8, 30)	(30, 30)	(30, 30)	(30, 30)	(11.9, 30)	(2.4, 5)

Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Data Quality and Integrity - Reviewers' Assessment

In general the submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. The reviewers could replicate the primary efficacy analysis results and main study results.

6.21 **Study 1030 - Combination study**

6.21.1 Study Design

Overview and Objective

Study 1030 evaluated the therapeutic efficacy of obiltoxaximab administered alone or in combination with levofloxacin to NZW rabbits following challenge with *Bacillus anthracis* spores. The primary objective was to assess the efficacy of obiltoxaximab (8 mg/kg, IV) in survival rate, when administered following a significant increase in body temperature, (SIBT) in NZW rabbits exposed to *Bacillus anthracis*.

Note: A significant increase in body temperature (SIBT) was defined as the first time the baseline body temperature threshold is exceeded for three consecutive hourly temperature measurements or the second occurrence of two consecutive elevated temperatures. A threshold for elevated temperature was defined as the individual animal's baseline average plus two times the animal's baseline standard deviation.

The secondary objective was to assess the efficacy of ETI-204 (8 mg/kg, IV) in combination with levofloxacin at a HED compared to levofloxacin on survival rate, when administered in a delayed fashion (96±1 hours post challenge).

Note: This review will focus on the secondary objective (i.e. survival) only with no comments on the primary objectives.

Trial Design

This was a randomized, controlled, open-label factorial design study with obiltoxaximab and levofloxacin, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and conducted at the (b) (4)

Table 6.116. Study 1030: Study Design

Group	Treatment	ETI-204 Dose	Levo Dose	Treatment Initiation	Therapy Duration	No. of Animals
1	ETI-204	8 mg/kg	N/A	SIBT	Single dose (IV)	16
2	Levofloxacin	N/A	50 mg/kg	96±1 hours	3 days (oral)	16
3	ETI-204+ Levo	8 mg/kg	50 mg/kg	96±1 hours	Single dose (ETI-204; IV) + 3 days (Levo; oral)	16
4	Control	N/A	N/A	N/A	N/A	6

N/A: not applicable; ETI-204: obiltoxaximab. Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

NZW rabbits were randomized, before challenge, into three groups of 16 (Group 1, 2 and 3) and one group of 6 (Group 4) with each group consisting of 50% male and 50% female animals. Rabbits in each group were then randomized to two challenge days (challenge day A and B) with a challenge order per day.

Rabbits were aerosol challenged with *B. anthracis* Ames strain spore dose of 200 LD_{50} via a plethysmography chamber passed in a Biological Class III safety cabinet system.

In Group 2 and 3, the corresponding treatments were initiated 96±1 hours following exposure. However, obiltoxaximab injection alone was administered to animals in Group 1 at the SIBT. Animals were confirmed to have been febrile (SIBT), bacteremic, and toxemic prior to treatment (PTT).

Study Endpoints

The primary endpoint was the survival rate by Day 28 post-challenge with *B. anthracis*.

Statistical Analysis Plan

Study Population
The sponsor analyzed the study using two populations, one including all animals and one including animals who survived to receive treatment and was bacteremic. This review referred to these populations as the Intent to treat (ITT) and modified intent to treat (mITT) populations, respectively.

Primary Analysis
The sponsor conducted one sided Fisher's exact test for comparison of survival rates among four study groups with Bonferroni-Holm adjustment at overall alpha level of 0.05. Additional pairwise comparison between treatment groups were also performed using log-rank test.

Dr. Lan's Comment: Pairwise comparisons among four study groups are not appropriate due to the different treatment initiation time in the ETI-204 group and the ETI-204 & Levo and Levo groups by study design. Therefore the primary analyses for this review compared the survival proportion of animals in the obiltoxaximab & Levo versus Levo group using a one-sided 0.025 level Fisher's exact test.

6.21.2 Study Results

Compliance with Good Clinical Practices

This is a non GLP study. The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

Animal Disposition

A total of 54 NZW rabbits were randomized to four study groups. The primary analysis population included the animals that survived to receive treatment.

Table 6.117. Study 1030: Animal Disposition Prior to Treatment

	ETI-204 8mg/kg	Levo 50mg/kg	ETI-204 & Levo	Control	Total
Animals challenged	16	16	16	6	54
Animals that died before treatment					23/48 (48%)
A(2009-09-14)	0	6	6		12
B(2009-09-21)	0	5	6		11
Animals that survived to be treated	16	5	4		25/48 (52%)
Analysis population					
Intent-to-Treat (ITT)	16	16	16	6	54
PA-ECL at or PTT	13	5	4	6	28
PA-ELISA at or PTT	9	5	3	6	23
Bacteremic at or PTT	13	4*	3**	6	26
SIBT at or PTT	16	16	16	6	54
Modified intent to treat (mITT)	13	4	3	6	26

ITT: intention to treat; PTT: prior to treatment;
*Animal L23016 in Levo group was never bacteremic.
** Animal L23040 in ETI-204 & Levo group become bacteremia post treatment.
Source: Table constructed by biostatistics reviewer, Ling Lan, Ph.D.

Table of Demographic Characteristics

The demographics and baseline characteristics of the subjects in each treatment group are summarized in

Table 6.118. Animals in levofloxacin and obiltoxaximab plus levofloxacin groups were comparable with regard to sex, age, and body weight at baseline, rate of bacteremia, and challenge inoculum. Quantitative bacteremia was not measured in this study per the protocol.

Table 6.118. Study 1030: Demographics and Baseline Characteristics

NZW Rabbits	ETI-204 8mg/kg n = 16	Levo 50mg/kg n = 16	ETI-204 & Levo n = 16	Control n = 6
Sex [n(%)]				
male	8(50.0%)	8(50.0%)	8(50.0%)	3(50.0%)
female	8(50.0%)	8(50.0%)	8(50.0%)	3(50.0%)
Body weight (kg) at challenge				
Mean ± SD	2.5±0.1	2.5±0.1	2.5±0.1	2.5±0.1
Median	2.6	2.5	2.6	2.6
(Min, Max)	(2.4, 2.6)	(2.4, 2.7)	(2.2, 2.7)	(2.4, 2.7)
Age (months)				
Mean ± SD	4.0±0	4.0±0	4.0±0	4.0±0
Median	4.0	4.0	4.0	4.0
(Min, Max)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)

The majority (70%) of animals received less than 200 LD_{50}; the mean and median challenge inoculum was 175 LD_{50} and 168 LD_{50} *B. anthracis* respectively, for all animals in the study.

Table 6.119. Study 1030: Extent of Exposure to *B. anthracis* spores

	ETI-204 8mg/kg n = 16	Levo 50mg/kg n = 16	ETI-204 & Levo n = 16	Control n = 6	Animals Died before Treatment n = 23	All Animals N = 54
Challenge dose (LD_{50})						
Mean ± SD	178.9±68.9	185.4±42.4	159.3±37.6	183.8±20.1	174.7±44.1	175.6±49.1
Median	166	188.5	151.5	183.5	166	168
(Min, Max)	(87, 362)	(83, 251)	(93, 227)	(157, 209)	(83, 251)	(83, 362)
Challenge dose (LD_{50}) [N(%)]						
< 200	11 (68.8)	9 (56.2)	13 (81.2)	5 (83.3)	15 (65.2)	38 (70.4)
200 or higher	5 (31.2)	7 (43.8)	3 (18.8)	1 (16.7)	8 (34.8)	16 (29.6)
***B. anthracis* LD_{50} by Challenge day**						
	A		B			
Mean ± SD	186.3±56.5		164.9±38.5			175.6±49.1
Median	180		157			168
(Min, Max)	(83, 362)		(93, 236)			(83, 362)

Efficacy Results - Primary Endpoint

The survival rates at Day 28 for levofloxacin and obiltoxaximab & levofloxacin groups are summarized in Table 6.120. The primary analysis demonstrated that, the obiltoxaximab plus levofloxacin had a significantly higher survival rate compared to levofloxacin alone, (100% versus 40%) with a difference of 60% (95% CI: -9%, 95%), p-value of 0.17. This comparison was not powered to detect the observed difference in survival rates.

Table 6.120. Study 1030: Survival Rates at Day 28

	Levo	ETI-204 & Levo	Difference (ETI-204 & Cipro – Cipro) 95% CI**	P-value*
Challenged and randomized	2/16 (12.5%)	4/16 (25%)	0.13 (-0.17, 0.41)	0.65
Survived to be treated	2/5 (40%)	4/4 (100%)	0.60 (-0.09, 0.95)	0.17
Bacteremic & Treated	2/4 (50%)	3/3 (100%)	0.50 (-0.30, 0.93)	0.43

*P-value based on a 1-sided Fisher's exact test compared to 0.025.
**Difference in % survivors with 95% exact confidence interval (CI) based on normal approximation. *Source: Biostatistics review by Ling Lan, Ph.D*.

Table 6.121. Study 1030: Survival Rates and Time to Death

	ETI-204 8mg/kg n = 16	Levo 50mg/kg n = 16	ETI-204 & Levo n = 16	Control n = 6
Survival rates [n(%)]	12 (75.0)	2 (12.5)	4 (25.0)	0 (0.0)

Source: Review by biostatistics reviewer, Ling Lan, Ph.D.; ETI-204: obiltoxaximab; levo: levofloxacin

There was a statistically significant difference in survival between the obiltoxaximab 8mg/kg group and the untreated control group. The difference in survival proportion compared with placebo was 0.75 [0.221, 0.927] p-value, 0.0008.

Table 6.122. Study NIAID 1030: Survival in NZW Rabbits at Day 28 by Treatment Group

	Control (N=6)	**ETI-204 8 mg/kg IV (N=16)**
All Animals		
n (%)	0 (0)	12 (75)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.75 [0.221, 0.927] 0.0008*
Adjusted exact 95% confidence interval		0.129, 0.952
Qualitative bacteremic animals		
n/N (%)		8/12 (66.7)

Two-sided 95% confidence interval and one-sided p-values from Boschloo's test were calculated by *the biostatistics reviewer, Xianbin Li, Ph.D.* *Statistically significant at the one-sided significance level of 0.025.

Data Quality and Integrity - Reviewers' Assessment

All datasets were submitted in AdaM and SEND standard format and were of high quality. The reviewers could replicate the primary efficacy analysis results and main study results.

Additional Analyses Conducted on the Individual Trial

The following table shows the results of subgroup analyses. The sample sizes were too small to see a reliable trend by gender and challenge dose.

Table 6.123. Study NIAID1030: Survival at Day 28 by Challenge Dose, Bacteremia, and PA-ELISA

	Control (N= 6)	**ETI-204 8 mg/kg IV (N= 16)**	**Total (N= 22)**
Gender			
Male	0/3	7/8 (87.5%)	7/11 (63.6%)
Female	0/3	5/8 (62.5%)	5/11 (45.5%)
Challenge dose of *B. anthracis*(LD_{50})			
<250	0/6	10/14 (71.4%)	10/20 (50%)
250 or higher	0	2/2 (100%)	2/2 (100%)
<200	0/5	8/11 (72.7%)	8/16 (50%)
PA prior to treatment (ng/mL)			
0 - < 10		10/12 (83.3%)	10/12 (83.3%)
10 - < 50		2/4 (50%)	2/4 (50%)

6.22 Study 1045 - Combination Study

6.22.1 Study Design

Overview and Objective

Study 1045 is entitled, "Determining the Therapeutic Efficacy of A Novel and anti-PA Antibody Administered Alone or in Combination with Levofloxacin to New Zealand White Rabbits following *Bacillus Anthracis* Inhalation Challenge." The primary objective was to determine the efficacy of treatment with obiltoxaximab, levofloxacin or obiltoxaximab combined with levofloxacin to NZW rabbits at 72 hours following exposure to *Bacillus anthracis.*

Trial Design

The proposed primary objective was to determine the efficacy of treatment with obiltoxaximab (8 mg/kg, IV), levofloxacin (50 mg/kg, HED) or ETI-204 in combination with levofloxacin to NZW rabbits 72 hours following exposure to B. *anthracis*.

This was a randomized, controlled, open label, factorial design study with obiltoxaximab and/or levofloxacin administered at a fixed time following inhalation of *B. anthracis* spores. The study was sponsored by the NIAID and was conducted at the (b) (4) Fifty- four rabbits were randomized, pre-challenge, into three groups of 16 rabbits (Group 1, 2 and 3) and one group of 6 rabbits (Group 4) with each group consisting of 50% male and 50% female rabbits. Animals in each group were then randomized to two challenge days (challenge Day A and B) with a challenge order per day. Rabbits were challenged with aerosolized *B. anthracis (*Ames) spores 200 LD_{50} via a plethysmography chamber passed in a Biological Class III safety cabinet system. The four treatment arms of study, obiltoxaximab (8 mg/kg, IV), levofloxacin (50 mg/kg, HED) or obiltoxaximab & levofloxacin are summarized in Table 6.124. All study treatments were initiated 72±1 hours following exposure. The control group received no treatment.

Table 6.124. Study 1045: Study Design

Group	Treatment	ETI-204 IV	Levofloxacin Dose	Treatment Initiation (median)	Therapy Duration	No. of Animals
1	Levofloxacin	N/A	50 mg/kg	72 ± 1 hours	3 days (oral)	16
2	ETI-204+ Levofloxacin	8 mg/kg	50 mg/kg	72 ± 1 hours	Single dose (ETI-204; IV) + 3 days (Levo; oral)	16
3	ETI-204	8 mg/kg	N/A*	72 ± 1 hours**	Single dose (IV)	16
4	Control	N/A	N/A	N/A		6

*N/A – Not applicable
** 72 ± 1 hours post median challenge
Source: *Source: Review by biostatistics reviewer,* Ling Lan, PhD

Study Endpoints

The primary endpoint was the survival rate by Day 28 post-challenge with *B. anthracis* spores.

Statistical Analysis Plan

Study Population

The sponsor analyzed the study using two populations, one including all animals and one including animals who survived to receive treatment. This review refers to these populations as the Intent to treat (ITT) and modified intent to treat (mITT) populations, respectively.

Primary analysis
The sponsor conducted one-sided Fisher's exact test for comparison of survival rates among four study groups with Bonferroni-Holm adjustment at overall alpha level of 0.05. Additional pairwise comparison between treatment groups were also performed using log-rank test.

Reviewer Comment: The primary analyses for this review compared the survival rates of animals in the ETI-204 plus levofloxacin with the survival rate in levofloxacin groups using a one-sided 0.025 level Fisher's exact test. The primary analysis population in this review is the population of rabbits who survived to receive treatment. A comparison of survival in the ETI-204 and control groups was also assessed.

The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

6.22.2 Study Results

Compliance with Good Clinical Practices

This is a non GLP study. The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

Animal Disposition

A total of 54 rabbits were randomized to four study groups in this study. The primary efficacy analysis populations for this review were the nine rabbits in levofloxacin group and eleven rabbits in ETI-204 plus levofloxacin group.

Table 6.125. Study 1045: Animal Disposition prior to Treatment

	Levo 50mg/kg	ETI-204 & Levo	ETI-204 8mg/kg	Control	Total
Animals challenged	16	16	16	6	54
Animals who died before treatment					17/48 (35%)
A(2010-01-07)	4	2	2		8
B(2010-01-14)	3	3	3		9
Animals who survived to be treated	9	11	11		31/48 (65%)
Analysis population*					
Intent-to-Treat (ITT)	16	16	16	6	54
PA-ECL at or PTT	9	11	11		52
PA-ELISA at or PTT	5	10	9		46
Bacteremic at or PTT	9	11	9		51
Modified intent to treat (mITT)	9	11	11		31

*1) ETI-204 group: Animals L20651 and L20655 were negative for PA-ECL, animals L20646, L20651 and L20655 were negative for PA- ELISA, and animals L20602, L20651 and L20655 were negative for bacteremia. Animals L20602 and L20651 both survived through Day

28, but Animal L20655 died prior to the 48 hour post-challenge blood collection and exhibited a negative culture at death.

2) Levo group: Animals L20614, L20625, L20644 and L20652 were negative of PA-ELISA.

3) ETI-204 & Levo group: L20624 was negative for PA-ELISA.

Data Quality

In general the submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. We could replicate the primary efficacy analysis results and main study results.

Table of Demographic Characteristics

Demographics and baseline characteristics of the study population in each treatment group are summarized in **Table 6.126**. The number of animals in the levofloxacin and obiltoxaximab& levofloxacin groups were well balanced across treatment groups with regard to sex, age, and baseline body weight, bacteremia, and challenge dose of *B. anthracis*. Quantitative bacteremia was not measured as per protocol.

Table 6.126. Study 1045: Demographics and Baseline Characteristics

	Levofloxacin 50mg/kg n = 16	ETI-204 & Levo n = 16	ETI-204 8mg/kg n = 16	Control n = 6
Sex [n(%)]				
Male	8(50.0%)	8(50.0%)	8(50.0%)	3(50.0%)
Female	8(50.0%)	8(50.0%)	8(50.0%)	3(50.0%)
Body weight (kg) at challenge				
Mean ± SD	2.7±0.1	2.8±0.1	2.7±0.2	2.8±0.2
Median	2.7	2.7	2.7	2.8
(Min, Max)	(2.5, 3)	(2.6, 2.9)	(2.5, 3.1)	(2.6, 3)
Age (months)				
Mean ± SD	5±0	4.8±1	5±0	5±0
Median	5	5	5	5
(Min, Max)	(5, 5)	(1, 5)*	(5, 5)	(5, 5)

*ETI-204 plus levofloxacin group: Age of animal L20615 was one month and other study animals aged 5 months.

Exposure to *B. anthracis* in all Animals

The mean challenge dose of *B. anthracis* (CFU/mL or LD_{50}) was similar across the three treatment and control groups including animals that died prior to treatment initiation. The mean and median challenge doses for all animals were 198 LD_{50} *B. anthracis* spores close to the target dose of 200 LD_{50}.

Table 6.127. Study 1045: Extent of Exposure to *B. anthracis*

	ETI-204 8mg/kg n = 16	Levo 50mg/kg n = 16	ETI-204 & Levo n = 16	Control n = 6	Animals Died before Treatment n = 17	All Animals N = 54
Challenge dose (LD_{50})						
Mean ± SD	178.5±30.4	213.9±38.3	194.4±57.9	202.3±30.3	181.2±42.4	196.3±43.6
Median	176.5	207	198.5	197.5	180	197.5
(Min, Max)	(120, 229)	(150, 289)	(108, 289)	(164, 247)	(108, 259)	(108, 289)
Challenge dose (LD_{50}) [n(%)]						
< 200	11 (68.8)	6 (37.5)	8 (50.0)	4 (66.7)	11 (64.7)	29 (53.7)
200 or higher	5 (31.2)	10 (62.5)	8 (50.0)	2 (33.3)	6 (35.3)	25 (46.3)
***B. anthracis* LD_{50} by Challenge day**						
	A		B			
Mean ± SD	202.7±44		190±43.1			196.3±43.6
Median	202		181			197.5
(Min, Max)	(112, 289)		(108, 289)			(108, 289)

Source: Biostatistics review by Ling Lan, Ph. D.

The time between challenge and first positive PA-ECL, PA-ELISA, and bacteremia, and time to treatment initiation are summarized in

Table 6.128. The time to treatment initiation was fixed at 72 ± 1 hour per protocol and there were no significant delays in treatment initiation. The median time to positive PA by ELISA or by ECL and time to development of bacteremia was shorter in the untreated controls as one would expect. There were no statistically significant differences in the parameters listed in

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Table **6.128** between the levofloxacin-treated group and the obiltoxaximab plus levofloxacin group (Wilcoxon rank sum test: p-value > 0.05, per Dr. Ling Lan's biostatistics review).

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Table 6.128. Study 1045: Time to First Detectable PA-ECL and Bacteremia by Study Group

	Levo 50mg/kg	ETI-204 & Levo	ETI-204 8mg/kg	Control
Time to first positive PA-ECL	n = 16	n = 16	n = 14	n = 6
Mean ± SD	36.5±11.8	40.9±11.1	43.6±13.3	36.1±13.2
Median	36.7	46.5	47.5	35.8
(Min, Max)	(21.9, 50.5)	(23.4, 50.5)	(22.2, 70.7)	(23.1, 49.2)
Time to first positive PA-ELISA	n = 12	n = 15	n = 13	n = 6
Mean ± SD	43.5±10.9	51.4±16.8	48.9±12.8	60±19.9
Median	46.1	48.1	49.2	49
(Min, Max)	(24.6, 60.2)	(25.7, 74.3)	(26.9, 72.2)	(47, 96.3)
Time to bacteremia	n = 16	n = 16	n = 13	n = 6
Mean ± SD	38±16.7	40.9±14.4	48.8±15.9	55.4±54.5
Median	27.9	46.4	47.8	35.8
(Min, Max)	(21.9, 73.6)	(23.4, 74.3)	(25.7, 72.9)	(23.1, 164)
Time to treatment initiation	n = 9	n = 11	n = 11	
Mean ± SD	73.2±2.1	72.2±1.8	73.2±2.1	
Median	73.7	72.2	73.7	
(Min, Max)	(69.5, 75.3)	(69.8, 74.8)	(69.8, 75.9)	

Levo: levofloxacin;
*P-value based on a 1-sided Fisher's exact test compared to 0.025.
**Difference in % survivors with 95% exact confidence interval (CI) based on normal approximation.

Efficacy Results - Primary Endpoint

The primary endpoint is the proportion of survivors alive at study Day 28. The survival rates were not statistically significant in the challenged animals or treated animals. Obiltoxaximab& levofloxacin had a numerically higher survival rate, 82% versus 78% (95% CI -36%, 44%) compared to levofloxacin- treated animals but the survival proportion was not statistically significant, p-value of 1.0; this comparison was not powered to detect the observed difference in survival rates. The survival proportion at study Day 28, for levofloxacin-treated group versus the obiltoxaximab plus levofloxacin groups are summarized in

Table 6.129.

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Table 6.129. Study 1045: Survival Rates at Day 28 Post-challenge in NZW Rabbits with *B. anthracis*

	Levo 50mg/kg	ETI-204 8mg/kg & Levo	Difference (ETI-204 & Cipro – Cipro) 95% CI**	P-value*
Challenged and randomized animals	7/16 (44%)	9/16 (56%)	0.12 (-0.22, 0.47)	0.72
Treated Animals	7/9 (78%)	9/11 (82%)	0.04 (-0.36, 0.44)	1.00

*P-value based on a 1-sided Fisher's exact test compared to 0.025.
**Difference in % survivors with 95% exact confidence interval (CI).

Source: Review by biostatistics reviewer, Ling Lan, Ph.D.

There was a statistically significant difference in survival (time to death) in the 11 animals that survived to receive a single dose of obiltoxaximab 8mg/kg IV at approximately 72 hours post challenge compared to the untreated controls, (obiltoxaximab , 64% vs. untreated control, 0%).

Table 6.130. Study NIAID 1045: Survival in NZW Rabbits at Day 28 by Treatment Group

	Control (N=6)	**ETI-204 8 mg/kg IV (N=16)**
All randomized animals		
n (%)	0 (0)	7 (43.8)
Difference in survival proportion compared with control [exact 95% confidence interval] one-sided p-value		0.438 [-0.054, 0.701] 0.0296
Animals that received treatment at 72 hours post-challenge		
n/N (%)	0/6 (0)	7/11 (63.6)
Difference in survival proportion compared with control [exact 95% confidence interval] one-sided p-value		0.636 [0.078, 0.891] 0.0052
Animals qualitatively bacteremic at or prior to 72 hours post challenge		
n/N (%)	0/5 (0)	5/9 (55.6)
Difference in survival proportion compared with control [exact 95% confidence interval] one-sided p-value		0.556 [-0.024, 0.863] 0.030

6.23 **Study AR034 – Re-challenge**

6.23.1 Study Design

Overview and Objective

Study AR034 is entitled, a "Re*challenge of rabbits treated previously for inhalational anthrax with intravenous obiltoxaximab to assess protective immunity*."
The **primary objective** was to demonstrate that obiltoxaximab administered alone or in combination with levofloxacin following primary challenge with *B. anthracis* spores resulted in development of protective immunity as measured by increased survival in the absence of treatment following secondary challenge (re-challenge) in NZW rabbits.
The **secondary objectives** were to determine whether rabbits treated with obiltoxaximab alone or in combination with levofloxacin following primary challenge were more likely to (i) survive a secondary challenge with *B. anthracis* spores, (ii) demonstrate longer time to death following secondary challenge, and (iii) have significant higher levels of circulating anti-P A IgG at the time of secondary challenge as compared to rabbits treated with levofloxacin alone.

Reviewer Comment: Phase 1 of this study, AR034, models a post-exposure scenario of treatment with an antibacterial drug +/- anti-PA monoclonal antibody following exposure to B. anthracis. The study provides data on survival rates in NZW rabbits treated with obiltoxaximab plus levofloxacin versus animals treated with levofloxacin alone following a delay in initiation of treatment. The study also provides data on the efficacy (survival rates) for animals treated obiltoxaximab alone versus placebo. This portion of the review focuses on survival rates in rabbits treated with obiltoxaximab plus levofloxacin versus animals treated with levofloxacin alone.

Trial Design

Study AR034 was a randomized, controlled, open-label, factorial design, rechallenge study with obiltoxaximab and levofloxacin in NZW rabbits, conducted at the (b) (4) in 2013. Healthy NZW rabbits were challenged with aerosolized *B. anthracis* spores twice, first in Phase I and nine months later in Phase II. Sixty-eight animals were placed on phase 1 of the study. Rabbits that were treated and survived in phase 1 were included in phase 2 of the study. Study treatments were initiated at 30 hours post-challenge in the treatment groups. The study design for phases I and II is outlined in **Table 6.131**.

Table 6.131. Study AR034 (Phase I & II): Study Design

Group	No. of Animals	Treatment	ETI-204 Dose	Levofloxacin Dose	Therapy Duration
Phase I					
1	20	ETI-204	16 mg/kg	0 (vehicle)	Single dose (IV)

2	20	Levofloxacin	0 (saline)	50 mg/kg	3 days (oral)
3	20	ETI-204+ Levofloxacin	16 mg/kg	50 mg/kg	Single dose (ETI-204; IV) + 3 days (Levo; oral)
4	8	Control	0 (saline)	0 (vehicle)	N/A
Phase II					
1	Survivors	None	None	None	N/A
2	Survivors	None	None	None	N/A
3	Survivors	None	None	None	N/A
4	12 naïve rabbits	None	None	None	N/A

N/A: not applicable;

In Phase 1, NZW rabbits were randomized by weight and sex, before challenge, into three groups of 20 (Group 1, 2 and 3) and one group of 8 (Group 4) with each group consisting of 50% male and 50% female animals. Animals in each group were then randomized to two challenge days (challenge Day A and B) with a challenge order per day. In phase 1, Day 0, rabbits were challenged with aerosolized *B. anthracis (*Ames) spores at a target dose of 200 LD_{50} (2.1×10^7 spores) via a plethysmography chamber in a Biological Class III safety cabinet system.

Treatment with obiltoxaximab 16 mg/kg IV in combination with oral levofloxacin 50mg/kg or placebo (saline) was administered at 30 ± 4 hours post mean challenge in Groups 1 and 3. Groups 2 and 4 received levofloxacin IV alone or IV placebo (vehicle).

The Phase II study included animals that survived through Phase I; 12 out of 14 naïve animals (13 males and 1 female) were assigned to the Phase II control group, respectively. Animals were then randomized into two challenge days. Each challenge day was then assigned a challenge order. Phase II animals were re-exposed to aerosolized *B. anthracis* (Ames) spores (target 200 LD_{50}, secondary challenge, or re-challenge) approximately nine months after first challenge. No monoclonal antibody or antibacterial treatment was administered in Phase II.

Anti-PA Ig G

Following the first spore challenge, anti-PA IgG levels were monitored (every 7 days following spore challenge until Day 28 and then monthly thereafter), with the second spore challenge scheduled to occur when endogenous anti-PA IgG levels dropped. However, endogenous levels did not drop as predicted and a decision was made to rechallenge the animals with *B. anthracis* spores at 9 months after the first spore challenge.

Study Endpoints

The primary endpoint was the survival proportion of the phase 2 population i.e. survival to 21 days after the secondary challenge with *B. anthracis* spores.

Statistical Analysis Plan

Excerpt from biostatistics review by Ling Lan, Ph.D.

Study Population
The Applicant analyzed Phase I of the study using the Intent to treat (ITT) population, including animals who survived to receive treatment regardless of bacteremia status.
Phase I, ITT: Includes animals surviving to receive treatment.
*Phase II, ITT***:** Includes all animals that were challenged in Phase II. All surviving animals from the treated groups in Phase I and newly added Phase II control group were included in the analysis population for the primary endpoint.

Primary analysis
For Phase I, the Applicant conducted f a comparison of survival rates among four study groups (using a one sided Fisher's exact test with Bonferroni-Holm adjustment at overall alpha level of 0.05).
A Phase II included animals that survived Phase I and 12 out of 14 naïve animals (13 males and 1 female) assigned to the Phase II control group, respectively. Animals were then randomized into two challenge days. Each challenge day was then assigned a challenge order. Phase II animals were exposed to aerosolized *B. anthracis* (Ames) spores (target 200 LD_{50}s, secondary challenge or re-challenge) approximately nine months after first challenge. No treatment was administered in Phase II.

Comment: *The primary analyses for this review compared the proportion of animals that survived in the obiltoxaximab and levofloxacin and levofloxacin groups in Phase I (using a one-sided 0.025 level Fisher's exact test). The primary analyses population for this review was the ITT population i.e., all animals that survived to receive treatment, and the modified ITT (mITT) population, i.e., bacteremic animals that survived to receive treatment. See biostatistics review by Dr. Ling Lan for further detail.*

Protocol Amendments

Not applicable to this review.

Data Quality and Integrity: Sponsor's Assurance

The Applicant provided a quality assurance statement that the study was inspected by their Quality Assurance Unit. The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

6.23.2 Study Results

Compliance with Good Clinical Practices

This is a non GLP study.

Patient Disposition

Sixty-eight rabbits were randomized to four study groups in Phase I. The disposition of the animals prior to treatment initiation is outlined in Table 6.132. The primary efficacy analysis population included 18 rabbits in levofloxacin group and 17 rabbits in ETI-204 & levofloxacin group. A total of 56 (82%) rabbits were bacteremic prior to therapy.

Table 6.132. Study AR034 (Phase 1): Animal Disposition before Treatment Initiation

	ETI-204 16mg/kg	Levo 50mg/kg	ETI-204 & Levo	Control	Total
Animals challenged	20	20	20	8	68
Animals who survived to be treated	20	20	20	8	68
Analysis population					
Intent-to-Treat (ITT)	20	20	20	8	68
PA-ELISA PTT*	4	1	4	0	9
Bacteremic PTT	17	18	17	4	56
Modified intent to treat (mITT)	17 (85%)	18 (90%)	17(85%)	4 (50%)	56 (82.3%)

*PTT: prior to treatment

Table of Demographic Characteristics

The demographics and baseline characteristics of the subjects in each treatment group are summarized in Table 6.133. Animals in the levofloxacin and obiltoxaximab plus levofloxacin groups were comparable with regard to sex, age, and body weight at baseline. In Phase I, the challenge dose, bacteremia, and PA-ELISA were slightly higher in the treated group. In Phase II, all naïve control animals were male and the survivors from Phase II were older than animals in phase I.

Table 6.133. Study AR034 (Phase 1): Demographics and Baseline Characteristics

	ETI-204 16mg/kg n = 20	Levo 50mg/kg n = 20	ETI-204 & Levo n = 20	Control n = 8
Sex [n(%)]				
Male	10(50)	10(50)	10(50)	4(50)
female	10(50)	10(50)	10(50)	4(50)
Body weight (kg) at challenge				
Mean ± SD	3.3±0.3	3.3±0.3	3.3±0.3	3.2±0.3
Median	3.2	3.3	3.4	3.2
(Min, Max)	(2.8, 4.1)	(2.8, 4.2)	(2.8, 4.1)	(2.8, 3.7)
Age (months)				
Mean ± SD	8.0±0	8.0±0	8.0±0	8.0±0
Median	8.0	8.0	8.0	8.0
(Min, Max)	(8.0, 8.0)	(8.0, 8.0)	(8.0, 8.0)	(8.0, 8.0)

The mean challenge doses of *B. anthracis* spores were comparable across treatment groups and across challenge days, Table 6.134, and

Table 6.135.

Table 6.134. Study AR034 (Phase 1): Exposure to *B. anthracis*

	ETI-204 16 mg/kg n = 20	Levo 50 mg/kg n = 20	ETI-204 & Levo n = 20	Control n = 8	All Animals N = 68
Challenge dose (LD_{50})					
Mean ± SD	238.1±58.6	209.2±41	207.1±37.4	221.9±47	218.5±47.6
Median	231.5	203.5	206.5	231	212.5
(Min, Max)	(136, 367)	(128, 320)	(149, 297)	(150, 279)	(128, 367)
Challenge dose (LD_{50}) [N(%)]					
< 200	4 (20.0)	8 (40.0)	9 (45.0)	3 (37.5)	24 (35.3)
200 or higher	16 (80.0)	12 (60.0)	11 (55.0)	5 (62.5)	44 (64.7)

Table 6.135. Study AR034 (Phase 1) Exposure *B. anthracis* LD_{50} by Challenge Day

***B. anthracis* LD_{50} by Challenge Day (phase 1)**			
	Day A	Day B	All Animals
Mean ± SD	241.1 ± 49	196 ± 33.8	218.5 ± 47.6
Median	232	191.5	212.5
(Min, Max)	(159, 367)	(128, 257)	(128, 367)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Levels of bacteremia were comparable among the three treatment groups and were lower in the control group in Phase 1. Protective antigen was measured in 9 of 68 animals and the results were below the limit of detection in all of them. The median time to treatment initiation was approximately 27 hours for the treatment and control groups.

Table 6.136. AR034 (Phase I): PA-ELISA and Bacteremia PTT and Time to Treatment

	ETI-204 n = 20	Levo n = 20	ETI-204 & Levo n = 20	Control n = 8
Log_{10} bacteremia (cfu/mL)	n = 17	n = 18	n = 17	n = 4
Mean ± SD	2.8±1.5	2.5±1.2	2.8±1.6	1.4±1.3
Median	2.9	2.6	2.9	1
(Min, Max)	(0.3, 5.2)	(0.3, 4.1)	(0.3, 5.3)	(0.3, 3.7)
Bacteremia (cfu/mL)	n = 17	n = 18	n = 17	n = 4
Geometric Mean	594.7	338	588	24.4
95% CI	(136.9, 2583.9)	(105.2, 1086)	(121.2, 2853.5)	(2.9, 202.6)
PA (ng/ml)	n = 4	n = 1	n = 4	n = 0
Geometric Mean	6.8	5.5	6.5	4.8
95% CI	(5, 9.4)	(4.3, 6.9)	(5, 8.5)	(4.8, 4.8)
Time to treatment initiation				
Mean ± SD	28±1.4	27.9±1.5	27.5±1.2	27.4±1.3
Median	28.1	27.9	27.5	27.2
(Min, Max)	(26, 30.3)	(25.7, 30.2)	(25.5, 29.5)	(25.8, 29.4)
Time to first positive bacteremia in Phase I	n = 17	n = 18	n = 17	n = 7
Mean ± SD	28.1±1.3	27.8±1.5	27.4±1.1	62.8±46.8
Median	28.1	27.5	27.4	28.4
(Min, Max)	(26, 30.1)	(25.6, 30.1)	(25.5, 29.5)	(25.7, 139.2)
Time to first positive bacteremia in Phase II	n = 1	n = 2	n = 4	n = 12
Mean ± SD	71.2	95.7±35.5	83.9±43.9	44.2±31.7
Median	71.2	95.7	95.6	24.6
(Min, Max)	(71.2, 71.2)	(70.6, 120.8)	(25.9, 118.6)	(22.9, 118.3)

PTT: prior to treatment

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable.

Efficacy Results - Primary Endpoint

Survival rates for rabbits treated with the combination of levofloxacin plus obiltoxaximab group versus the levofloxacin-treated group are summarized in Table 6.137. All animals in the control

group succumbed to *B. anthracis* infection indicating that the inoculum was sufficient to cause lethal disease. All animals in the levofloxacin-treated group survived.
In the ITT population, animals treated with obiltoxaximab and levofloxacin had lower survival rates than animals treated with levofloxacin alone, 95% versus 100%, respectively. In bacteremic animals, obiltoxaximab plus levofloxacin had a lower survival rate than the levofloxacin-treated animals, 94% versus 100% with a difference of 0.6% (95% CI -29%, 11%), p-value of 0.49; this comparison was not powered to detect the observed difference in survival rates.

Table 6.137. Study AR034: Survival Rates at Month 9 Post-Challenge for Combination Therapy

	Group 2 ETI-204 16mg/kg	Group 3 ETI-204 & Levo	Difference (ETI-204 & Cipro – Cipro) 95% CI**	P-value*
Challenged and randomized	20/20 (100%)	19/20 (95%)	-0.05 (-0.26, 0.11)	1.00
(Bacteremic and Treated)	18/18 (100%)	16/17 (94%)	-0.06 (-0.29, 0.11)	0.49

*P-value based on a 1-sided Fisher's exact test compared to 0.025.
**Difference in % survivors with 95% exact confidence interval (CI) based on normal approximation.

No treatment was administered in Phase II. In the ETI-204 treatment group, 13 of 20 (65%) animals survived to Phase II and the survival rate in this group was 100%, compared with 0% in the control group. Phase II animals were exposed to aerosolized *B. anthracis* (Ames) spores (target 200 LD_{50}, secondary challenge or re-challenge) approximately nine months after the first challenge with *B. anthracis* spores.

The survival rate for the 16mg/kg dose was 65% and 100% survival in phase I and phase II respectively compared to 0% in the control arms. These differences in survival rates were statistically significant,

Table 6.138.

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Table 6.138. Study AR034 (Phase I and II): Survival Rates for ETI-204 and Placebo at Month 9 Post-Challenge

	Phase I		Phase II	
	Group 4 Placebo (N=8)	**Group 1 ETI-204 16 mg/kg 30 hrs PC (N=20)**	**Placebo (N=12)**	**ETI-204 16 mg/kg Survivors (N=13)**
N (%)	0	13 (65.0)	0	13 (100)
Difference in survival proportion compared with placebo [exact 95% confidence interval] one-sided p-value		0.65 [0.156, 0.846] 0.0008		1 [0.724, 1] <0.0001
Adjusted exact 95% confidence interval		0.300, 0.969		0.677, 1
Including only bacteremic animals prior to treatment				
n/N(%)	0/4 (0)	10/17 (58.82)	12	1 (100)
		0.588 [-0.072, 0.822]	0	1

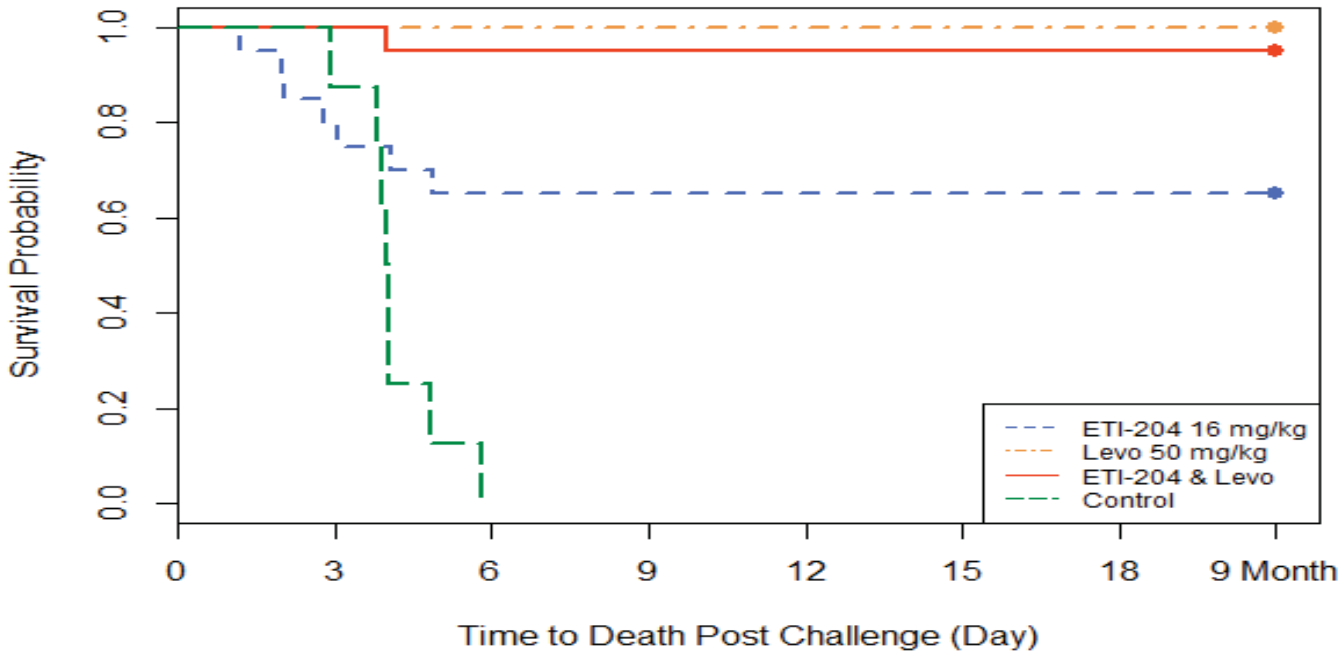
Note: Two-sided 95% confidence interval and one-sided p-values were calculated by the biostatistics reviewer, Xianbin Li, Ph.D.

Rechallenge at 9 months

The survivors from the primary challenge received a secondary challenge, in addition to 12 naïve control rabbits, with an average dose of 301 (± 69) LD_{50} equivalents of *B. anthracis* spores via aerosol exposure nine months post the initial challenge. The time from challenge to death was similar in the levofloxacin treatment arm, obiltoxaximab, or the combination of obiltoxaximab/ levofloxacin. *One dose of obiltoxaximab 16mg/kg IV was protective against anthrax following rechallenge with 200 LD_{50} B. anthracis spores at 9 months after the initial challenge.*

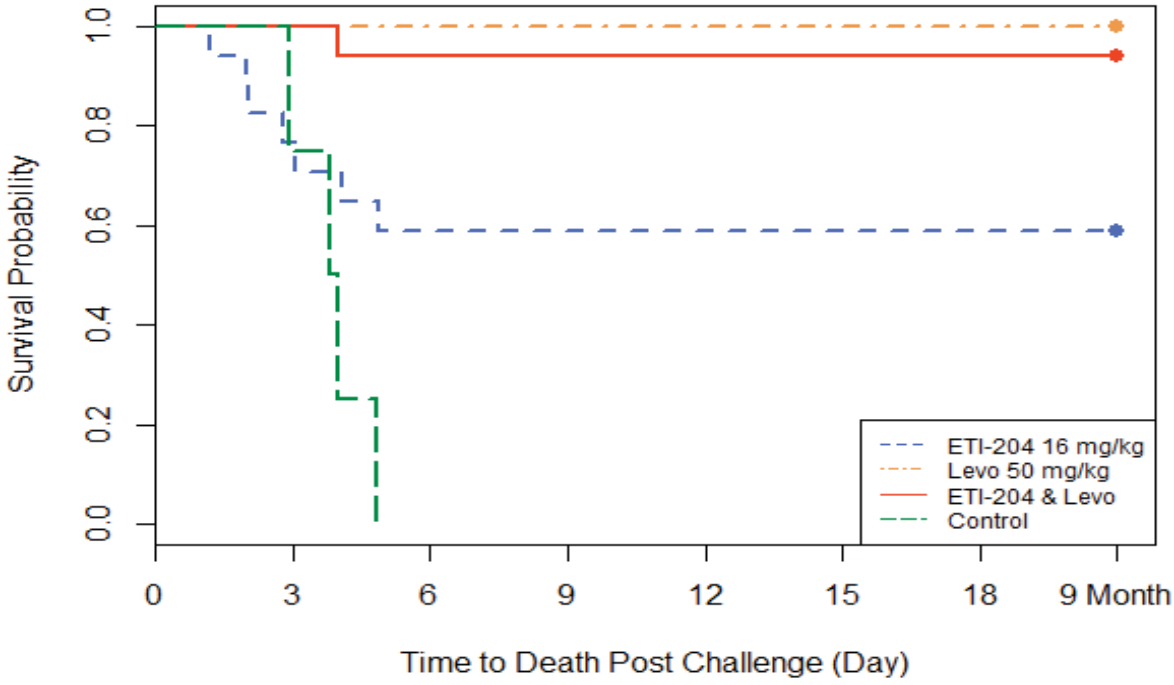
Reviewer Comment: The survival rates in the combination of obiltoxaximab&levofloxacin versus levofloxacin alone were 94% and 100%, respectively. The combination of levofloxacin plus obiltoxaximab did not offer an advantage over levofloxacin alone for the survival endpoint. It should be emphasized that these findings are from one study in one animal model and in a relatively small number of animals. Clinical situations where single treatment with obiltoxaximab monotherapy would be beneficial could include an infection with a multi-drug resistant isolate of B. anthracis and in the setting of significant antibacterial drug allergy or intolerance. See section 7.3 for further discussion.

Figure 6.46. Study AR034: Kaplan-Meier survival curves by Treatment Group – All Animals



Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.

Figure 6.47. Study AR034: Kaplan-Meier Curve for Treated Animals with Bacteremia



Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.

Data Quality and Integrity - Reviewers' Assessment

The data was of high quality and study results could be replicated from the datasets.

Efficacy Results - Secondary and other relevant endpoints

Immune response: Anti-PA-IgG and TNA

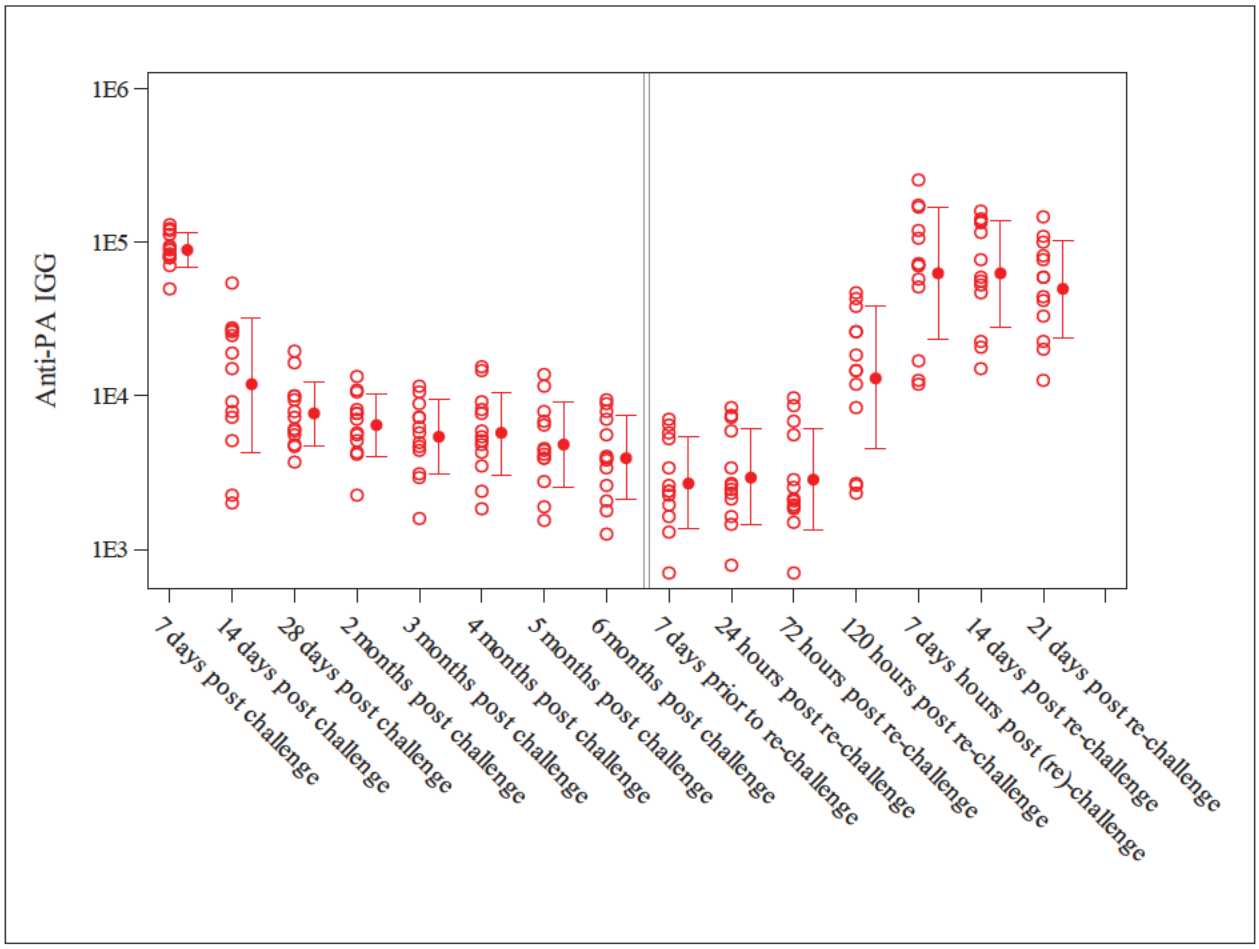
The development of an immune response for the animals was assessed through measurements of anti-PA IgG levels and the functional ability of serum to neutralize *B. anthracis* lethal toxin activity (TNA primary endpoints: ED_{50}/NF_{50} titers).

The following figure shows the anti-PA-IgG levels over time for the 13 surviving (treated) animals from Phase I and Phase II. The anti-PA-IgG levels were highest at Day 7 post-challenge, then gradually reduced until 5 days post re-challenge. Anti-PA IgG levels increased to a level

similar to the level at Day 7 post re-challenge and antibody levels continued to increase through Day 21 post re-challenge indicating the development of an immune response to re-challenge with *B. anthracis* spores.

Reviewer Comment: The anti-PA IGG ELISA assay utilized PA as a capture reagent and protein A/G as a detection reagent and both ETI-204 and endogenous anti-PA IgG are detected in the assay. It should be noted that the results in this assay are measured against ETI-204 as a standard (ETI-204 equivalents). See microbiology review the specifications of the anti-PA IgG assay by Lynette Berkeley, Ph.D.

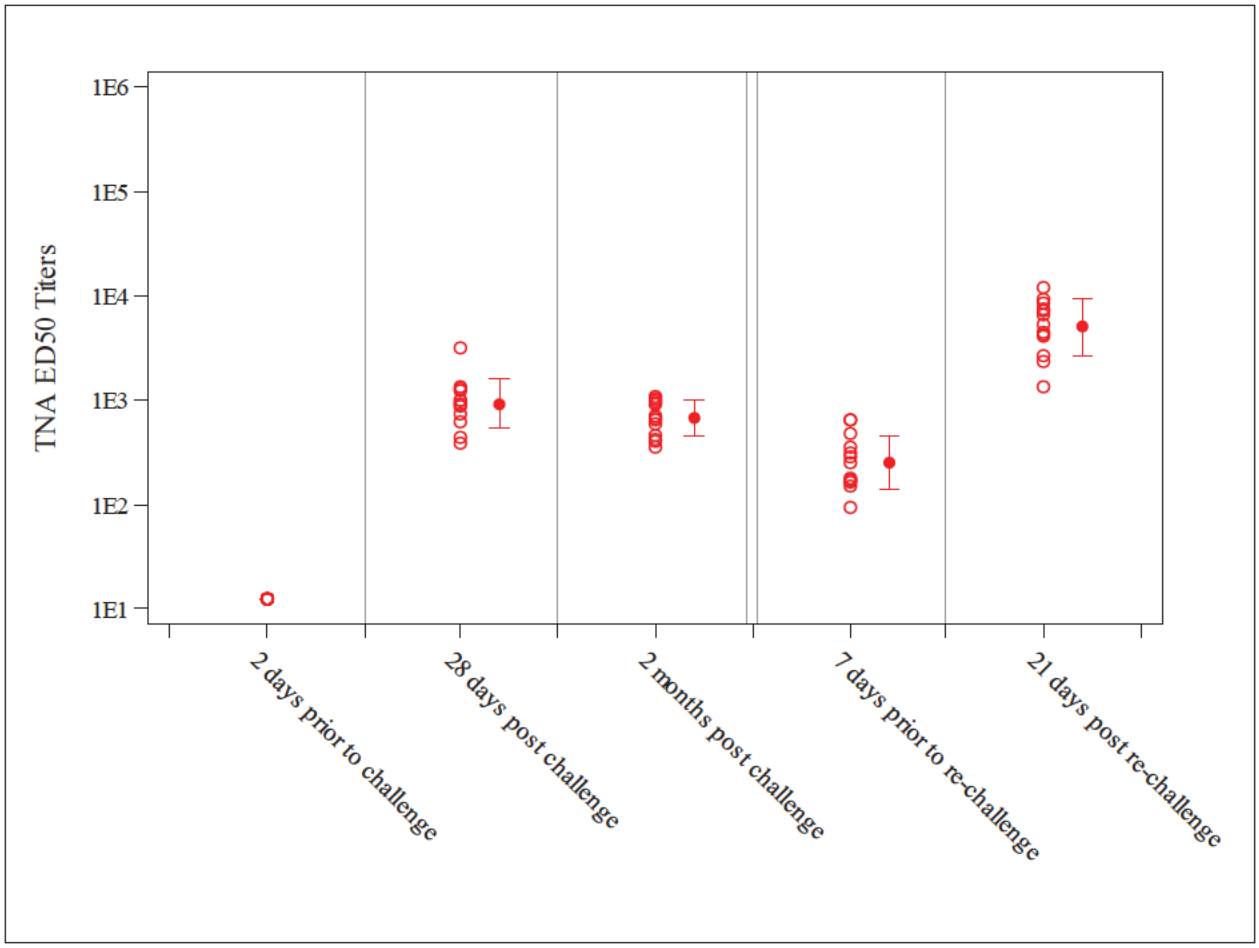
Figure 6.48. Study AR034 (Phase I&II): Anti-PA-IgG levels (geometric mean and standard deviation) in surviving treated animals



Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.

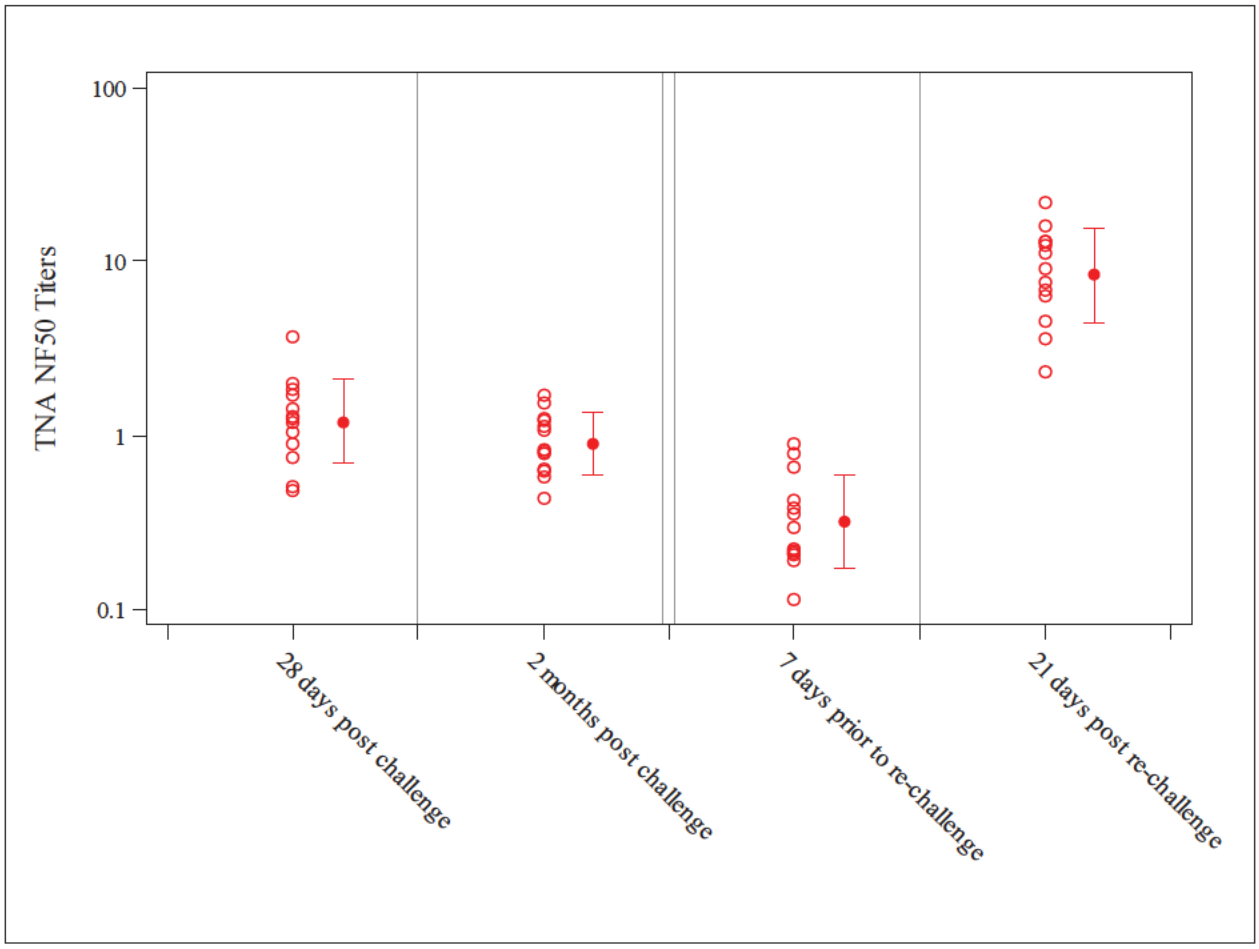
The following two figures are a summary of the toxin neutralizing ability (geometric mean and 95% confidence intervals) for the TNA ED_{50} and NF_{50} titers for treated animals in Phase I and Phase II. These variables measured the functional ability of serum to neutralize *B. anthracis* lethal toxin activity. The ETI-204 group (n=13) consistently exhibited an ED_{50} or NF_{50} 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.

Figure 6.49. Study AR034 Phase I and Phase II: *TNA ED_{50} for surviving treated animals -



Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.
*geometric mean and standard deviation

Figure 6.50. Study AR034: TNA NF_{50} for surviving treated NZW rabbits - Phase I and Phase II



Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.
Note: TNA titers geometric mean and standard deviation are shown.

Tissue bacterial assessments and pathological findings in the brain

Reviewer Comment: Anti-PA IgG had toxin neutralizing ability as demonstrated in the TNF assay. The immune response was effective because there was a 100% survival rate in the 13 animals that were re-challenged in phase II of the study.

See review of histopathological findings by Amy Nostrandt, DVM.

Durability of Response

There was no recurrence of anthrax in surviving animals within the 28 day study period following a single-dose of obiltoxaximab. A second dose of obiltoxaximab 16mg/kg was

protective against rechallenge with *B. anthracis* when administered at nine months post the initial challenge with *B. anthracis*.

Table 6.139. Study AR034: Time between Challenge and Bacteremia

	Phase I		**Phase II**	
	Placebo (N=8)	**ETI-204 16 mg/kg 30 hrs PC (N=20)**	**Phase II placebo (N=12)**	**ETI-204 16 mg/kg (N=13) Phase I Survivors**
Time to qualitative bacteremia (hours)				
N	7	17	12	1
Mean (SD)	62.7 (46.8)	28.0 (1.32)	44.2 (31.7)	71.2
Range	25.7, 139.2	25.98, 30.1	22.9, 118.2	

Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.

The results of subgroup analyses by gender, body weight, challenge dose, bacteremia levels, and PA-ELISA at baseline are summarized in

Table 6.140. In Phase I, a higher bacteremia or PA level prior to treatment was associated with a lower survival in the treated group at the end of the study (Month 9). The numbers of subjects were too small to make a conclusion in other subgroups.

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Table 6.140. Study AP034: Survival in NZW Rabbits at End of Study by Challenge Dose, Bacteremia, and PA-ELISA

	Phase I		Phase II	
	Placebo (N= 8)	ETI-204 8 mg/kg IV (N= 20)	Placebo (N=12)	ETI-204 16 mg/kg (N=13) Phase I Survivors
Gender				
Male	0/3			8/8 (100)
Female	0/3		0/12	5/5 (100)
Challenge dose (LD_{50})				
<250	0/6	7/13 (53.8%)	0/3	3/3 (100%)
250 or higher	0/2	6/7 (85.7%)	0/9	10/10 (100%)
<200	0/3		0	0
Bacteremia prior to treatment (cfu/mL)				
$<10^2$	0/6	6/6 (100%)	0/7	13/13 (100%)
10^2 - $<10^4$	0/2	6/9 (66.7%)	0/3	
10^4 or higher	0	1/5 (20%)	0/2	
PA-ELISA (ng/mL)				
0 - < 10		10/12 (83.3%)		
10 - < 50		2/4 (50%)	0/2	1/1 (100%)

Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D.

6.24 **AP10-055 - Combination Study**

6.24.1 Study Design

Overview and Objective

Study AP10-055 of evaluated obiltoxaximab as an adjunct therapy in a NZW Rabbit partial survival model for inhalational anthrax. The primary objective of this study was to determine the added-benefit of *obiltoxaximab* 8 mg/kg, IV in combination with doxycycline (2 mg/kg) in comparison to doxycycline alone in NZW rabbits following aerosol exposure to *B. anthracis*.

Note: This review will focus on the primary objective on the comparison of survival rates between obiltoxaximab & doxycycline versus doxycycline group alone.

Trial Design

This was a non-randomized, controlled, open-label study of obiltoxaximab plus doxycycline, doxycycline and saline control. The study was conducted by Center for Aerobiological Sciences United States Army Medical Research Institute of Infectious Diseases (USAMRIID), Frederick MD. Obiltoxaximab was administered as a single dose of 8 mg/kg IV and doxycycline was administered at a dose of 2 mg per kilogram IV twice a day for three days. Details of the study design are outlined in Table 6.141.

Table 6.141. Study AP 10-055: Study design

Group	Treatment	ETI-204 IV Dose	Doxy IV Dose	Treatment Initiation	Therapy Duration	No. of Animals
1	Doxycycline	8 mg/kg	2 mg/kg	PA-ECL+ or 30 hours post challenge	3 days (oral)	10
2	ETI-204+ Doxycycline	8 mg/kg	2 mg/kg	PA-ECL+ or 30 hours post challenge	Single dose (ETI-204; IV) + 3 days (Levo; oral)	10
3	Control (Saline)	N/A	N/A	N/A	N/A	4

*N/A – Not applicable; *Source Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D.*

All NZW rabbits received a target challenge with *B. anthracis* (Ames) strain spore dose of 200±50 LD_{50}. Treatments were initiated at positive PA-ECL by 30 hours post-challenge or at 30 hours post-challenge if PA-ECL was negative. Animals that survived to receive treatment were divided into two groups of ten animals and one group of 4 animals.

Study Endpoints

The primary endpoint was survival by Day 28 or 29 post-challenge.

Statistical Analysis Plan

Excerpt from biostatistics review by Ling Lan, PhD:
Study Population
The sponsor analyzed the study using two populations, one including all animals received treatment and one including treated animals with positive bacteremia result at any time prior to treatment. This review referred to these populations as the intent to treat (ITT) and modified ITT (mITT) populations, respectively.

Primary Analysis
The sponsor compared survival rates among three study groups using exact permutation Cochran-Armitage trend tests stratified by experimental iteration with p-values corrected by permutation to account for multiple comparisons. Additional comparisons were performed for mean time to death using a generalized linear model stratified by experimental iteration with p-values corrected by permutation to account for multiple comparisons.

Comment: T*he primary analyses for this review compared the survival proportion of animals in the obiltoxaximab plus doxycycline versus doxycycline groups used a one-sided 0.025 level Fisher's exact test. The primary analyses population included animals that survived to receive treatment.*

Data Quality and Integrity: Sponsor's Assurance

The study was conducted according to the study protocol as amended, and standard operating procedures (SOPs) at USAMRIID.

6.24.2 Study Results

Compliance with Good Laboratory Practices

This was a non- GLP study.

Patient Disposition

The primary efficacy analysis population included 10 rabbits in the obiltoxaximab and doxycycline groups versus 10 animals in the doxycycline group.

Table of Demographic Characteristics

A total of 24 rabbits were randomized to three study groups. Animals were all adult rabbits weighted 3-5 kg. Animals in doxycycline and obiltoxaximab & doxycycline groups were comparable in sex and challenge dose of *B. anthracis*. Control animals received a lower challenge dose of *B. anthracis* compared to other treatment groups. Time to treatment initiation was not calculable because neither treatment initiation time nor challenge time was provided.

Table 6.142. Study AP10-055: Extent exposure to *B. anthracis*

	Doxy 2mg/kg IV **n = 10**	**ETI-204 8mg/kg IV& Doxy 2mg/kg IV** **n = 10**	**Control** **n = 4**	**All Animals** **N = 24**
Sex [n(%)]				
Male	5 (50.0)	5 (50.0)	3 (75.0)	13 (54.2)
Challenge dose ($\times 10^7$ cfu)				
Mean ± SD	4.0±2.5	4.8±1.9	1.8±2.1	4.0±2.4
Median	4.0	4.7	9.0	4.0
(Min, Max)	(0.4, 7.4)	(2.2, 8.1)	(0.5, 4.9)	(0.4, 8.1)
Challenge dose (LD_{50})*				
Mean ± SD	381±239.8	458.6±182.2	173.5±198.3	378.8±225.2
Median	378.8	444.3	88.1	378.8
(Min, Max)	(33.6, 708.3)	(209.7, 773.3)	(50.4, 467.4)	(33.6, 773.3)

Challenge dose (LD_{50}) [n(%)]				
< 200	4 (40.0)	0 (0.0)	3 (75.0)	7 (29.2)
200 or higher	6 (60.0)	10 (100.0)	1 (25.0)	17 (70.8)

Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D.

Efficacy Results - Primary Endpoint

The primary analysis demonstrated that ETI-204 and Doxy group had higher survival rate versus doxycycline (90% versus 50%) with a difference of 40% (95% CI: -2%, 72%), p-value of 0.14. This comparison was not powered to detect the observed difference in survival rates.

Table 6.143. Study AP 10-055: Survival in NZW Rabbits at Day 28 or 29

	Doxy n = 10	**ETI-204 & Doxy n = 10**	**Control n = 4**
Survival Rates [n(%)]	5 (50)	9 (90)	0 (0.0)
Time to Death (hour)			
Mean ± SD	17.7±10.9	26.3±7.1	1.8±0.5
Median	18.5	28.5	2
(Min, Max)	(6, 28)	(6, 29)	(1, 2)

P-value from one-sided Fisher's Exact Test; *Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D*.

Data Quality and Integrity - Reviewers' Assessment

There was no electronic dataset submitted for this study. Study reports included tables for gender, exposure, obiltoxaximab dose, outcome, time to death post exposure in days and results for quantitative bacteremia and PA-ECL. The reviewers could replicate the main study results from the submitted data.

6.25 Study AR028 - Combination Study

6.25.1 Study Design

Overview and Objective

Study AR028 was an exploratory study to evaluate the effects of obiltoxaximab when given in combination with levofloxacin on survival in anthrax-challenged NZW rabbits.

The primary objective was to determine whether ETI-204 (16 mg/kg, IV) improved survival rate when co-administered with levofloxacin at 6.5 mg/kg (less than HED), compared to levofloxacin alone in NZW rabbits following aerosol exposure to *B. anthracis*, with a delayed treatment resulted in 50% survival at 72±4 hours after post-median challenge time.
The secondary objective was to determine whether ETI-204 reduced survival rate when co-administered with levofloxacin at a lower than HED compared to levofloxacin alone in NZW rabbits following exposure to *B. anthracis*, with the delayed treatment

Trial Design

This was a randomized, placebo-controlled, open-label, study of three treatment groups, levofloxacin oral , obiltoxaximab IV plus levofloxacin oral versus control in NZW rabbits, conducted at the (b) (4) The study design (phase 1 and 2) is summarized in

Table 6.144.

Table 6.144. Study AR028: Study Design

	Group	Therapy	ETI-204 Dose	Levo Dose	Treatment Initiation	Therapy Duration	NZW rabbits challenged, n=120	No. of Rabbits Survived to Randomization
Phase I	1	Control	0 (saline)	0 (water)	72±4 hours post-median challenge time*	Levo once daily 3 days (oral) ETI-204 Single dose (IV)	60	8
	2	Levo	0 (saline)	6.5 mg/kg				19
	3	ETI-204 + Levo	16 mg/kg	6.5 mg/kg				17
Phase II	4	Control	0 (saline)	0 (water)			60	4
	5	Levo	0 (saline)	6.5 mg/kg				19
	6	ETI-204 + Levo	16 mg/kg	6.5 mg/kg				17

* Hours post-median challenge time, where the median challenge time is calculated by averaging the end time of the first animal and the end time of the last animal within each day. Levo: levofloxacin; *Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D*.

Sixty rabbits in Phase I and 60 in Phase II were challenged with 200 LD_{50} of aerosolized *B. anthracis* (Ames) spores. Study treatments were initiated 72±4 hours after post-median challenge time. Eighty-four animals survived long enough to receive study drugs.
Animals were randomized by sex into three groups in each phase. In Phase I, the controls (Group 1) consisted of 8 rabbits (4 males and 4 females). Groups 2 and 3 each consisted of approximately half of the remaining rabbits. In Phase II, the controls (Group 4) consisted of 4 rabbits (2 males and 2 females). Groups 5 and 6 each consisted of approximately half of the remaining rabbits treated. PA-ECL was not measured in this study per protocol.

Study Endpoints

The primary endpoint was survival at Day 28 post challenge with *B. anthracis* spores.

Statistical Analysis Plan

Study Population
The Applicant analyzed the study using two populations, one including all animals survived to receive treatment and one including treated animals with bacteremia at any time prior to treatment; this review referred to these populations as the Intent to treat (ITT) and modified intent to treat (mITT) populations, respectively.

Primary Analysis
The Applicant conducted one sided Fisher's exact test for comparison of survival rates between obiltoxaximab plus levofloxacin and levofloxacin only groups, at alpha level of 0.05 each time, without adjustment of multiple comparisons. Additional comparisons were performed for time to death endpoint using log-rank test.

Interim Analysis
An interim analysis of survival results from Phase I was conducted following completion of Phase I to select dose for Phase II. A statistically significant difference in the survival rate obiltoxaximab & levofloxacin group compared to levofloxacin group would have resulted in selection of lower dose of ETI-204 in Phase II. Because statistical significance was not achieved based on survival results of Phase I, ETI-204 was administered at 16 mg/kg in Phase II, same as that in Phase I. As stipulated in the statistical analysis plan, groups with the same treatment regimen were combined in a single study population for statistical calculations.

*Reviewer Comment: **T**he primary analyses for this review compared the survival rate of animals in the obiltoxaximab plus levofloxacin versus levofloxacin groups (using a one-sided 0.025 level Fisher's exact test). The primary analysis population was the combined populations from Phase I & II that survived to receive treatment.*

Data Quality and Integrity: Sponsor's Assurance

The Applicant provided a quality assurance statement that the study was inspected by their Quality Assurance Unit. The study was conducted according to the study protocol as amended, and (b) (4) standard operating procedures (SOPs).

6.25.2 Study Results

Compliance with Good Laboratory Practices

This is a non GLP study.

Patient Disposition

The disposition of NZW rabbits prior to treatment is outlined in Table 6.145.

Table 6.145. Study AR028: Disposition of NZW rabbits Prior to Treatment

	Phase I			Total (Phase I & II)		
Treatment group	**Levo**	**ETI-204 & Levo**	**Control**	**Levo**	**ETI-204 & Levo**	**Control**
Animals challenged	60			120		
Animals survived to treatment	19	17	8	38	34	12
Analysis population						
Intent-to-Treat (ITT)	19	17	8	38	34	12
Bacteremia at or PTT	18	17	8	37	34	12
Modified intent to treat (mITT)	18	17	8	37	34	12

PTT: prior to treatment ; *Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D*.

Table of Demographic Characteristics

Demographics and baseline characteristics of NZW rabbits are summarized in

Table 6.146. Animals were evenly distributed among treatment groups with respect to age, gender, and body weight.

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Table 6.146. Study AR028: Demographics and Baseline Characteristics

	Levo 6.5mg/kg PO n = 38	**ETI-204 16mg/kg IV & Levo 6.5mg/kg PO n = 34**	**Control n = 12**
Sex [n(%)]			
male	20 (52.6)	18 (52.9)	6 (50.0)
female	18 (47.4)	16 (47.1)	6 (50.0)
Body weight (kg) at challenge			
Mean ± SD	3.2±0.1	3.2±0.2	3.2±0.2
Median	3.2	3.2	3.2
(Min, Max)	(3, 3.6)	(2.9, 3.6)	(2.8, 3.4)
Age (months) – Phase I	n = 19	n = 17	n = 8
Mean ± SD	7.8±1.1	8.2±0.8	7.6±1.1
Median	8	8	8
(Min, Max)	(6, 9)	(6, 9)	(6, 9)

Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D.

The mean and median challenge doses of *B. anthracis* spores were similar across treatments groups. The mean challenge dose was slightly lower in the control group however, all control animals died indicating that the challenge inoculum caused lethal disease.

Table 6.147. Study AR028: Extent Exposure to *B. anthracis* in NZW Rabbits

	Levo 6.5mg/kg PO n = 38	**ETI-204 16mg/kg IV & Levo 6.5mg/kg PO n = 34**	**Control n = 12**	**All Animals N = 84**
Challenge dose (LD_{50})				
Mean ± SD	215.8±41	232.2±40.1	191.8±52.2	219±44
Median	213.3	229.4	181.5	222.3
(Min, Max)	(114.7, 316.6)	(160.2, 326.1)	(94.7, 270.1)	(94.7, 326.1)
Challenge dose (LD_{50}) in animals, [n(%)]				
< 200	14 (36.8)	5 (14.7)	7 (58.3)	26 (31.0)
200 or higher	24 (63.2)	29 (85.3)	5 (41.7)	58 (69.0)
LD_{50} by Challenge day	A	B	C	D
Mean ± SD	230.1±39.7	211.8±33.2	204.3±53.8	226.1±47.4
Median	226.1	212.8	213.3	228.4
(Min, Max)	(155.5, 316.6)	(161.1, 271.1)	(94.7, 296.7)	(141.2, 326.1)

Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D.

Bacteremia and Protective Antigen

The level of bacteremia was slightly higher in the control group compared to other two treatment groups. Bacteremia levels and PA-ELISA are summarized in **Table 6.148**. PA-ECL was not measured as per protocol.

Table 6.148. AR028: Bacteremia and PA-ELISA PTT in Animals that Survived to be Treated

	Levo 6.5mg/kg PO n = 38	**ETI-204 16mg/kg IV & Levo 6.5mg/kg PO n = 34**	**Control n = 12**	**All Animals N = 84**
Log_{10} bacteremia* (cfu/mL)	n = 37			
Mean ± SD	3.9±1.2	3.8±1.5	4.3±0.9	3.9±1.3
Median	3.9	4	4.1	4
(Min, Max)	(1.7, 6.9)	(0.3, 7.5)	(3.2, 6.7)	(0.3, 7.5)
Bacteremia (× 10^4 cfu/mL)				
Geometric Mean	0.7	0.7	1.9	0.8
95% CI	(0.3, 1.8)	(0.2, 2.1)	(0.6, 6.2)	(0.4, 1.5)
PA-ELISA (ng/ml)**	n = 35			
Mean ± SD	203.1±530.9	273.6±719.1	254.7±620.5	240.3±622.2

Median	17.4	32	58.2	28.3
(Min, Max)	(4.9, 2540)	(4.9, 3870)	(4.9, 2210)	(4.9, 3870)
Log_{10} PA-ELISA (ng/ml)				
Mean ± SD	1.4±0.8	1.6±0.9	1.8±0.7	1.5±0.8
Median	1.2	1.5	1.8	1.5
(Min, Max)	(0.7, 3.4)	(0.7, 3.6)	(0.7, 3.3)	(0.7, 3.6)
PA-ELISA (ng/ml)				
Geometric Mean	27.1	37.3	58.3	34.7
95% CI	(14.8, 49.6)	(19.2, 72.5)	(22.3, 152.4)	(23.3, 51.8)

* In analysis of quantitative bacteremia in animal L43132 (ETI-204 & Levo, Phase I), the colony count was <LOD (3 cfu/ml) and this value was replaced by 2; six animals were "+" (<LOQ = 100 cfu/ml) and this value was replaced by 50. Animal L43701 (Levo, Phase II) was negative for bacteremia prior to and at the treatment initiation and was not included in the analyses of bacteremia.

**In the analysis, PA-ELISA levels for 24 animals was <LLOQ (9.68 ng/ml) and was replaced with 4.84 ng/ml. Three animals, L43139 (Levo, Phase I), L43720 & L43744 (Levo, Phase II) had missing values for PA-ELISA prior to treatment and were excluded from this analysis.

Source: Adapted from Table 45 of biostatistics review, Ling Lan, Ph.D.

Efficacy Results - Primary Endpoint

Obiltoxaximab and levofloxacin group had higher survival rate compared to the levofloxacin group, of (68% versus 58%), respectively with a difference of 10% (95% CI: -12%, 32%), p-value of 0.47 (one-sided Fisher's exact test). This comparison was not powered to detect the observed difference in survival rates. All control animals died indicating that the challenge dose caused lethal disease.

Table 6.149. Study AR028: Survival at Day 28 in NZW Rabbits

	Levofloxacin 6.5mg/kg n = 38	ETI-204 & Levo n = 34	Control n = 12
Survival rates [n(%)]	22 (58)	23 (68)	0
Death [n(%)]	16 (42)	11 (32)	12 (100)
Time to death (hours)			
Mean ± SD	433.4±284	486.1±273.1	96.3±16.2
Median	672	672	98.6
(Min, Max)	(75, 672)	(74.5, 672)	(74.2, 118.3)

Source: Review by biostatistics reviewers, Ling Lan, PhD. and Xianbin Li, Ph.D.

Data Quality and Integrity - Reviewers' Assessment

The submitted data sets were of high quality. All data sets were submitted in AdaM and SEND standard format. The reviewers could replicate the primary efficacy analysis results and main study results.

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy Across TrialsPrimary Endpoints

The primary efficacy endpoint in the cynomolgus macaque and NZW rabbit monotherapy and post-exposure prophylaxis studies was the survival rate at the end of the study, Day 28 or Day 30, defined as the percentage of animals alive at the time of scheduled study termination.

7.1.2 Secondary and Other Endpoints

Not applicable.

7.1.3 Subpopulations

Not applicable.

7.1.4 Dose and Dose-Response

In cynomolgus macaques and NZW rabbits, the highest survival rates were reported that were treated with the highest dose of obiltoxaximab i.e., 16 mg/kg single dose. The dose response for survival was more evident in the NZW rabbit studies than in the NHP monotherapy efficacy studies.

7.1.5 Onset, Duration, and Durability of Efficacy Effects

There was no delayed occurrence of inhalational anthrax in animals that were initially successfully treated with a single dose of intravenous obiltoxaximab.

7.2 Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Postmarket Setting

See the benefit-risk assessment, section 1.3.

7.2.2 Other Relevant Benefits

Not applicable.

7.3 Integrated Assessment of Effectiveness

This section summarizes the overall survival outcomes of the monotherapy studies, combination studies with monoclonal antibody ± antibacterial drugs, and the survival in post exposure prophylaxis and pre-exposure prophylaxis studies.

Obiltoxaximab Monotherapy Efficacy Studies
Survival rates for five monotherapy efficacy studies in cynomolgus macaques are summarized in Table 7.1. All cynomolgus macaques were challenged with a 200 LD_{50} dose of *B. anthracis.* Obiltoxaximab was efficacious for the treatment of anthrax with statistically significant results for survival compared to placebo/control in four of the five studies (except study AP203). Highly variable rates for survival were observed in the obiltoxaximab and the placebo groups across studies. Survival rates across studies ranged from 31 to 50% for the 16 mg/kg IVdose, 6.25 to73% for the 8mg/kg IV dose, 25% to 79% for the 4 mg/kg IV dose, and 37.5% for the 32mg/kg IV dose (one study). The highest survival rate (79%) in cynomolgus macaques was observed in Study AP201 and the lowest survival rate was 6.25% in study AP203. The proposed therapeutic dose, 16mg/kg IV single-dose, had a statistically significant survival rate of 31% or 35% in study AP201) and 50% instudies AP204 and NIAID 1056. A total of 205/219 (94%) of animals were bacteremic prior to treatment indicating that obiltoxaximab was efficacious in animals that

were systemically ill with anthrax.

Table 7.1. Survival Rates in Obiltoxaximab IV Monotherapy Studies in all Cynomolgus Macaques

	Dose (mg/kg)	n/N (%)	Difference in proportion [95% CI]	P-value
AP202	0	0/17 (0)		
Lonza vs Baxter	16 (Lonza)	5/16 (31)	0.31 [0.08, 0.59]	0.0085
	16 (Baxter)	6/17 (35)	0.35 [0.11, 0.62]	0.0046
AP203 Lonza	0	2/16 (12.50)		
	8	1/16 (6.25)	0.625 [-0.329,0.194]	0.761
	32	6/16 (37.50)	0.375 [-0.065, 0.541]	0.064
AP204 Baxter	0	1/16 (6.3)		
	4	4/16 (25.0)	0.188 [-0.090, 0.473]	0.1077
	16	8/16 (50.0)	0.438 [0.113, 0.703]	0.0036
AP201 Baxter	0	2/14 (14.3)		
	4	11/14 (78.6)	0.643 [0.260, 0.879]	0.00046
	8	11/15 (73.3)	0.590 [0.207, 0.841]	0.00075
NIAID 1056	0†	0/8 (0)		
	8	4/8 (50)	0.50 [0.058, 0.843]	0.014

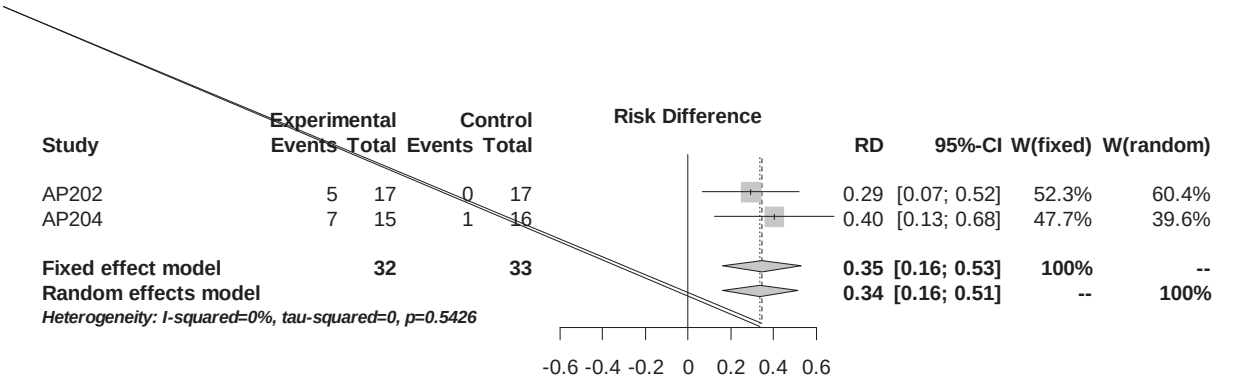
Significant p-values are in red text.
*95% CI and p-values from exact method and Boschloo's one-sided test; †Excluded one animal that did not have bacteremia prior to treatment in 16mg/dose group in Study 204;
Included the one animal that did not have bacteremia prior to treatment in 16mg/dose group in Study AP204: 8/16 (50) [0.113, 0.703] 0.0036; Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.
†Control animals in study NIAID 1056 were untreated i.e., did not receive a placebo.

Reviewer Comment: The survival results for the Baxter and Lonza obiltoxaximab products studied in Study AP202 were similar, therefore, monotherapy efficacy studies that used the Baxter ETI-204 were analyzed to support the survival results observed in study AP202. The differences in survival among the studies were most likely due to differences in bacteremia or PA levels prior to treatment as well as possible innate immunity to anthrax in some animals as evidenced by the five survivors in the placebo groups in the nonhuman primate studies.

Meta-analysis of Nonhuman Primate Monotherapy Studies
The following graph presents the results from a fixed-effect model and random-effects model for the obiltoxaximab16mg/kg IV dose used in Studies AP202 and AP204. The diamond shapes in the graph show the 95% confidence intervals from a fixed-effect model and random effects model. A statistically significant treatment effect is indicated if the lower limit is greater than 0.

The risk difference (RD) is the difference in survival proportions.
The point estimates and confidence intervals (CI) for both fixed effect and random effects models for the 16mg/kg dose tested in two studies are shown in Figure 7.1. The 16mg/kg IV dose showed significant differences in survival in both models. The lower limit of the CI in both models is 0.16; therefore, the results demonstrate that treatment with obiltoxaximab 16mg/kg IV is significantly better than the placebo for the survival outcome.

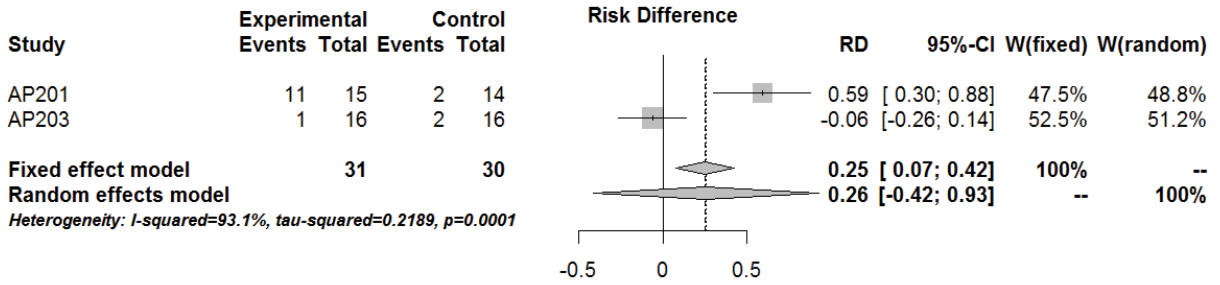
Figure 7.1. Meta-analysis Results for Difference in Survival Proportions between Treatment (16mg/kg ETI-204) and Placebo Group in Cynomolgus Macaques



Note: One animal was excluded because it was not bacteremic prior to therapy.
Source: Biostatistics review by Xianbin Li, Ph.D.

The results from a fixed-effect model and random-effects model for the 8mg/kg dose tested in Studies AP201 and AP203 are presented in **Figure 7.2**. There was a significant result for testing heterogeneity (p value = 0.0001, I-squared 88.6%) as shown indicating the high percentage of variation in survival across studies is due to heterogeneity rather than chance.

Figure 7.2. Meta-analysis: Results for Differences in Survival Proportions between Treatment (8mg/kg ETI-204) and Placebo Group in Cynomolgus Macaques



Source: Biostatistics review, section 5.2.1, by Xianbin Li, Ph.D.

Median time to death across nonhuman primate studies

The median time to death ranged from 75 to 84 hours in studies AP202, AP203 and AP 204. The median time to death was 134 hours in the study AP201. Study AP201 had the lowest mean bacteremia levels and the smallest proportion of animals with high levels of bacteremia (e.g., *B. anthracis*> 10^5 CFU/mL) prior to treatment compared to the other three studies.

Table 7.2. Comparison of Time to Death in IV ETI-204 Monotherapy Treatment Studies in Cynomolgus Macaques

	AP202[a]	**AP203**	**AP204**	**AP201**
Median Time (hours) to death	75	84	82	134
Mean time (hours) to death	76	70	87	110
Geometric mean bacteremia at PTT (95% CI) (CFU/mL)	1.50e+05 (6.26e+04, 3.59e+05)	5.57e+04 (2.2e+04, 1.39e+05)	8.27e+03 (3.89e+03, 1.76e+04)	1.67e+03 (8.22e+02, 3.38e+03)
Geometric mean time to abnormal PA-ECL (95% CI) (hours)	35.08 (33.69, 36.47)	32.73 (31.41, 34.11)	36.77 (34.94, 38.70)	37.81 (35.31, 40.49)
Geometric mean time to abnormal bacteremia (95% CI) (hours)	28.59[b] (27.13, 30.05)	29.21 (27.79, 30.70)	30.91 (29.14, 32.80)	35.07 (33.17, 37.07)
Proportion of animals with >10^5 CFU/mL *B. anthracis* at PTT, % (n/N)	45% (23/51)	42% (20/48)	19% (9/48)	7% (3/44)

[a]Includes one challenged animal that died after PTT sample collection and prior to treatment administration. This

animal was not randomized to a treatment group.
[b]By enriched bacteremia.
IV: intravenous; CI: confidence interval; CFU/mL: colony forming units/milliliter; PA-ECL: protective antigen electrochemiluminescence; PTT: prior to treatment; NA: not available.
Source: Adapted from Table 18, page 73 of "Summary of Clinical Efficacy", BLA 125509, SDN1.

Bacteremia and Survival Outcomes

Survival outcomes in bacteremic (*B. anthracis*) cynomolgus macaques in five obiltoxaximab IV monotherapy studies are summarized in

Table 7.3. All macaques were challenged with a 200 LD_{50} dose of *B. anthracis.* A significant improvement in survival in bacteremic animals treated with obiltoxaximab 4mg/kg, 8 mg/kg, and 16 mg/kg IV doses was observed in four of the five studies. There was no recurrence of inhalational anthrax / bacteremia in the animals once PA and bacteremia were initially cleared.

Table 7.3. Survival in Monotherapy Treatment Studies in Bacteremic Cynomolgus Macaques

Study # and manufacturer of ETI-204	ETI-204 Dose (mg/kg)	n/N (%)	Difference in proportion [95% CI] [Adjusted 95% CI]	p-value (significance level)
AP202 Lonza vs Baxter	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	0	2/16 (12.50)		
	8	1/16 (6.25)	-0.063 [-0.329, 0.194] [-0.358, 0.238]	0.761 (0.0125)
	32	**5/15 (33.33)**	0.208 [-0.104, 0.510] [-0.148, 0.550]	0.104 (0.0125)
AP204 Baxter	0	1/16 (6.3)		
	4	4/16 (25.0)	0.188 [-0.090, 0.473] [-0.135, 0.513]	0.1077 (0.0125)
	16	**7/15 (46.7)**	0.404 [0.089, 0.381] [0.048, 0.712]	0.0058 (0.0125)
AP201 Baxter	0	2/14 (14.3)		
	4	**10/13 (76.9)**	0.626 [0.226, 0.867] [0.179, 0.888]	0.00078 (0.0125)
	8	11/15 (73.3)	0.590 [0.207, 0.841] [0.162, 0.864]	0.00075 (0.0125)
NIAID 1056 Baxter	0	0/8 (0)		
	8	4/8 (50)	0.50 [0.058, 0.843] [-0.014, 0.871]	0.014 (0.0125)
		203		

Source: Table constructed by the biostatistics reviewer, Xianbin Li, Ph.D.

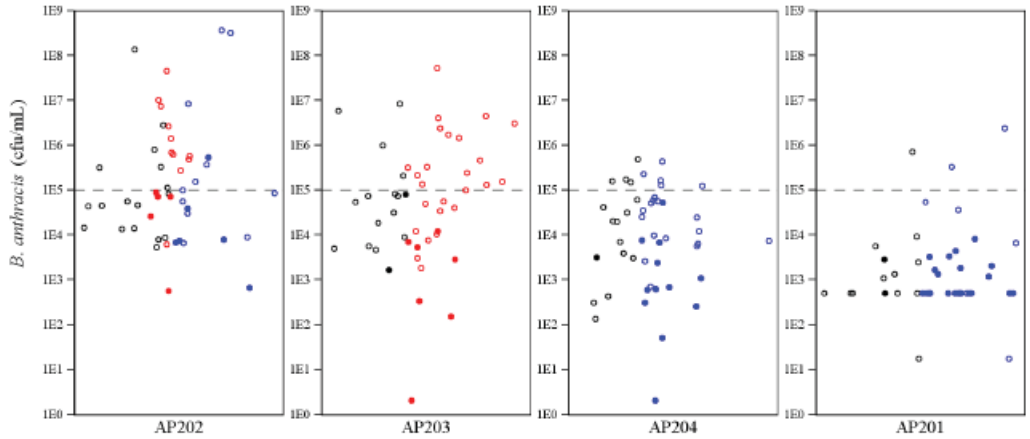
Bacteremia

There was considerable variability in mean bacteremia levels prior to treatment across the intravenous monotherapy studies, Figure 7.3. Animals in study AP201 had the lowest mean bacteremia levels and highest proportion of survivors compared to the other four nonhuman primate monotherapy studies including the study NIAID 1056. Animals in study AP202 and study AP203 had the highest mean bacteremia levels and the lowest proportion of survivors.

The results for survival demonstrated a significant treatment effect of obiltoxaximab 16mg/kg IV in study AP202 and in study AP204. The 8mg/kg dose demonstrated a significant treatment effect in study AP201 and in study NIAID 1056, however the 8 mg/kg and 32 mg/kg treatment

groups failed to show efficacy compared to placebo in study AP203. Animals with the lowest mean bacteremia levels (< 10^4 cfu/mL) prior to treatment were more likely to survive, Figure 7.3.

Figure 7.3. Obiltoxaximab IV Monotherapy Studies in Cynomolgus Macaques: Bacteremia (Geometric mean ± SD) prior to Treatment by Study and Dose Group



cfu = colony forming unit. Shown are bacteremia levels for individual animals at PTT (Prior to Treatment). Terminal samples are not included
Filled symbols represent the survivors and open symbols represent the non-survivors; Blue symbols represent ETI-204 (Baxter); Red symbols represent ETI-204 (Lonza); Black symbols represent Placebo.
Dotted line is drawn at 10^5(1E5) cfu/ml to visually indicate animals with PTT bacteremia above or below that level.
Limit of detection (LOD) and limit of quantification (LOQ) value in each study were as follows:
AP201: LOD = 33 cfu/mL and LOQ = 1000 cfu/mL, respectively; for computational purposes, values below LOD are replaced with 17 cfu/mL (1/2 LOD) and values below LOQ are replaced with 500 cfu/mL (1/2 LOQ). AP204 and AP203: LOD = 3 cfu/mL and LOQ = 100 cfu/mL, respectively; for computational purposes, values below LOD are replaced with 2 cfu/mL (1/2 LOD rounded to the nearest integer); values below LOQ are replaced with 50 cfu/mL (1/2 LOQ). AP202: LOD = 3 cfu/mL; for computational purposes, values below LOD are replaced with 2 cfu/mL (1/2 LOD rounded to the nearest integer) and values reported as positive are replaced with 50 cfu/mL.
Project Code\Study Number\Analysis:Elusys\AP201\Program: f_lb_jittered_time_qbacteremia_ttt.sas (03FEB2015 09:22)

Open symbols are non-survivors. Closed symbols are survivors.
Source: BLA 125509, SDN 1, study report, integrated summary of efficacy, Figure 20.

The level of bacteremia prior to treatment was inversely associated with survival in the intravenous monotherapy studies in cynomolgus macaques. Survival proportions decreased as the bacteremia levels (prior to treatment) increased within each dose group and in the placebo group, Table 7.4. However, because the dose groups came from different studies, comparisons among the dose group should be interpreted with caution. Animals with lowest bacteremia levels prior to treatment had the highest survival rates. Animals that had >10^6 cfu/mL *B. anthracis* bacteremia prior to treatment did not survive.

Table 7.4. Survival in Cynomolgus Macaque Studies by Bacteremia level and by Dose group

Bacteremia PTT CFU/mL	ETI- 204 0 mg/kg N=63	ETI 204 4 mg/kg N=30	ETI-204 8 mg/kg N=39	ETI-204 16 mg/kg N=49	ETI-204 32 mg/kg N=16
$<10^4$	4/28 (14.3%)	15/20 (75%)	12/19 (63.2%)	12/18 (66.7%)	5/5 (100%)
10^4 - $<10^6$	1/31 (3.2%)	0/10 (0)	4/15 (26.7%)	7/23 (30.4%)	1/8 (12.5%)
$>10^6$	0/4	0	0/5	0/8	0/3

PTT: prior to treatment

Protective Antigen and Survival

Animals with lowest PA-ELISA levels prior to treatment had the highest survival rates among the dose groups. PA-ELISA levels prior to treatment in obiltoxaximab monotherapy efficacy studies in nonhuman primates are summarized in Table 7.5. The results for survival for the 0 mg (placebo), 4 mg/kg, 8 mg/kg, and 16 mg/kg doses are from two or more studies, and the results for the 32mg/kg are from one study. Comparisons of the dose groups should be interpreted with caution because the groups come from different studies.

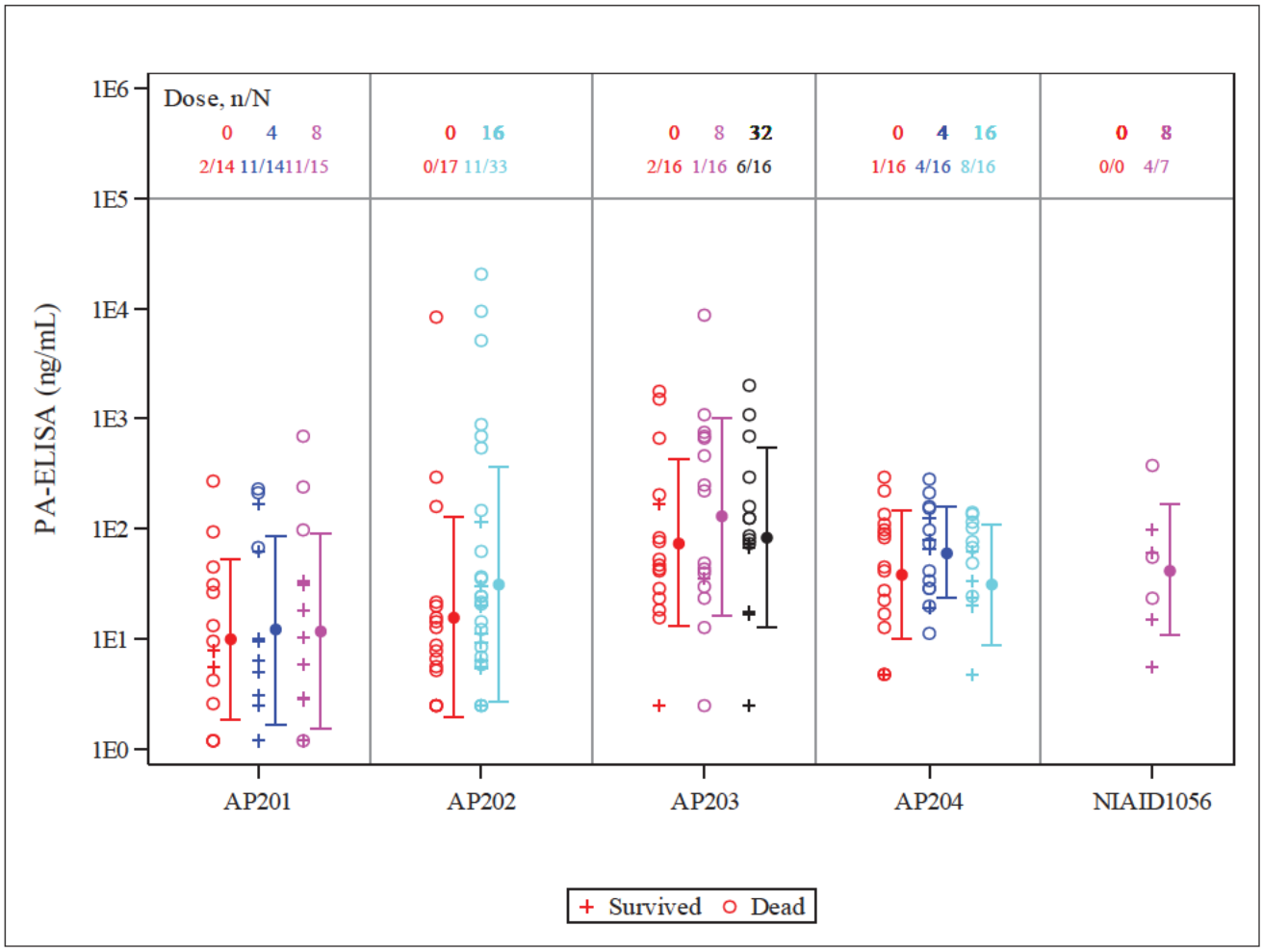
Table 7.5. Survival in Nonhuman Primate Studies by PA Levels prior to Treatment with Obiltoxaximab (ETI-204)

PA-ELISA ng/mL	**ETI-204 0 mg/kg N=60**	**ETI-204 4 mg/kg N=30**	**ETI-204 8 mg/kg N=38**	**ETI-204 16 mg/kg N=45**	**ETI-204 32 mg/kg N=16**
<10	3/18 (16.7%)	8/8 (100%)	7/9 (77.8%)	7/13 (53.9%)	2/2 (100%)
10 - <50	0/22 (0%)	2/8 (25%)	7/14 (50%)	6/16 (37.5%)	2/2 (100%)
50 or higher	1/20 (5%)	5/14 (35.7%)	2/15 (13.3)	2/16 (12.5%)	2/12 (16.7%)

PA-ELISA: Protective Antigen measured by ELISA;

In Study AP201, the PA-ELISA levels were lower than in other studies. Macaques in study AP203 had the highest mean PA-ELISA levels prior to treatment and the lowest survival proportions in the treated groups, Figure 7.4.

Figure 7.4. Obiltoxaximab IV Monotherapy Studies: PA-ELISA (Geometric mean ± SD) prior to Treatment in Nonhuman Primates by study and dose groups



Color Legend: placebo 0mg/kg (red); 4mg/kg (blue); 8mg/kg (pink); 16mg/kg (turquoise); 32mg/kg (black).
"o" = non-survivor; "+" = survivor
Source: Biostatistics review by Xianbin Li, Ph.D.

The levels of PA post treatment with obiltoxaximab were evaluated to determine if the levels were predictive of survival. Data on PA levels from five monotherapy efficacy studies in cynomolgus macaques, AP201, AP202, AP203, AP204, and NIAID 1056 are included in the analysis. In treated macaques (excluding placebo), 62 of 65 (96%), animals had PA levels < 10ng/mL at 10 of 15 minutes post treatment with obiltoxaximab. A PA level < 10 ng/mL was associated with a survival rate of 29% in all obiltoxaximab - dose groups combined. Animals with the lowest PA level at 15min post treatment had the greatest chance of survival, see Table 7.6.

Table 7.6. Protective Antigen Levels Post Treatment with Obiltoxaximab by Survival Status in Cynomolgus Macaques

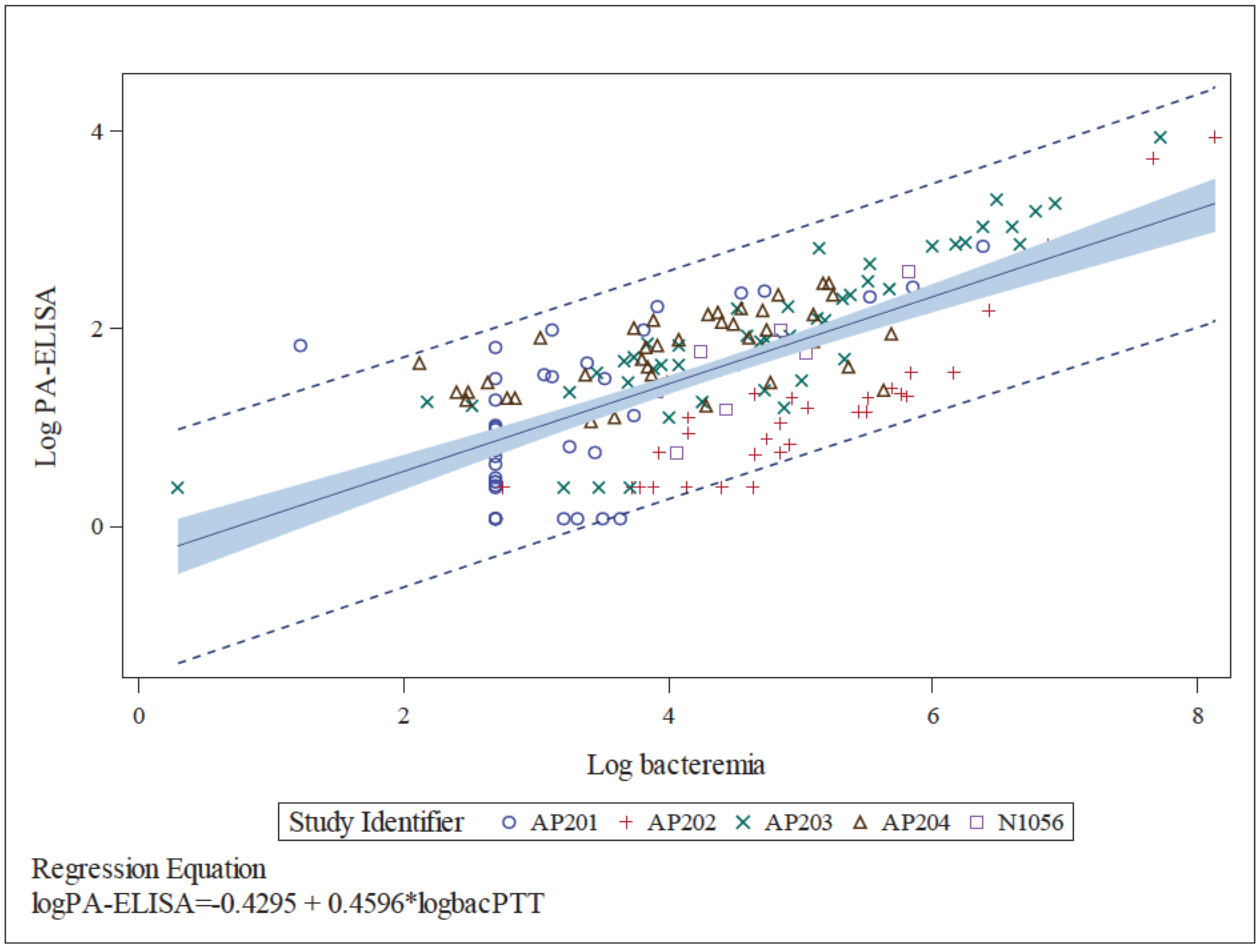
Protective Antigen Levels Post Treatment with Obiltoxaximab by Survival Status in Five Monotherapy Efficacy Studies in Cynomolgus Macaques			
PA (ng/mL) at 15min post treatment	Survival Status at End of the Studies		
	Died	Survived	Total
A. <10	44 70.97	18 29.03	62
B. 10+	2 100.00	0 0.00	2
C. 50+	1 100.00	0 0.00	1
Total	47	18	65

Correlation between Bacteremia and Protective Antigen Levels

Bacteremia and PA levels are strongly correlated in the efficacy studies of cynomolgus macaques. The relationship between bacteremia and PA-ELISA prior to treatment in the intravenous monotherapy studies in cynomolgus macaques is presented in Figure 7.5. The solid line in the middle of the graph is the regression line, and the dotted lines are the 95% upper and lower confidence limits for an individual predicted value and the shaded band is the 95% upper and lower confidence limits for the expected mean values of log PA-ELISA level. The correlation coefficient was 0.723 (p-value <0.0001), indicting a strong positive linear relationship between bacteremia and protective antigen levels.

The data points from study AP202 were more likely to be under the fitted line and data points from AP203 and AP204 were more likely to be above the fitted line. Although study AP202 and AP203 had similar bacteremia levels, animals in AP203 had the highest PA-ELISA level prior to treatment. The high bacteremia levels and non-proportionally high PA-ELISA levels relative to bacteremia in study AP203 may explain the failure of this study to demonstrate a survival benefit for obiltoxaximab.

Figure 7.5. Obiltoxaximab IV Monotherapy Studies: Log_{10} PA-ELISA and Log_{10} Bacteremia Prior to Treatment by Study



Source: graph constructed by biostatistics reviewer, Xianbin Li, Ph.D.

Reviewer Comment: A regression analysis of survival with covariates of bacteremia and PA-ELISA was performed by the biostatistics reviewer, Dr. Xianbin Li. Bacteremia and PA-ELISA were associated with survival and after adjusting for one of them and the 16 mg/kg ETI-204 had the strongest treatment effect among all dose groups. It is noted that after adjusting for bacteremia, the 32 mg/kg dose had the second strongest treatment effect, followed by the 4 mg/kg and 8 mg/kg groups.

Rabbit Monotherapy Studies

In study AR021, treatment was triggered for the majority of animals in the placebo, 1 mg/kg ETI-204, and levofloxacin groups by a positive result in the PA-ECL assay and by a SIBT in the 4

mg/kg and 16 mg/kg ETI-204 groups. In study AR033, treatment was triggered for the majority of animals in each group by a significant increase in body temperature, SIBT.
No animals in any of the treatment groups in either study AR021 or study AR033 were treated based on time from challenge. Additionally, median time to trigger for treatment and median time to positive bacteremia were similar across the groups in each study. A statistically significant difference in survival compared with placebo occurred in the 4mg/kg, 8mg/kg, and 16mg/kg dose groups in studies AR021, AR033, and 1030,Table 7.7. Survival increased as the dose of obiltoxaximab IV increased except in study AR033 where the 16mg/kg dose and the 8mg/kg dose group had similar survival rates.

The dose response for survival was more evident in the NZW rabbit studies than in the nonhuman primate studies. The 16 mg/kg IV dose of obiltoxaximab had the highest survival rate (94%) in NZW rabbits.

Table 7.7. Obiltoxaximab Monotherapy Studies in NZW Rabbits: Survival at Day 28 by Study and Treatment Group

Study # and manufacturer of ETI-204	ETI-204, mg/kg	NZW Rabbits n/N (%)	Difference in proportion [95% CI]	P-value*
AR021 Baxter	0	1/10 (10)		
	1	4 /10 (40)	0.3 [-0.107, 0.659]	0.0755
	4	13/17 (76.5)	0.665 [0.249, 0.878]	0.0005
	16	16/17 (94.1)	0.841 [0.443, 0.978]	<0.0001
AR033 Baxter	0	0/14 (0)		
	1	4/14 (28.6)	0.286 [0.012, 0.581]	0.02081
	4	6 /14 (42.9)	0.429 [0.135, 0.711]	0.003
	8	10/14 (71.4)	0.714 [0.406,0.916]	<0.001
	16	9/14 (64.3)	0.643[0.334,0.872]	0.001
1030 Baxter	0	0/6 (0)		
	8	12/16 (75)	0.75 [0.221, 0.927]	0.0008

*Significant p-values in red text; Source: Biostatistics review by Xianbin Li, Ph.D.

Dose Response

The dose-response relationship was further explored in the NZW rabbit study AR033, in which an intermediate dose of obiltoxaximab 8 mg/kg was included. In macaques, the dose-response relationship was further explored in Studies AP204 and AP203, in which additional doses of 16 mg/kg and 32 mg/kg were evaluated, respectively. The primary objective of study AP202 was to confirm the efficacy of the 16 mg/kg obiltoxaximab dose in the treatment of inhalational anthrax in cynomolgus macaques.

Anti-PA IgG levels

The anti-PA IgG antibodies and/or toxin neutralizing antibodies were measured prior to challenge in one study, AP202. Other nonhuman primate studies (AP201, AP203, and AP204) did not test for Anti-PA IgG. The Applicant tested for anti-PA IgG antibodies in the serum from five control animals that survived in the four nonhuman primate studies, AP201, AP202, AP203, and AP204; these sera were collected prior to challenge and stored. No anti-PA IgG antibodies were detected, prior to challenge, in these five survivors.

COMBINATION STUDIES

Results from eight studies of obiltoxaximab in combination with antibacterial drugs versus antibacterial drug alone are compiled in this section. The eight studies were randomized, controlled, open-label, parallel-group, factorial design studies that were conducted (b) (4). Six studies were conducted in NZW rabbit model and two studies in the cynomolgus macaque model of inhalational anthrax. These studies explored a range of intravenous obiltoxaximab doses with human equivalent doses (HED) or subtherapeutic doses (less than HED) of the antibacterial drug and delayed treatment times post exposure to inhalational *B. anthracis*. Control groups in all of the NIAID-sponsored studies were untreated and control groups in the Elusys-sponsored studies received a placebo. The target challenge dose was 200 LD_{50} *B. anthracis* in the majority animals. Delayed initiation of treatment post-challenge and use of less than HED doses of the antibacterial drug were utilized in order to demonstrate a difference in survival rates in the obiltoxaximab plus antibacterial drug combinations over the antibacterial drugs alone. Obiltoxaximab was administered as a single-dose, 8mg/kg or 16 mg/kg, and one study (AR007) used a single-dose of 10mg. Antibacterial drugs used in combination with obiltoxaximab included ciprofloxacin, levofloxacin, or doxycycline.
Four studies evaluated a human equivalent dose (HED) of antibacterial drug, i.e. levofloxacin 50mg/kg and four studies evaluated doses less than the HED of the other antibacterial drugs listed above. Antibacterial drugs such as ciprofloxacin and levofloxacin have high efficacy (approximately 90% to 100%) when administered as soon as an animal develops a a positive PA or SIBT.

Reviewer Comment: The FDA requested that the development program for anti-PA monoclonal antibodies for treatment of anthrax should include evidence that the Mab plus antibacterial drug resulted in higher survival outcomes ("added-benefit") compared to the antimicrobial drug alone. The mechanisms of action of the mAb and antibacterial drugs are different therefore no antagonism was expected between the two treatments. Previous combination or "added-benefit" studies suggested that the time to 50 percent mortality was at approximately 84 hours post-exposure in rabbits. The rationale for co-administration of a mAb and antimicrobials in the post-exposure prophylaxis setting is based on findings in experimental animal models indicating

that antibacterial treatment early after challenge with B. anthracis may lead to persistence of spores and disease development following cessation of antibacterial drugs.[22]

Studies that Evaluated a Human Equivalent Dose of Antibacterial Drug
Studies that investigated a HED of the antibacterial drug are more applicable to the treatment of human anthrax than the studies that employed less than the HED of the antibacterial drug. Four studies (AR007, 1030, 1045, AR034) in the NZW rabbit model evaluated a human equivalent dose (HED) of levofloxacin administered orally, in combination with obiltoxaximab. Study treatments (obiltoxaximab + antibacterial or levofloxacin alone) were delayed until 9 hours, 30 hours, 72 hours, and 96 hours post challenge with *B. anthracis* in the four studies. The survival rates for animals treated with the comparator, levofloxacin monotherapy at the HED, were 33% at 9 hours post-challenge, 100% at 30 hours post-challenge, and 78% at 72 hours post-challenge, and 40% at 96 hours post-challenge.
The low survival rate (33%) in levofloxacin-treated animals in Study AR007 is discussed below. In studies 1030, 1045, AR034, the survival rates in the levofloxacin arm decreased as delays in treatment initiation increased. In three of the combination studies (AR007, 1030, 1045), survival rates in the obiltoxaximab &levofloxacin study arms numerically increased survival rates from 33 to 89% (9 hours post-challenge), 78 to 82% (72 hours post-challenge), 40 to 100% (96 hours post challenge), 100 to 95% (30 hours post challenge), Table 7.8.
Study AR034 was the only study that tested the proposed human dose of obiltoxaximab 16mg/kg with a HED of levofloxacin, 50mg/kg. The survival rate for levofloxacin alone (100%) in this study is consistent with prior treatment studies of levofloxacin in animal models of anthrax. In study AR034, there was no significant difference in survival rate between obiltoxaximab 16mg/kg plus levofloxacin 50mg/kg (95%) versus levofloxacin alone (100%), respectively.

Reviewer Comment: Study AR007 was the only NZW rabbit study that demonstrated a statistically significant difference in survival rates favoring the combination obiltoxaximab plus a HED of levofloxacin versus levofloxacin alone. The fixed dose of 10mg (~4mg/kg) is well below the proposed human dose of obiltoxaximab 16mg/kg IV and the survival outcomes with this low dose suggests that a 16mg/kg would be more efficacious when combined with levofloxacin if administered early post-exposure. The anti-PA monoclonal antibody in this study was manufactured by (b) (4) *and it may not be identical to the current mAb manufactured by Lonza but this does not negate the survival results. The survival rate of 33% for the comparator, levofloxacin was low, however this has been observed in other studies in which initiation of antibacterial treatment within 6 to 12 hours after B. anthracis spore challenge led to persistence*

[22] *Vietri NJ, Purcell BK, Tobery SA et al. A short course of antibiotic treatment is effective in preventing death from experimental inhalational anthrax after discontinuing antibiotics. Jour of Infect Diseases. 2009;199:336-41.*

of spores and disease development with low survival outcomes following discontinuation of the antibacterial drug. See section 6.20.2 for a more detailed discussion of study results.

Studies that Evaluated less than Human Equivalent Dose of Antibacterial Drug
Among the four studies that used a less than HED of the antibacterial drug, one study, NIAID 1056, demonstrated a significant difference in survival in cynomolgus macaques favoring obiltoxaximab 8mg/kg & ciprofloxacin 10mg/kg versus ciprofloxacin alone, 62% versus 15%. Study treatments were administered 24 ± 12 hours post-challenge. The 10mg/kg dose of ciprofloxacin is less than half of the HED i.e., ~26mg/kg. Survival rates of > 90% for ciprofloxacin (HED) have been reported in the cynomolgus macaque model of inhalational anthrax.[22]

The survival rates for each of the eight combination studies are summarized in Table 7.8.

Table 7.8. Survival Outcomes for Combination ("Added-Benefit") Studies

Study	Dose of Abx	ETI-204 Dose mg	Treatment Initiation (hours)	Survival % (# survived / # treated)		Difference and 95%CI (ETI-204&Anti – Anti)
				ETI-204 + Abx[4]	Abx	
Rabbits						
AR007 (b) (4)	HED[1]	10 mg IV	9 ± 3	89% (8/9)	33% (4/12) Levo	56% (11, 82)
1030 **Baxter**	HED	8 mg/kg IV	96±1	100% (4/4)	40% (2/5) Levo	60% (-9, 95)
1045 **Baxter**	HED	8 mg/kg IV	PMC[2] + 72±1	82% (9/11)	78% (7/9) Levo	4% (-36, 44)
AR034 (Phase I) **Lonza**	HED	16 mg/kg IV	30	95% (19/20)	100% (20/20) Levo	-5% (-26, 11)
AR028 **Baxter**	< HED	16 mg/kg IV	72±4	68% (23/34)	58% (22/38) Levo	10% (-12, 32)
AP-10-55[3] **Baxter**	< HED	8 mg/kg IV	PA Positive by 30	90% (9/10)	50% (5/10) Doxy	40% (-2, 72)
Monkeys						
1056 **Baxter**	< HED	8 mg/kg IV	PA Positive + 24±12	62% (8/13)	15% (2/13) Cipro	46% (4, 77)
2469 **Baxter**	< HED	8 mg/kg IV	PA Positive + 24±12	57% (8/14)	31% (4/13) Cipro	26% (-14, 60)

[1] HED: human equivalent dose of antibacterial drug; Abx: antibacterial drug; Levo: levofloxacin
[2] PMC: post median challenge time
[3] No electronic data provided (USAMRIID).
[4] Doxycycline given at 2 mg/kg bid, treatment was initiated at 30 hours after elevated PA.

Source: Adapted from biostatistics review by Ling Lan, Ph.D.

The majority of the combination studies had numerical improvements in survival rates for cynomolgus macaques and rabbits treated with the combination of obiltoxaximab plus an antibacterial drug over the antibacterial drug alone for the treatment of inhalational anthrax. One study demonstrated a statistically significant improvement in survival with the combination of the anti-PA monoclonal antibody and a HED of levofloxacin which was initiated at 9±3 hours post-exposure to *B. anthracis* spores. There were no statistically significant survival results in studies in which initiation of treatment with the monoclonal antibody ± antibacterial drug was delayed longer than 24±12 hours.

Reviewer Comment: The efficacy results in the eight combination studies provided 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. In the studies that used a HED of the antibacterial drug, one study demonstrated a statistically significant survival benefit for the monoclonal antibody with the antibacterial drug and the other studies showed numerical improvements in survival outcomes for the combination. The studies were not powered to show differences between the two arms. The limited data from these combination studies suggest that the combination of obiltoxaximab IV plus an IV antibacterial drug would be beneficial in human anthrax. Obiltoxaximab neutralizes protective antigen, a critical component of B. anthracis toxins. It is biologically plausible that, based on the different mechanisms of actions of the monoclonal antibody and the antibacterial drug and the long half-life of the monoclonal antibody, the combination would be beneficial for treatment of anthrax. In the 2001 anthrax attack in the US, the mortality rate was 45% in humans with inhalational anthrax despite treatment with multiple antibacterial drugs and intensive supportive care. It is therefore necessary to have adjunctive effective therapies to improve survival outcomes in humans. The limited data from the combination studies does not negatively impact the approval of obiltoxaximab because there are also 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 active against B. anthracis.

PROPHYLAXIS STUDIES

Post-exposure Prophylaxis (PEP) Studies

Three studies in macaques (AP107, AP301, and AP307) were conducted to evaluate the use of obiltoxaximab in the post-exposure prophylaxis setting. Six studies in NZW rabbits (AR004, AR007, AR012, AR035, AR037, and AR0315) were conducted to evaluate the efficacy of obiltoxaximab for PEP in rabbits. All the post-exposure prophylaxis studies, except for study AP301, were essentially open-label studies. Obiltoxaximab was administered at 18 to 72 hours

post challenge with *B. anthracis* spores. In re-challenge study, AR034 Phase I, obiltoxaximab was administered at 30 hours post challenge.

Reviewer Comment: Survival outcomes in the rabbit PEP studies are challenging to interpret because disease progression in rabbits is rapid and the time window within which the therapeutic intervention can be effective is often too narrow to allow for an evaluation of the efficacy of obiltoxaximab administered intramuscularly. Peak obiltoxaximab exposure may occur after the animal has progressed to advanced systemic anthrax and a point of no return in its disease. In human PK/safety studies, the IM doses achieved approximately 70% of the exposure achieved by the IV doses of obiltoxaximab. Please refer to the clinical pharmacology review by Grace Yan, Ph.D., for a comprehensive assessment of the human pharmacokinetics of obiltoxaximab.

Pre-exposure Prophylaxis Studies in Nonhuman Primates

Survival data from three pre-exposure prophylaxis (PEP) studies in cynomolgus macaques treated with obiltoxaximab IM or IV administration at 18, 24, or 36 hours post-challenge are summarized in Table 7.9. In study AP107, there were no statistically significant differences in survival outcomes between any obiltoxaximab treatment group and the placebo group. However, a dose-response relationship trend was observed in the obiltoxaximab IV groups but not in the obiltoxaximab IM groups.

In macaques, the 16 mg/kg dose IM administered at 18 hours post challenge improved survival significantly in one study (AP301) and at 24 hours post challenge survival outcomes improved significantly in two studies (AP301 and AP307). Studies AP301 and AP307 used obiltoxaximab manufactured at Lonza. The survival benefits with obiltoxaximab 8mg/kg and 16mg/kg were time-dependent with higher survival observed with earlier treatment after exposure *to B. anthracis* spores. Obiltoxaximab administered at or after 36 hours post-challenge did not show a significant improvement in survival.

In macaques, obiltoxaximab 8 mg/kg administered IM at 18 hours demonstrated a significant improvement in survival rate over placebo in Study AP301 which supports the survival outcomes observed with the obiltoxaximab 16mg/kg dose in the study. In study AP107, an 8 mg/kg IV dose administered 24 hours post challenge was not statistically significant (after adjustment for multiple comparisons) for a survival outcome but the proportion of survivors in this group was numerically high at 75%, 0.583 [0.018, 0.902], Table **7.9**.

Numerically higher survival rates and longer survival times were seen with the 16 mg/kg IM dose compared to placebo when administered at > 24 hours following spore exposure (AP301), however, these differences were not statistically significant. At these later time points, PA toxemia and bacteremia were established in most animals before study drug administration and this observation is consistent with results for PA toxemia and bacteremia in animals in the

treatment studies.

In summary, obiltoxaximab 16mg/kg IV (proposed human dose) prevented the development of inhalational anthrax when administered as a monotherapy post-exposure intervention to macaques exposed to an inoculum of 200 LD_{50} *B. anthracis* spores. In macaques, the 16 mg/kg dose administered IM at 18 hours post challenge (study AP301) and at 24 hours post challenge (studies AP301 and AP307) significantly improved survival outcomes compared to placebo. The survival benefits with obiltoxaximab were time-dependent with higher survival observed with earlier treatment after inhalational exposure *to B. anthracis* spores. A 16 mg/kg IV dose administered 24 hours post challenge was not studied, however, a 16 mg/kg IM administration was effective and a 16mg/kg IV dose is expected to be effective for prophylaxis because systemic levels of drug are higher and achieved faster following IV administration. Treatment with obiltoxaximab started at or after 36 hours did not show a significant improvement in survival outcomes. Latent development of PA toxemia, bacteremia, or delayed occurrence of inhalational anthrax in macaques did not occur following treatment with obiltoxaximab through the end of the studies.

Table 7.9. Survival Rates in Post-Exposure Prophylaxis Studies in Cynomolgus Macaques that received Treatment

Study	**Route**	**Hours post challenge**	**ETI-204 mg/kg**	**n/N(%) Survival**	**Difference [95% CI] [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 [-0.295, 0.641] [-0.391, 0.765]	0.210 (0.0063)
	IV	24	8	6/8 (75.0)	0.583 [0.018, 0.902] [-0.130, 0.941]	0.020 (0.0063)
	IM	24	4	6/8 (75.0)	0.583 [0.018, 0.902] [-0.130	0.020 (0.0063)
	IM	24	8	5/9 (55.6)	0.389 [-0.158, 0.777] [-0.292,	0.087 (0.0063)
AP301 Lonza Day 28 or Day 56 survival[a]		18	0	0/6 (0)		
	IM	18	8	6/6 (100)	1 [0.471, 1] [0.438, 1]	0.0012 (0.0042)

	IM	18	16	6/6 (100)	1 [0.471, 1] [0.438, 1]	0.0012 (0.0042)
	IM	24	8	5/6 (83)	0.83 [0.230, 0.996] [0.196, 0.998]	0.0042 (0.0042)
	IM	24	16	5/6 (83)	0.83 [0.230, 0.996] [0.196, 0.998]	0.0042 (0.0042)
	IM	36	8	0/6 (0)		1.0000 (0.0042)
	IM	36	16	3/6 (50)	0.5 [-0.037, 0.882] [-0.069, 0.893]	0.0345 (0.0042)
AP307	IM	24	0	1/10 (10)		
Lonza Day 28 survival	IM	24	16	13/14 (93)	0.83 [0.431, 0.976] [0.347, 0.987]	0.001

[a]Survival assessed after *B. anthracis* spore challenge (28 days) except for the 16 mg/kg IM dose in AP301 which was assessed at 56 days post- challenge.
Adapted from Table 9 from Clinical Overview, BLA125509, SDN1.
Source: Biostatistics review, Xianbin Li, Ph.D.

Post-Exposure Prophylaxis Studies in NZW rabbits
Six of the seven rabbit studies demonstrated a survival benefit over placebo in one or more dose groups.
Three studies tested the Lonza product (AR034 Phase I, AR035 and AR037), Table 7.10. In the re-challenge study, AR034 Phase I, a 16 mg/kg IV administered 30 hours post challenge demonstrated a statistically significantly improvement in survival (65%) compared to the placebo group (0%) at Day 28.
In study AR035, the dose of 16 mg/kg IM administered 18 or 24 hours post-challenge with *B. anthracis* demonstrated a significant beneficial effect on survival outcomes. However, the 16mg/kg or 32mg/kg IM doses in study AR037 failed to replicate a significant effect on survival.

A single-dose of 10 mg IV per animal (approximately 3 mg/kg) in two studies (AR004 and AR007) demonstrated a statistically significant improvement in survival with IV administration at 9 or 24 hours post-challenge in rabbits. A previous formulation of the monoclonal antibody made by (b) (4) was tested in Study AR007 and is not further discussed.

In study AR012, the FDA biostatistics reviewer, Dr. Xianbin Li, concluded that only the 20 mg IV per animal had a significantly higher survival rate than the placebo group (using a one-sided significance level of 0.025/7=0.0036). A dose of 20mg IV per animal (approximately 7mg/kg) was effective if administered by 24 hours post-challenge, however, a delay of treatment

beyond 24 hours did not show an improvement in the survival outcome over placebo. The 40mg IM dose is approximately 13mg/kg but it did not show a significant improvement in survival. Three studies (AR035, AR315 and AR034) showed a survival benefit in rabbits when ETI-204 16 mg/kg was administered IM at 18 or 24 hours post challenge. ETI-204 administered as a 10 mg IV (approximately 4 mg/kg) at 9 or 24 hours post challenge, or at 20mg IV (approximately 8 mg/kg) per animal at 24 hours post-challenge.

Reviewer Comment: These results provide limited evidence for the efficacy of obiltoxaximab as a post-exposure prophylactic treatment. There are a number of issues that make the interpretation of results from the rabbit studies difficult. Anthrax infection progresses rapidly in rabbits and they succumb quickly once they become bacteremic. Therefore, administration of an ETI 204 by the IM route beyond 24 hours post challenge may be too late to achieve effective ETI-204 exposure in time to prevent death. Two rabbit studies, AR012 and AR037, were dose-ranging studies and there were multiple comparisons, thereby limiting their statistical power.

Table 7.10. Survival Rates in Post-Exposure Prophylaxis Studies in NZW Rabbits

Study	Route	Hours post challenge	ETI-204 mg	n/N (%) Survival	95% CI Adjusted 95% CI	Unadjusted one-sided p-value
AR004 Elusys Day 28	IV	48	0	0/9 (0)		
		24	10	8/10 (80.0)	0.80 [0.402, 0.975] [0.303, 0.986]	0.0001 (0.0083)
		36	10	5/10 (50.0)	0.50 [0.084, 0.813] [-0.017, 0.856]	0.010 (0.0083)
		48	10	3/7 (42.9)	0.429 [0.012, 0.816] [-0.084, 0.865]	0.0226 (0.0083)
AR007 (b) (4) Day 34	IV	9	0	0/9 (0)		
	IV		10	9/9 (100)	1 [0.629, 1]	<0.0001 (0.0125)
	IM		20	9/9 (100)	1 [0.629, 1]	<0.0001 (0.0125)
AR012 Elusys Day 14	IM	24	0	0/9 (0)		
	IV		2.5	1/9 (11.1)	0.111 [-0.224, 0.483] [-0.436, 0.610]	0.4073
			10	6/12 (50)	0.50 [0.094, 0.789] [-0.057, 0.859]	0.0074

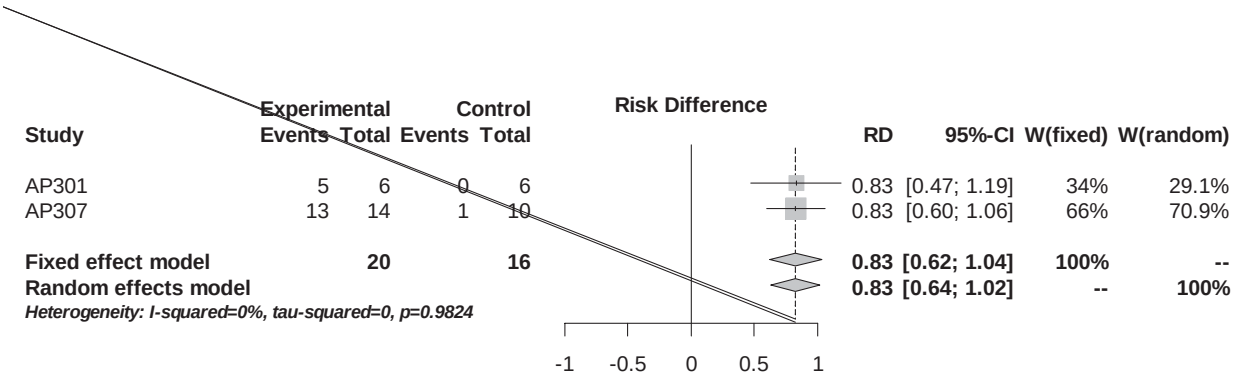
			20	7/12 (58.3)	0.583 [0.187, 0.848] [-0.018, 0.904]	0.0026 (0.0036)
	IM		5	1/9 (11.1)	0.111 [-0.224, 0.483] [-0.436, 0.610]	0.4073
			10	3/9 (33.3)	0.333 [-0.071, 0.701] [-0.238, 0.794]	0.049
			20	5/12 (41.7)	0.417 [0.034, 0.725] [-0.134, 0.806]	0.0186
			40	4/12 (33.3)	0.333 [-0.066, 0.655] [-0.217, 0.749]	0.051
AR0315 Baxter Day 28	IM	24	0	0/10 (0)		
		18	4 mg/kg	11/12 (91.7)	0.917 [0.535, 0.998] [0.425, 1]	<0.0001 (0.0063)
		24	4 mg/kg	5/12 (41.7)	0.417 [0.065, 0.723] [-0.058, 0.786]	0.0131 (0.0063)
		18	16 mg/kg	11/12 (91.7)	0.917 [0.535, 0.998] [0.425, 1]	<0.0001 (0.0063)
		24	16 mg/kg	8/12 (66.7)	0.667 [0.290, 0.901] [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 [0.156, 0.846] [0.300, 0.969]	0.0008 (0.0125)
AR035 Lonza Day 28	IM	18	0	0/10 (0)		
		18	16 mg/kg	6/10 (60)	0.60 [0.213, 0.878] [0.119, 0.912]	0.0018
		24	16 mg/kg	6/10 (60)	0.60 [0.213, 0.878] [0.119, 0.912]	0.0018
		36	16 mg/kg	0/8 (0)	0 -0.309, 0.369 -0.387, 0.480	0.5
AR037 Lonza	IM	24	0	0/10		
			8 mg/kg	5/16 (31.3)	0.313	0.33

Day 28					[-0.019, 0.587]	
			16 mg/kg	5/16 (31.3)	0.313 [-0.019, 0.587]	0.33
			32 mg/kg	5/16 (31.3)	0.303 [-0.019, 0.587]	0.33

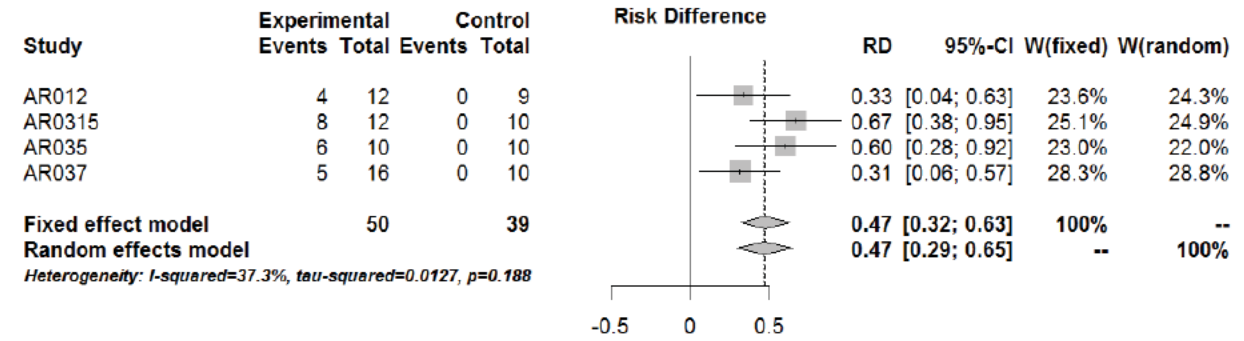
Source: Biostatistics review by Xianbin Li, Ph.D.

Meta-analysis of the post-exposure prophylaxis (PEP) studies that contained 16 mg /kg dose

Two studies (AP301 and AP307) conducted in cynomolgus macaques evaluated the efficacy of 16 mg/kg administered intramuscularly at 24 hours post challenge. Both of the studies demonstrated a statistically significant treatment effect in the prevention of death. The biostatistics reviewer, Dr. Xianbin Li, evaluated a fixed effect model and random effects model which yielded almost identical results for the risk difference. Results of the meta-analysis are summarized in the following graphic.



There were four post-exposure prophylaxis studies in NZW rabbits which included a 16 mg/kg group IM 24 hours post challenge. In the analysis of each individual study, two studies (AR0315 and AR035) showed a significant treatment effect for survival, and the remaining two studies (AR012 and AR037) did not (using an exact confidence interval with Bonferroni's adjustment). In the following graph, the results of the meta-analysis indicate that the overall treatment effect was statistically significant.



Source: Biostatistics review by Xianbin Li, Ph.D.

Reviewer Comment: (b) (4)

Please refer to the clinical pharmaceutical review by Grace Yan, Ph.D., for a comprehensive assessment of the pharmacokinetics of obiltoxaximab/ETI-204.

Pre-Exposure Prophylaxis Studies

The efficacy of ETI-204 as a monotherapy for the pre-exposure prophylaxis for inhalational anthrax was evaluated in one study in cynomolgus macaques (AP305) and two studies in NZW rabbits (AP305, AR001, and AR003) to define the dose, time, and window of protection. Study AP305 was the only blinded study. The target challenge dose was 100 LD_{50} spores in AP305 and AR001 and 200 LD_{50} spores in AR003. PA toxemia was not assessed in the pre-exposure prophylaxis studies.

In Study AP305, obiltoxaximab 16 mg/kg administered IM to monkeys at 1, 2, or 3 days prior to challenge with *B. anthracis* significantly increased survival rates compared to placebo,

Table 7.11. All animals survived and the protective effect was sustained until the end of the study at Day 56.

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Table 7.11. Study AP305: Survival at Day 56 in Pre-exposure Prophylaxis in Nonhuman Primates

ETI-204 Lonza mg/kg IM	**Days before challenge**	**n/N (%) Survival**	**Difference [95% CI]**	**Unadjusted P-value (sig. level)**
0		1/10 (10)		
16	3	15/15(100)	0.9 [0.554, 0.998]	<0.0001 (0.0083)
	2	14/14(100)	0.9 [0.554, 0.998]	<0.0001 (0.0083)
	1	14/14(100)	0.9 [0.554, 0.998]	<0.0001 (0.0083)

The analysis was performed used a Closed Comparison procedure as described in the statistical analysis plan, therefore, no additional adjustment for multiple comparisons is needed.
Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.

The results from the two rabbit studies are summarized in Table 7.12. The targeted challenge dose of *B. anthracis* 100 LD_{50} than standard challenge dose of 200 LD_{50} used in the treatment and post exposure prophylaxis studies; however, all placebo animals succumbed to anthrax infection by Day 5.
These two rabbit studies showed that the doses ≥ 2.5mg/animal in rabbits administered intravenously and a dose of 20 mg IM /animal administered about 30 to 45 minutes prior to challenge provided significant protection against anthrax.
In summary, a 16 mg/kg ETI-204 IM administered at 24 to 72 hours prior to challenge in monkeys or 2.5, 5 mg IM, 10 mg IV, or 20 mg IM about 30 minutes prior to challenge in rabbits provided statistically significant protection against inhalational anthrax.

Table 7.12. Survival at Day 28 in Pre-Exposure Prophylaxis Studies in NZW Rabbits

ETI-204 mg	Route	n/N(%) Survival	Difference 95% CI Adjusted 95% CI	Unadjusted P-value (sig. level)
AR001 Elusys, 30-45 minutes prior to a targeted 100 LD_{50} exposure				
0	IV	0/5 (0)		
10		9/9 (100)	1 [0.474, 1]	0.0001 (0.05)
AR003 Elusys, within 35 minutes prior to a targeted 200 LD_{50} exposure				
0	IV	0/8 (0)		
1.25		1/8 (12.5)	0.125 [-0.292, 0.527] [-0.427, 0.632]	0.402 (0.005)
2.5		5/8 (62.5)	0.625 [0.173, 0.915] [0.019, 0.953]	0.004 (0.005)
5		5/8 (62.5)	0.625 [0.173, 0.915] [0.019, 0.953]	0.004 (0.005)
10		7/8 (87.5)	0.875 [0.395, 0.997] [0.237, 0.999]	0.0003 (0.005)
20	IM	8/8 (100)	1 [0.588, 1] [0.436, 1]	<0.0001 (0.005)

Source: Review by biostatistics reviewer, Xianbin Li, Ph.D.

Obiltoxaximab prevented the development of anthrax when administered as pre-exposure prophylaxis to monkeys and rabbits that were subsequently exposed to a lethal inoculum of *B. anthracis* spores. There was no delayed occurrence of inhalational anthrax in the animals that were initially successfully treated. In cynomolgus monkeys, a 16 mg/kg IM dose administered 24-72 hours before exposure B. anthracis significantly increased survival rate and survival time and prevented the development of bacteremia through 56 days after spore challenge. In NZW rabbits, 4 mg/kg IV and 8 mg/kg IM administered within 30-45 minutes before exposure to *B. anthracis* spore significantly increased survival rates and survival times compared to placebo and prevented the development of bacteremia through 28 days after spore challenge.

Reviewer Comment: (b) (4)

(b) (4)

Use of Obiltoxaximab for Prophylaxis against Anthrax in Humans
Concerns with regard to the use of obiltoxaximab for prophylaxis against anthrax in humans are discussed in the following comment.

Reviewer Comment: In the phase 1, human pharmacokinetic/safety studies of obiltoxaximab, hypersensitivity reactions during IV infusion were reported at a rate of 3.1%. Hypersensitivity reactions included seven (2.2%) cases of anaphylactic reactions that were treated by stopping the infusion of ETI-204 and use of diphenhydramine +/- steroids, (see safety review, section 8.0, by Dr. Ramya Gopinath, MD). It should be noted that the cases of hypersensitivity occurred in patients with and without premedication with diphenhydramine. A 3.1% rate of hypersensitivity reactions which included cases of anaphylaxis brings into question whether intravenous obiltoxaximab could be safely used for prophylaxis (pre- and post-exposure) against anthrax. The use of intravenous obiltoxaximab is less than ideal for prophylaxis because of the risk of hypersensitivity reactions and an infusion time of 90 minutes. Obiltoxaximab could be used in circumstances where IV administration and monitoring for potential adverse reactions by trained personnel is possible such as in hospitals, field hospitals, and some medical clinics. The risk/ benefit assessment of obiltoxaximab use for pre- and post-exposure will depend on the availability of other prophylactic antibacterial drugs and the FDA-approved monoclonal antibody, raxibacumab, which had a lower rate of hypersensitivity reactions in its phase 1, PK/safety studies . The raxibacumab USPI states that, (b) (4) *four subjects (1.2%) had their infusion of raxibacumab discontinued for adverse reactions: 2 subjects (neither of whom received diphenhydramine premedication) due to urticaria (mild), and one subject each discontinued for clonus (mild) and dyspnea (moderate). In the event of intentional exposure to inhalational B. anthracis, the use of the obiltoxaximab IV for prophylaxis could be justified in the setting of release of a multi-drug resistant B. anthracis or in individuals with contraindications to the use of the available effective antibacterial drugs for anthrax. Because obiltoxaximab appears to have a higher rate of hypersensitivity than the FDA-approved monoclonal antibody, raxibacumab, it would be prudent to use obiltoxaximab IV as a third- line agent for prophylaxis after antibacterial drugs and raxibacumab. Hypersensitivity reactions and the limitations of obiltoxaximab for prophylaxis should be addressed in labeling of the product.*

Summary of Nonclinical Efficacy
The following is a summary of the survival outcomes in studies of obiltoxaximab in cynomolgus macaque and NZW rabbit models of inhalational anthrax. This BLA contains studies of treatment, post-exposure prophylaxis, pre-exposure prophylaxis, and re-challenge.

Table 7.13. Survival Results in Nonclinical Studies

Animal and administration time	Difference in survival proportion compared with controls	Obiltoxaximab Doses	Study #
Cynomolgus monkeys			
3, 2, 1 days pre-exposure	90%	16 mg/kg IM	AP305
18 hours post-challenge	100%	16 mg/kg IM	AP301
24 hours post-challenge	58-83%	8 mg/kg IV or 16 mg/kg IM	AP107, AP301, AP307
39–44 hours post-challenge	31-44%	16 mg/kg IV	AP202, AP204
New Zealand White rabbits			
30-45 minutes pre-challenge	88-100%	4 mg/kg IV or 8 mg/kg IM	AR001, AR003
9 hours post-challenge	100%	4 mg/kg IV or 8 mg/kg IM	AR007
18 hours post-challenge	60-92%	16 mg/kg IM	AR035, AR0315
24 hours post-challenge	31-67%	8 mg/kg IV or 16 mg/kg IM	AR035, AR012, AR037, AR0315
28-30 hours post-challenge	64-84%	16 mg/kg IV	AR021, AR033, AR034

Source: Adapted from biostatistics review by Xianbin Li, Ph.D.

Key Efficacy Findings for Obiltoxaximab 16mg/kg

- In the monotherapy efficacy studies, a single dose of obiltoxaximab 16 mg/kg IV showed a significant survival benefit over placebo in both the cynomolgus macaque and rabbit models of inhalational anthrax. The majority of the animals were bacteremic prior to treatment with obiltoxaximab indicating severe anthrax disease.
- The failed monotherapy efficacy study, AP203, may be explained by the high bacteremia levels and high PA-ELISA levels prior to treatment observed in animals in this study.

- The efficacy was supported by prophylaxis studies using this product. The majority of the prophylaxis studies evaluated IM obiltoxaximab. In post-exposure prophylaxis studies, doses given early post- challenge resulted in higher survival rates than at later time points post-challenge. A 16 mg/kg IM dose, was administered to macaques and NZW rabbits within 24 hours of exposure to *B. anthracis* spores, was effective in preventing anthrax. Intramuscular doses of obiltoxaximab achieved lower exposures than the IV doses therefore the IV obiltoxaximab would also be effective. [See reviewer

comments above and in Section 8 regarding the safety of the obiltoxaximab for the prophylaxis indication].

- In pre-exposure studies, a 16 mg/kg IM dose was effective when treatment was given 30 minutes and up to 3 days prior to challenge. The IV dose should also be effective.
- In a re-challenge study, 100% of the animals who were previously treated with obiltoxaximab 16 mg/kg IV survived a second challenge with aerosolized B. anthracis spores and 89% of the animals who were previously treated with obiltoxaximab 16 mg/kg IV and levofloxacin survived a second challenge.

In summary, obiltoxaximab 16 mg/kg IV, which is the proposed human dose, was effective in the treatment, post-exposure prophylaxis, and pre-exposure prophylaxis of inhalational anthrax in the cynomolgus macaque and rabbit models of inhalational anthrax. See the Risk/Benefit Assessment, section 1.3.

8 Review of Safety

8.1 Safety Review Approach

The primary objectives of the intravenous (IV) development program of obiltoxaximab (code name: ETI-204) were to evaluate the safety and tolerability of a single IV dose of obiltoxaximab, both alone and in the presence of ciprofloxacin, and to evaluate the safety and tolerability of repeat administration (i.e., two doses) of IV obiltoxaximab, in humans. Secondary objectives were to evaluate the pharmacokinetics (PK) and immunogenicity of obiltoxaximab.
The IV development program included:

- A pivotal safety study, AH104, with single-dose 16 mg/kg IV obiltoxaximab vs. placebo
- A repeat-dose safety study, AH109, with 16 mg/kg IV obiltoxaximab given twice either 14 days or ≥120 days apart
- A drug-drug interaction study, AH110, with single-dose 16 mg/kg IV obiltoxaximab with or without IV ciprofloxacin followed by oral ciprofloxacin
- A dose-escalation study, AH101, with fixed single doses of obiltoxaximab vs. placebo, and obiltoxaximab plus ciprofloxacin vs. placebo plus ciprofloxacin
- A dose-escalation study, AH102, with higher fixed doses of obiltoxaximab vs. placebo

- A dose-escalation study, AH105, of single-dose 4, 8, and 16 mg/kg obiltoxaximab vs. placebo

In addition, there was a single dose, dose-escalation study, AH106, of obiltoxaximab vs. placebo, given intramuscularly (IM). As this product was developed under the Animal Rule, there were no clinical trials involving human patients with anthrax infections. All human studies enrolled healthy humans to study the safety, tolerability and pharmacokinetics of obiltoxaximab, alone and in combination with ciprofloxacin.

Details of these studies are provided in Table 8.1.

Table 8.1 Clinical Studies of Obiltoxaximab

Study Identifier	Study Title	Design	Phase	Test Product(s)* Dosage Regime Administration route	Number (gender) of subjects per group	Duration of study (days)
AH101	Dose-escalation study of a single IV dose of obiltoxaximab and ciprofloxacin	R, DB, PC	1	**Part 1**: obiltoxaximab or placebo single dose 0, 19, 57, or 114 mg IV **Part 2**: obiltoxaximab 114 mg IV + cipro PO bid x 14d or placebo + cipro PO bid x 14d	**Part 1**: 15M, 9F 6 obiltoxaximab per dose 6 placebo **Part 2**: 8M, 4F 6 obiltoxaximab + cipro 6 placebo + cipro	42
AH102	Dose-escalation study of a single IV dose of obiltoxaximab	R, DB, PC	1	obiltoxaximab or placebo single dose (0, 120, 240 or 360 mg) IV	33M, 12F 12 obiltoxaximab per dose 9 placebo	42
AH105	Sequential group dose-escalation study of a single IV dose of obiltoxaximab	R, DB, PC	1	obiltoxaximab or placebo single dose 0, 4, 8, 16 mg/kg IV	78M, 30F 30 obiltoxaximab per dose 18 placebo	71
AH104	Study of a single 16 mg/kg IV dose of obiltoxaximab	R, DB, PC	1	obiltoxaximab or placebo 0 or 16 mg/kg IV	144M, 136F 210 obiltoxaximab 70 placebo	71
AH109	Study of repeat administration of 16 mg/kg obiltoxaximab IV	R, DB, PC		Sequence A: 16 mg/kg IV obiltoxaximab on days 1 and 14, placebo on day 120 or Sequence B: 16 mg/kg IV obiltoxaximab on days 1 and 120, placebo on day 14	44M, 26F A: 35 B: 35	191
AH110	Study of 16 mg/kg IV obiltoxaximab alone or with Cipro	Open-label, R, parallel group		obiltoxaximab 16mg/kg IV or obiltoxaximab 16 mg/kg IV +single dose Cipro on day 1, then PO Cipro q12h days 2-9	24M, 16F 20 obiltoxaximab 20 obiltoxaximab + cipro	71
AH106	Dose-escalation study of IM obiltoxaximab	R, DB, PC		(b) (4)		

					9 placebo	

*AH101, AH102, and AH105 used the investigational (Baxter) preparation of obiltoxaximab, while studies AH104, AH109, AH110 and (b) (4) used the commercial (Lonza) preparation
Cipro: Ciprofloxacin; R: randomized; DB: double-blind; PC: placebo-controlled; M: male; F: female
Adapted from Table 1, p. 14, Summary of Clinical Safety

There were no unexpected safety issues identified during drug development, either in the pre-clinical or early clinical studies (AH101, AH102). The first part of study AH101 was a fixed dose, dose-escalation study in healthy humans, and the second part was a drug-drug interaction study of obiltoxaximab with ciprofloxacin. Study AH102 was also a single-dose dose-escalation study with higher fixed doses of obiltoxaximab. Both of these used the Baxter preparation, and the doses of obiltoxaximab used ranged from 0.3 mg/kg (for a 60 kg person) to 6 mg/kg. Study AH105 was also reviewed because there were 30 subjects who received 16 mg/kg of obiltoxaximab (Baxter product) compared with placebo, which added to the single-dose pool. Study AH106 was reviewed as the single dose-escalation study utilizing the intramuscular route of administration of obiltoxaximab (b) (4)

Reviewer Comment: Because the recommended human equivalent of the fully effective dose of obiltoxaximab in animals was 16 mg/kg, (b) (4) this reviewer focused the review on studies AH104 (single-dose), AH109 (repeat-dose) and AH110 (drug-drug interaction study), as these were the studies which used the recommended IV dose of obiltoxaximab and the Lonza formulation which is intended for commercial application.

Because obiltoxaximab is a monoclonal antibody, the common side effects of mAbs such as hypersensitivity, were particularly sought in the review of data. The clinical reviewer used JMP®, JMP Clinical®, MAED, and Empirica® for independent data analysis.

Reviewer Comment: Since this product was developed under the Animal Rule, all the efficacy studies are in New Zealand white (NZW) rabbits and cynomolgus macaques as described in sections 5, 6 and 7. The main human safety studies, AH104, AH109 and AH110 will therefore be described in this section prior to the analysis of the safety database.

8.1.1 AH104 Study Protocol

Since this was the main human safety study, the study design is fully described.

8.1.1.1 Study Objectives

Primary: to evaluate the safety and tolerability a single IV dose of obiltoxaximab in adult subjects. Secondary: to evaluate the a) PK and b) immunogenicity of a single 16 mg/kg dose of obiltoxaximab in adult subjects.

8.1.1.2 Ethics and Administrative Structure

The study protocol, Informed Consent Form (ICF), and relevant supporting information were submitted to the Institutional Review Board (IRB) by the investigators for review and approval before the study was initiated. Subsequent protocol amendments were submitted for review and approval to the IRB for the sites that were still enrolling subjects at the time of the amendment. The study was conducted in accordance with the applicable FDA guidelines and IRB requirements, and monitored in accordance with the procedures of the Applicant and the Covance Clinical Research Unit (CCRU); these comply with Good Clinical Practice (GCP) in accordance with the Declaration of Helsinki. All subjects were required to provide written informed consent before any screening tests were conducted.

The study was conducted at 4 Covance Clinical Research Units – in Daytona Beach FL, Dallas TX, Evansville IN, and Madison WI. Study monitoring was performed by CCRU with Applicant oversight. Data were recorded using electronic case report forms (eCRFs). Data were entered into a database created and administered by Covance Clinical Data Analysis and Reporting Organization (CDARO).

Clinical Trial Steering Committee (CTSC): Safety data from this study and other ETI-204 clinical trials were monitored by an external Clinical Trial Steering Committee (CTSC). After the first 12 subjects were dosed in this study, a blinded review of all available safety data, up to and including Day 2, was to be completed by the CTSC and investigators before any additional subjects were dosed. However, this review did not occur before each study site had dosed an additional 12 subjects. When the missed review was discussed with the Applicant, relevant investigators, and the CTSC on 23 July 2013, all agreed that this lapse was a protocol deviation, but none considered it to have had any impact on subject safety because relevant safety data for each of the first 12 subjects who were dosed were disseminated by e-mail in near real-time during the dosing period and were discussed during weekly phone calls, instead of a single phone call in which a data summary from the first 12 subjects dosed was discussed. The Applicant and IRB were notified of this lapse and the IRB did not consider this to be a reportable event. Review of a summary of the first 12 subjects' data occurred after additional subjects at each investigational site were dosed (12 subjects at each of 3 sites and 14 subjects at the fourth site); however, the CTSC concluded that it was safe to proceed with subsequent subjects.

Reviewer comment: The protocol deviation is noted; further, the Applicant does not specify whether the first 12 subjects had any AEs though they note that safety data from each of them were discussed. Overall, there is no evidence that this protocol deviation had an impact on the overall conduct of the study.

In addition, occurrence of any of the following events across the ongoing clinical program was to trigger a review of safety data by the CTSC and a pause in subject enrollment in all ongoing clinical studies:

• Two of the following events: symptomatic hypotension, respiratory distress (defined as either bronchospasm or central cyanosis), anaphylactic reaction, or any intravenous (IV) infusion-related serious adverse event (SAE)
• Two generalized urticarial reactions of severe intensity related to study drug infusion
• The first five generalized urticarial reactions of mild to moderate intensity related to the infusion of study drug and without diphenhydramine premedication
• Generalized mild to moderate urticarial reactions related to the infusion of study drug in ≥ 5% of subjects with diphenhydramine pretreatment (instituted after the occurrence of the first five mild to moderate urticarial reactions in the absence of diphenhydramine premedication)
• Any other safety event which either the investigators or Applicant considered a reason to pause the clinical study or clinical program until review by the CTSC. In the event of a pause in study enrollment, the clinical studies were not to be restarted until the CTSC agreed to a course of action and the IRBs were notified.

A total of five generalized urticarial reactions occurred in AH104 and the other ongoing obiltoxaximab clinical studies as of July 30 2013; as a result, all ongoing studies were paused. The CTSC agreed that all subsequent subjects should be premedicated with 50 mg diphenhydramine orally approximately 30 minutes before study drug infusion. By this time, 86 subjects had been enrolled in AH104 and had received study medication without diphenhydramine premedication.

Reviewer comment: No generalized urticarial reactions or more severe hypersensitivity occurred in the earlier studies – AH101 and AH102 - with administration of a lower mg/kg dose of IV obiltoxaximab. In AH105, only 30 subjects received 16 mg/kg obiltoxaximab. Of this group, one subject experienced hypersensitivity severe enough to stop the infusion; though initially thought to have no exposure, this subject was ultimately found to have been immunized with anthrax vaccine (AVA) in the past. Thus, the administration of diphenhydramine did not appear necessary until the fully effective dose of 16 mg/kg IV obiltoxaximab was consistently used in a larger population in studies AH104, AH109 and AH110. This suggests a dose-response relationship for hypersensitivity in relationship to administration of obiltoxaximab: i.e., increasing doses of the product could lead to increased incidence of hypersensitivity. Though biologically plausible, this was not borne out in the only study (AH105) with dose-escalation close enough to the fully effective dose (4, 8 and 16 mg/kg) to be meaningful. However, there were only 30 subjects in each arm so this study may not have been powered to show a dose-response. The possible relevance of this observation to future studies will be discussed in a later section. The effect of diphenhydramine on AEs will be discussed in detail in Section 8.5.1.

8.1.1.3 Study Design and Investigational Plan

Study Design: This was a Phase I, double-blind, randomized, placebo-controlled, multicenter study which took place between July 9, 2013 and November 29, 2013 in 4 sites of CCRU as detailed above.

Randomization: In AH104, 280 adults were randomized in a block design in a 3:1 ratio to receive either: a) a single 16 mg/kg IV dose of obiltoxaximab (210 subjects) or b) matching placebo (70 subjects).

After a screening visit (Day -28 to Day -2), subjects arrived at the CRU on Day -1. On Day 1, qualified subjects were randomized to receive either of the study treatments. Subjects were discharged from the CRU on Day 2 after completion of study assessments and returned to the CRU for 5 additional visits on Days 8 (±2 days), 15, 29 and 43 (±days), and 71 (±4 days). The total duration of each subject's participation in the study was 100 days. The end of the study was defined as the date of the last visit of the last subject in the study.

Reviewer Comment: This study design was appropriate to address the safety and tolerability of obiltoxaximab.

Study Population: The target population was adults ≥18 years of age; they had to participate in the informed consent process and sign and date the ICF before enrollment. Subjects who did not meet the inclusion criteria or who met any of the exclusion criteria at Screening or on Day -1 were not eligible for study participation.

Inclusion Criteria – all the following criteria had to be met for the subject to be enrolled:

1. Was female or male ≥ 18 years of age

2. Had a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test at Screening and Day -1 (all females regardless of childbearing potential)

3. Agreed to practice abstinence or to use a medically accepted method of contraception from the time of Screening through 30 days after the final study visit (females of childbearing potential [i.e., not postmenopausal or surgically sterile])

4. Was a postmenopausal female (amenorrhea for at least 12 months prior to the start of the study), either naturally or following cessation of all exogenous hormonal treatments, with a follicle-stimulating hormone (FSH) level of > 40 mIU/mL at Screening

5. Was a female who was surgically sterilized, including by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, tubal ligation, or tubal Essure® procedure, ≥3 months prior to screening; the latter required radiological confirmation of occlusion of the fallopian tubes

6. Was a male who practiced abstinence or used a condom with spermicide and refrained from sperm donation during the study and for 30 days after the final study visit

7. Provided written informed consent and was willing to comply with study restrictions

Exclusion Criteria

1. A pregnant or lactating woman

2. Had a clinically-significant comorbidity that would interfere with completion of the study procedures or objectives or compromise the subject's safety

3. Had a seated systolic blood pressure ≥ 150 mmHg or ≤ 90 mmHg or diastolic blood pressure ≥ 95 mmHg (Note: blood pressure measurements could be repeated once at the discretion of the investigator)

4. Had used H1 receptor antagonists (ie, antihistamines) within 5 days prior to Day 1

5. Had evidence of drug or alcohol abuse, as determined by the investigator, within 6 months of Day 1

6. Had a positive test result for drugs of abuse (with the exception of medically-prescribed drugs) at Screening or on Day -1

7. Had a positive test result for alcohol at Screening; exclusion was subject to the investigator's discretion. Subjects who tested positive for alcohol on Day -1 were excluded from the study

8. Had been treated with an investigational agent within 30 days of Day 1 or within five half-lives of the investigational agent at Day 1 (whichever was longer)

9. Had a congenital or acquired immunodeficiency syndrome

10. Had a prior solid organ or bone marrow transplant

11. Had a positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening

12. Had a history of prior treatment for anthrax exposure or prior anthrax infection

13. Had prior immunization with any approved or investigational anthrax vaccine or prior treatment with an investigational anthrax treatment (i.e., obiltoxaximab, raxibacumab, or anthrax immune globulin)

14. Was military personnel deployed in 1990 or after, unless the subject provided documentation demonstrating he/she had not previously received any approved or investigational anthrax vaccine

15. Had therapeutic use of systemic steroids, immunosuppressive agents, anticoagulants, or anti-arrhythmics within 1 year prior to Day 1. A single short course (<14 days) of systemic steroid therapy was allowed provided it concluded more than 6 months prior to Day 1

16. Had a donation or loss of > 500 mL of blood within 30 days, or plasma within 7 days of Day 1

17. Had a prior stroke, epilepsy, relapsing or degenerative central nervous system disease or relapsing or degenerative ocular disease.

18. Had a myocardial infarction or acute coronary syndrome in the past 5 years, active angina pectoris, or heart failure (New York Heart Association scale > 1).

19. Had a history of chronic liver disease.

20. Had a calculated creatinine clearance (CrCl) of < 30 mL/min using the Cockcroft-Gault equation

21. Had any clinically significant abnormality, in the investigator's opinion, on electrocardiogram (ECG) or clinical laboratory tests (hematology, clinical chemistry, or urinalysis) at Screening; out of range results may have been repeated to confirm.

22. Had a history of allergic or hypersensitivity reactions to other therapeutic antibodies or immunoglobulins (Ig).

23. Had a history of any malignant neoplasm within the last 5 years, with the exception of adequately treated localized or in situ non-melanoma carcinoma of the skin (i.e., basal cell carcinoma) or the cervix.

24. Was not a suitable candidate for enrollment or may not have complied with the study requirements, in the opinion of the investigator.

Reviewer Comment: All of the human studies are Phase 1 – therefore, their study designs had the same extensive exclusion criteria and only adults who were completely healthy or had stable co-morbidities were enrolled. Additionally, there were no pregnant women or children. Given the paucity of naturally occurring cases of inhalational anthrax and the life-threatening nature of this disease, it would not be possible or ethical to study patients suffering from inhalational anthrax. Thus, while the Applicant's approach fulfilled the purpose of phase 1 trials, and provided a medically uncomplicated population in which to evaluate the safety of obiltoxaximab, the applicability of study findings to pregnant women, children and adults with significant co-morbidities may be limited.

Removal of subjects from therapy or assessment: All subjects had the right to withdraw their consent at any point in the study for any reason. In addition, the investigator could discontinue the subject at any point if medically necessary in the event of: an adverse event, abnormal laboratory value, abnormal results from a study procedure, protocol violation, subject withdrawal of consent, loss to follow-up or administrative problems. Subjects who withdrew prior to completing the study were not replaced.

Study Treatment: Obiltoxaximab was supplied as a sterile, clear to pale yellow solution consisting of 100 mg/ml obiltoxaximab, 40 mM histidine, 200 mM sorbitol, and 0.01% polysorbate 80 with a pH of 5.5. Translucent particles were sometimes present. Matching placebo had the same inactive ingredients as the study drug, and was provided in identical vials. Obiltoxaximab bulk drug substance was manufactured (b) (4) in accordance with GMP at Lonza Biologics, Portsmouth, NH. Final drug product and placebo were manufactured, packaged and labeled in accordance with GMP at (b) (4) . The obiltoxaximab and placebo lots used for this study were 3-FIN-1513 and 3-FIN-1491, respectively.

At the study site, an unblinded pharmacist calculated the correct concentration of obiltoxaximab in 0.9% sodium chloride (NS) to deliver a dose of 16 mg/kg in a volume of 250 mL. Single doses of obiltoxaximab were infused IV over 90 minutes at a rate of approximately 3 mL/min using an infusion set with a 0.2µ in-line filter and an infusion pump. This duration of administration was chosen to allow the investigator to limit exposure through infusion interruption in the event of a hypersensitivity reaction. When the IV bag was empty, the infusion bag and line were flushed with an additional 40 mL of sterile NS to ensure that the entire contents of the infusion bag and IV line were administered. Placebo was administered in an identical fashion. After Protocol Amendment 1 in September, 2013, all subjects were premedicated with 50 mg oral diphenhydramine approximately 30 minutes prior to the start of the infusion of study drug on Day 1.

Selection of Dose: Selection of the 16 mg/kg obiltoxaximab dose was based on data from nonclinical efficacy studies of this product in rabbits and macaques, as detailed in previous sections, and on modeling of animal exposures to human exposures. See the Clinical Pharmacology review by Dr. Zhixia Yan for further details. Obiltoxaximab was to be administered over 90 minutes in order to allow the investigator to limit exposure through infusion interruption in the event of a hypersensitivity reaction.

Reviewer comment: The Clinical Pharmacology team reviewing this product evaluated the dose selection of obiltoxaximab extensively. Although they felt that 16 mg/kg was the human equivalent of the fully effective dose of obiltoxaximab in animals, there was a question of whether a higher mg/kg dose in humans would provide greater exposure and possibly an enhanced clinical effect. The possibility of studying an increased dose should be considered by the Applicant, but needs to be weighed against the possibility of an increased risk of hypersensitivity. This is addressed in more detail in a later section.

Method of Assigning Subjects: Subjects were randomized in a block design in a 3:1 ratio to either obiltoxaximab or matching placebo by an unblinded pharmacist at the study center using a randomization schedule provided by Covance CDARO. Randomization was stratified by study center.

Blinding: The investigator, study center staff, and subjects were blinded to the treatment assignment. The site pharmacist was the only team member at the site level unblinded to treatment assignment; this individual was not involved in study assessments. The expiration date and time were placed on study drug label rather than the preparation date and time to avoid potential unblinding because of the perceived order of obiltoxaximab and placebo preparation. No subjects were unblinded during the study.

Reviewer Comment: Since hypersensitivity may be expected to occur with some frequency after exposure to a monoclonal antibody like obiltoxaximab, the occurrence of any form of hypersensitivity might have led to unintended unblinding. For example, the investigator may infer that any subject with a rash or urticaria received obiltoxaximab rather than placebo.

Prior and Concomitant Therapy: The therapeutic use of systemic steroids, immunosuppressive agents, anticoagulants or anti-arrhythmics within 1 year prior to Day 1 was prohibited. A single short course (<14 days) of systemic steroid was allowed provided it concluded more than 6 months prior to Day 1. No investigational agents were allowed within 30 days or 5 half-lives of study drug on Day 1 (whichever was longer). In addition, no investigational therapies other than obiltoxaximab were allowed during the study.

After protocol amendment 1, subjects were premedicated with 50 mg oral diphenhydramine approximately 30 minutes before the start of study drug infusion. All medications taken or used

within 30 days prior to the start of obiltoxaximab administration were recorded on the appropriate eCRF page. All concomitant medications, including those used for management of an AE, were recorded on the appropriate eCRF page.

Management of Hypersensitivity Reactions: The infusion of study drug was stopped under the following circumstances and reported to the Applicant and the CTSC: symptomatic hypotension, respiratory distress (bronchospasm or central cyanosis), generalized urticaria considered by the investigator to be of severe intensity, anaphylactic reaction, development of any SAE considered by the investigator as related to the study drug, and other event at the discretion of the investigator. The investigator decided whether infusions were to be restarted. Subjects who did not complete infusion of study drug remained in the study and completed all prescribed study visits and procedures unless they withdrew consent.

Management of Anaphylaxis: A complete treatment plan is provided by the Applicant in Appendix A of the Clinical Study Report (CSR) of AH104; the plan is summarized here. Therapy was divided into initial and secondary treatment and the Applicant noted that the therapy must be individualized. The following therapies were suggested:

- Initial therapy: stop the infusion, maintain the airway with 100% oxygen (though subjects may require intubation if severe cardiopulmonary collapse occurs), administer intravascular volume, administer epinephrine for shock.
- Secondary therapy: administer antihistamines, consider catecholamine infusions (epinephrine, dopamine, norepinephrine or dobutamine), consider phosphodiesterase inhibitors such as aminophylline, administer corticosteroids, consider sodium bicarbonate, secure the airway, administer bronchodilators such as albuterol.

Treatment Compliance: Accountability and subject compliance were assessed by maintaining adequate study drug dispensing records. The study site's unblinded pharmacist recorded all information related to study drug preparation. The investigator was responsible for ensuring that study drug was administered in compliance with the protocol.

Reviewer Comment: Compliance was easily assessed and recorded with this product since there was a single infusion administered under direct supervision of the investigator. In the event of discontinuation of the study infusion, fairly precise measurements of the actual volume or amount of study drug administered were available. Further, serum levels of obiltoxaximab were followed over the study period as part of the PK evaluation.

8.1.1.4 Safety, Pharmacokinetic and Pharmacodynamic Assessments

Table 8.2 Study AH104: Schedule of Assessments

Procedures and Assessments	Screen D -28 to -2	D -1	D 1	D 2	D 8 ±2d	D15 ±3d	D 29 ±3d	D 43 ±3 d	D71 ±4 d
Informed Consent	X								
Medical History	X	X							
Prior Medication	X	X							
Inclusion/Exclusion	X	X							
Clinical Hematology Tests[a] and Serum Chemistry[a]	X	X		X	X	X	X	X	X
Dipstick Urinalysis[b]	X	X		X	X	X	X	X	X
Virology Panel (HBsAg,HCV, HIV-Ab)	X								
Urine Drug Screen[c]	X	X							
Calculated Creatinine Clearance[d]	X								X
Free T3, Free T4, TSH, and Anti-thyroid peroxidase		X							X
Physical Examination[e]		X				X		X	X
Height (BMI)[f]	X								
Weight	X	X							X
Percent Body Fat[g]		X							
Vital Signs Measurement[h]	X	X	X	X	X	X	X	X	X
Electrocardiography[i]	X	X	X	X					X
Serum Pregnancy Test	X	X					X		X
Follicle-Stimulating Hormone Level[j]	X								
Randomization			X						
In-Unit Period		X	X	X					
Discharge from In-Unit Study Center				X					
Diphenhydramine Preinfusion[k]			X						

Administer ETI-204 or Matching Placebo			X						
Blood Samples for ETI-204 (PK)[l]			X	X	X	X	X	X	X
Blood Samples for Anti-ETI-204 Antibodies[m]			X		X			X	X
Blood Samples for Cytokines[n]			X		X				
Blood Samples for IgE and Histamine[o]			X						
Concomitant Medication Review		X	X	X	X	X	X	X	X
AE Assessments[p]	X	X	X	X	X	X	X	X	X
Skin Assessments[q]			X	X					
Infusion Site Assessments[r]			X	X					

Source: AH104 CSR, Table 1, p. 23-25
BMI=body mass index; HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV-Ab=human immunodeficiency virus antibody; TSH=thyroid stimulating hormone.
a. Subjects fasted for at least 10 hours prior to blood collection for clinical laboratory evaluations. Clinical hematology assessments included red blood cells, hemoglobin, hematocrit, platelets, prothrombin time, activated partial thromboplastin time, white blood cells with differential, and International Normalized Ratio. Clinical chemistry assessments included sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, glucose, calcium, albumin, cholesterol, phosphorus, lactate dehydrogenase, amylase, total protein, uric acid, and creatine phosphokinase.
b. Dipstick urinalysis assessments included protein, white blood cell esterase, and blood.
c. Urine drug screen included alcohol, amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolites, methadone, opiate metabolites, phencyclidine, and marijuana metabolites.
d. Using Cockcroft-Gault equation.
e. A full physical examination was required on Day -1 (at check-in) and Day 71 (final visit). A brief physical examination (evaluation of general appearance, respiratory, gastrointestinal, neurological, and other systems as determined by the investigator) was required on Days 15 and 43.
f. BMI was calculated only once at Day -1 using the Screening height and Day -1 weight.
g. Estimated percent body fat was measured on Day -1 using calipers at the back of upper arm (triceps), front of upper arm (biceps), back, below the shoulder blade (subscapular), and waist (suprailiac).
h. Vital signs, including temperature, heart rate, respiratory rate, and blood pressure, were taken in a supine position after the subject was supine for at least 5 minutes and were repeated once per investigator's discretion. On Day 1, temperature, heart rate, respiratory rate, and blood pressure were measured predose and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours, and 8 hours after the start of infusion. On Days 1 and 2, deviations of ±5 minutes for time points <1.5 hours post start of infusion and ±10 minutes for time points ≥1.5 hours post start of infusion were allowed.
i. On Day 1, ECGs were recorded in triplicate at predose, end of infusion, 3 and 8 hours after the start of infusion, and on Day 2 (at 24 hours after the start of infusion). ECGs were recorded before collection of blood samples for PK assessments (see footnote 'l' below). Predose ECGs were done within 1 hour prior to dosing; postdose ECGs were done within +/- 15 minutes of the specified time.
j. Required for postmenopausal females only.
k. After protocol amendment 1, subjects were premedicated with 50 mg oral diphenhydramine approximately 30 minutes before the start of study drug infusion.

l. Blood samples (3.5 mL) for analysis of ETI-204 serum concentrations (PK) were obtained on Day 1 predose, at the end of infusion, and 3 and 8 hours after the start of infusion. Additional blood samples were taken on Day 2 (24 hours after the start of infusion), and on Days 8, 15, 29, 43, and 71; blood samples for PK were collected after ECGs and vital signs were recorded. On Days 1 and 2, deviations of up to ±15 minutes from specified postdose time points were allowed.
m. Blood samples (3.5 mL) for screening of serum anti-ETI-204 antibody levels were collected on Day 1 (prior to dosing), and on Days 8, 43, and 71.
n. Blood samples (3.5 mL) for serum cytokine evaluation were obtained from the first 80 subjects only and were collected on Day 1 at predose, at the end of infusion, and on Day 8 (+/- 2 days).
o. Blood samples for analysis of serum IgE (3.5 mL) and analysis of plasma histamine levels (3 mL) were obtained on Day 1 at predose from all subjects and postdose from only those subjects who experienced a hypersensitivity reaction. Postdose samples were collected as close to the time of onset of the AE as possible. The predose and postdose samples from only those subjects experiencing a hypersensitivity reaction were analyzed for IgE and histamine. The predose samples for subjects who did not experience a hypersensitivity reaction were not analyzed and were destroyed by the study center 14 days after dosing.
p. AE assessments began after the ICF was signed.
q. Skin assessments for presence or absence of rash were performed by the investigator or designee on Day 1 at predose and 1, 2, 4, and 12 hours after the start of infusion, and again on Day 2 (at 24 hours after the start of the infusion). If any evidence of rash was present, it was evaluated by the investigator.
r. The infusion site and vein were examined after insertion of the IV cannula prior to infusion, immediately following infusion, and 4, 8, and 24 hours after the start of infusion. Visual signs of irritation (swelling, tenderness, and erythema) were rated using a 4-point scale (0=absent to 3=severe). Venous tolerability was assessed by monitoring the IV infusion site and checking for evidence of phlebitis.

Blood samples for analysis of serum concentrations of obiltoxaximab, and anti-obiltoxaximab antibodies (ATA) were collected as outlined in footnotes *l* and *m* in Table 8.2 above. Post-treatment samples were identified as positive for ATA as follows: a) if the subject had a positive ATA titer at baseline, the titer of the postdose sample(s) had to be ≥4 times higher than baseline to be considered ATA positive, b) if the subject had a negative ATA titer at baseline, the postdose sample(s) required a titer of at least 1:20 to be considered ATA positive. Positive postdose samples of ≥ 1:40 were considered potentially meaningful and were isotyped for Ig class. Blood samples for exploratory assessment of cytokine (interleukin [IL]-1β, IL-2, IL-6, tumor necrosis factor alpha [TNF-α], and interferon gamma [IFN-γ]), histamine and IgE levels were taken as outlined in footnotes *n* and *o* in Table 8.2.

Safety Assessments: Safety assessments, including AEs, SAEs, clinical laboratory tests, vital signs, ECGs, physical examinations, and skin and infusion site assessments, were collected at the time points indicated in Table 8.2. AEs were collected from the day the subject gave informed consent until 30 days after the final dose of study drug or until resolution of all SAEs. Subjects with AEs that were ongoing at their last study visit were followed: 1) until the AE resolved; 2) the AE became stable and was not expected to further improve; or 3) for 30 days after the subject's last study visit, whichever came first, with the exception of an SAE, which was followed until the event resolved, or the event or any sequelae stabilized.

Blood and urine samples were collected after at least a 10-hour fast. In the event of any unexplained abnormal laboratory test values, the tests were repeated and followed up until results returned to baseline or were considered clinically acceptable.

Vital signs (supine) were taken and ECGs were performed before and after infusion of study drug as described in the Schedule of Assessments. ECG tracings were read by the investigator at each study center.

Physical examinations (conducted on Day -1 and the Final Visit) included an evaluation of the head, eye, ear, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Brief physical examinations (conducted on Days 15 and 43) included general appearance, the respiratory, gastrointestinal and neurological systems, and symptom-directed evaluations. Abnormal findings on physical examinations were reported as AEs.

Reviewer comment: It would have been good clinical practice to have a physical examination conducted and recorded at the time of an adverse event that resulted in discontinuation of the study drug. Since this was not done, it was challenging to accurately evaluate the complete clinical picture at these times. Though individual data points are presented in the clinical narratives of these subjects, a complete physical examination is a critical aspect of clinical evaluation.

Skin assessments for rash were performed before and after study drug infusion. Any rash was reported as an AE and described in the eCRF, including date of onset, nature and extent of the rash and date of resolution, if applicable. The infusion site and vein were monitored at the time points in the Schedule of Assessments for visible signs of irritation (swelling, tenderness, erythema, and phlebitis) using a 4-point scale (0=absent, 1=mild, 2=moderate, and 3=severe).

IgE and Histamine: Predose and postdose levels of IgE and histamine were assayed for subjects who the investigator believed had a hypersensitivity reaction. Additionally, predose levels only were analyzed inadvertently for several subjects without hypersensitivity reactions.

Reviewer comment: The IgE/histamine measurement database for subjects with hypersensitivity was not complete. The Applicant did not always explain why these measurements were not done. Therefore, this reviewer's ability to comment on these changes in relation to the occurrence of hypersensitivity is limited.

Clinical Laboratory Parameters: The following parameters were measured:

Hematology: Red blood cells, hemoglobin, hematocrit, platelets, white blood cells with differential, prothrombin time, activated partial thromboplastin time, and International Normalized Ratio
Serum biochemistry: Sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, glucose, calcium, albumin, cholesterol, phosphorus, lactate dehydrogenase, amylase, total protein, uric acid, and creatine phosphokinase

Additional tests: Free T3, free T4, thyroid stimulating hormone, and anti-thyroid peroxidase antibodies

Dipstick urinalysis: Protein, blood, and white blood cell esterase

Electrocardiograms: ECG data included the PR, RR, QT, QT interval corrected (QTc) using Bazett's formula (QTcB) and Fridericia's formula (QTcF), heart rate, and QRS duration.

Vital signs: Blood pressure, heart rate, respiration rate, and oral body temperature.

Skin and Infusion Site Parameters: The presence or absence of skin rash was assessed. Infusion site parameters included tenderness, erythema, and phlebitis.

Data Quality Assurance: Accurate and reliable data collection was assured by verification and cross–check of the eCRF against the investigator's records by qualified trial monitors (source document verification) and the maintenance of a study drug dispensing log by the investigator or designated individual. Data for this study was recorded via an electronic data capture system using eCRFs and was transcribed by the study center from the paper source documents onto the eCRF. A comprehensive validation check program was used to verify the data. Discrepancies were generated accordingly and transferred electronically to the eCRF at the study center for resolution by the investigator. Internal audits including annual facility, departmental, and randomly selected project audits were performed by Covance's Quality Assurance (QA) department, which operated independently of the trial monitors. The main purpose was to provide assurance that all aspects of the clinical trial were carried out in compliance with GCP, ICH, and all applicable regulations. The Covance QA audit and the trial monitoring process provide assurance that trial conclusions were based on valid procedures for data management and analysis and that the clinical trial was performed in accordance with GCP guidelines.

8.1.1.5 Statistical Analysis Plan

A detailed Statistical Analysis Plan (SAP) was provided by the Applicant. Data analysis was performed using SAS version 9.3. All safety data were summarized using descriptive statistics.

Determination of Sample Size: Based on the randomization ratio, approximately 210 subjects were expected to receive a single infusion of obiltoxaximab at the proposed therapeutic dose. According to the SAP, this sample size was considered sufficient to provide an 88% probability of detecting an adverse event (AE) that occurred at a frequency of 1.0%. Further, these subjects would add to the total number of subjects exposed to a single 16 mg/kg IV dose of this product in the clinical development program. A total of 300 subjects (including subjects in other studies) was considered sufficient to provide a 95% probability of detecting an AE that occurred at a frequency of 1%.

Reviewer comment: These determinations were based on previous consultations and agreement between FDA and the Applicant (see Section 3.2).

Data Handling Rules: For continuous data, summary statistics included the mean, standard deviation, median, minimum, maximum and the number of subjects analyzed. For categorical data, frequency counts and percentages were calculated. Summary statistics and statistical analyses were performed for subjects included in the relevant analysis population using unrounded data. Mean change from baseline was the mean of all individual subjects' change from baseline values. Each individual change from baseline was calculated by subtracting the individual subject's baseline value from the value at the specified time point. Data listings were provided for all subjects up to the point of withdrawal or study completion.

Missing dates and missing data: Missing values were generally not imputed, with the following exceptions: AEs with a start date on study Day 1, but missing start time, were imputed as treatment-emergent, and AEs entered into the eCRF on study Day 1 or later with a missing or invalid start date, were imputed as treatment-emergent.

Unscheduled/Repeat Visits: Repeat visit values in the listings were presented in parentheses. Values obtained during unscheduled visits were not included in summary tables, except when an unscheduled assessment was the last value prior to dose administration. All unscheduled visits were listed.

Analysis Populations**:** The Safety population consisted of all subjects who received study drug, whether prematurely withdrawn from the study or not. Safety analyses were based on the study drug actually received.

Subject Disposition and Withdrawal from Study Treatment: Study drug discontinuation (i.e., temporary or permanent infusion discontinuation) and the reasons for discontinuation were summarized by group (obiltoxaximab or placebo) in the Safety Population. Study discontinuation was similarly presented. Listings of treatment discontinuations and study discontinuations by subject were also provided.

Demographics: Baseline demographics, including age, gender, race, ethnicity, body weight, height, BMI (calculated as weight [kg]/height^2 [m^2]), and percent body fat were summarized by group in the Safety Population. A listing of demographics by subject was provided.

Previous and Concomitant Medications: Previous and concomitant medications were summarized by Anatomical Therapeutic Chemical classification and group in the Safety Population. A listing of previous and concomitant medications, non-required and required [i.e., diphenhydramine premedication], by subject was provided.

Pharmacodynamic Analyses: Anti-therapeutic antibodies (ATA): Subjects positive for ATA were summarized by group and study visit. ATA titer and ATA isotype were listed by subject. Cytokine levels of those listed above were summarized by group over time. Mean cytokine levels over time were plotted by group. IgE and histamine levels for subjects with a hypersensitivity reaction were listed.

8.1.1.6 Safety Analysis

All safety data were summarized using descriptive statistics.

Extent of Exposure: Duration of infusion (first segment only of the infusion for those situations where it was interrupted), total volume infused, the percentage of subjects with a completed infusion, and the percentage of subjects with an interrupted infusion, with subcategories for the reason for interruption were summarized. A listing was provided of subjects who received study drug, including duration, rate of infusion, concentration, and volume infused. A listing of subjects with infusion interruptions was also provided. The listing included the reason for interruption (i.e., AE, equipment, or other). If the reason for interruption was “other,” then the specified reason, as collected in the eCRF, was also presented.

Adverse Events: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. Treatment-emergent AEs were identified as AEs with either a start or worsening time after the start of study drug infusion through Study Day 191. Worsening of a pre-existing condition was calculated based on any increase in severity or elevation in seriousness to an SAE. AEs with a start date on Study Day 1, but missing a start time, were imputed as treatment-emergent. AEs entered into the eCRF on Study Day 1 or later with a missing or invalid start date were imputed as treatment-emergent. In general, AEs were

assigned to the last dose prior to onset. If an AE increased in severity after the next dose, it was assigned to the last dose prior to the increase in severity. If an AE occurred after a dose and resolved after the next dose without a change in severity, it was assigned to the dose prior to onset. Subjects who reported AEs of different severity were counted for each severity; however, subjects with an AE that changed in severity were only counted once at the highest severity grade.

AEs (number and percentage of subjects experiencing an AE) were summarized by treatment sequence, system organ class (SOC), and preferred term (PT). Separate AE summaries were provided by treatment sequence, severity and relationship to study drug. A subject with multiple AEs (different PTs) coded to the same SOC were counted only once for that SOC, but were counted each time for the PTs within the SOC. A subject with separate events of the same PT (different start/stop dates) was counted only once for that PT. SAEs were tabulated by treatment. AEs resulting in study discontinuation were listed.

AEs were summarized for the overall Safety Population, and an AE listing was provided for subjects who did not receive diphenhydramine prior to dosing.

Hypersensitivity Reactions: The incidence of hypersensitivity reactions was analyzed using both time-based and specific searches. In the time-based search, potential hypersensitivity reactions were defined as AEs that occurred either within the first 3 hours of the start of study drug infusion or AEs that occurred between 3 to 24 hours of the start of study drug infusion. Separate summaries were provided for AEs occurring within these two time periods by treatment sequence and by SOC and PT. These analyses were reviewed by Elusys Medical Monitoring and Pharmacovigilance staff to identify AEs possibly indicative of hypersensitivity. In the specific search for hypersensitivity, the database was searched for the following AEs: symptomatic hypotension, respiratory distress (bronchospasm or central cyanosis), generalized urticaria considered by the investigator to be severe; anaphylactic reaction, and SAEs considered by the investigator to be related to study drug. A listing of these AEs was provided.

Clinical Laboratory Data: Laboratory data were presented using the International System of Units. For serum biochemistry and hematology data, observed values were summarized by treatment sequence at each scheduled time point. The Day -1 value or the last unscheduled value between Day -1 and dosing was the baseline value. Laboratory data were listed by subject with values outside the clinical reference range flagged. Serum biochemistry, hematology, and urinalysis parameters outside the clinical reference ranges were summarized and listed by parameter and treatment sequence. Unscheduled laboratory values were not included in summary statistics but were included in the listings.

Vital signs: Observed and change from baseline values for vital signs were summarized descriptively at each scheduled time point and listed by subject. The baseline value was the last

measurement collected prior to starting study drug on Day 1. A plot of the mean observed values with standard deviations was provided by treatment sequence. Unscheduled vital sign values were not included in summary statistics but were included in the listings. For each vital sign parameter, the incidence rates of potentially clinically significant changes from baseline were summarized by treatment sequence for subjects without clinically significant values at baseline. Individual subject vital sign values were listed with potentially clinically significant changes flagged. Unscheduled vital sign values were also listed.

Table 8.3 Criteria for Potentially Clinically Significant Changes in Vital Signs

Parameter	High	Low
Systolic blood pressure	>140 mmHg and >20 mmHg increase from baseline	<90 mmHg and decrease of >10 mmHg from baseline
Diastolic blood pressure	>90 mmHg and >15 mmHg increase from baseline	<60 mmHg and decrease of >10 mmHg from baseline
Heart Rate	>100bpm and >15 bpm increase from baseline	<60 mmHg and decrease of >10 bpm from baseline

Source: AH104 CSR, Table 2, p. 37

Electrocardiograms: ECG data were obtained directly from the 12-lead ECG tracings. The mean of the triplicate ECG values was used in the calculation of summary statistics. ECG data were summarized by treatment sequence together with changes from baseline, where baseline was defined as the last value prior to dosing on Day 1, including unscheduled values. Unscheduled post dose readings were excluded from summary statistics. Unscheduled readings were labeled as unscheduled in the listings. The frequency of subjects with a maximum increase from baseline in QTcB or QTcF of ≤30, >30 and >60 milliseconds (ms) and of those with postdose QTcB or QTcF values ≤450, >450, >480, and >500 ms were summarized by treatment sequence. Increases of >30 and >60 ms and values >450, >480, and >500 ms were flagged on the listing as potentially clinically significant.

Skin and Infusion Site Assessment: Findings of skin assessments were summarized by sequence and severity and listed by subject. The number of subjects with a skin rash was summarized by treatment sequence and listed by subject. The number of subjects with findings of tenderness, erythema, and phlebitis at either the infusion site or vein was summarized by treatment sequence and severity and listed by subject.

8.1.1.7 Changes in Conduct of the Study

Protocol Amendments: The original protocol was dated April 29, 2013. The protocol was amended twice, and key changes are in Table 4. All amendments were submitted to the Applicant's IND and the IRB for the sites that were still enrolling subjects at the time of the protocol amendment.

Table 8.4 Protocol Amendments in AH104

Amendment 1 September 3, 2013	Revised inclusion criterion for female subjects who underwent surgical sterilization by tubal essure to have done so at least 3 months prior to Screening and to provide radiological confirmation or agree to follow the protocol-specified methods of contraception
	Revised exclusion criterion to clarify that previous systemic steroid use pertained to therapeutic use of systemic steroids
	Required premedication with 50 mg oral diphenhydramine approximately 30 minutes before infusion of study drug on Day 1
Amendment 2 January 28, 2014	Clarified that PK parameters included terminal $t_{1/2}$
	Provided specific criteria for determining which ATA samples would be assayed for neutralizing antibodies and isotyped

Source: Adapted from AH104 CSR, Table 3, p. 38

There were no changes from the protocol-specified statistical analyses. Errors found after database lock and unblinding and finalization of the tables and listings were provided.

8.1.2 AH109 Study Protocol

This study was the only repeat-dose study in the Application.

8.1.2.1 Study Objectives

The primary objective was to evaluate the safety and tolerability of repeat administration (2 doses) of 16 mg/kg of obiltoxaximab IV in adult volunteers. Secondary objectives were to evaluate: a) the PK of obiltoxaximab after repeat IV administration and b) the immunogenicity of obiltoxaximab after repeat IV administration.

Study Design: Phase I, double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety, tolerability, PK and potential immunogenicity of repeat administration (2 doses) of IV obiltoxaximab either 14 or 120 days following the initial dose in adult subjects. The study took place between July 23, 2013 and April 19, 2014 at Quintiles, Overland Park, KS and DaVita Clinical Research, Minneapolis, MN.

8.1.2.2 Ethics and Administrative Structure

These were similar to the structure for study AH104. (See Section 8.1.1.2)

8.1.2.3 Study Design

Subjects were admitted to the Clinical Research Unit for an overnight stay on Days -1, 13, and 119. Clinic evaluations were done at screening and on Days -1, 1, 2, 8, 13, 28, 43, 71, 85, 119, 128, 134, 149, 163 and 191. Following completion of screening, all subjects were administered a single IV dose of 16 mg/kg obiltoxaximab on Day 1. All but 8 subjects (who were randomized prior to the implementation of Amendment 1) were pretreated with 50 mg oral diphenhydramine prior to study drug administration. On Day 14, after premedication with diphenhydramine, subjects received either obiltoxaximab or placebo IV, depending on the sequence in which they were enrolled. For the third dose, subjects again received either obiltoxaximab or placebo depending on the sequence they were in. The total duration of the study for each subject including screening, was approximately 220 days. The end of the study was defined as the date of the last visit of the last subject in the study.

Study Population: The target population was adults ≥18 years of age. Subjects had to have participated in the informed consent process, and signed and dated the ICF before any procedures were performed.

Inclusion/Exclusion Criteria: These criteria were identical to those listed in Section 8.1.1.3.

Removal of Subjects from Therapy or Assessment: General rules were the same as in AH104 (see Section 8.1.1.3). In addition, if the investigator determined that the subject should not receive a second dose of study drug due to a significant drug-related AE, all assessments related to the first dose (Days 15, 28, 43, 71, and 85) were completed and the subject was withdrawn from the study at Day 85. The subject was not readmitted to the CRU on Day 14.

Similarly, if a subject had a significant drug-related AE after the second study treatment on Day 14 and the investigator determined that the subject should not receive a third dose, all assessments related to the second dose (Days 15, 28, 43, 71, and 85) were completed and the subject was withdrawn from the study at Day 85. The subject was not readmitted to the CRU on Day 119. Subjects who received the third study treatment on Day 120 were to complete all remaining study assessments. Subjects who withdrew prior to completing the study were not replaced.

Treatment and Administration of Study Drug: See Section 8.1.1.3. The obiltoxaximab and placebo lots used for this study were 3-FIN-1513 and 3-FIN-1491 respectively. After Protocol Amendment 1, subjects were premedicated with 50 mg oral diphenhydramine approximately 30 minutes prior to the start of the infusion of study drug on Days 1, 14 and 120.

Method of Assigning Subjects to Treatment Groups: Subjects were randomized to one of the following treatment sequences by an unblinded pharmacist at the study center using a randomization schedule provided by Covance CDARO:

Sequence A: obiltoxaximab on Days 1 and 14 and placebo on Day 120 (N=35)
Sequence B: obiltoxaximab on Days 1 and 120 and placebo on Day 14 (N=35)

Seventy adults (70) were randomized in a 1:1 ratio; the randomization schedule was generated using SAS software in a randomized block design and stratified by site.

Selection of Dose in the Study, Blinding, Prior and Concomitant Therapy: See Section 8.1.1.3.

Study Restrictions (not specified in AH104 protocol): Subjects were asked to avoid alcohol and herbal preparations for 5 days prior to dosing on Day 1 and for 5 days prior to each subsequent visit after discharge from the CRU. There were no restrictions on smoking or the use of caffeine either prior to or during the study. During their stay in the CRU, meals and a snack were served, and they could continue their usual diet (except for the noted restrictions) while outside the CRU. Subjects were also asked to avoid strenuous exercise for 5 days prior to dosing on Day 1 and for 5 days prior to each subsequent visit after discharge from the CRU.

Management of Hypersensitivity Reactions: See Section 8.1.1.3

Treatment Compliance: Accountability and subject compliance were assessed by maintaining adequate study drug dispensing records. The study center's unblinded pharmacist recorded all information related to study drug preparation. The investigator was responsible for ensuring that study drug was administered in compliance with the protocol.

8.1.2.4 Safety, Pharmacokinetic and Pharmacodynamic Parameters

Table 8.5 Study AH109: Schedule of Assessments

	D																				
	-28 to	-1	1	2	8 (±2 d)	13	14	15	28 (±3 d)	43 (±3 d)	71 (±3 d)	85 (±3 d)	119	120	121	128 (±3 d)	134 (±3 d)	149 (±3 d)	163 (±3 d)	191 (±3 d)
Informed Consent	X																			
Medical History	X	X																		
Prior Medication History	X	X																		
Inclusion/Exclusion Criteria	X	X																		
Clinical Hematology /Serum Chemistry[a]	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X	X	X
Dipstick Urinalysis[b]	X	X		X	X	X		X	X			X	X		X	X		X		X
T3, T4, TSH, and Thyroid Antibodies		X										X	X							X
Urine Drug Screen[c]	X	X											X							
Calculate Creatinine Clearance	X																			X
Virology Panel (HBsAg, HCV, HIVAb)	X																			
Physical Examination[d]	X	X				X						X	X							X
Height/Weight (BMI)[e]	X	X											X							X
Percent Body Fat[f]		X																		
Vital Signs[g]	X	X	X	X	X	X	X	X	X			X	X	X	X	X		X		X
Electrocardiogram[h]	X	X	X	X		X	X	X					X	X	X					X
Serum Pregnancy Test	X	X				X			X	X	X	X	X					X		X
Follicle-Stimulating Hormone[i]	X																			
Randomization			X																	

In-Unit Period		X	X	X		X	X	X					X	X	X					
Discharge from In-Unit Study Center				X				X							X					
Administer Diphenhydramine Pre-infusion[j]			X				X							X						
Administer Study Medication			X				X							X						
Blood Samples for PK[k]			X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
Blood for Anti-ETI-204 Antibodies (PD)[l]			X		X		X			X		X		X		X			X	X
Blood Samples for IgE and Histamine[m]			X				X							X						
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessments[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin Assessments[o]			X	X			X	X						X	X					
Infusion Site Assessment[p]			X	X			X	X						X	X					

Source: AH109, CSR, Schedule of Assessments

BMI=body mass index; HBsAG=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV-Ab=human immunodeficiency virus antibody; TSH=thyroid stimulating hormone

[a] a. Subjects fasted for at least 10 hours prior to blood collection for clinical laboratory evaluations. Clinical hematology assessments included red blood cells, hemoglobin, hematocrit, platelets, prothrombin time, activated partial thromboplastin time, International Normalized Ratio, and white blood cells with differential. Clinical chemistry assessments included sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, AST, ALT, total bilirubin, blood urea nitrogen, creatinine, glucose, calcium, albumin, cholesterol, phosphorus, lactate dehydrogenase, amylase, total protein, uric acid, and creatine phosphokinase.

b. Dipstick urinalysis assessments included protein, white blood cell esterase, and blood.

c. Urine drug screen included alcohol, amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolites, methadone, opiate metabolites, phencyclidine, propoxyphene, and marijuana metabolites.

d. A full physical examination was required at Screening and Day 191 (final visit). A brief physical examination (evaluation of general appearance, respiratory, gastrointestinal, neurological, and other systems as determined by the investigator) was required on Days -1, 13, 85, and 119.

e. Weight was recorded at Screening, Day -1, Day 119 and Day 191. Height was recorded at Screening only. BMI was calculated using Day -1 weight and height at Screening. If a subject's weight changed by >10% between Day -1 and Day 119, the Sponsor was notified prior to adjusting the dose calculation.
f. Estimated percent body fat was measured on Day-1 using calipers at the following locations: back of upper arm (triceps), front of upper arm (biceps), back, below the shoulder blade (subscapular) and waist (suprailiac).
g. Vital signs, including temperature, heart rate, respiratory rate, and blood pressure, were taken in a supine position after the subject had been supine for at least 5 minutes and may have been repeated once if the investigator felt an initial value was inappropriate. On Days 1, 14 and 120, temperature, heart rate, respiratory rate, and blood pressure were measured predose and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours and 8 hours after the start of the infusion. On Days 1, 14 and 120 deviations of +/- 5 minutes for time points < 1.5 hours post start of infusion and +/- 10 minutes for time points ≥ 1.5 hours post start of infusion were allowed.
h. On Days 1, 14, and 120, ECGs were recorded predose, at the end of infusion, and 3 and 8 hours after the start of the infusion. On Days 2, 15, and 121, ECGs were recorded at 24 hours after the start of the infusion. ECGs were recorded before collection of blood samples for PK assessments (see footnote 'k' below). All ECGs were recorded in triplicate. Predose ECGs were done within 1 hour prior to dosing; postdose ECGs were done within +/- 15 minutes of the specified time.
i. Follicle-stimulating hormone level required for postmenopausal females only
j. Subjects were premedicated with 50 mg oral diphenhydramine approximately 30 minutes before the start of study drug infusion (or as recommended by the Clinical Trial Steering Committee).
k. Blood samples (3.5 mL) for analysis of ETI-204 serum concentrations (PK) were obtained on Days 1, 14, and 120 predose, at the end of infusion, and 3 and 8 hours after the start of infusion, after ECG recordings. A single PK sample was obtained on Days 2, 8, 15, 28, 43,71 ,85, 121, 128, 134, 149, 163, and 191. On Days 2, 15, and 121, the PK sample was taken 24 hrs after the start of the infusion on the previous day. The actual time of sample collection was recorded. On Days 1, 2, 14, 15, 120, and 121, deviations of up to +/- 15 minutes from specified postdose time points were allowed.
l. Blood samples (3.5 mL) for screening of serum anti-ETI-204 antibody titers (PD) were collected on Days 1, 14, and 120 prior to dosing, and on Days 8, 43, 85,128, 163, and 191.
m. Blood samples for analysis of serum IgE (3.5 mL) and plasma histamine concentrations (3 mL) were obtained on Days 1, 14, and 120 at predose from all subjects and postdose ONLY from subjects who experienced a hypersensitivity reaction. The postdose samples were collected as close to the time of onset of the hypersensitivity reaction as possible. Only the pre- and postdose samples from subjects experiencing a hypersensitivity reaction were analyzed for IgE and histamine. The predose samples for subjects who did not experience a hypersensitivity reaction were not analyzed and were destroyed by the site 14 days after dosing.
n. AE assessments began after signing of the informed consent form.
o. Skin assessments for presence or absence of rash were performed by an investigator or designee, on Days 1, 14, and 120 at predose, and 1, 2, 4, and 12 hours after the start of the infusion. Skin assessments were performed again on Days 2, 15 and 121 (at 24 hours after the start of the infusion on Days 1, 14 and 120, respectively). If any evidence of rash was present, it was evaluated by the investigator.
p. The infusion site and vein were examined after insertion of the IV cannula prior to dose, immediately following the infusion, and 4, 8 and 24 hours after the start of the infusion. Visual signs of irritation (swelling, tenderness, and erythema) were rated using a 4-point scale (0=absent to 3=severe). Venous tolerability was assessed by monitoring the IV infusion site and checking for evidence of phlebitis.

Blood samples for obiltoxaximab, ATA, IgE and histamine levels were collected and handled in an identical manner to study AH104 (Section 8.1.1.4); exploratory assessment of cytokine levels was not done.

Safety Assessments: AEs, SAEs, clinical laboratory tests, vital signs, ECGs, physical examinations and skin and infusion site assessments were collected at the time points indicated in the Schedule of Assessments.

Adverse events: See Section 8.1.1.3

Safety Parameters: Adverse Events: See Section 8.3.2 Categorization of Adverse Events.

Clinical Laboratory Parameters, ECGs, Vital signs: See Section 8.1.1.3

Data Quality Assurance: See Section 8.1.1.3

8.1.2.5 Statistical Methods

Statistical Analytical Plan: There were no changes from the protocol-specified statistical analysis. Data analysis was performed using SAS® Version 9.3.

Determination of Sample Size: No formal sample size calculation was performed since formal statistical comparisons were not planned.

Reviewer comment: The sample size of 70 subjects was adequate to characterize the safety and PK profiles of the repeat dosing of obiltoxaximab.

8.1.2.6 Safety Analyses

Extent of Exposure, Adverse events, hypersensitivity reactions, clinical laboratory data, ECGs, vital signs and skin and infusion site assessments: See Section 8.1.1.6

8.1.2.7 Changes in the Conduct of the Study or Planned Analyses

Protocol Amendments: The original protocol was dated April 29 2013. Key changes are tabulated below. All amendments were submitted to the Applicant's IND and the IRBs.

Table 8.6 Protocol Amendments in AH109

Protocol Amendment and Date	Key Changes
Amendment 1 September 11, 2013	Clarified the total duration of study as 220 days
	Revised inclusion criteria for female subjects who underwent tubal ensure to have had this procedure at least 3 months prior to screening, and to provide radiological confirmation or agree to follow the protocol-specified method of contraception.
	Clarified that previous systemic steroid use in the exclusion criteria pertained to therapeutic use.
	Required premedication with 50 mg oral diphenhydramine 30 minutes prior to infusion.
	Explanation of staggered dosing for the first 8 subjects to allow for safety monitoring.
Amendment 2 January 20, 2014	Provided specific criteria for determining which ATA samples would be assayed for neutralizing antibodies and isotyped.

Source: Adapted from AH109 CSR, Table 3, p. 40,

Changes to the Statistical Analysis Plan: The baseline value for clinical laboratory parameters was the last measurement collected prior to starting study drug on Day 1, including unscheduled visits, instead of Day -1 values, as stated in the SAP.

8.1.3 AH110 Study Protocol

AH101 was an initial study of obiltoxaximab in combination with ciprofloxacin – 6 subjects received a single 114 mg dose of obiltoxaximab in combination with 500 mg of oral ciprofloxacin every 12 hours for 14 days. This combination was well-tolerated with no evidence of a pharmacokinetic interaction between the two agents. AH110 was conducted to further assess the safety, tolerability and PK of obiltoxaximab at 16 mg/kg IV when administered alone and in the presence of ciprofloxacin administered by the IV and oral routes.

Reviewer comment: This study of potential drug-drug interactions is critical since the proposed indication for obiltoxaximab is as an adjunct to antimicrobial therapy. It may indeed be clinically relevant to study the PK and safety of obiltoxaximab with other antibiotics as well in the future, since combination antimicrobial therapy is recommended for treatment of inhalational anthrax. Further, there is no data on the potential interactions or safety profiles of obiltoxaximab when administered in combination with anthrax vaccine (AVA). To this reviewer's knowledge, these data do not exist with raxibacumab either. Characterizing these potential interactions - for example, whether the anti-PA antibodies induced by AVA interfere with, abrogate, or enhance

the effects of obiltoxaximab, or vice versa, or if the combination leads to a higher incidence of hypersensitivity would be critical to know a priori as therapy for inhalational anthrax may include all 3 modes of therapy – ABT, AVA and obiltoxaximab.

8.1.3.1 Study Objectives

The **primary** objective of study AH110 was to evaluate the safety and tolerability of IV obiltoxaximab alone and in the presence of IV and oral ciprofloxacin. The **secondary** objectives were to evaluate the PK of IV obiltoxaximab alone and in the presence of IV and oral ciprofloxacin, and to evaluate the immunogenicity of IV obiltoxaximab.

Study Design: This was a Phase I, open-label, randomized, parallel group study of IV obiltoxaximab administered alone and in the presence of IV and PO ciprofloxacin. It was conducted between October 9, 2013 and April 9, 2014 at Quintiles Phase I Services in Overland Park, KS.

8.1.3.2 Ethics and Administrative Structure

These were similar to study AH104. See section 8.1.1.2.

8.1.3.3 Investigational Plan

40 adults volunteers were randomized in a 1:1 ratio to either:

Group 1: IV obiltoxaximab followed by IV ciprofloxacin followed by oral ciprofloxacin, or

Group 2: IV obiltoxaximab alone

The total duration of the study for each subject was approximately 100 days. After the screening period, all subjects had an in-unit phase of Days -1, 1 and 2, and Days 8, 9 and 10 (Group 1). Out-of-unit visits: Day 9, Day 16, Day 29 and Day 43. Final visit: Day 71. On Day 1, subjects were randomized in a 1:1 ratio to receive obiltoxaximab + ciprofloxacin (PO and IV) (Group 1) or obiltoxaximab alone (Group 2). All subjects were pretreated with 50 mg oral diphenhydramine approximately 30 minutes prior to the start of the obiltoxaximab infusion.

Subjects in Group 1 received a single IV dose of obiltoxaximab 16 mg/kg infused over 90 minutes, followed immediately by a single IV dose of ciprofloxacin (400 mg) infused over 60 minutes. Subjects in Group 2 received a single IV dose of obiltoxaximab 16 mg/kg infused over 90 minutes. All subjects were discharged from the CRU on Day 2 following completion of study assessments.

On Days 2 through 8, subjects in Group 1 received oral ciprofloxacin (750 mg every 12 hours) with the final 750 mg dose administered on the morning of Day 9. Oral ciprofloxacin dosing began 24 hours after the initiation of the ciprofloxacin infusion on Day 1. Subjects in Group 1 returned to the CRU on Day 8 and were discharged following completion of PK sampling on Day 10. Subjects in Group 2 returned to the unit for an out-patient visit on Day 9 but were not re-admitted to the CRU for an overnight stay.

Study Population: Females or males between 18 and 60 years of age.

Inclusion/Exclusion Criteria: See Section 8.1.1.3. In addition, there were exclusion criteria specific to the use of ciprofloxacin. Subjects were excluded who:

1. Had a history of hypersensitivity to any fluoroquinolone

2. Were at increased risk of *Clostridium difficile* infection (CDI) (e.g., received prior systemic antibiotic therapy or had an in-hospital stay of greater than 2 nights over the past 6 months, had abdominal surgery within 3 months prior to Day 1, had a history of a chronic inflammatory bowel disease or prior CDI)

3. Had any medical condition that required repeat courses of antibiotics, e.g., recurrent urinary tract or respiratory infections. A short course (i.e., ≤ 10 days) of antibiotics within 6 months prior to Day 1 was not exclusionary.

4. Had a history of any tendon rupture

5. Were smokers or had used tobacco or nicotine containing products within 3 months of Day 1

6. Had used cation-containing drugs or food supplements within 2 days prior to Day 1

7. Had used protheophylline, theophylline, methylxanthine, tizanidine, or other drugs metabolized via cytochrome P450 1A (CYP1A) within 30 days prior to Day 1

8. Had used glyburide, cyclosporine, didanosine, methotrexate, or probenecid and medications that prolong the QT interval within 30 days prior to Day 1 or within 5 half-lives of Day 1, whichever was longer

9. Were subjects at high risk for QT prolongation, including having:
   a. Baseline prolongation of QT interval corrected using Fridericia's formula (QTcF) ≥ 500 milliseconds (ms)
   b. Risk factors for torsade de pointes, including hypocalcemia, hypokalemia, sudden death of unknown cause in a close family member (ie, biological mother, father or siblings), a

near drowning episode, a family history of either Romano-Ward syndrome or Jervell and Lange-Nielsen syndrome

c. Used concomitant medications that prolonged the QT interval within 30 days prior to Day 1

Removal of subjects from therapy or assessment: See Section 8.1.1.3. All subjects in AH110 received premedication with diphenhydramine.

Study Treatment: See Section 8.1.1.3. for details of obiltoxaximab administration. Commercially available ciprofloxacin was obtained for IV and oral administration by the investigator – 400 mg in 200 ml in 5% dextrose premixed solution for IV infusion and 750 mg tablets for oral dosing. In addition, subjects randomized to Group 1 received single IV doses of 400 mg of ciprofloxacin infused over 60 minutes on Day 1, immediately following the obiltoxaximab administration. They then received ciprofloxacin 750 mg PO every 12 hours on Days 2 through 8 and a single 750 mg dose of oral ciprofloxacin on the morning of Day 9.

Method of Assigning Subjects: This was an open-label, randomized, parallel group study. Subjects were randomized in a 1:1 ratio by the pharmacist at the study center to Group 1 or Group 2.

Selection of Dose: See Section 8.1.1.3. The ciprofloxacin doses were the standard recommended IV and oral doses for patients with normal renal function.

Blinding: AH110 was an open-label study but all subjects remained blinded to treatment assignment until Day 1, just before dosing.

Prior/Concomitant Therapy and Restrictions: See Section 8.1.1.3 and the additional exclusion criteria outlined above. In addition, the use of the following medications was prohibited during the study: cation-containing products including dietary supplements, nicotine and nicotine-containing products, medications metabolized via CYP1A, glyburide, cyclosporine, didanosine, methotrexate, probenecid, and all medications that prolong the QT interval. Subjects were asked to take ciprofloxacin orally on an empty stomach. They were asked to avoid strenuous exercise for 5 days prior to dosing on Day 1 and for 5 days prior to each visit after discharge from the CRU, and to avoid exposure to natural and artificial sunlight from 5 days prior to receiving ciprofloxacin on Day 1 until 5 days after receiving the last dose of ciprofloxacin on Day 9.

Management of hypersensitivity reactions: See Section 8.1.1.3.

Management of antibiotic-associated diarrhea: This is a potential risk especially with fluoroquinolone use. All subjects were advised to report to the clinic if they developed diarrhea (identified as 3 or more loose/watery stools in 24 hours) or severe abdominal pain, while taking

ciprofloxacin or within 30 days of the last dose. Subjects with diarrhea were to submit a stool specimen for local *C. difficile* testing and unless the individual's diarrhea could definitively be attributed to another cause, ciprofloxacin was discontinued. Anti-peristaltic agents were to be avoided. Fluid and electrolytes were to be replaced as needed. Mild to moderate CDI was treated with oral metronidazole 500 mg three times daily for 10-14 days. Severe CDI was to be treated with oral vancomycin 125 mg four times daily for 10-14 days. Management of recurrent CDI was to be discussed with the Elusys medical monitor. Subjects who did not complete the course of ciprofloxacin or who developed CDI after completion of ciprofloxacin were to be encouraged to remain in the study and complete all scheduled safety assessments.

Treatment Compliance: See Section 8.1.1.3 regarding obiltoxaximab treatment compliance.

8.1.3.4 Safety, Pharmacokinetic and Pharmacodynamic Assessments

Schedule of Assessments and Procedures: The schedule of assessments and blood sampling times for obiltoxaximab concentrations were the same as for study AH104 (see Section 8.1.1.4.). In addition to standard sampling for obiltoxaximab levels, blood was taken for ciprofloxacin levels on Days 1 and 2, and oral ciprofloxacin levels on Days 9 and 10. Blood sampling for cytokine levels was not done.

Safety and PK Parameters: safety and PK assessments were consistent with trial AH104. (See Section 8.1.1.4.)

8.1.3.5 Statistical Analysis Plan

See Section 8.1.1.5. In addition, the sample size of 20 per arm was based on the assumption of 20% between-subject arithmetic coefficient of variation (CV) for both AUC and Cmax for obiltoxaximab and there was no difference in true geometric means in the presence or absence of ciprofloxacin. Based on this assumption, completion of treatment by 18 subjects/group in the parallel group design would yield 80% overall power to conclude that there was no effect of ciprofloxacin on the PK of obiltoxaximab.

8.1.3.6 Safety Analyses

See Section 8.1.1.6.

8.1.3.7 Changes in the Conduct of the Study

Table 8.7: Protocol Amendments in AH110

Protocol Amendment and Date	Key Changes
Amendment 1 September 16, 2013	Required premedication with 50 mg oral diphenhydramine approximately 30 minutes before infusion of ETI-204
	Revised exclusion criterion to clarify that previous systemic steroid use pertained to therapeutic use of systemic steroids
	Clarified inclusion criterion to include that female subjects who had undergone surgical sterilization by tubal essure had to have had it done at least 3 months prior to Screening and had to provide radiological confirmation or agree to follow the protocol- specified methods of contraception to be eligible
	Clarified that oral ciprofloxacin had to be administered to subjects in Group 1 on Days 2 through 9 on an empty stomach (i.e., at least 2 hours after a meal)
	Removed free T3, free T4, TSH and thyroid antibodies from the screening evaluations and added them to the list of evaluations to be done on Day -1
	Clarified that the thyroid antibodies to be evaluated included only anti-thyroid peroxidase antibodies and not anti-microsomal thyroid antibodies
Amendment 2 December 19, 2013	Clarified that Inclusion Criterion #6 did not apply to males who had undergone a vasectomy and could provide documentation of confirmatory sperm count 3 months post procedure
	Modified the exclusion criteria to indicate that subjects who test positive for alcohol at Screening or Day -1 are excluded
	Clarified that a short course (ie, ≤ 10 days) of antibiotics taken within 6 months of Day 1 was acceptable and did not exclude a subject from participating in the trial
	Clarified in the exclusion criterion pertaining to risk factors for Torsade de Pointes, that a close family member was defined as a biological mother, father or siblings

Source: Adapted from AH110 CSR Table 4, p. 43

8.2 Review of the Safety Database

8.2.1 Overall Exposure

Overall, 497 subjects received obiltoxaximab (all doses; both commercial formulation and investigational material; both IV and IM routes of administration). The total safety database for IV obiltoxaximab is comprised of 470 subjects (Table 8.8):

Table 8.8 Summary of Subjects Exposed to Obiltoxaximab in the Clinical Studies

	Any Obiltoxaximab dose	16 mg/kg Obiltoxaximab
Studies with IV obiltoxaximab (Lonza commercial formulation)		
AH104	210	210
AH109	70	70
AH110	40	40
Subtotal for commercial formulation	320	320
Studies with IV obiltoxaximab (Baxter investigational formulation)		
AH105	90*	30
AH102	36	0
AH101	24	0
Subtotal for Investigational material	150	30
Overall total for IV obiltoxaximab	470	350
Studies with IM obiltoxaximab (Lonza commercial formulation)		
AH 106	27**	6
Overall Total: Subjects Exposed to obiltoxaximab	497	356

*includes the 30 subjects who received 16 mg/kg IV obiltoxaximab as well as 30 who received 4 mg/kg and 30 who received 8 mg/kg
**includes the 6 subjects who received 16 mg/kg obiltoxaximab IM as well as 21 subjects who received other obiltoxaximab IM doses (4 mg/kg (3 subjects), 8 mg/kg (6), 20 mg/kg (6) and 24 mg/kg (6)
Adapted from Table 2, p.16, Summary of Clinical Safety

For purposes of this review, this reviewer focused on subjects who received 16 mg/kg IV of the Lonza preparation of obiltoxaximab since this is the one to be used commercially. The ISS submitted by the Applicant combined studies AH104, AH109, AH110 and AH105 for a total of 498 subjects. AH104 included 210 subjects in the obiltoxaximab arm and 70 in the placebo arm. In AH109, all 70 subjects received at least one dose of obiltoxaximab, then 35 subjects were assigned to receive a second dose of obiltoxaximab in 2 weeks, and 35 subjects were assigned

to receive a second dose in ≥ 4 months. AH110 had 20 subjects in the obiltoxaximab group and 20 subjects in the obiltoxaximab plus ciprofloxacin group. All of these studies (AH104, AH109 and AH110) used 16 mg/kg IV of the Lonza (commercial) preparation as the dose of obiltoxaximab. Study AH105 (described in Section 8.6.3) was a dose-escalation study of a single dose of 4 mg/kg, 8 mg/kg and 16 mg/kg IV of obiltoxaximab vs. placebo which used the Baxter formulation (investigational) of obiltoxaximab; of the 108 subjects in this study, only 30 received the 16 mg/kg dose and 18 received placebo.

Pooling: Table 8.9 summarizes the Applicant's pooling strategy.

Table 8.9 Applicant's Pooling Strategy for Analysis of Safety

Primary Safety Population (16 mg/kg dose of obiltoxaximab or placebo, DDI study)		
Single-dose Pool		
	Subjects in treatment arm (n)	Subjects in placebo arm (n)
AH104	210	70
AH110 (DDI)	20 obiltoxaximab	0
	20 obiltoxaximab + cipro	
Total	250	70
Repeat-dose Pool		
AH109 (repeat dose)	A: 1st dose: 35; 2nddose:34 B: 1st dose: 35; 2nd dose: 31	
Total	70	
Expanded Safety Population (single 16 mg/kg dose of obiltoxaximab or placebo)		
AH104	210	70
AH110	40	0
AH105	30	18
Total	280	88
Supportive Data (Fixed or Smaller Doses of obiltoxaximab IV)*		
AH101	Part 1: 18	6
	Part 2: obiltoxaximab + cipro: 6; placebo + Cipro: 6	
AH102	36	9
AH105	60	18
Total		
Intramuscular Administration of obiltoxaximab		
AH106	(b) (4)	

Source: Adapted from Section 1.3, Integrated Summary of Safety (ISS)

*19-360 mg obiltoxaximab in AH101 and AH102, and weight-based dosing of 4, 8, or 16 mg/kg in AH105. These were not pooled with the exception of the 16 mg/kg dose arm and placebo arm from AH105 which were included in the expanded safety population.
**4, 8, 16, 20, 24 mg/kg obiltoxaximab (3, 6, 6, 6, 6 subjects respectively)

Reviewer comment: This reviewer agreed that the studies that utilized 16 mg/kg of the Lonza preparation of ETI-204 were the most relevant for analysis as this is the dose and formulation proposed for marketing. However, the reviewer separately analyzed AH110, and felt that inclusion of both arms of AH110 in the Applicant's Primary Single-dose Pool would not allow a "clean" analysis of adverse events related to obiltoxaximab alone. Therefore, in the reviewer's pooling, only the 20 subjects who received ETI-204 alone were included in the single-dose pool, named the FDA Primary Safety Population (FDA PSP). However, the addition of ciprofloxacin obviously provided relevant clinical context as obiltoxaximab is intended for use with antimicrobial therapy. Therefore, all subjects in both arms of AH110 were included in analysis of the entire population exposed to 16 mg/kg of the Lonza preparation of ETI-204, named the FDA Expanded Safety Population (FDA ESP). The individual analysis of AH110 is also presented.

Further, this reviewer felt that the 70 subjects who received obiltoxaximab as the first infusion in AH109 were a valuable population to include in the analysis of single-dose administration, as many of the adverse events of interest occurred within the first 13 days after infusion, especially those associated with hypersensitivity. Thus, all 70 subjects who received ETI-204 in the first treatment period (Days 1-13, inclusive) of AH109 were included in the single-dose population (FDA PSP). Because many of the adverse events related to infusion of a monoclonal antibody might be anticipated at the time of infusion or shortly thereafter, this pooling strategy was considered not only appropriate, but helpful to increase the single-dose safety database.

Analysis of AH109 alone was important to compare adverse events associated with repeat doses over time, and this was performed separately. However, all subjects in AH109 at all time points were also included in the FDA ESP as this represented an overall analysis of all subjects at all exposures to the Lonza formulation of ETI-204 at 16 mg/kg.

The supportive study AH105, was considered relevant because of the dose-escalation design, including a dose of 16 mg/kg in 30 subjects. AH105 was analyzed separately by this reviewer. Finally, AH106, the only study in the human safety database utilizing the intramuscular administration of ETI-204, was analyzed separately (b) (4) *.*

This reviewer's pooling strategy is reflected in Table 8.10.

Table 8.10 FDA Pooling and Summary of Studies

FDA Primary Safety Population – Studies	Obiltoxaximab Formulation	Dose of Obiltoxaximab	Number of subjects in treatment arm	Number of subjects in placebo arm
AH104	Commercial	16 mg/kg	210	70
AH109	Commercial	16 mg/kg	70*	0
AH110	Commercial	16 mg/kg	20**	0
Total			300	70
FDA Expanded Safety Population – Studies				
AH104	Commercial	16 mg/kg	210	70
AH109	Commercial	16 mg/kg	70*	0
AH110	Commercial	16 mg/kg	40	0
Total			320	70
Combination Studies* **				
AH110	Commercial	16 mg/kg	40	0
AH101	Investigational	114 mg	6	6
Supportive Studies				
AH105	Investigational	4 or 8 mg/kg	30	18
AH102	Investigational	120, 240 or 360 mg	36	9
AH101 (part 1)	Investigational	19, 57, 114 mg	18	6
AH101 (part 2)	Investigational	114 mg	6	6
IM Study				
[redacted]				(b) (4)

*First treatment period after initial dose of obiltoxaximab: Days 1 through 13
**obiltoxaximab alone
***obiltoxaximab with and without ciprofloxacin for 8 days (AH110) or obiltoxaximab plus ciprofloxacin vs. placebo plus ciprofloxacin for 14 days (AH101)

The FDA Single-Dose Primary Safety Population, hereafter referred to as FDA PSP, consisted of subjects who received a single dose of 16 mg/kg of the commercial (Lonza) formulation of obiltoxaximab:

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

The FDA ESP contained all subjects at all time points in AH104, AH109, and AH110. Lastly, AH104 was the largest human safety study with a direct comparison of ETI-204 and placebo; therefore, its analysis is presented alongside FDA PSP and FDA ESP in the following sections. In discussions between the Applicant and FDA, a safety database of at least 300 subjects receiving the intended dose of obiltoxaximab was recommended. In the IV development program of obiltoxaximab, these numbers were met; the safety database was therefore considered adequate.

Disposition of Subjects

Table 8.11 FDA Analysis of Disposition of Subjects in the FDA PSP, FDA ESP and AH104

		Placebo (n=70) N(%)	Obiltoxaximab N(%)		
			FDA PSP* (N=300)	FDA ESP** (N=320)	AH104 N=210
Completed Study		69 (98.6%)	294 (98%)	304 (95%)	205 (97.6%)
Terminated Study Prematurely		1 (1.4%)	6 (2%)	16 (5%)	5 (2.4%)
	Adverse Event	0	1 (0.3%)	2 (0.6%)	0
	Death	0	0	0	0
	Withdrawal of Consent	1 (1.4%)	1 (0.3%)	3 (0.9%)	1 (0.5%)
	Lost to Follow-up	0	4 (1.2%)	8 (2.5%)	4 (1.9%)
	Protocol Violation	0	0	2 (0.6%)	0
	Other	0	0	1 (0.3%)	0

*FDA PSP – AH104, first 13 days of AH109, obiltoxaximab alone arm of AH110
**FDA Expanded Safety Population – all subjects in AH104, AH109, AH110

Consideration of duration of dosing does not apply in this instance as the intended use is a single dose.

Based on recommendations from the Clinical Trial Steering Committee (CTSC), 50 mg oral diphenhydramine approximately 30 minutes prior to study drug administration was a required pretreatment to limit infusion-related reactions 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. All subjects in AH110 received diphenhydramine pretreatment.

8.2.2 Relevant characteristics of the safety population: The demographics of the subjects in AH104, the FDA PSP and the FDA ESP are tabulated below**:**

Table 8.12 FDA Analysis: Demographics of Subjects in AH104, FDA PSP and FDA ESP

Demographic Parameters	Placebo (N=70) n(%)	Obiltoxaximab			Total (N=390) n(%)
		AH104 (N=210) n (%)	FDA PSP (N=300) n (%)	FDA ESP (N=320) n (%)	
Sex					
Male	38 (54.2%)	106 (50.4%)	162 (54%)	174 (54.3%)	212 (54.4%)
Female	32 (45.7%)	104 (49.5%)	138 (46%)	146 (45.6%)	178 (45.6%)
Age					
Mean (years)	41.5	42.4	41.9	**47.2**	**44.3**
Median (years)	40	43	42	**47**	**43.5**
Min, Max (years)	20, 78	18, 79	18, 79	**18, 79**	
Age Group					
< 18 years	0	0	0	0	0
≥ 18 < 65 years	66 (94.3%)	189 (90%)	270 (90%)	290 (90.6%)	356 (91.2%)
≥ 65 years	4 (5.7%)	21 (10%)	30 (10%)	30 (9.4%)	34 (8.7%)
> 65 < 75 years	3 (4.3%)	18 (8.6%)	23 (7.7%)	23 (7.2%)	
≥ 75 years	1 (1.4%)	3 (0.5%)	5 (1.7%)	5 (1.6%)	6 (1.5%)
BMI (kg/m^2)					
Mean	27.1	27.7	27.7	28.5	27.8
Median	26.3	26.9	26.9	27.8	27.1
Min, Max	19.4, 43.8	18.1, 52.3	18, 52.3	18, 52.3	
Body Weight (kg)					
Mean	77.6	81.2	81.1	81.3	79.5
Median	75.9	79.2	79.6	79.8	77.9
Min, Max	55.4, 110.6	48.4, 149.5	48.4, 149.5	48.4, 149.5	
Race					
White	44 (62.9%)	151 (71.9%)	210 (70%)	224 (70%)	254 (68.6%)
Black or AA[1]	23 (32.9%)	53 (25.2%)	80 (26.7%)	83 (25.9%)	103 (27.8%)
Asian	2 (2.9%)	3 (1.4%)	3 (1%)	3 (0.9%)	5 (1.3%)
AI[2] or AN[3]	0	0	3 (1%)	6 (1.8%)	3 (0.8%)
NH[4]	0	0	0	0	0
Other	1 (1.4%)[5]	3(1.4%)[6]	4 (1.3%)[7]	4 (1.2%)[7]	5 (1.3%)
Ethnicity					
H/L[8]	9 (12.8%)	20 (9.5%)	25 (8.3%)	31 (9.7%)	43 (11%)
Not H/L	61 (87.1%)	189 (90%)	274 (91.3%)	288 (90%)	349 (89.5%)

[1]AA:African American; [2]AI:American Indian; [3]AN:Alaska native; [4]NH:native Hawaiian/Pacific islander;[5]South East Asian/White; [6]AA/white; AI/AA/white; AA/white; [7]AA/white; AI/AA/white; AA/white; AI/white); [8]Hispanic/Latino

The demographics of the subjects studied in the FDA PSP were felt to be generally representative of the US population, though the proportions of some groups, e.g. Asians or subjects >65 years, were numerically small. The important exceptions in the subject database were the pediatric population, pregnant and lactating women, and adults with significant co-morbidities. Clinical trials did not include pediatric age groups and pregnancy and lactation was an exclusion criteria, due to concerns for safety.

8.2.3 Adequacy of the safety database:

All subjects were healthy volunteers, but 90 subjects from AH104 (21 in the placebo arm, 69 in the obiltoxaximab arm) 64 subjects from AH109 (31 in Sequence A, 33 in Sequence B) and 34 subjects from AH110 (17 in the obiltoxaximab arm, 17 in the obiltoxaximab + ciprofloxacin arm) had stable co-existing medical conditions as summarized in the following table.

Table 8.13 FDA Analysis: Common stable co-morbidities in the FDA PSP

Condition	Number of subjects	
	Obiltoxaximab	Placebo
Hypertension	5	1
Hypercholesterolemia	6	0
Dyslipidemia	3	0
Hypothyroidism	5	1
Type 2 diabetes mellitus	1	0
History of drug hypersensitivity	3[1]	0
History of migraine headache	4	0
History of headaches	11	0
History of urticaria	1	0
Asthma	2	0
Chronic renal disease (mild)	1	0
Seasonal allergies	17	0
Myopia	28	0
Presbyopia	22	0
Carcinoma in situ of cervix	1	0

[1]Allergies to penicillin, amoxicillin and cephalexin

Many had had surgical procedures in the past, such as adenoidectomy, tonsillectomy, appendectomy, arthroscopy, caesarean section, bunion operation, ASD repair (1), cholecystectomy, female sterilization procedures (41), knee operation, hysterectomy, polypectomy, bilateral salpingo-oophorectomy, wisdom teeth removal and others. No subject had immunodeficiency or history of repeated upper respiratory tract infections, sinusitis or bronchitis.

There were no major differences in the use of concomitant medications between the two groups. The most common medications used were diphenhydramine (protocol after July 2013 amended to include premedication with 50 mg PO half an hour prior to infusion of obiltoxaximab), paracetamol (49 subjects), naproxen (11 subjects), multivitamins (24 subjects), methylprednisolone (3 subjects), medroxyprogesterone (6 subjects), ibuprofen (50 subjects), amoxicillin (10 subjects), and ASA (20 subjects).

Reviewer comment: Since obiltoxaximab is intended for administration to an entire population in an outbreak situation, the lack of pediatric subjects, pregnant women, and subjects with chronic medical conditions, especially renal and hepatic insufficiency or immunosuppression from whatever cause in this study, is potentially a significant drawback to evaluation of safety. The Applicant should ideally consider obtaining data on the safety profile of obiltoxaximab in subjects with active co-morbidities, but this may not be ethical or practicable due to safety concerns. The percentages of white, AA and Hispanic subjects in the safety database are reflective of U.S demographics (2014 Census – white: 77.4%, black: 13.2%, Hispanic: 17.4%), but the other races are under-represented.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

Overall, the Applicant's clinical safety assessments were acceptable because relevant laboratory parameters were measured with a reasonable schedule for laboratory evaluation. The plan for evaluation of subjects in AH104 is outlined in the Schedule of Assessments, Section 8.1.1.3. Exploratory measurements of cytokines in the first 80 subjects in AH104, and IgE and histamine levels in subjects with hypersensitivity, were done. Complete physical examinations were done at Day -1 and at Day 71, with limited examinations at Days 15 and 43, in accordance with the protocol. However, a complete physical exam at the time of an adverse event, especially if the AE resulted in discontinuation of study drug, should have been done in order to correctly characterize these events clinically as anaphylaxis or hypersensitivity.

Reviewer comment: Though not part of the protocol, this information should have been provided as part of the narrative to clarify the clinical reaction. This reviewer obtained information about the various cases by review of the clinical narratives, adverse event tables provided by the Applicant and independent analysis of the dataset.

Overall, the submission was well-organized and information was relatively easy to find. However, a few problems were identified:

1. Electronic case report forms (eCRF's) from the 4 study sites of Covance were each 900+ pages long, with only 1 or 2 variables per page, and extensive audit information was

included which was not relevant to the review of safety data. This made it difficult to review, both in terms of the time spent and the inability to easily appreciate a time course.

2. Datasets for AH101 and AH102 had to be requested from the Applicant for supportive safety data.

3. Additional CRF's were requested from the Applicant for all patients who were discontinued from the study.

4. The tables of adverse events listed per individual were confusing to interpret for AEs that occurred PRIOR to infusion of obiltoxaximab. These events were marked but appeared to be assigned a time of occurrence AFTER the start of the infusion. The clinical reviewer conducted an independent analysis regarding timing of adverse event onset using JMP and based on the study day of the AE. SI units were used for some of the biochemical tests, especially liver enzymes. This made is difficult to evaluate laboratory test results without conversion to the standard units used in the U.S.

5. The study sites which enrolled the largest numbers of subjects in the pivotal safety study, AH104, were chosen for site inspection, in addition to the sites for the repeat-dose study, AH109. The reports are still pending. Bioequivalence and GLP inspection of the (b) (4) was requested as several of the subjects had measurable obiltoxaximab in their blood PRIOR to the infusion.

Reviewer comment: After discussion with the Clinical Pharmacology review team, this finding was felt to be non-significant since the serum levels of obiltoxaximab were very low and likely reflective of cross-reactivity of the assay. Please see the Clinical Pharmacology review by Dr. Zhixia Yan for further discussion of this issue.

6. Many more subjects in AH109 were listed as having experienced somnolence which was marked as an adverse event. The investigators appeared to relate this to pre-medication with diphenhydramine. Since 192 out of 280 subjects in AH104, all subjects in AH110 and 62 subjects out of 70 in AH109 received premedication with diphenhydramine, it was unclear why somnolence was identified as an AE only in AH109 and AH110. An Information Request was sent to the Applicant regarding this – they did not offer a clear explanation other than that there was a difference in assessment of AEs, and specifically, of somnolence by different investigators.

Reviewer comment: Information requests were sent to the Applicant regarding #s 1, 2, 3, and 7. With regard to #1, the Applicant explained that these were the eCRF's provided by Covance, and that they could not change them. Supportive databases from AH101 and 102 and CRF's for all subjects who were discontinued from the study for any reason were provided by the Applicant.

7. Categorization of subjects with significant hypersensitivity or anaphylaxis was problematic in the human safety studies. While the Applicant identified and tabulated characteristics of subjects in whom infusion was discontinued and provided narratives for those subjects, the AE's that each experienced were identified as Preferred Terms (PTs) without an overall clinical interpretation.

Reviewer comment: The lack of a physical examination at the time of occurrence of the hypersensitivity reaction or the lack of overall clinical interpretation led to an under-estimation of significant hypersensitivity and anaphylaxis in these studies. This reviewer's clinical interpretation of their significance is therefore different from that of the Applicant.

8. Several measurements of IgE and histamine levels are missing or not available. This was a hindrance in evaluation of the mechanism of hypersensitivity.

8.3.2 Categorization of Adverse Events

The definitions of adverse events (AE), serious adverse events (SAE), and treatment-emergent adverse events (TEAE) used in the application are standard – for reference, they are reproduced briefly below.

An adverse event (AE) was defined by the Applicant as an "untoward medical occurrence in a subject, which did not necessarily have to have a causal relationship with study treatment." An AE could therefore be an unfavorable or unintended sign (including an abnormal laboratory finding), symptoms or disease temporally associated with the use of an investigational product, whether or not it was considered to be related to the product.

AEs were collected from the day the subject gave informed consent until 30 days after the final dose of study drug or until resolution of all SAEs. Subjects with AEs that were ongoing at their last study visit were followed: 1) until the AE resolved; 2) the AE became stable and was not expected to further improve; or 3) for 30 days after the subject's last study visit, whichever came first. The exception was a serious adverse event (SAE), which was followed until the event resolved or the event or any sequelae stabilized.

The severity of each AE was graded on a 3-point scale:

1 = mild. Discomfort noticed but no disruption of normal daily activity

2 = moderate. Discomfort sufficient to reduce or affect daily activity
3 = severe. Inability to work or perform normal daily activity

The relationship of the AE to study drug was evaluated using the following criteria:

- Related AE
  - Followed a reasonable temporal sequence from drug administration; and/or
  - Abated upon discontinuation of study drug; and/or
  - Was confirmed by reappearance of the reaction on repeat exposure (rechallenge); and/or
  - Was associated with use of a study device/procedure; and/or
  - Could not be reasonably explained by the known characteristics of the subject's clinical state; and/or
  - Could not have been produced by the subject's clinical state or by other modes of therapy administered to the subject

- Unrelated AE: was most likely produced by the subject's clinical state or by other modes of therapy administered to the subject

Reviewer comment: The clinical reviewer evaluated "relatedness" for certain AEs independent of the Applicant's evaluation.

A **treatment-emergent AE** (TEAE) was defined as an AE that started or worsened (relative to the pretreatment state) at any time from the start of the study drug infusion through Day 71 (nominal date of last visit in studies AH104 and AH110), and through Day 191 (last study day in AH109). Pre-existing conditions that worsened during the study were reported as AEs.
The Applicant used MedDRA version 16.0 to code AEs.

Serious AEs were defined by the Applicant as fulfilling the following criteria:

- Fatal
- Life-threatening
- Required or prolonged hospitalization
- Significantly or permanently disabling or incapacitating
- Was a congenital anomaly or birth defect
- Jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above

Reviewer comment: The last criterion was used by the clinical reviewer to re-classify the aggregate of some adverse events associated with hypersensitivity which were listed by the Applicant as moderate or mild. These will be discussed in detail in Section 8.5.1,

Hypersensitivity. An explanation for the Applicant's classification and interpretation of these events was sought through an Information Request. The Applicant's response to the request did not, in this reviewer's opinion, clarify their approach or justify their reliance on the use of Preferred Terms rather than a full clinical interpretation of their significance.

The infusion of study drug was stopped under the following circumstances:

- Symptomatic hypotension
- Respiratory distress (bronchospasm or central cyanosis)
- Generalized urticaria considered by the investigator to be of severe intensity
- Anaphylactic reaction
- The development of any other SAE considered by the Investigator to be related to study drug
- Any other event at the Investigator's discretion

Upon the discretion of the Investigator, agents such as diphenhydramine, epinephrine, famotidine, albuterol, methylprednisolone injection, and acetaminophen could be used in urgent situations such as anaphylactic shock or allergic reactions. Infusions could be restarted at the discretion of the investigator.

Subjects who did not receive the complete infusion remained in the study and completed all prescribed study visits and procedures unless the subject withdrew consent and chose not to continue in the study.

For each subject randomized and treated, including those who failed to complete the study, an eCRF was completed by the study staff. If a subject withdrew from the study, the reason was to be noted on the eCRF. If a subject was withdrawn from the study because of a treatment-limiting AE, thorough efforts were to be made to clearly document the outcome.

Reviewer comment: The definitions of adverse events, and treatment-emergent AEs are standard and, except for the identification of somnolence, appeared to be applied appropriately by the study sites. The Applicant's criteria for stopping the infusion due to an adverse event were also thought to be reasonable, and they also provided a clear and reasonable definition of SAEs.

Definition of Hypersensitivity and Anaphylaxis

A major potential concern with administration of monoclonal antibodies in general is the occurrence of immediate or delayed hypersensitivity or anaphylaxis; thus careful attention was paid to the occurrence of these AEs.

Reviewer comment: This definition is considered separately because this clinical reviewer identified it as the most significant safety signal in this Application, and differed with the Applicant's approach to its analysis.

The Applicant defined hypersensitivity to include the following: symptomatic hypotension, respiratory distress (bronchospasm or central cyanosis), generalized urticaria considered by the investigator to be of severe intensity, anaphylactic reaction, and SAEs considered by the investigator to be related to study drug.

This reviewer used the Summary Report of the Second NIH Symposium on the Definition and Management of Anaphylaxis[23] as the basis for evaluation of possible anaphylaxis. This document specifies a working definition of anaphylaxis to be "a serious allergic reaction that is rapid in onset and may cause death"; the diagnosis is highly likely when any ONE of the following 3 criteria is fulfilled:

1. 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:*

    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)

    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch/flush, swollen lips/tongue/uvula)

    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

[23] Sampson HA et al. Second Symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infection Disease/Food Allergy and Anaphylaxis Network symposium. J All Clin Immunol. 2006; 117(2): 391-7

d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

The Applicant provided a Treatment Plan for Anaphylaxis (Appendix A; AH104 CSR). The summary of this plan is outlined in Section 8.1.1.4.

The Applicant's discussion of hypersensitivity in the ISS was reviewed. In their broad review of all unique terms of potential hypersensitivity and rash, terms such as chest discomfort, conjunctivitis, pneumonitis, seasonal allergy, acarodermatitis, application site erythema, dermatitis contact, eczema, and infusion site erythema were included. The Applicant then did a more focused review resulting in exclusion of many of those broader terms; this reviewer conducted an independent analysis and agreed that those terms were not relevant to identification of potential hypersensitivity (for example, acarodermatitis is skin inflammation or eruption produced in response to a mite).

This reviewer independently looked for hypersensitivity using the Broad SMQ's of Hypersensitivity, Anaphylactic Reaction and Angioedema through MAED analysis, and compared the subjects identified through this with the group identified by grouping subjects in JMP by the Hypersensitivity (HYPER) and Hypersensitivity with Clinical Review (HYPER2FL) flags. The Preferred Terms (PTs) included under the Anaphylactic Reaction SMQ in MAED were rash generalized, rash, pruritus, cough, rash erythematous, flushing, dyspnea, cyanosis, and anaphylactic reaction. The PTs under Hypersensitivity included rash generalized, seasonal allergy, rash, pruritus, urticaria, dermatitis allergic, skin exfoliation, rash erythematous, hypersensitivity, dermatitis, anaphylactic reaction, dermatitis contact, flushing and conjunctivitis, while the Angioedema SMQ included urticaria and hypersensitivity.

Reviewer comment: Using the Second NIH Symposium criteria for definition of anaphylaxis, this reviewer identified several subjects who potentially fit the criteria for anaphylaxis, compared to the single subject identified by the Applicant. A full discussion of hypersensitivity is found in Section 8.5.1.

MedDRA version 16.0 was utilized to code AEs. In general, the Applicant's coding appeared to be acceptable with reasonable agreement between the verbatim terms for AEs and the preferred term. Though all AEs were listed by SOC and PT by the Applicant, it was felt that for

some categories, SOCs were preferred as this gave a more accurate picture of certain AEs such as those related to the skin or hypersensitivity. It was felt that the Applicant "split" certain terms – this is discussed in more detail in a later section.

Reviewer Comment: The analysis of AEs, as described in Section 8.1.1.5 was considered adequate. This reviewer's independent analysis of AEs was performed in a similar way: by SOC (System Organ Class) and by PT (Preferred Term). For analysis of SOCs, the number of subjects with even one TEAE in that SOC was counted, while within each SOC, the number of events were counted separately. Thus, one subject may have had more than one TEAE in the same SOC.

8.3.3 Routine Clinical Tests

The frequency of physical examinations as outlined in the Schedule of Assessments was considered reasonable overall, but lacked the specification for a physical examination at the time of a hypersensitivity reaction, especially one that resulted in discontinuation of study drug infusion.

Reviewer Comment: A physical examination should have been done and recorded during hypersensitivity reactions, in a way that did not interfere with clinical treatment of the reaction. Although the subject narratives provide the context, the list of symptoms and their chronological sequence of appearance and resolution, there is no detailing of the subject's overall appearance, voiced complaints, level of objective or subjective distress or results of pulmonary or cardiac auscultation. These and other parameters are very important when considering the clinical relevance of the observed symptoms and signs of hypersensitivity. In a real clinical situation, they would be a critical part of bed-side decision-making about whether or not to continue the infusion or how to treat adverse events related to it; in this Application, an accurate categorization of serious hypersensitivity or anaphylaxis was difficult in the absence of these data.

The clinical laboratory parameters evaluated during these studies are outlined in the Schedule of Assessments in Section 8.1.1.3. The specified parameters and timing were considered to be reasonable by this reviewer. Blood draws were done after a 10-hour fast, and the methodology of handling samples was considered to be adequate. The laboratories utilized for PD measurements were specified in Section 8.1.1.3. Since hypersensitivity may be anticipated with infusion of obiltoxaximab, frequent vital signs during and after infusion would be key to detect hypotension, tachycardia or fever. On Day 1, temperature, heart rate, respiratory rate, and blood pressure were measured predose and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours, and 8 hours after the start of infusion. On Days 1 and 2, deviations of ±5 minutes for time points <1.5 hours post start of infusion and ±10 minutes for time points ≥1.5 hours post start of infusion were allowed. The protocol did not specify measurement of postural changes in blood pressure in the event of dizziness. Out of range vital signs were evaluated according to

criteria specified in Section 8.1.1.3. Abnormal laboratory values were followed up until values returned to baseline. Because all human studies were Phase I and involved only healthy humans with near-normal renal and hepatic function, there were few serious changes in laboratory parameters.

Reviewer comment: Renal and hepatic dysfunction were exclusion criteria for the human studies. However, because obiltoxaximab is a monoclonal antibody, i.e,. a protein which is ultimately broken down endogenously, neither the kidney nor liver are important routes of elimination.Therefore, impairment of either renal or hepatic function is not anticipated to change recommendations for administration of obiltoxaximab. In non-clinical animal models, there was one animal with immunohistochemical staining of a part of the glomerular membrane. However, this was not uniform, and there was no other evidence that obiltoxaximab binds to glomeruli.

Because obiltoxaximab is intended as a single dose monoclonal antibody, no other alterations in laboratory values are anticipated, except in the context of hypersensitivity. Thus, the schedule detailed by the Applicant for hematology, clinical biochemistry, thyroid testing and urinalysis was considered suitable.

The Applicant also performed exploratory analyses for cytokine production and variation after administration of obiltoxaximab, as well as pre- and postdose measurements of IgE and histamine in subjects with hypersensitivity in order to try and define its mechanism. The laboratories which performed these measurements were detailed in Section 8.1.1.3; all protocols used were validated. The methodology of sample collection and storage was considered to be reasonable.

Reviewer comment: These exploratory analyses were useful to try and define the cytokine milieu following infusion of obiltoxaximab and its possible relevance to the occurrence of adverse events, as well as to identify a possible mechanism of hypersensitivity. However, data collection was incomplete for the IgE and histamine levels as samples at relevant time points in some subjects are missing. Thus, even in the 10 subjects with significant hypersensitivity, although there appears to be an intriguing increase in histamine release during hypersensitivity in some of them, one cannot reasonably infer a pattern partly because of the missing data. Defining this would potentially be very relevant in determining the most effective method and timing of premedication to prevent hypersensitivity to obiltoxaximab. Further, the Applicant should have considered performing histamine and IgE assays in all subjects, or at least in a larger population, regardless of whether they developed hypersensitivity. This would have provided a context in which to determine whether the increase in histamine release following infusion of study drug in some subjects was really connected with hypersensitivity.

Finally, it would have been useful for the Applicant to consider exploratory analyses of other factors that may be important in causation of upper respiratory infections, since the incidence of these seemed greater in the repeat-dose groups of AH109 (see Section 8.5.2). For example, pulmonary function testing,and measurements of CD4, CD8, serum complement levels or IgA, and IgM levels in addition to IgE, may have been useful. IgG levels would not have been useful since they would have included obiltoxaximab also.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in any of the studies in the clinical development program of obiltoxaximab.

8.4.2 Serious Adverse Events

In the FDA ESP, including all subjects in AH104, AH109 and AH110, there were 2 subjects who were classified by the Applicant as having a serious AE.

Table 8.14 Serious Adverse Events in FDA ESP

Subject ID	Infusion Received	Demo	PT	Study day of onset	Course	Related
109-002-232	Sequence B	46 YOM/WAI	Ankle fracture	166	Hospitalized, ORIF	unrelated
104-002-216	Placebo	42 YOF/W	Ovarian cyst	12	Hospitalized d101, Bilateral oophorectomy	unrelated

Source: FDA Analysis from Applicant's narratives and CRF's

These cases were reviewed by perusing the CRF's as well as the Applicant's narratives.

Subject 109-002-232 experienced an ankle fracture on day 166 and had to be hospitalized. He was a 46 year old white/American Indian male randomized to sequence B. He had a history of seasonal allergies, hay fever, sleep apnea, gastroesophageal reflux disease, headache, tonsillectomy/adenoidectomy, anterior cruciate ligament tear in the knee with reconstruction. He was on omeprazole and intermittent ibuprofen. All 3 infusions were completed as scheduled. After the obiltoxaximab infusion on Day 1, the subject reported a dry mouth (5 hours later), swelling and tenderness at the site (8 hours later). These were classified as mild, and resolved in 16 hours. At the final study visit, he informed the investigators that he had slipped on ice while at work on Day 166 and sustained a severe fracture and dislocation of his right ankle. He required an open reduction and internal fixation, was hospitalized overnight for

this, and required general anesthesia, local anesthesia, pre-operative antibiotics, ibuprofen, hydrocodone and acetaminophen as concomitant medications. The investigator categorized this event as a severe, serious AE unrelated to study medication.

Subject 104-002-216 had a left-sided ovarian cyst – although the Applicant classified it as of moderate severity, it was included as a serious adverse event since the subject required hospitalization. She was a 42-year-old, white female with a medical history of hysterectomy, breast augmentation, lithotripsy, and bladder stent. The subject received an IV infusion of placebo on Day 1. On Day 12, the subject reported to the emergency room with abdominal pain, and an abdominal ultrasound identified an ovarian cyst on the left side. The subject was treated with fentanyl, hydromorphone, and ondansetron and discharged; the ovarian cyst was reported as an AE of moderate severity and was judged as unrelated to study drug by the investigator. The subject completed the study on Day 71, but the event continued for 87 days. On Day 101, (30 days after the final study visit), the subject underwent surgery for removal of her left ovary. Due to complications discovered during surgery, both ovaries and her appendix were removed and the subject was hospitalized. The investigator reported an unrelated serious AE of ovarian cyst of moderate severity on Day 101 that resolved after 1 day. The subject recovered and was discharged from the hospital on Day 102.

Reviewer comment: This reviewer agreed with the Applicant's assessment that neither of these SAEs were related to infusion of study drug.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

The pre-specified safety withdrawal criteria used in all 3 major safety studies are outlined in Section 8.1.1.3 Study Design and Investigational Plan. This reviewer considered them to be reasonable.

A total of 17 subjects or 5.3% of the FDA ESP (320 subjects) withdrew from the 3 main studies prematurely. Their reasons for withdrawal, study arm, and study day of withdrawal are shown in Table 8.15.

Table 8.15 Details of Subjects Discontinued from the 3 Studies in the FDA ESP

Study/subject ID	Study arm*	Study day	Lost to follow up	With-drawal of consent	Protocol violation	Adverse event	Other
110-001-113	Obiltoxaximab + cipro	1					Personal Reasons
109-001-108	Sequence A	71	Y				
109-001-120	Sequence B	43	Y				
109-001-121	Sequence A	43	Y				
109-001-131	Sequence B	134	Y				
109-001-119	Sequence A	85			Y		
109-001-127	Sequence B	119			Y		
109-002-214	Sequence B	79		Y			
109-002-216	Sequence A	41		Y			
109-002-204	Sequence B	106				Y	
109-002-205	Sequence A	1				Y	
104-001-038	ETI-204	71	Y				
104-002-226	ETI-204	15	Y				
104-003-118	ETI-204	43	Y				
104-004-316	ETI-204	47	Y				
104-002-236	ETI-204	13		Y			
104-002-247	Placebo	8		Y			

Adapted from CSR's of AH104, AH109 and AH110; Y: yes
*Sequences A and B are in AH109. Sequence A: obiltoxaximab/obiltoxaximab/placebo; Sequence B: obtiltoxaximab/ placebo/obiltoxaximab.

Six subjects from AH104 (2.1%) withdrew from the study – 5 in the obiltoxaximab arm (2.4%) and 1 in the placebo arm (1.4%). Of these, 4 were lost to follow-up (all in the obiltoxaximab arm) and 2 withdrew consent (1 in the placebo, and 1 in the obiltoxaximab arm).

Ten subjects from AH109 (14.3%) withdrew from the study – 5 (7.1% of the total, 14.3% of the subjects in the arm) from Sequence A, and 5 (7.1% of the total, 14.3% of the 35 subjects in the arm) from Sequence B. Four were lost to follow-up, 2 withdrew consent, 2 had a protocol violation and 2 were withdrawn due to an AE. Subjects 109-001-119 and 109-001-127 had protocol deviations due to positive urine drug screens at Days 85 and 119 respectively, and were withdrawn on those days.

Reviewer comment: There were a higher percentage of subjects who withdrew from study AH109 as compared with the other studies. Of these, only 2 were due to an adverse event (both of which occurred on Day 1). It is possible that the lower completion rate was related to the long study period (191 days) as compared with 71 days for studies AH104 and AH110.

One subject from AH110 (2.5%) discontinued from the study for personal reasons.

Reviewer comment: An Information Request was submitted to the Applicant in order to obtain eCRFs for all subjects who were discontinued from, or dropped out of the study for reasons other than AEs (since these were already provided the Applicant). These eCRFs were reviewed to make sure that subjects who were identified as lost to follow-up, withdrawal of consent or had other reasons to withdraw from the study did not actually have an AE to account for the withdrawal. Of those reviewed, none seemed to have withdrawn due to an AE.

Subject 104-001-026 had a protocol deviation as the study drug administration record could not be found. However, this subject was not discontinued from the study, and is included in the safety analysis.

There were no abnormalities of laboratory testing that necessitated discontinuation of any subject from a study.

Ten subjects in the FDA ESP had significant hypersensitivity; 8 of them had infusion of study drug (all obiltoxaximab) discontinued, but completed the study. These subjects are not included in this section, but discussed in detail in Section 8.5.1 Hypersensitivity. Two subjects in AH109 had hypersensitivity to infusion of obiltoxaximab on Day 1, and were discontinued from the study so that they would not receive another dose; these 2 subjects are also reflected in Table 8.15.

8.4.4 Significant Adverse Events

The focus of this review is on treatment-emergent AEs as these are relevant to study drug administration. Adverse events were characterized as mild, moderate or severe using the definition outlined in Section 8.3.2. The majority of subjects with AEs in the placebo arm and the obiltoxaximab arm of all study populations – AH104, FDA PSP and FDA ESP - had mild AEs. Many fewer had moderate or severe AEs in either arm. The distribution of AE severity in the various populations is tabulated below in Table 8.16.

Table 8.16 FDA Analysis: Frequency of Mild, Moderate and Severe AEs in AH104, FDA PSP and FDA ESP

	TREATMENT ARM			
AE Severity	**Placebo**	**Obiltoxaximab**		
	N=70 n (%)	**AH104 N=210 n (%)**	**FDA PSP N=300 n (%)**	**FDA ESP N=320 n (%)**
Mild	27 (38.6%)	86 (40.9%)	134 (44.7%)	172 (53.7%)
Moderate	2 (2.6%)	14 (6.7%)	18 (6%)	34 (10.6%)
Severe	0	1 (0.5%)	2 (0.7%)	5 (1.6%)

Reviewer comment: Mild AEs occurred in a similar percentage of subjects in both the placebo (38.6%) and obiltoxaximab (40.9%) arms of AH104, while moderate AEs occurred more frequently in the obiltoxaximab arm (6.7%) than in the placebo arm (2.6%). There was one subject with a severe AE in the entire safety population of AH104. In the FDA PSP, mild AE's were reported in 134/300 (44.6%) of subjects in the obiltoxaximab arm, moderate AE's were reported in 6%, while 2 of 300 (0.7%) subjects were categorized by the Applicant as having severe AE's. Subject 104-002-058 had pruritus and urticaria, both classified as severe, on study Day 1, and subject 109-002-204 had severe back pain, also on study Day 1; these 3 AEs were clearly related to obiltoxaximab infusion and occurred in the context of significant hypersensitivity. These AEs will be discussed in detail in Section 8.5.1.

In the FDA ESP, all AE's occurred in a higher percentage of subjects compared with the other populations – mild AEs occurred in 172 of 320 subjects (53.7%), moderate AEs in 34 subjects (10.6%) and severe AEs in 5 subjects (1.6%). In this reviewer's opinion, this difference is accounted for by the inclusion of the obiltoxaximab + ciprofloxacin arm of AH110 and all time points of AH109 in FDA ESP. The longer study period in AH109 may have driven the increased numbers of subjects with mild, moderate and severe AEs.

In order to better characterize the subjects with severe AEs in the entire population, the relevant details were investigated and tabulated in Table 8.17. There were 5 subjects who were listed by the Applicant as having a severe AE.

Table 8.17 FDA Analysis: Characteristics of Subjects in the FDA ESP with Severe AE's

Subject Identifier	SAE	Study Arm	Study Day of Occurrence	Need for concomitant medications or hospitalization	Drug Withdrawn	Relatedness*
104-002-053	Pruritus	obiltoxaximab	1	Yes	Yes	Yes
104-002-053	Hives	obiltoxaximab	1	Yes	Yes	Yes
109-001-129	Elevated CPK	Sequence B	28	No	No	Unlikely
109-002-204	Back pain	Sequence B	1	Yes	Yes	Yes
109-002-218	Gingivitis	Sequence A	15	Yes	No	No
109-002-232	Fracture dislocation – right ankle	Sequence B	166	Yes	No	No

Adapted from ISS; *FDA evaluation of relatedness

As noted above, six severe AEs occurred in 5 subjects (1.6%) in the FDA ESP. In contrast to the 3 severe AEs in 2 subjects identified in the FDA PSP, there were 3 other subjects in the FDA ESP who had severe AEs in treatment periods 2 and 3 (i.e., ≥14 days) of AH109.

The narrative for Subject 109-002-232 is outlined in Section 8.4.2. Subjects 104-002-053 and 109-002-204 had significant hypersensitivity reactions to the infusion of obiltoxaximab and the drug was withdrawn – the narratives for these subjects are found in Section 8.5.1.

Subject 109-001-129 was randomized to sequence B. On day 28 (i.e., 14 days after infusion of placebo on day 14), he was found to have elevated ALT, AST and LDH; none were reported as AE's, and all returned to baseline at the subsequent time point. No symptoms were recorded, and no physical examination appears to have been done. He also had a markedly elevated creatine phosphokinase (CPK) which was reported as a serious AE. The CPK value was 227.4 µkat/L (reference range: 0.53-4.9 µkat/L). At an unscheduled visit 2 weeks later, his serum CPK was normal. Of note, this subject's CPK were mildly elevated on days -1, 2, 8, and 71-191; these were not considered clinically significant. He reported having exercised, including lifting weights, 5 or 6 days prior to the SAE.

Reviewer comment: The heavy exercise may account for an elevated CK – there was no record of muscle pain or abnormal urinalysis to suggest muscle breakdown of another cause, and he was otherwise healthy. There is also no record to suggest ingestion of health supplements, but this may be a possibility in someone who works out; such supplements can sometimes contain active drug substances leading to abnormal laboratory values which are not labeled since these products are unregulated.

Subject 109-002-218 was a 51 year old male randomized to sequence A; on day 15, one day after receiving a second infusion of obiltoxaximab, he was classified as having worsening gingivitis. This was counted by the investigator as a severe AE, and the subject required concomitant medication as well as a procedure. This AE was not thought to be related to the infusion. A narrative was not provided by the Applicant.

This reviewer also analyzed moderate AEs in the FDA ESP - there were 60 such AE's in 36 subjects.

Table 8.18 FDA Analysis of Subjects with Moderate SAE's in the FDA ESP Stratified by Study

	AH104 (n)	Arm/Rel (Y/N)	AH109 (n)	Sequence/Rel (Y/N)	AH110 (n)	Arm/Rel (Y/N)
Pruritus	2	obiltoxaximab/Y	0	-	0	-
Hives	3	obiltoxaximab/Y	0	-	0	-
Rash	3	obiltoxaximab/Y	1[a]	B/N	0	-
Chills	1	obiltoxaximab/Y	1	B/Y	0	-
Dizziness	1	obiltoxaximab/Y	1	B/N	0	-
Nausea/emesis	1	obiltoxaximab/Y	2	B/N	0	-
Ankle fracture dislocation	1	obiltoxaximab/N	1	B/N	0	-
Ovarian cyst	1	placebo/N	0	-	0	-
Positive serum pregnancy test	1	obiltoxaximab/N	0	-	0	-
Acute anaphylactic allergic reaction	1	obiltoxaximab/Y	0	-	0	-
Headache	1	obiltoxaximab/Y	1	B/Y	0	-
Urticaria	0	-	2	A/Y; B/N	2	obiltoxaximab/Y
Gastroenteritis	0	-	2	A/N; B/N	0	-
Other	8*	obiltoxaximab/N	19**	Various**	2***	O+C[b]/Y; O+C/N

Rel: Related; Y: yes; N: no
*Feeling anxious, lack of energy, insomnia – all in subject 104-004-309; laceration left palm, situational depression, dental pain, elevated blood pressure, upper respiratory infection – all in one subject each
**Acrocyanosis, dyspnea, generalized myalgias, pallor, restlessness, decreased neutrophil count all occurred in subject 109-002-204 (B/Y); bilateral inguinal hernia, low back pain, dental pain, left gastrocnemius contracture, cough (B/Y), heartburn, sinusitis, labyrinthitis, pneumonitis, syncope, bacterial vaginosis, yeast vaginitis, Streptococcal pharyngitis – all in one subject each (those that were related are indicated in parentheses)
***Postural light-headedness, upper respiratory infection – in one subject each
[a]Scabies
[b]Obiltoxaximab + ciprofloxacin

Twenty-three moderate AE's (including those in the table and in the footnotes) occurred in subjects who had significant hypersensitivity (see section 8.5.1); these include pruritus, hives, rash, chills, dizziness, and urticaria, but also acrocyanosis, dyspnea, pallor, restlessness, decreased neutrophil count, and cough. The two subjects who had SAEs of left ankle fracture and ovarian cyst (described in Section 8.4.2), were also ascribed AEs of moderate severity by the investigator at different time points, as noted in Table 8.18. Subject 104-002-230 with a positive pregnancy test is described in detail in 8.7.2. The acute anaphylactic allergic reaction was rated as moderate in severity by the Applicant. This was the only event specifically identified as acute anaphylaxis and will be discussed further in Section 8.5.1.

Reviewer comment: As noted previously, the utility of either a single diagnosis of anaphylaxis such as in this table, or multiple individual preferred terms (PTs) to describe hypersensitivity, is

limited. There may be variability among on-site investigators in assigning PTs to clinical conditions which further underscores the importance of physical examinations in combination with other clinical data to aid in the critical evaluation of hypersensitivity in this Application. Further, a single term may not convey an accurate picture of a particular condition. For example, this reviewer questions the categorization by the investigators of an acute anaphylactic allergic reaction as a moderately severe event, rather than a severe event.

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

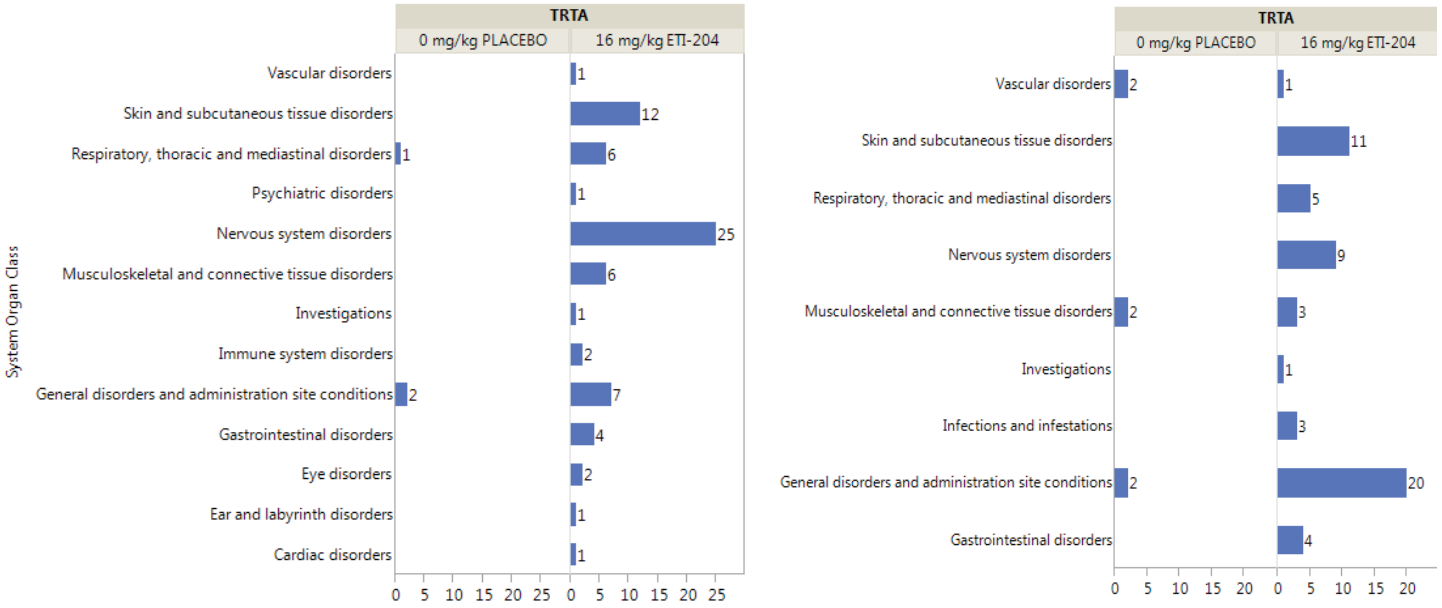
Treatment-emergent adverse events (TEAEs) are the most relevant to the safety analysis because they are directly related to infusion of study drug. The definition of a TEAE is outlined in section 8.3.2. Because obiltoxaximab is a monoclonal antibody and administered intravenously, infusion-related reactions, specifically hypersensitivity, would be expected. Thus, the Applicant recorded TEAEs occurring in the first 3 hours and between 3 and 24 hours, in addition to TEAEs across the study period and analyzed them using descriptive statistics.

Reviewer comment: The Applicant's identification of TEAEs occurring in two time periods within the first 24 hours was clinically relevant. Therefore, this clinical reviewer performed an independent analysis of TEAEs occurring in the first 3 hours, between 3 and 24 hours, and overall in AH 104, the FDA PSP and the FDA ESP. Because this reviewer's pooling strategy differed from the Applicant's for analysis of integrated safety, the percentages obtained in the independent analysis are not identical to the Applicant's numbers, though overall trends are similar.

FDA PSP

In the FDA PSP, 72 TEAEs emerged within the first 3 hours in 50 subjects (16.7%), and 63 TEAE's in 54 subjects (18%) occurred between 3 and 24 hours after start of study drug infusion. The occurrence of TEAEs in these two time periods by SOC is depicted graphically in Figure 8.1.

Figure 8.1 FDA Analysis of Subjects with TEAEs within 3 hours, and Between 3 and 24 hours after Start of Study Drug Infusion, by SOC, in the FDA PSP



<u>Reviewer comment</u>: In this graphical representation of subjects with TEAEs within the first 24 hours, several general patterns are easily visible. First, TEAEs are clearly more common in the obiltoxaximab arm (50 subjects [16.7%]) compared with placebo (3 subjects [4.3%]) within 3 hours, and this pattern holds true between 3-24 hours as well (49 subjects [16.3%] vs. 5 subjects [7.1%] in the obiltoxaximab and placebo arms respectively). Second, nervous system disorders occurred more commonly in the obiltoxaximab group within 3 hours compared to 3-24 hours (8.3% vs. 3% respectively), and not at all in the placebo group. Third, TEAEs in the general disorders and administration site conditions SOC occurred more frequently in the obiltoxaximab group at the later time period than within 3 hours (6.7% vs 2.3% respectively). Fourth, TEAEs in the skin and subcutaneous tissue disorders SOC, and the gastrointestinal disorders SOC seemed to occur almost equally at the two different time periods in the obiltoxaximab group, and not at all in the placebo group. Finally, 2 subjects had TEAEs within 3 hours in the immune system disorders SOC – the PTs were anaphylactic reaction and hypersensitivity.

The Preferred Terms within each SOC were analyzed more closely – these results are depicted in Table 8.19.

Table 8.19 FDA Analysis of TEAEs Occurring in the First 24 Hours after Infusion in the FDA PSP (with an incidence ≥ 2 subjects)

		Within 3 hours		3-24 hours	
System Organ Class	**Preferred Term**	**Obiltoxaximab, N=300 N(%)**	**Placebo, N=70 N(%)**	**Obiltoxaximab, N=300 N(%)**	**Placebo, N=70 N(%)**
Nervous System Disorders		**25 (8.3%)**	**0**	**9 (3%)**	**0**
	Dizziness	3 (1%)	0	0	0
	Headache	4 (1.3%)	0	8 (2.6%)	0
	Somnolence	17 (5.7%)	0	0	0
Skin and Subcutaneous Tissue Disorders		**12 (4%)**	**0**	**11 (3.7%)**	**0**
	Pruritus	8 (2.7%)	0	1 (0.3%)	0
	Rash	4 (1.3%)	0	1 (0.3%)	0
	Urticaria	3 (1%)	0	2 (0.7%)	0
	Dermatitis contact	0	0	5 (1.6%)	0
Respiratory, Thoracic and Mediastinal Disorders		**6 (2%)**	**1 (1.4%)**	**5 (1.7%)**	**0**
	Cough	4 (1.3%)	0	1 (0.3%)	0
	Throat irritation	2 (0.6%)	1 (1.4%)	0	0
	Dry Throat	0	0	2 (0.6%)	0
General and Administration Site Reactions		**7 (2.3%)**	**2 (2.9%)**	**20 (6.7%)**	**2 (2.9%)**
	Chills	2 (0.6%)	1 (1.4%)	0	0
	Infusion site pain	2 (0.6%)	0	5 (1.6%)	0
	Injection site swelling	0	1 (1.4%)	5 (1.6%)	0
	Vessel puncture site bruise	1 (0.3%)	0	6 (2%)	1 (1.4%)
	Infusion site discoloration	0	0	3 (1%)	0
	Infusion site erythema	0	0	4 (1.3%)	2 (2.8%)
Immune System Disorders		**2 (0.7%)**	**0**	**0**	**0**
	Anaphylactic Reaction	1 (0.3%)	0	0	0
	Hypersensitivity	1 (0.3%)	0	0	0

Reviewer comment: Independent analysis demonstrated that most of the TEAEs within the Nervous System Disorder SOC are driven by the occurrence of somnolence in 17 (5.7%) subjects, and occur within the first 3 hours. As noted previously, the occurrence of somnolence was mostly seen in AH109 and AH110. Since it is not biologically plausible that somnolence would

occur only in these studies with a single dose of obiltoxaximab, and not in AH104 with administration of either the same dose of obiltoxaximab or placebo, it suggests instead that the investigators recorded this probable side effect of diphenhydramine inconsistently among the studies. Thus, this reviewer feels that the observed occurrence of somnolence within the first 3 hours after infusion is likely not attributable to obiltotoxaximab.

Headache occurred less commonly within 3 hours (1.3%) compared to the 3-24 hour window (2.6%), and both rates were less common than the occurrence in the entire study period. This will be discussed further below.

Those PTs that occurred in only 1 subject were deleted from the table, and are as follows: Hypoesthesia and skin irritation occurred in 1 subject each within 3 hours, along with dyspnea and nasal congestion, non-cardiac pain and pain, cyanosis, anaphylactic reaction and hypersensitivity – all these occurred in the obiltoxaximab arm. Between 3 and 24 hours, vessel puncture site hemorrhage, rhinorrhea, dysphonia, petechiae, rash erythematous and dermatitis, and lethargy occurred in 1 subject each in the obiltoxaximab arm.

Reviewer comment: Again, this method of accounting shades the actual clinical significance of these findings. For example, hypoesthesia, dyspnea, non-cardiac pain, anaphylactic reaction and hypersensitivity all occurred in 2 of the subjects with severe hypersensitivity, in whom infusion of study drug was discontinued. This is discussed further in Section 8.5.1.

Pruritus occurred in 8 subjects (2.7%) within 3 hours compared to its occurrence in 1 subject (0.3%) between 3 and 24 hours. Rash occurred in 4 subjects (1.3%) compared to 1 (0.3%), and urticaria occurred in 3 (1%) compared to 2 (0.7%) within 3 hours and between 3 and 24 hours respectively. Contact dermatitis referred to local reactions to ECG pads, etc., and these were not counted as hypersensitivity – available data from all subjects identified with dermatitis was evaluated by this reviewer to ascertain relevance to hypersensitivity. Cough appeared to be a manifestation of hypersensitivity and occurred in 1.3% vs. 0.3% of subjects within 3, and between 3 and 24 hours after infusion, respectively.

By contrast, infusion site reactions such as infusion site pain (5 [1.6%] vs. 2 [0.6%] – obiltoxaximab arm), injection site swelling (5 [1.6%] in the obiltoxaximab arm vs 1 [1.4%] in the placebo group), vessel puncture site bruise (6 [2%] vs 1 [0.3%] – obiltoxaximab arm) and infusion site discoloration (3 [1%] vs 0 in the obiltoxaximab arm) occurred more often at 3-24 hours compared to within 3 hours.

Reviewer comment: The later occurrence of infusion site reactions seems reasonable from a clinical perspective. The greater occurrence of these reactions in the obiltoxaximab arm vs. placebo suggests that this is an effect of the product itself. In this reviewer's opinion, all the PTs

listed above were related to infusion of study drug and were clearly more prominent with obiltoxaximab infusion.
Six subjects (2%) had musculoskeletal AE's within the first 3 hours – all in the obiltoxaximab arm – these consisted of 1 occurrence each of back pain, muscle spasms, muscle twitching, musculoskeletal pain, myalgia, pain in extremity. Four subjects (1.3%) experienced gastrointestinal AE's consisting of abdominal pain, eructation, dry mouth, nausea and vomiting within the first 3 hours.

Reviewer comment: Although not obvious from this listing, the occurrence of back pain, myalgia and muscle twitching all occurred in the context of a hypersensitivity event.

Between 3 and 24 hours, nausea occurred in 2 subjects. Upper respiratory infection, folliculitis, and asymptomatic bacteriuria occurred in 3 subjects – these were judged not related to study drug infusion. A decrease in total white count, neutrophil count and lymphocyte count occurred in 1 subject; these were in the obiltoxaximab group and occurred in the context of anaphylaxis. Back pain occurred in 1 subject in the placebo arm, and 2 in the obiltoxaximab arm, while muscle spasms occurred in 1 subject in the placebo arm, and pain in the extremity in 1 subject in the obiltoxaximab arm.

FDA ESP

One hundred TEAEs occurred in 68 subjects within the first 3 hours after study drug infusion in the FDA ESP; 82 TEAE's occurred in 65 subjects between 3 and 24 hours after study drug infusion. The percentages of subjects with the main SOCs and PT's in the most commonly occurring SOC's are listed below in Table 8-21.

Table 8.20 FDA Analysis: TEAEs Occurring in the First 24 hours Following Infusion of Study Drug in the FDA ESP (incidence ≥ 2 subjects)

		Within 3 hours		3-24 hours	
System Organ Class	**Preferred Term**	**Obiltoxaximab, n=320**	**Placebo, n=70**	**Pbiltoxaximab, n=320**	**Placebo, n=70**
Nervous System Disorders		**39 (12.2%)**	**0**	**9 (2.8%)**	**0**
	Dizziness	4 (1.3%)	0	0	0
	Headache	4 (1.3%)	0	8 (2.5%)	0
	Somnolence	29 (9.1%)	0	0	0
Skin and Subcutaneous Tissue Disorders		**16 (5%)**	**0**	**17 (5.3%)**	**0**
	Dermatitis contact	0	0	8 (2.5%)	0
	Pruritus	8 (2.5%)	0	2 (0.6%)	0
	Rash	4 (1.3%)	0	1 (0.3%)	0
	Urticaria	6 (1.9%)	0	2 (0.6%)	0
Respiratory, Thoracic and Mediastinal Disorders		**6 (1.9%)**	**1 (1.4%)**	**6 (1.9%)**	**0**
	Cough	4 (1.3%)	0	1 (0.3%)	0
	Dry throat	0	0	2 (0.6%)	0
	Throat irritation	2 (0.6%)	1	0	0
	Chills	2 (0.6%)	1 (1.4%)	0	0
General Disorders and Administration Site Conditions		**12 (3.8%)**	**2 (2.9%)**	**23 (7.2%)**	**2 (2.9%)**
	Infusion site extravasation	2 (0.6%)	0	0	0
	Infusion site pain	2 (0.6%)	0	6 (1.9%)	0
	Injection site swelling	0	1 (1.4%)	5 (1.6%)	0
	Infusion site discoloration	0	0	3 (0.9%)	0
	Infusion site erythema	0	0	4 (1.2%)	2 (2.8%)
	Vessel puncture site bruise	1 (0.3%)	0	6 (1.9%)	1 (1.4%)
	Vessel puncture site hemorrhage	0	0	2 (0.6%)	0
Immune System Disorders		**2 (0.6%)**	**0**	**0**	**0**
	Hypersensitivity	1 (0.3%)	0	0	0
	Anaphylactic Rxn	1 (0.3%)	0	0	0

Reviewer comment: Similar trends were seen in the FDA ESP as in the FDA PSP. Nervous system disorders occurred in 39 (12.2%) subjects in the obiltoxaximab arm within 3 hours as against 9 (2.8%) at 3-24 hours and 0 in the placebo group in those time periods. Again, the incidence within 3 hours was primarily driven by the incidence of somnolence which was discussed above. Headache occurred in 8 subjects (2.5%) during the later time period compared to 4 (1.3%) within 3 hours.

The occurrence of TEAEs in the skin and subcutaneous tissue disorder SOC and the respiratory, thoracic and mediastinal disorders SOC were roughly equivalent between the two time periods in the obiltoxaximab group, and there was no occurrence of the former SOC in the placebo group. The incidence of infusion site pain (1.9%), injection site swelling (1.6%), and vessel puncture site bruise (1.9%) occurring between 3 and 24 hours was greater than the incidence of these PTs within 3 hours (0.6%, 0, and 0.3% respectively). The overall incidence of TEAEs within the general disorders and administration site conditions was 3.8% within 3 hours but rose to 7.2% at 3-24 hours.

Many other TEAEs occurred once during the first 24 hours in the obiltoxaximab group; some are detailed in the discussion of the FDA PSP as they occur in subjects common to both populations. In the 20 additional subjects and additional time points with TEAEs in the first 24 hours included in the FDA ESP, chest discomfort, postural dizziness, dysarthria, pain in jaw each occurred once in the first 3 hours after infusion of obiltoxaximab in a single subject – AH110-001-103 – and are part of this subject's hypersensitivity reaction. Palpitations occurred once between 3 and 24 hours – also in the same subject. Back pain, contusion, dry mouth, feeling cold, injury associated with a device, nausea, skin lesion, and syncope all also occurred in 1 subject each within 3 hours, while arthropod bite, dermatitis acneiform, nausea, oropharyngeal pain, vomiting, superficial phlebitis, rash maculopapular, and vulvovaginal infection occurred in one subject each between 3 and 24 hours after infusion.

Reviewer comment: In this reviewer's opinion, almost all these TEAEs were related to study drug infusion and most were manifestations of hypersensitivity. Some obvious exceptions are arthropod bite, and vulvovaginal infection. Once again, considering each PT separately does not convey the full clinical picture.

Dizziness and syncope were more closely examined as possible markers of more serious manifestations of hypersensitivity. Dizziness occurred in 4 subjects, and postural dizziness in 1 subject, in the FDA ESP within the first 3 hours after infusion. The one occurrence of postural dizziness (AH110-001-103) and one (AH104-002-068) of the 4 occurrences of dizziness were in the context of hypersensitivity reactions to infusion of obiltoxaximab. In subject AH109-001-122, randomized to sequence B, dizziness occurred together with the single occurrence of syncope and nausea 1 hour and 40 minutes after the start of the infusion of placebo on day 14. The

syncope lasted for 2 minutes and there was also a head contusion recorded; it is therefore a possibility, (though not specified by the Applicant), that the subject lost consciousness and fell. Her blood pressure was not recorded as part of the description of her AE, but her dizziness was recorded as lasting for 92 days. Subject AH109-002-226 experienced dizziness of mild severity starting 15 minutes into the infusion of obiltoxaximab on Day 1; this lasted for 53 minutes and was accompanied by mild transient pruritus. Concomitant medication was not required. Finally, subject AH104-002-224 experienced mild dizziness starting 1 hour and 19 minutes after starting the infusion of obiltoxaximab; this lasted for 6 minutes and did not require any intervention.

Study AH104 – First 24 Hours

Forty-two TEAE's occurred in 27 subjects (12.9%) in AH104 within the first 3 hours after study drug infusion – 39 of these were in the obiltoxaximab group, 3 in the placebo group. Thirty-six TEAE's occurred in 32 subjects between 3 and 24 hours after study drug infusion. The breakdown of these AE's are outlined in Table 8.21.

Table 8.21 FDA Analysis of Occurrence of TEAE's in AH104 within the First 24 Hours after Study Drug Infusion

		Within 3 hours		3-24 hours	
System Organ Class	**Preferred Term**	**Obiltoxaximab, n=210**	**Placebo, n=70**	**Obiltoxaximab, n=210**	**Placebo, n=70**
Nervous System Disorders		**7 (3.3%)**	**0**	**8 (3.8%)**	**0**
	Dizziness	2 (0.9%)	0	0	0
	Headache	4 (1.9%)	0	8 (3.8%)	0
Skin and Subcutaneous Tissue Disorders		**10 (4.8%)**	**0**	**6 (2.9%)**	**0**
	Dermatitis	0	0	1 (0.5%)	0
	Dermatitis contact	0	0	2 (0.9%)	0
	Pruritus	7 (3.3%)	0	1 (0.5%)	0
	Rash	3 (1.4%)	0	1 (0.5%)	0
	Urticaria	3 (1.4%)	0	1 (0.5%)	0
Respiratory, Thoracic and Mediastinal Disorders		**2 (1%)**	**1 (1.4%)**	**4 (1.9%)**	**0**
	Cough	2 (0.9%)	0	1 (0.5%)	0
	Throat irritation	2 (0.9%)	1 (1.4%)	0	0
General Disorders and Administration Site Reactions		**6 (2.9%)**	**2**	**9 (4.3%)**	**2 (2.8%)**
	Chills	1 (0.5%)	1 (1.4%)	0	0
	Infusion site discoloration	0	0	3 (1.4%)	0
		Within 3 hours		**3-24 hours**	
System Organ Class	**Preferred Term**	**obiltoxaximab, n=210**	**Placebo, n=70**	**obiltoxaximab, n=210**	**Placebo, n=70**
	Infusion site erythema	0	0	0	2
	Infusion site pain	2 (0.9%)	0	2 (0.9%)	0
	Injection site swelling	0	1 (1.4%)	1 (0.5%)	0
	Vessel puncture site bruise	1 (0.5%)	0	5 (2.4%)	1 (1.4%)
Immune System Disorders		**2 (0.9%)**	**0**	**0**	**0**
	Anaphylactic Reaction	1 (0.5%)	0	0	0
	Hypersensitivity	1 (0.5%)	0	0	0

Reviewer comment: The incidence of TEAEs in the nervous system disorders is roughly equivalent in the obiltoxaximab arm between the two time periods. However, there is no record of somnolence in AH104 alone, and though there is a higher incidence of headache between 3 and 24 hours after infusion (3.8%) compared with within 3 hours (1.9%), it is not enough to account for a large difference between the two groups. Pruritus, rash and urticaria occurred more often within 3 hours (3.3%, 1.4% and 1.4%) compared with their occurrence between 3 and 24 hours (0.5%, 0.5%, and 0.5% respectively). This difference is likely accounted for by the fact that in AH104, there were 6 subjects with significant hypersensitivity resulting in discontinuation of obiltoxaximab infusion; all these occurred in the first 3 hours. Despite the knowledge that 6 subjects had significant hypersensitivity, the tabulation of PT occurrence does not allow that inference to be made.

As in the FDA PSP and FDA ESP, infusion site reactions in AH104 occurred more frequently in the 3-24 hour time period rather than within 3 hours after the infusion.

TEAE's in the Total Study Period for AH104, FDA PSP and FDA ESP

In the AH104 CSR, a total of 88 subjects (41.9%) in the obiltoxaximab arm were recorded as having a total of 189 TEAE's, while in the placebo group, 27 subjects (38.6%) had 49 TEAE's.

Reviewer comment: The clinical reviewer also independently identified a total of 88 subjects with TEAE's in the obiltoxaximab arm with 189 TEAE's, while 27 subjects in the placebo arm had 50 TEAE's. The following table summarizes the relevant information for AH104, FDA PSP and FDA ESP.

Table 8.22 FDA Analysis: Summary of Occurrence of TEAEs in AH104, FDA PSP, and FDA ESP

	Placebo N=70 n (%)	Obiltoxaximab n (%)		
		AH104 N=210	FDA PSP N=300	FDA ESP N=320
Subjects with TEAE's	27 (38.6%)	88 (41.9%)	138 (46%)	176 (55%)
Number of TEAE's	50	189	279	450
Subjects with serious adverse events	1	0	0	1
Subjects discontinued study drug due to AE	0	6	8	8
Subjects discontinued from the study due to AE	0	0	1	1
Number of deaths due to AE	0	0	0	0
Subjects with severe AE's	0	1	2	5
Subjects with severe related AE's	0	1	2	2
Subjects with related AE's (N=66)	9	31	50	57

Reviewer comment: The percentage occurrence of TEAEs in AH104 and FDA PSP were reasonably similar, but significantly higher in FDA ESP – this again may reflect the longer study duration of AH109.

The verbatim term (AETEXT) and dictionary-derived term (AEDECOD) for TEAE's were compared and were reasonably concordant. The frequency of various SOCs within AH104, FDA PSP and FDA ESP was then analyzed, and compared with an independent analysis of the Applicant's Single-dose Pool. These results are tabulated below.

Table 8.23 FDA Analysis of Subjects with TEAE's in AH104, FDA PSP, ESP, and the Applicant's Single-Dose Pool by SOC and Arm

	AH104		FDA PSP	FDA ESP	Applicant's Single-Dose Pool*
Body System Class	Placebo	Obiltoxaximab	Obiltoxaximab		
	N=70	N=210	N=300	N=320	N=250
Cardiac disorders	0	1 (0.5%)	2 (0.7%)	3 (0.9%)	2 (0.8%)
Ear and labyrinth disorders	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	1 (0.4%)
Eye disorders	2 (2.9%)	2 (0.9%)	3 (1.0%)	3 (0.9%)	2 (0.8%)
Gastrointestinal disorders	2(2.9%)	11 (5.2%)	14 (4.7%)	27 (8.4%)	16 (6.4%)
General disorders and administration site conditions	7 (10.0%)	24 (11.4%)	38 (12.7%)	48 (15%)	26 (10.4%)
Immune system disorders	0	3 (1.4%)	3 (1.0%)	3 (0.9%)	3 (1.2%)
Infections and infestations	4 (5.7%)	9 (4.3%)	19 (6.3%)	47 (14.6%)	20 (8%)
Injury, poisoning and procedural complications	2 (2.9%)	8 (3.1%)	9 (3.0%)	18 (5.6%)	8 (3.2%)
Investigations	0	5 (2.4%)	6 (2.0%)	8 (2.5%)	5 (2%)
Metabolic Disorders	0	0	0	1 (0.3%)	1 (0.4%)
Musculoskeletal and connective tissue disorders	6 (8.6%)	14 (6.7%)	20 (6.7%)	27 (8.4%)	19 (7.6%)
Nervous system disorders	4 (5.7%)	25 (11.9%)	47 (15.7%)	63 (19.7%)	38 (15.2%)
Pregnancy	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	1 (0.4%)
Psychiatric disorders	0	2 (0.9%)	3 (1.0%)	3 (0.9%)	2 (0.8%)
Renal and urinary disorders	1 (1.4%)	0	1 (0.3%)	1 (0.3%)	0
Reproductive system and breast disorders	3 (4.3%)	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Respiratory, thoracic and mediastinal disorders	2 (2.9%)	14 (6.7%)	19 (6.3%)	23 (7.2%)	15 (6%)
Skin and subcutaneous tissue disorders	5 (7.1%)	21 (10.0%)	30 (10%)	46 (14.4%)	26 (10.4%)
Vascular disorders	2 (2.9%)	1 (0.4%)	3 (1.0%)	7 (2.2%)	1 (0.4%)

*Applicant's Single Dose Pool of the Primary Safety Population: AH104 and AH110 (both arms). Independent analysis by FDA yielded numbers and percentages that agreed with the Applicant's for this column.

Reviewer comment: The reviewer's analysis of TEAEs in each SOC in AH104 is identical to the Applicant's analysis presented in Table 10, p. 57 of the ISS; independent analysis of the Applicant's Single-Dose Pool by this reviewer also yielded identical results to the Applicant's analysis of that population. The same methodology was applied to analysis of the FDA PSP and FDA ESP though the numbers do not equate with Applicant's Single-Dose or Expanded-Dose Pools since the pooling strategy differed.

Table 8.23 shows the numbers of subjects with at least 1 AE in a particular system organ class – each subject is counted once even though they may have had more than one TEAE in that SOC. System organ classes with percentages above 5% are highlighted and will be discussed further below. Some of the subjects had more than one TEAE in a particular SOC.

In the FDA PSP (also reflected in AH104 and the FDA ESP), there was a marked increase in TEAEs in the obiltoxaximab arm compared with placebo in the following SOCs: Nervous System Disorders (15.7% vs. 5.7%), Respiratory, Thoracic and Mediastinal Disorders (6.3% vs. 2.9%) and Skin and Subcutaneous Tissue Disorders (10% vs. 7.1%). There was also a greater incidence of TEAEs in the Gastrointestinal Disorders (4.7% vs. 2.9%), General Disorders and Administration Site Conditions (12.7% vs. 10%), and Infections and Infestations (6.3% vs. 5.7%) SOCs in the obiltoxaximab arm compared to placebo, though the difference was slighter.

Reviewer comment: The percentages of subjects with TEAEs in a particular SOC in the FDA PSP accorded well with the Applicant's calculations in their Single-Dose Pool. The immune system disorders SOC did not reveal the full picture of hypersensitivity. The SOCs represented in the most frequently-occurring TEAEs are biologically plausible after infusion of a monoclonal antibody. The frequency of TEAEs in the Cardiac Disorders, Eye Disorders, Ear and Labyrinth Disorders, Investigations, Metabolic, Renal and Urinary Disorders, and Reproductive and Breast Disorders SOCs was similarly low in AH104, FDA PSP and FDA ESP – again these results are biologically plausible. In general, the incidence of TEAEs in the most frequently-occurring SOCs was even higher in the FDA ESP as compared to the FDA PSP or even the Applicant's Single-Dose Pool. For example, in the FDA ESP, Nervous System Disorders (19.7%), Infections and Infestations (14.6%), General Disorders and Administration Site Conditions (15%), Skin and Subcutaneous Tissue Disorders (14.4%), Gastrointestinal Disorders (8.4%) all occurred more frequently than in the FDA PSP (15.7%, 6.3%, 12.7%, 10% and 4.7% respectively.

Thus, it appears that either the addition of a second dose of obiltoxaximab in AH109 or its longer study period (191 days), the addition of the obiltoxaximab + ciprofloxacin arm from AH110 or a combination of these factors drove the numbers and percentages higher in the FDA ESP. In the reviewer's opinion, the longer study period likely accounted for many of the

differences, though there may also have been an effect from the repeat dose of obiltoxaximab in study AH109. A separate analysis of this study is presented in Section 8.6.1, and may help to clarify this.

Hypersensitivity as a syndrome will be discussed in 8.5.1.

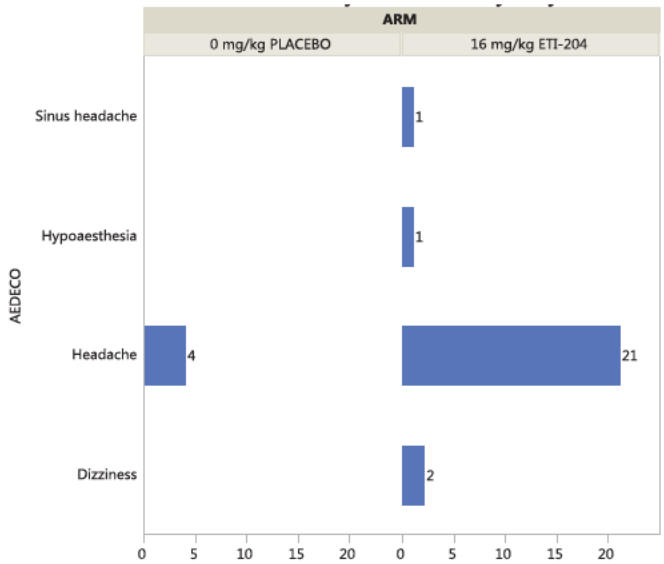
The most commonly occurring Body System Organ Classes were further analyzed in AH104 and the pooled populations to determine the distribution of Preferred Terms within them.

Reviewer comment: The percentage of subjects in either arm who suffered at least one TEAE is likely skewed due to the low numbers, especially in the placebo arm. It is noted that there were some subjects who had more than one TEAE and these occurrences were analyzed as detailed below.

FDA Analysis of Individuals System Organ Classes in AH104 and the Pooled Populations

Reviewer comment: This reviewer's independent descriptive analysis of the occurrence of SOCs and PTs in AH104 agreed with the Applicant's, and the same methodology was applied to analysis of the FDA PSP and FDA ESP. Because nervous system disorders were one of the frequently occurring SOCs in this Application, an in-depth analysis was independently performed by this reviewer, first on the largest safety study, AH104, and then on the pooled populations. The results are presented in Figure 8.2:

Figure 8.2 FDA Analysis of Nervous System Disorders in AH104



In all, 21 subjects experienced headache in the obiltoxaximab arm and 4 in the placebo arm; 20 of the headaches were characterized by the Applicant as mild, one was moderate in intensity. The time of onset of these TEAEs in the obiltoxaximab arm ranged from 10 minutes to 65 days after the start of the infusion.

Reviewer comment: Headaches were strikingly more common in the obiltoxaximab arm than in the placebo arm, and the details of these cases were examined more closely in terms of time of occurrence, etc. The incidence of headache in this Application was similar to that occurring with raxibacumab, an anti-PA monoclonal antibody which is FDA-approved. Pre-clinical animal studies showed changes in the nervous system of animals infected with anthrax and treated with obiltoxaximab, but increased changes were not seen in animals which were treated with obiltoxaximab alone in the absence of infection.

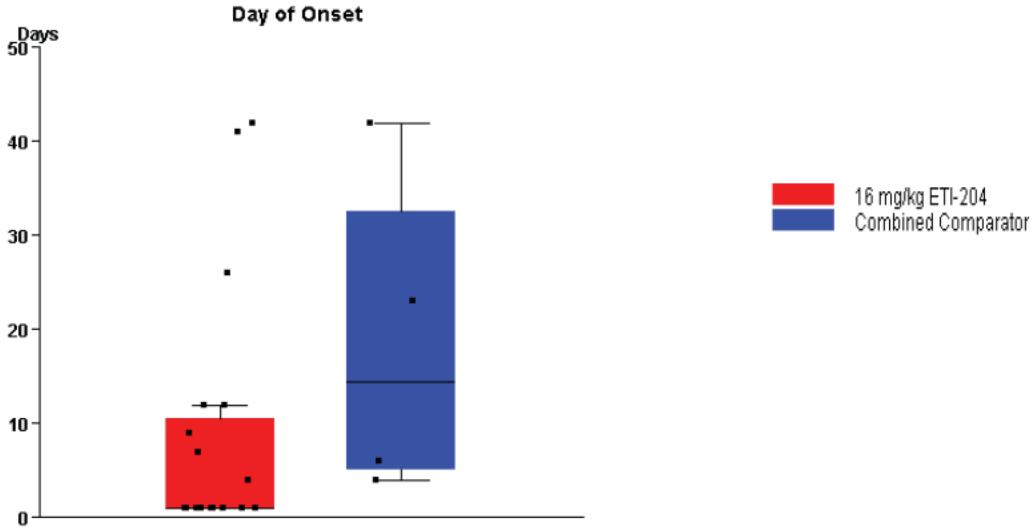
The mechanism of headache after infusion of obiltoxaximab in the human studies is unclear. There was a paucity of additional clinical information on which to judge whether headaches were related to obiltoxaximab or not. For purposes of exploratory FDA analysis, an arbitrary and conservative cut-off of 7 days after the infusion was used to designate relatedness.

Independent FDA analysis of the data using this cut-off time period highlighted 10 subjects (47.6% of 21 subjects with a headache or 4.8% of 210 total subjects in AH104) in the obiltoxaximab arm in whom the headache was almost certainly related to the infusion. The time of onset in these subjects ranged from 10 minutes to almost 13 hours after the start of the infusion. However, based on the fact that effective serum levels of obiltoxaximab persist for about 20 days, it is possible that headaches that occurred at 6, 8, 11 or 12 days could also be related to study infusion.

Reviewer comment: If the data is re-analyzed using 20 days as the cut-off for relatedness, 17 subjects (81% of the 21 subjects with headache, or 8.1% of 210 total subjects) in the obiltoxaximab arm had a headache related to the study drug.

The box plot in Figure 8.3 shows that the occurrence of headache seemed by and large, to cluster within the first 15 days after administration of obiltoxaximab.

Figure 8.3 FDA Analysis of Occurrence of Headache by Day of Onset Relative to Study Drug Infusion



Nervous System Disorders in Pooled Populations

Similar trends in occurrence of Nervous System Disorders was seen in the pooled populations, as depicted in Table 8.24.

Table 8.24 FDA Analysis of Nervous System Disorders in Study AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

Preferred Term	Placebo n=70 N (%)	Obiltoxaximab			
		AH104 N=210 n (%)	FDA PSP N=300 n (%)	FDA ESP N=320 n (%)	Applicant's Single-Dose Pool N=250, n (%)
Dizziness	0	2 (0.9%)	3 (1%)	5 (1.6%)	2 (0.8%)
Dizziness postural	0	0	0	1 (0.3%)	0
Dysarthria	0	0	0	1 (0.3%)	0
Dysgeusia	0	0	0	1 (0.3%)	0
Headache	4 (5.7%)	21 (10%)	24 (8%)	29 (9.1%)	23 (9.2%)
Hypoaesthesia	0	1 (0.5%)	1 (1%)	1 (0.3%)	0
Lethargy	0	0	1 (1%)	1 (0.3%)	0
Migraine with aura	0	0	1 (1%)	1 (0.3%)	0
Sinus headache	0	1 (0.5%)	1 (1%)	1 (0.3%)	0
Somnolence	0	0	17 (5.6%)	31 (9.7%)	11 (4.4%)
Syncope	0	0	0	1 (0.3%)	0

The predominant TEAEs in the nervous system SOC were headaches and somnolence. Of the 31 TEAEs of somnolence in the FDA ESP, all occurred in AH109 (20) and in AH110 (11). As can be seen from the table, no somnolence was reported in AH104. The Applicant thought it was most likely that the somnolence was related to administration of diphenhydramine. Since all subjects in AH110, all but 8 subjects in AH109, and the majority in AH104 (192 subjects) received diphenhydramine, the lack of occurrence of this TEAE in AH104 was surprising and not clinically plausible; this was addressed in a previous section. Headache was clearly associated with the use of obiltoxaximab in all populations. Categorization of TEAEs into the ≤3hr or 3-24hr groups shows that headache appears to occur primarily after the first 3 hours, but that throughout the study period, there is a cumulative increased risk for occurrence of headache.

The occurrence of dizziness and syncope was discussed earlier in this section.

Skin and Subcutaneous Tissue Disorders – AH104

Skin assessments for presence or absence of rash were performed by the investigator or designated person on Day 1 predose and at 1, 2, 4, and 12 hours after the start of infusion, and again on Day 2 (24 hours after the start of the infusion). If any evidence of rash was present, it was evaluated by the investigator.

Skin and subcutaneous disorders were common in the subjects who received obiltoxaximab.

Clinical Reviewer comment: Many of these AE's are related to hypersensitivity; see Section 8.5.1.

Though there were multiple dictionary-derived terms used in this SOC, as noted in Table 8.25, this reviewer felt that for the purposes of evaluating adverse events, and because of possible overlap between the terms, some of these should be counted together. Therefore, urticaria, skin exfoliation, skin irritation, rash generalized, rash erythematous, rash papular, rash, pruritus, hyperhidrosis, dermatitis allergic and dermatitis were considered together as related to infusion of obiltoxaximab.

Among the 210 subjects therefore, 27 subjects in the obiltoxaximab arm (12.8%) had a skin-related adverse event, while only 3 of 70 (4.2%) in the placebo group had a similar event (2 with rash, 1 with pruritus).

The three subjects with urticaria were among the 6 patients who had obiltoxaximab infusion withdrawn due to an AE (ie. subjects 104-002-053, 104-002-068, and 104-002-350). Two subjects had a generalized rash (104-001-001, and 104-001-182). Subject 104-001-001 was a 45 year old black woman in whom the rash occurred on Day 71, while T-wave inversion on her ECG occurred 2 hours and 45 mins after the obiltoxaximab infusion began – it is unclear whether this finding was related to the infusion or not. Subject 104-001-184 was a 32 year old black woman in whom a rash occurred on Day 3 after infusion of obiltoxaximab. She had a baseline amylase of 134 at screening (N=21-129). It rose steadily after the infusion to a high of 173 on Day 44, and 134 on Day 71. Liver enzymes remained normal, but her total bilirubin was elevated at baseline at 1.3 U/L, and bumped briefly to 1.5 U/L on Day 2, before returning to normal on Day 8.

Subject 104-002-065 tolerated the infusion of obiltoxaximab but then developed allergic dermatitis on Day 3 which lasted until Day 10. He received diphenhydramine as pre-medication, but then required diphenhydramine again on Day 3, along with Claritin, then methylprednisolone orally on Days 8-13. His ECG was marked as abnormal on Day 2 and again on Day 71, but no further description was given. His alkaline phosphatase was higher than the upper limit of normal at baseline (113 U/L, Normal range = 44-103 U/L), and remained slightly above the upper limit of normal throughout (max=124 U/L) the study period. Other liver enzymes were normal. He then developed desquamation of the skin on Day 23 which lasted until Day 36.

Reviewer comment: Presumably skin desquamation was related to the allergic dermatitis and both were related to infusion of obiltoxaximab. However, because allergic dermatitis often

refers to cutaneous contact with a known allergen, it is unclear whether this was truly a precise description of a reaction related to an intravenously administered medication.
Subject 004-156 was classified as contact dermatitis but also had pruritus that started on Day 8 and resolved on Day 9 without treatment.

Of the 5 subjects characterized with rash, two had to discontinue the infusion (104-003-101 and 104-003-107) due to hypersensitivity; subject 104-003-111 was able to complete the infusion but required additional diphenhydramine and famotidine to manage the rash.

In the pooled populations, the distribution of skin and subcutaneous tissue disorders is shown in Table 8.25.

Table 8.25 FDA Analysis of Occurrence of Skin and Subcutaneous Tissue Disorders in AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

Preferred Term		Obiltoxaximab			
	Placebo N=70 n (%)	AH104 N=210 n (%)	FDA PSP N=300 n (%)	FDA ESP N=320 n (%)	Applicant's Single-Dose Pool N=250 n(%)
Rash generalised	0	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Cold sweat	1 (1.4%)	0	0	0	-
Urticaria	0	3 (1.4%)	4 (1.3%)	8 (2.5%)	6 (2.4%)
Dermatitis contact	1 (1.4%)	2 (0.9%)	6 (2.0%)	14 (4.4%)	4 (1.6%)
Rash papular	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Dermatitis allergic	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Skin exfoliation	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Rash	2 (2.8%)	5 (2.4%)	6 (2.0%)	6 (1.9%)	5 (2%)
Papule	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Rash erythematous	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Dermatitis	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Hyperhidrosis	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Skin irritation	0	1 (0.5%)	0	1 (0.3%)	-
Pruritus	1 (1.4%)	10 (4.8%)	11 (3.7%)	13 (4.1%)	10 (4%)
Rash maculo-papular	0	0	0	2 (0.6%)	-
Rash macular	0	0	0	1 (0.3%)	-
Ecchymosis	0	0	1 (0.3%)	1 (0.3%)	-
Petechiae	0	0	1 (0.3%)	1 (0.3%)	-

Reviewer comment: As seen in Table 8.25, pruritus occurred at a frequency of ≥4% in AH104, FDA ESP and the Applicant's Single-Dose Pool, and in 3.7% of subjects in FDA PSP, but only in 1.4% of the placebo group. Rash occurred with approximately 2% frequency in all populations,

including the placebo group (2.8%). Urticaria occurred in >2% of subjects in the FDA ESP and the Applicant's Single-Dose Pool. Many recorded PTs within this SOC are related to hypersensitivity.

General Disorders and Administration Site Reactions – AH104

There were various verbatim terms and dictionary-derived terms applied to infusion site changes, but these reactions occurred more frequently in the obiltoxaximab group in AH104 than in the placebo group. FDA analysis grouped vessel puncture site pain, vessel puncture site bruise, tenderness, pain, injection site swelling, infusion site swelling, infusion site pain, infusion site erythema, infusion site discolouration, application site erythema into the class of infusion-related events. In all, 23 subjects (10.9%) in the obiltoxaximab group in AH104 experienced AE's related to the infusion site, compared to 6 of 70 (8.5%) in the placebo arm.

Further, 2 of 3 subjects with an AE identified by the dictionary-derived term "pain" actually had pain referable to the infusion site. These subjects, 104-004-145 and 104-004-317, were included in the above group for purposes of analysis.

The infusion site and vein were examined after insertion of the IV cannula prior to infusion, immediately following infusion, and 4, 8, and 24 hours after the start of infusion. Visual signs of irritation (swelling, tenderness, and erythema) were rated using a 4-point scale (0=absent to 3=severe). Venous tolerability was assessed by monitoring the IV infusion site and checking for evidence of phlebitis.

General Disorders and Administration Site Reactions – All Populations

Table 8.26 FDA Analysis of Occurrence of General Disorders and Administration Site Reactions in AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

	Obiltoxaximab				
Preferred Term	**Placebo n=70 N (%)**	**AH104 n=210 N (%)**	**FDA PSP n=300 N (%)**	**FDA ESP n=320 N (%)**	**Applicant's Single-Dose Pool N=250 n(%)**
Chills	1 (1.4%)	1 (0.5%)	2 (0.7%)	2 (0.6%)	-
Vessel puncture site pain	0	2 (0.9%)	2 (0.7%)	5 (1.6%)	2 (0.8%)
Influenza like illness	0	1 (0.5%)	1 (0.3%)	3 (0.9%)	-
Pain	2 (2.8%)	3 (1.4%)	3 (1.0%)	3 (0.9%)	3 (1.2%)
Vessel puncture site bruise	1 (1.4%)	7 (3.3%)	8 (2.7%)	8 (2.5%)	8 (3.2%)
Asthenia	0	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Injection site swelling	1 (1.4%)	0	8 (2.7%)	0	-
Infusion site pain	0	4 (1.9%)	7 (2.3%)	8 (2.5%)	4 (1.6%)
Infusion site erythema	2 (2.8%)	0	4 (1.3%)	5 (1.6%)	-
Facial pain	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Tenderness	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Infusion site discolouration	0	3 (1.4%)	3 (1.0%)	3 (0.9%)	3 (1.2%)
Non-cardiac chest pain	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Fatigue	0	3 (1.4%)	3 (1.0%)	5 (1.6%)	4 (1.6%)
Edema	0	0	0	0	-
Pyrexia	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Application site erythema	0	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Feeling abnormal	1 (1.4%)	0	0	0	-

Reviewer comment: Infusion of obiltoxaximab appeared to be associated with more vessel puncture site bruises (incidence from 2.5-3.3% in the various pooled populations depicted in the table above) than with infusion of placebo (1.4%). Similarly, infusion site pain occurred in 1.6-2.5% in the pooled populations, while it did not occur in the placebo group. Conversely, pain and

infusion site erythema occurred slightly more in the placebo compared to the obiltoxaximab group.

Respiratory, Thoracic and Mediastinal Disorders – AH104

Respiratory, thoracic and mediastinal disorders occurred in 14 subjects (6.7%) in the obiltoxaximab arm of AH104 vs. 2 of 70 subjects in the placebo arm (2.9%). There were 6 subjects in the obiltoxaximab arm with cough which was treatment-emergent, while 4 had nasal congestion and 2 had rhinorrhea. Only 1 patient in the placebo arm experienced throat irritation and nasal congestion.

Cough occurred as a treatment-emergent AE in 6 subjects in the obiltoxaximab arm and was analyzed further. Of the six subjects with cough in AH104, three subjects (104-002-053, 104-003-101 and 104-003-107) experienced this AE as part of a hypersensitivity reaction severe enough to result in discontinuation of the obiltoxaximab infusion. Two of these subjects (104-002-053 and 104-003-101), also had throat irritation which occurred concurrently; in addition, the former experienced dysphonia.

Table 8.27 FDA Analysis of Respiratory, Thoracic and Mediastinal Disorders in AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

Preferred Term		Obiltoxaximab			
	Placebo n=70 N (%)	AH104 n=210 N (%)	FDA PSP n=300 N (%)	FDA ESP n=320 N (%)	Applicant's Single-Dose Pool N=250 n(%)
Oropharyngeal pain	0	3 (1.4%)	3 (1.0%)	4 (1.3%)	3 (1.2%)
Rhinorrhoea	0	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Dry throat	0	1 (0.5%)	2 (0.7%)	2 (0.6%)	-
Sinus congestion	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Nasal congestion	1 (1.4%)	4 (1.9%)	5 (1.7%)	6 (1.9%)	4 (1.6%)
Dysphonia	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Cough	0	6 (2.8%)	9 (3.0%)	10 (3.1%)	7 (2.8%)
Throat irritation	1 (1.4%)	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Dyspnea	0	0	1 (0.3%)	1 (0.3%)	-

Reviewer comment: The occurrence of cough and throat irritation in subjects 104-002-053 and 104-003-101 (and dysphonia in the former) in the setting of hypersensitivity severe enough to result in discontinuation of obiltoxaximab, is very suggestive of angioedema. The one subject designated by the Applicant with the PT anaphylactic reaction – 104-003-058 – also experienced cough according to his subject narrative, but was not listed as part of the 6 subjects with cough

in the ISS database. Finally, subjects 104-003-258 and 109-002-204 experienced dyspnea as part of severe hypersensitivity, underscoring the fact that the TEAEs in this SOC, as in others, have to be considered in their clinical context to understand their true significance.

Musculoskeletal and Connective Tissue Disorders – AH104
Out of 4 subjects in the obiltoxaximab arm in AH104 with the "Pain in extremity" PT, subject 104-004-138 had pain related to the IV site and was counted in the appropriate group under General Disorders.

Table 8.28 FDA Analysis of Musculoskeletal and Connective Tissue Disorders in AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

Preferred Term		Obiltoxaximab			
	Placebo N=70 n (%)	AH104 N=210 n (%)	FDA PSP N=300 n (%)	FDA ESP N=320 n (%)	Applicant's Single-Dose Pool N=250 n (%)
Groin pain	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Muscle spasms	1 (1.4%)	2 (0.9%)	2 (0.7%)	2 (0.6%)	2 (0.8%)
Back pain	3 (4.3%)	1 (0.5%)	5 (1.7%)	7 (2.2%)	3 (1.2%)
Myalgia	0	2 (0.9%)	3 (1.0%)	3 (0.9%)	2 (0.8%)
Pain in extremity	1 (1.4%)	4 (1.9%)	5 (1.7%)	6 (1.9%)	5 (2.0%)
Muscle twitching	0	1 (0.5%)	1 (0.3%)	2 (0.6%)	2 (0.8%)
Muscle tightness	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Musculoskeletal chest pain	1 (1.4%)	0	1 (0.3%)	1 (0.3%)	-
Musculoskeletal pain	0	2 (0.9%)	1 (0.3%)	2 (0.6%)	2 (0.8%)
Neck pain	1 (1.4%)	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Arthralgia	0	0	1 (0.3%)	1 (0.3%)	-

Reviewer comment: No specific patterns were discernible in the occurrence of AEs in this SOC. Although there were several subjects with back pain, it did not occur predominantly in the obiltoxaximab arm, except in one subject in AH109 who had severe back pain as part of her hypersensitivity reaction.

Gastrointestinal Disorders – AH104
In this SOC, nausea and vomiting are considered together, therefore, 8 subjects in the obiltoxaximab arm vs. 2 in the placebo arm experienced this TEAE. (For purposes of this review, they are considered together, but the same patient may have experienced one of the nausea episodes PLUS one of the vomiting episodes).

Table 8.29 FDA Analysis of Occurrence of Gastrointestinal Disorders in AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

Preferred Term	Placebo	Obiltoxaximab			
		AH104	FDA PSP	FDA ESP	Applicant's Single-Dose Pool N=250 n(%)
Abdominal pain	1 (1.4%)	0	1 (0.3%)	1 (0.3%)	-
Diarrhea	2 (2.8%)	0	0	5 (1.6%)	2 (0.8%)
Dry mouth	0	1 (0.5%)	2 (0.7%)	3 (0.9%)	-
Eructation	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Hiatus hernia	0	1 (0.5%)1	1 (0.3%)	1 (0.3%)	-
Lip pain	0	1 (0.5%)1	1 (0.3%)	1 (0.3%)	-
Nausea	2 (2.8%)	5 (2.4%)	6 (2.0%)	10 (3.1%)	7 (2.8%)
Toothache	0	2 (0.9%)	2 (0.7%)	5 (1.6%)	3 (1.2%)
Vomiting	0	3 (1.4%)	3 (1.0%)	4 (1.3%)	3 (1.2%)
Anal Fissure	0	0	0	1 (0.3%)	-

Reviewer comment: *Nausea was the most commonly-occurring PT in this SOC, but because it also occurred in 2.8% of subjects in the placebo group, could not be causally related to obiltoxaximab infusion.*

Cardiac Disorders – All Populations

One subject (104-001-046), a 23 year old black woman, experienced palpitations on Days 4-7 after infusion of obiltoxaximab. Her ECG was characterized as abnormal at screening, predose and at 3 hours postdose; it was normal at 8 hours postdose, and on Day 2. It was abnormal again on Day 71. It is unclear whether this was a recurring or significant problem.
Two subjects had palpitations (104-001-046 and 110-001-103), and one had cyanosis (109-002-204) which occurred as part of her hypersensitivity reaction.

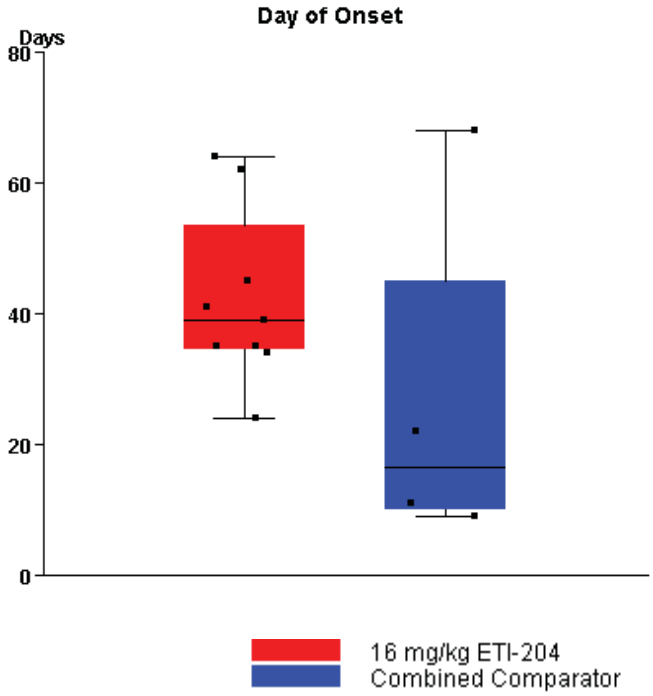
Injury, Poisoning and Procedural Complications – All Populations

Several subjects had an AE in this SOC in the various populations, but none were thought to be related to the infusion of obiltoxaximab.

Infections and Infestations – AH104

Nine (9) subjects in the obiltoxaximab group of AH104 had an AE in this category. One had Streptococcal pharyngitis, one had bronchitis, 5 had upper respiratory tract infections (URTI), 1 had a vaginal yeast infection, and one had a viral infection. In the placebo group, 2 subjects had an UTI, and 2 had an URTI.

Figure 8.4 FDA Analysis of Occurrence of Upper Respiratory Tract Infections in AH104



All subjects in AH104 diagnosed with an URTI in either the obiltoxaximab (n=5) or placebo (n=2) group, or bronchitis (n=1) or viral infection (n=1) in the obiltoxaximab group received their infusion either in late July or August and completed the study at various time points in October. This is prior to the expected peak of influenza and respiratory infections that usually occurs over the winter months.

Infections and Infestations – Pooled Populations

Table 8.30 shows the occurrence of infections in the pooled populations after administration of obiltoxaximab or placebo.

Table 8.30 FDA Analysis of Occurrence of Infections in AH104, FDA PSP, FDA ESP and the Applicant's Single-Dose Pool

Preferred Term	Placebo	Obiltoxaximab			
		AH104	FDA PSP	FDA ESP	Applicant's Single-Dose Pool N=250 n(%)
Upper respiratory tract infection (URTI)	2 (2.9%)	5 (2.4%)	11 (3.7%)	29 (9.1%)	12 (4.8%)
Bronchitis	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Pharyngitis Streptococcal	0	1 (0.5%)	1 (0.3%)	2 (0.6%)	-
Pharyngitis	0	0	0	2 (0.6%)	-
Viral infection	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	-
Viral upper respiratory tract infection		0	0	1 (0.3%)	-
Laryngitis	0	0	0	1 (0.3%)	-
Sinusitis	0	0	0	2 (0.6%)	-
Rhinitis	0	0	0	1 (0.3%)	-
Pneumonia	0	0	1 (0.3%)	1 (0.3%)	-
Vulvovaginal mycotic infection	0	1 (0.5%)	1 (0.3%)	3 (0.9%)	2 (0.8%)
Urinary tract infection	2 (2.9%)	0	0	0	-
Cystitis	0	0	1 (0.3%)	1 (0.3%)	-
Asymptomatic bacteriuria	0	0	1 (0.3%)	1 (0.3%)	-
Folliculitis	0	0	1 (0.3%)	1 (0.3%)	-
Gastroenteritis	0	0	0	2 (0.6%)	-
Gastroenteritis viral	0	0	0	1 (0.3%)	-
Gingivitis	0	0	0	1 (0.3%)	-
Labyrinthitis	0	0	0	1 (0.3%)	-
Vaginitis bacterial	0	0	1 (0.3%)	2 (0.6%)	-
Postoperative wound infection	0	0	0	1 (0.3%)	-
Acarodermatitis	0	0	0	1 (0.3%)	-

Reviewer comment: URTIs occurred with similar frequency in the obiltoxaximab and placebo arms in AH104. The incidence of URTIs was higher in the pooled populations as seen in the table above, and especially in the FDA ESP, possibly due to the contribution of the longer study duration in AH109. As in other SOCs, this reviewer felt that counting infections only according to PT would "split" and therefore probably underestimate the true incidence, as several of the terms used in the table could refer to very similar syndromes – for example, URTI, viral infection, viral upper respiratory tract infection. A safety signal could thus potentially be missed. If these

and other terms are combined, there appears to be a clear predominance of various infections of the upper respiratory tract.
Subjects in AH109 had the greatest incidence of URTIs; the study started in July 2013, and finished in April 2014. This includes the months usually associated with the highest seasonal incidence of URTI's. Study AH110 was carried out between October 2013 and April 2014, also during the peak winter months for respiratory infections.

The occurrence of infections in the human safety studies is discussed in more detail in section 8.5.2.

The occurrence of TEAEs in the Eye Disorders SOC, the Renal and Urinary Disorders SOC, and the Psychiatric Disorders SOC was low, occurred after administration of both placebo and obiltoxaximab, and seemed unrelated to infusion of either drug.

Vascular Disorders

In the entire study population – FDA ESP – 4 subjects (1 in AH104, 3 in AH109) experienced phlebitis after obiltoxaximab, 3 had hot flushes, and 1 subject had pallor. Two subjects who received placebo also had AEs under this SOC – one subject with a flushing reaction, one subject with a hematoma of her right wrist.

Reviewer comment: Although all these TEAEs seemed clearly associated with IV administration of study drug, they did not seem to be related specifically to obiltoxaximab.

Reproductive System and Breast Disorders
One subject (104-001-017) in the obiltoxaximab group experienced left nipple pain, one (104-004-130) had spotting in between her menstrual cycles. One subject in the placebo group, (104-001-020) experienced dysmennorhea, while subject 104-002-216 had an ovarian cyst which led to hospitalization and was characterized by the Applicant as a serious AE. Her narrative is provided in section 8.4.2. Both the Applicant and FDA judged this SAE not to be related to the infusion. Another subject in the placebo group missed a period (104-002-228).

Immune System Disorders
Subjects 104-001-016 had a seasonal allergy, 104-002-351 had hypersensitivity, and 104-003-258 had anaphylactic reaction. The latter two will be described more fully in Section 8.5.1.

Investigations
In the FDA ESP, 1 subject each in the obiltoxaximab arm of AH104 had a T wave inversion on their ECG (104-001-001), increase in serum creatine phosphokinase [CPK] (104-002-078), a positive pregnancy test (104-002-230), increase in blood pressure (104-003-110), and a decrease in blood TSH level (104-004-307). Subject 109-001-129 also had an increase in serum

CPK, and subject 109-001-114 had an increased WBC – both were in the obiltoxaximab arm. Subject 109-002-204 had a decrease in WBC count, lymphocyte count and neutrophil count after the infusion of obiltoxaximab; this occurred in the context of a serious hypersensitivity reaction.

8.4.6 Laboratory Findings

Laboratory tests were done routinely according to the schedule outlined in section 8.1.1.3. This reviewer examined the Applicant's review of laboratory data. In addition, graphs of specific hematological and biochemical indices in each of the main human safety studies were independently constructed by this reviewer from the datasets provided by the Applicant. These included variations over time as well as plots of toxicity shifts from baseline. Shifts from baseline to post baseline were assessed for major laboratory parameters using a standard toxicity grade. In addition, laboratory-related AEs from the FDA ESP were analyzed in JMP® (Table 8.31).

Reviewer comment: For this reviewer's analysis, all biochemistry data provided by the Applicant in µkat/L were converted by the reviewer to U/L, the standard unit of measurement in the U.S.

Baseline laboratory values for hematological and biochemical indices were similar between the treatment and placebo groups in AH104 and similar between the two arms in both AH109 and AH110. Laboratory-related adverse events were infrequent in the FDA ESP and all occurred with administration of obiltoxaximab; there were none in the placebo group.

Table 8.31 FDA Analysis of Laboratory-related AE's in the FDA ESP*

Subject ID	Preferred Term	Day of Event
AH104-001-001	Electrocardiogram T wave inversion	1
AH104-002-078	Blood creatinine phosphokinase increased	71
AH104-002-230	Pregnancy test positive	71
AH104-003-110	Blood pressure increased	36
AH104-004-307	Blood thyroid stimulating hormone decreased	71
AH109-001-114	White blood cell count increased	28
AH109-001-129	Blood creatinine phosphokinase increased	28
AH109-002-204	Lymphocyte count decreased	2
	Neutrophil count decreased	2
	White blood cell count decreased	2

*All with obiltoxaximab infusion

Reviewer comment: The decreases in white cell count and its component cell lineages in AH109-002-204 likely reflect temporary bone marrow suppression in the context of this subject's anaphylaxis in response to infusion of obiltoxaximab on Day 1. The narrative of subject AH104-002-230 with a positive pregnancy test is provided in Section 8.7.2. T wave inversion on the ECG of subject AH104-001-001 was noted on Day 1 starting 3 hours after the start of obiltoxaximab infusion but was not associated with other symptoms. This subject had a normal ECG at baseline at 1 hour and 15 minutes after the abnormal ECG.

Subject 104-002-078 was a 25 year old white female with an increase in CPK from 94 U/L at baseline to 3324 U/l on Day 71. No abnormalities were recorded on examination. CK levels decreased to 2000 U/L on Day 72, and to 171 U/L by Day 78 when the AE was reported to be resolved. Subject 104-004-307 was a 22 year old white/African-American male with a normal TSH at baseline, but a slightly reduced level at Day 71 (0.46 mIU/L, reference range: 0.55-4.8 mIU/L). He was referred to his primary care physician for followup.

All except the hematological changes in subject AH109-002-204 were unlikely related to infusion of obiltoxaximab.

Hematology: Mean values and changes in baseline in hemoglobin, lymphocytes, neutrophils, white blood cell (WBC) count, platelets and differential counts were similar in the obiltoxaximab and placebo groups over the individual study periods. In particular, there were no specific changes noted in eosinophil counts as might be expected to occur with hypersensitivity after infusion of obiltoxaximab.

In the Applicant's Single-Dose Pool (AH104 + AH110), 3 subjects (1.2%) had a ≥ 2-grade increase in partial thromboplastin time (PTT) postbaseline, 4 subjects (1.6%) had a ≥ 2-grade decrease in neutrophils, 2 subjects had a ≥ 2-grade increase each in prothrombin time (PT) and white blood cell count (WBC), while 1 subject had a ≥ 2-grade decrease in hemoglobin, lymphocyte count and platelet count. In the same population, there were a similar percentage of subjects with a hematology value outside the reference range in both the obiltoxaximab and placebo groups. None of these were reported as an AE.

Biochemistry: In the Applicant's Single-Dose Pool, mean values over time and changes from baseline in ALT, AST, bilirubin, creatinine, albumin and other serum biochemistry parameters were similar in the obiltoxaximab and placebo groups. Most subjects who received either obiltoxaximab or placebo had a toxicity grade of 0 at baseline and no changes in toxicity grade postbaseline. However, 16.9% of subjects in the obiltoxaximab arm and 18.6% of subjects in the placebo arm had a ≥ 2-grade increase in cholesterol levels, while 10% and 15.7% respectively had a ≥ 2-grade increase in creatine kinase levels.

Reviewer comment: *Given the greater incidence of changes in cholesterol levels in the placebo group compared with the obiltoxaximab group, this is unlikely to be related to the infusion of obiltoxaximab. Increases in creatine kinase levels were also seen in a significant proportion of subjects. There is no obvious biologically plausible mechanism by which a monoclonal antibody would cause increases in CK. It is known that CK levels can increase significantly in healthy individuals with normal levels of exercise. In those subjects with elevated CKs for whom narratives are available (detailed previously), exercise seemed to be responsible.*

No liver function tests were reported as AEs. There were no subjects who fulfilled the criteria for Hy's Law in all the human studies of obiltoxaximab. The percentage of subjects with a serum biochemistry value outside the reference range at any time postbaseline was similar between the arms in the Applicant's Single-Dose Pool.

Most subjects in AH104, the largest placebo-controlled study, with an elevation in a liver function test had an increase <2X the ULN. Only 2 subjects had a liver function test value > 2X ULN.

- Subject AH104-003-090 had an AST increase from 22 U/L at baseline to 225 U/L (reference range 5-40 U/L) on Day 43. Other liver function tests on Day 43 were either just above the ULN (ALT at 94 U/L; reference range, 7-56 U/L) or within normal range (total bilirubin and alkaline phosphatase of 10.3 µmol/L [reference range, 1.7 to 20.5 µmol/L] and 76.5 U/L [reference range 20-140 U/L], respectively). Creatine phosphokinase (CPK) was also elevated from 62 U/L (reference range, 96-140 U/L for women) at baseline to 6917 U/L on Day 43. Thus, it is likely that the AST elevation was of skeletal origin.

- Subject 104-004-313 had an ALT increase from 30 U/L at baseline to 120 U/L (reference range, 7-56 U/L) on Day 71. AST was slightly increased from 29 U/L to 59 U/L (reference range, 5-40 U/L) on Day 71, while total bilirubin and alkaline phosphatase were within normal range at the same time point. ALT and AST decreased to 92 U/L and 55 U/L, respectively, at 1 week following Day 71 and to 65 U/L and 41 U/L respectively, 2 weeks following Day 71.

Reviewer comment: Subject AH104-003-090 had a rise in both CK and AST on Day 43, and no apparent symptoms, suggesting that the rises were related to skeletal muscle activity, ie. exercise, though no clinical details are provided. The reasons for the mild changes in ALT and AST in subject 104-004-313 are not clear from the information provided.

Potassium levels had a greater incidence of ≥ 2-grade increase in the population that received obiltoxaximab in the Applicant's Single-Dose Pool vs. placebo (3.6% vs. 0 respectively), but none were considered significant by the investigator, none required medical treatment and none were reported as an adverse event.
Thyroid function evaluation was part of the study protocols as there were changes noted in the only FDA-approved anti-PA monoclonal antibody, raxibacumab, including staining of thyroid tissue in their pre-clinical studies. The Applicant did not examine shifts from baseline in thyroid function parameters because the FDA Guidance for toxicity grading in volunteers does not assign grades for thyroid function laboratory parameters. However, mean values and changes from baseline in T3, T4, thyroid stimulating hormone (TSH) and anti-thyroid peroxidase antibodies were similar in the obiltoxaximab and placebo groups of the Applicant's Single-Dose Pool, as were percentages of subjects with a thyroid function value outside the reference range at any time postbaseline.

Urinalysis parameters did not differ significantly between the groups.

AH109

Laboratory parameters in the repeat-dose study was considered independently since the data from the single-dose studies is presented above, and there may be more changes expected with 2 doses of obiltoxaximab. The two arms in AH109 are referred to as: Sequence A: obiltoxaximab on Day 1, obiltoxaximab on Day 14 and placebo on Day 120, and Sequence B: obiltoxaximab on Day 1, placebo on Day 14, and obiltoxaximab on Day 120.

Hematology:
RBC and Platelets: Baseline values were very similar between the arms for mean erythrocyte measurements, hematocrit, hemoglobin levels and platelet count (109-002-227 had a count of 625,000/mm^3). The variation in these values by study visit was also similar with overlapping confidence intervals – the mean Hb level ranged between 14-15 g/dL, and mean platelet count stayed around 250,000/mm^3 over time. The mean hemoglobin level at baseline was slightly lower in the sequence B at baseline compared with sequence A (13.6 vs. 14.75).

White blood cell count: Total white count was similar between the two arms at baseline, as were the constituent populations including eosinophils. The mean eosinophil percentage in sequence A was 2% while in sequence B it was 2.7%. However, more subjects in sequence A (n=5) had increased maximal change from baseline in eosinophil count. The neutrophil count and total white count over time of the study period were similar between the two arms.

Atypical lymphocytes were seen in subject 109-001-130 on day 134 coincident with a flu-like illness that began on day 132. Subjects 109-001-114 and 109-001-126 developed elevated WBC counts coincident with URTIs in both.

Chemistry: Lipids: Mean cholesterol level in sequence B at baseline was 165 mg/dl vs. 186 mg/dl in sequence A. Mean values in both arms appeared to drop slightly at visit 10 but mean changes over time were similar.

Liver tests: Baseline mean ALP, ALT, AST, and bilirubin were normal in most subjects in both arms. Subject 109-002-223 in sequence B however, had an elevated ALT (77U/L), ALP (152U/L) and AST (61U/L) at baseline. The ALP went up to 152, then down to 126 at the end of the study period. Clinical details were not available. Subject 109-001-123 in Sequence B had an elevated ALT on Day 163 of 79 U/L (reference range: 7-56 U/L), and on Day 191 (67 U/L). No clinical information is provided.

Subject 109-001-129 in sequence B had an elevated ALT of 102 on Day 28 along with an elevated AST of 144 (reference range: 5-40 U/L), and lactate dehydrogenase of 429 (reference range: 140-280 U/L) – these were not reported as AEs and all values subsequently returned to normal. He also had an elevated CK on that day – 13,352 U/L (reference range: 96-140 U/L for women); this was considered a severe unrelated AE. At an unscheduled visit 2 weeks later, his CK was normal. Of note, he had had elevated CK levels on Day -1, Day 2, Day 8 and then again, from Day 71 to Day 191; none of these were considered clinically significant by the investigator. He reported having exercised, including lifting weights, 5-6 days prior to the severe AE.

Reviewer comment: No laboratory parameters seemed obviously related to infusion of obiltoxaximab. Five subjects in sequence A compared to sequence B had mild eosinophil elevation suggesting that 2 doses of obiltoxaximab two weeks apart might be more associated with allergy than 2 doses of obiltoxaximab 120 days apart. However, the hypersensitivity data did not bear this out. From the information provided, the CK elevation in subject 109-001-129 appeared related to exercise.

8.4.7 Vital Signs

Information on vital signs was obtained from perusal of the Applicant's submission and FDA analysis of the Applicant's single-study and ISS datasets. Mean systolic and diastolic blood pressures, pulse rates, respiratory rates, and oral body temperatures were comparable between the groups that received obiltoxaximab vs. placebo, and did not vary significantly over time. The exceptions occurred in some subjects with hypersensitivity – these are detailed in Section 8.5.1. Subject 104-003-110 had a moderate rise in blood pressure reported as an AE on day 36. Actual BP measurements on that day were unavailable as the subject was seen by his primary care physician. BP was 137/91 mmHg on day 43 and 142/89 on Day 71. This was reported as an unresolved AE.

8.4.8 Electrocardiograms (ECGs)

There were no specific concerns regarding ECG changes during the development of obiltoxaximab. During the conduct of the trials, multiple ECG's were collected at various time points during the first 24 hours following study drug administration; the schedule is outlined in the Table of Clinical Assessments, Section 8.1.1.3. ECGs from AH110 were read by an external ECG Core Laboratory, while ECGs in AH104, AH105, and AH109 were reviewed by the investigator.

In the Applicant's Single-Dose Pool, mean PR, QRS, QT, QTcB, QTcF, RR and ventricular heart rate were similar in the obiltoxaximab and placebo groups; mean changes from baseline for each parameter were small and not considered clinically significant. One subject, 104-001-001, had mild, asymptomatic, T-wave inversion noted prior to the start of obiltoxaximab infusion which did not change at any time point post-treatment (See Section 8.4.6)

8.4.9 QT

The assistance of the CDER QT Interdisciplinary Review Team was sought for analysis of any potential cardiac safety concerns with obiltoxaximab. The following is a summary of their findings: Because this product is a large protein, direct ion channel interactions were not anticipated and a thorough QT study was not needed. Pre-clinical cardiac safety was evaluated in two monkey studies - one (AP106) after a single dose of 5 mg/kg IV bolus or 10 mg/kg IM in anesthetized animals, and one (AP115) after two IV infusions of up to 30 mg/kg/dose 8 days apart in conscious, telemetered animals. In AP106, transient non-biologically significant increases in heart rate and QT (but not QTc) and blood pressure (BP) were observed about 2-4 hour postdose but all resolved by 24 hours postdose. In AP115, with two infusions of obiltoxaximab, there were no effects on heart rate, QTc, BP, mean arterial pressure, or ECG waveform.

In the human Phase I studies, serial ECG readings were obtained in all subjects, with most done within 24 hours following infusion of study drug. Therefore, multiple readings were available before and during the time when drug concentrations were maximal. There were no serious cardiac AEs reported, and specifically no cases of torsades de pointes, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, or seizures.

The QTcB and QTcF were not found to be > 480 ms in any subject at any post-baseline time point. In the Applicant's single-dose pool (AH104 and AH110), post-baseline QTcB > 450ms was found in 3/70 (4.3%) placebo-treated subjects and 14/250 (5.6%) subjects treated with obiltoxaximab. The QTcB and QTcF did not increase > 60 ms in any subject at any post-baseline determination, but QTcB did increase by > 30ms in 5.7% of placebo-treated, and 5.2% of obiltoxaximab-treated subjects in the single-dose pool.

Reviewer comment: Problems with arrhythmias, conduction abnormalities or QT prolongation are not anticipated with a monoclonal antibody, and indeed were not found in the human trials with obiltoxaximab. Increased risk of these findings may also be encountered if there were significant changes in serum potassium level, but this too, was not seen.

8.4.10 Immunogenicity

Immunogenicity was low. Subjects who developed anti-therapeutic antibodies (ATA) at any study time point in the FDA ESP are tabulated in Table 8.32, along with TEAEs, if any.

Table 8.32 Subjects with Anti-therapeutic Antibodies and their AEs in the FDA ESP

Subject ID	Obiltoxaximab**	ATA results	Highest Titer	AE Preferred Term	AE Study Day (post-infusion)
AH104-001-160	16 mg/kg	Neg at BL,d8,d43; Pos d71	1:320	Affective disorder	*
AH104-001-160	16 mg/kg			Papule	*
AH104-001-160	16 mg/kg			Rash	16
AH104-001-177	16 mg/kg	Neg at BL,d8,d43; Pos d71	1:20	None	-
AH104-003-271	16 mg/kg	Neg at BL,d8,d43; Pos d71	1:40	Dermatitis	2
AH109-001-114	Sequence B	Neg at BL; Pos d120, d191	1:40	Upper respiratory tract infection	28
AH109-001-114	Sequence B			White blood cell count increased	28
AH109-002-211	Sequence A	Neg at BL; Pos d128, d163	1:20	Rash maculo-papular	111
AH109-002-211	Sequence A			Vessel puncture site swelling	1
AH109-002-224	Sequence A	Neg at BL: Pos d128	1:20	None	-
AH109-002-231	Sequence A	Neg at BL; Pos d163, d191	1:80	Gastroenteritis	95
AH109-002-231	Sequence A			Infusion site pain	1
AH109-002-231	Sequence A			Infusion site swelling	1
AH109-002-231	Sequence A			Pharyngitis	15
AH109-002-	Sequence A			Upper respiratory tract	111

231				infection	
AH110-001-135	16 mg/kg	Neg at BL, d9, d29, d43: Pos d71	1:80	Somnolence	1
AH110-001-135	16 mg/kg			Upper respiratory tract infection	28
AH110-001-135	16 mg/kg			Upper respiratory tract infection	53

*AE occurred prior to infusion
**All occurred only with obiltoxaximab; the dose or sequence are listed

There were 8/320 (2.5%) subjects in the FDA ESP who developed anti-therapeutic antibodies during the study period. Of these, 5 subjects were African-American, 3 subjects were white; males and females were equally represented (4 each).

Reviewer comment: Only one subject had an ATA titer > 1:80. There was no obvious correlation between time of development of ATA and TEAEs. Note: there were several other subjects, as noted by the Applicant, who were positive for ATA at screening only or at both screening and each postdose assessment, but did not have at least a 4-fold increase from baseline titer. These subjects are not represented in Table 8.32.

In the Applicant's analysis of 470 subjects who received at least one dose of IV obiltoxaximab in the clinical development program, 14 subjects (3.0%) were positive for a treatment-emergent ATA response. In addition to the 8 subjects listed above, there was 1 subject from AH 101 who received 19 mg IV ETI-204, 1 subject from AH102 who received 120 mg IV ETI-204, and 4 subjects from AH105 (1 received 16 mg/kg IV ETI-204, 2 received 4 mg/kg, 1 received 8 mg/kg). Of these, all were negative for ATA at baseline; 2 subjects in AH105 had a titer of 1:160, but all others had titers of ≤ 1:80.

In AH109, 8.8% (3/34) and 3.2% (1/31) of subjects in sequence A (2 weeks) and sequence B (≥4 months apart), respectively, were positive for a treatment-emergent ATA response.

The presence of ATA did not appear to have an impact on the pharmacokinetics of obiltoxaximab.

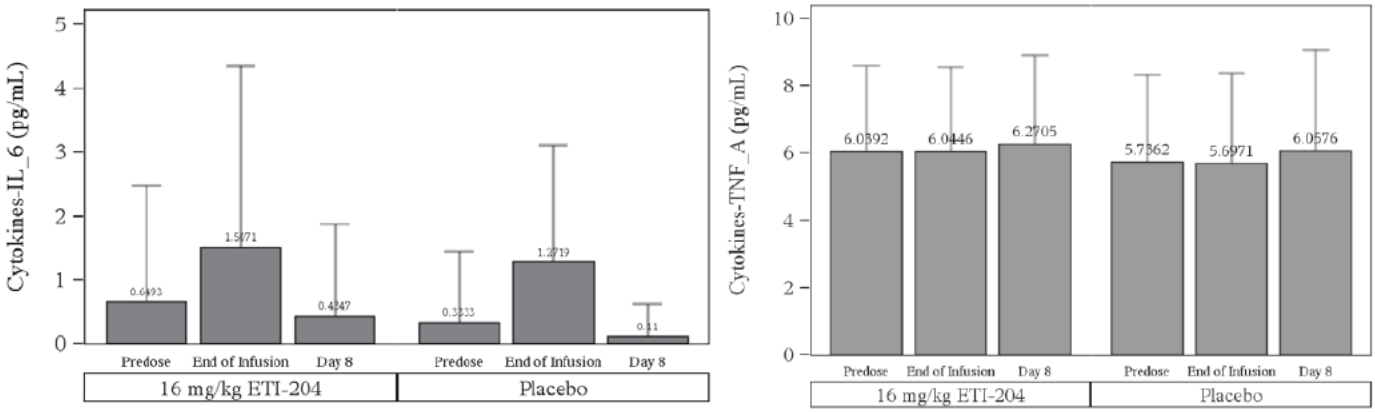
Reviewer comment: The higher incidence of treatment-emergent ATA response in the 2 week apart group of AH109 (sequence A) as compared to the 4 months apart group (sequence B) – 8.8% vs. 3.2% - suggests that the development of anti-obiltoxaximab antibodies could be prompted by an increased dose or frequency of obiltoxaximab administration. The incidence in the 4 months apart group (3.2%) is similar to that found in the entire population who received at least one dose of obiltoxaximab (3%). Levels of obiltoxaximab close to C_{max} are measurable in

the serum for approximately 20 days after infusion, which may lead to a temporary window of further increase in obiltoxaximab levels after a 2nd infusion of it 2 weeks after the first.

Exploratory Assessments: Cytokines

Blood for measurement of IL-6, IL-2, IL-1β, IFNγ and TNF-α was taken from the first 80 subjects in AH104. In the subjects that received obiltoxaximab, levels of IFNγ, IL-1β, and IL-2 were similar before and after study drug infusion; these cytokines were below the limit of quantification in the placebo group. IL-6 and TNF-α were similar in the obiltoxaximab and placebo groups, as shown in Figure 6.

Figure 8.5 IL-6 and TNF-α Levels in Recipients of Obiltoxaximab and Placebo



Source: AH104 Clinical Study Report, p.50

One subject in the obiltoxaximab group had a transient elevation in IL-1β – <0.78 pg/ml at baseline which rose to 9.5 pg/ml at the end of infusion. All vital signs were normal, laboratory parameters showed no change, and IFNγ and IL-2 levels were not elevated. Mild back pain 4 hours following the infusion on Day 1 was the only AE in this subject.

Reviewer comment: In these 80 subjects, there were no cytokine variations to suggest an inflammatory response to infusion of obiltoxaximab

8.5 Analysis of Submission-Specific Safety Issues

Hypersensitivity and the occurrence of infections were identified as the two main safety issues specific to this Application.

8.5.1 Hypersensitivity

Hypersensitivity was an issue in the clinical development program of obiltoxaximab. Eight subjects out of 320 (2.5%) who received obiltoxaximab in the three main safety studies, had a hypersensitivity reaction serious enough for the on-site investigator to discontinue the infusion; 2 other subjects were withdrawn from study AH109 for hypersensitivity severe enough to avoid repeat administration of obiltoxaximab. Thus, a total of 10 or 3.1% had serious hypersensitivity to obiltoxaximab.

The Applicant's analysis of hypersensitivity was reviewed thoroughly; this reviewer also conducted an independent analysis. The Applicant's approach to management of hypersensitivity was outlined in Sections 8.1.1.3 and 8.1.1.6. This reviewer used the Summary Report of the Second NIH Symposium on the Definition and Management of Anaphylaxis as the basis for definition of hypersensitivity and possible anaphylaxis. This document specifies a working definition of anaphylaxis to be "a serious allergic reaction that is rapid in onset and may cause death" and presented criteria to aid in identifying cases. Please see Section 8.3.2 Categorization of Adverse Events for an outline of this reviewer's approach to analysis of hypersensitivity. Broadly, the HYPERFL and HYPER2FL, AE3h and AE324h, and RASH flags provided by the Applicant in the ISS database, along with subject narratives, were utilized by this reviewer for independent analysis in combination with MAED analysis of the broad SMQs of Hypersensitivity, Anaphylactic Reaction and Angioedema.

8.5.1.1 Hypersensitivity in the Pooled Populations (FDA PSP and FDA ESP)

This reviewer's analysis of the occurrence of hypersensitivity in the FDA PSP (using the methodology outlined in section 8.3.2) identified 29, 25 and 5 subjects who received single-dose obiltoxaximab and 5, 4, and 0 subjects who received placebo in the Hypersensitivity, Anaphylactic Reaction and Angioedema SMQs respectively. Some subjects were represented in more than one of these SMQ's; they were counted just once. A total of 35 subjects **(35/300 or 11.6%)** with any symptom compatible with hypersensitivity were identified in the obiltoxaximab arm by this method, along with 5 subjects **(5/70 or 7.1%)** in the placebo arm.

In order to ensure that only PTs actually related to hypersensitivity were counted, this reviewer drilled down to individual subject profiles for subjects with AEs such as conjunctivitis, dermatitis contact, cough, seasonal allergy, allergic dermatitis and skin exfoliation which may have been related to conditions other than hypersensitivity. Those subjects whose information did not fit the clinical profile of hypersensitivity were excluded from this analysis. Further, subjects identified by the HYPERFL and the HYPER2FL flags in the Applicant's ISS datasets were grouped by this reviewer; the adverse event profile of each subject within these groups was then reviewed to ensure that the clinical reviewer agreed with the Applicant's classification. For example, subject 104-001-101 had a cough on Day 11; this was not felt by the reviewer to represent hypersensitivity. Subject 104-001-160 experienced a rash on the lower back on Day

16; this was included by the reviewer as hypersensitivity. Subject 104-002-236 had an erythematous rash on the left thigh on Day 1; this was thought to be related by the reviewer to study drug. Subject 104-004-318 had a cough on Day 6; this was thought related by the reviewer and the Applicant.

With this analysis and multiple cross-checks, **27 subjects with any symptom of hypersensitivity were identified in the obiltoxaximab arm of the FDA PSP (27/300=9%), along with 4 subjects in the placebo arm (4/70=5.7%).** Further, 8 subjects in the obiltoxaximab arm (2.5%) of the FDA PSP and 0 subjects in the placebo arm (0%) had their infusion discontinued (6 in AH104) or were discontinued from the study (2 in AH109) due to hypersensitivity.

The analysis was then redone using the FDA ESP (all subjects in AH104, both arms of AH110, and all time points in AH109). **Thirty-four (34) subjects in the obiltoxaximab arm had any clinically-relevant symptom of hypersensitivity (34/320=10.6%) vs. 4 subjects in the placebo arm (5.7%).** In this population, 10 subjects (10/320=3.1%) had significant hypersensitivity such that the infusion of obiltoxaximab was discontinued in 6 subjects in AH104 and 2 subjects in AH110; in addition, 2 subjects with significant hypersensitivity in AH109 were discontinued from the study to avoid potential risk with a second infusion of obiltoxaximab. The two subjects in AH110 in whom infusion of obiltoxaximab was discontinued due to hypersensitivity were also not given ciprofloxacin.

The most common hypersensitivity-related PTs are shown in Table 8.33.

Table 8.33 FDA Analysis of Subjects with Preferred Terms Compatible with Hypersensitivity

Hypersensitivity (PT)	Placebo, N=70 n (%)	FDA PSP, N=300 n (%)	FDA ESP, N=320 n (%)
Pruritus	1 (1.4%)	9 (3%)	9 (2.8%)
cough	0 (0%)	8 (2.6%)	8 (2.5%)
Urticaria	0 (0%)	4 (1.3%)	7 (2.1%)
Rash maculopapular	0	0	2 (0.6%)
Rash macular	0	0	1 (0.3%)
Rash papular	0 (0%)	1 (0.3)	1 (0.3%)
Rash generalised	0 (0%)	1 (0.3%)	1 (0.3%)
Rash erythematous	0 (0%)	1 (0.3%)	1 (0.3%)
Rash	2 (2.8%)	6 (2%)	6 (1.9%)
Dermatitis allergic	0 (0%)	1 (0.3%)	1 (0.3%)
Dermatitis acneiform	0 (0%)	0 (0%)	1 (0.3%)
Anaphylactic Reaction	0 (0%)	1 (0.3%)	1 (0.3%)
Hypersensitivity	0 (0%)	1 (0.3%)	1 (0.3%)
Dermatitis	0 (0%)	1 (0.3%)	1 (0.3%)

Cyanosis	0 (0%)	1 (0.3%)	1 (0.3%)
Flushing	1 (1.4%)	1 (0.3%)	1 (0.3%)
Dyspnea	0 (0%)	1 (0.3%)	1 (0.3%)
Chest discomfort	0	0	1 (0.3%)

Reviewer comment: This count identifies the numbers of subjects with the relevant PT compatible with hypersensitivity. However, as has been indicated through this review, there is limited clinical utility to consideration of individual symptoms or signs, because their aggregate into a clinically meaningful syndrome is much more relevant to overall safety. Some subjects experienced more than one AE counted as hypersensitivity. Further, the terms Anaphylactic Reaction and Hypersensitivity as used in this table and as used by the Applicant in Table 34 of the ISS (p.118), are misleading. Using this term, there was only one subject (AH104-003-258) who was thought to have anaphylaxis.

A narrative of the subject identified with the PT of anaphylactic reaction by the Applicant is provided below:

Subject AH104-003-258 was a 62-year-old white male, essentially healthy, with a past history of vasectomy. He was noted to have first-degree block on his ECG at baseline. The subject was pre-medicated with diphenhydramine as per protocol. Thirty-three minutes into the infusion of obiltoxaximab, the subject needed to be escorted to the bathroom. The infusion was resumed 4 minutes later, continued for 21 minutes, then stopped again at 55 minutes after the start of dosing; by then, 164 mL had been infused. A diffuse pruritic urticarial rash developed over his neck, chest, back, abdomen, arms and legs and was accompanied by shortness of breath and coughing. His ECG showed PVC's and subsequent non-specific ST-T changes. He had moderate infusion site erythema. The subject received an additional 25 mg diphenhydramine IV, followed by 20 mg famotidine. Despite this, his rash worsened, and other symptoms persisted. He then received 125 mg IV methylprednisolone followed by 2.5 mg salbutamol by nebulizer, and 0.3 mg epinephrine IM. The dyspnea and cough resolved, but the rash and pruritus persisted. No hypotension, hypoxia, ECG or lab changes were reported. No physical examination at the time of reaction was reported. On Day 2, the subject received 2 more oral doses of 50 mg diphenhydramine and the AE resolved 24 hours after the start of the infusion. All of these AEs were individually counted by the investigator as being of moderate severity. The subject recovered and completed the study.

However, there were several other subjects who had a constellation of symptoms indicating serious hypersensitivity, despite the fact that they were not identified with the PT "anaphylactic reaction". Some of these subjects, using the definition provided in Section 8.3.2., had reactions that should be considered as anaphylaxis.

Reviewer comment: The definition and clinical recognition of anaphylaxis depends on the clinical context in which the reaction occurs, physical examination of the subject, the signs and

symptoms present, vital signs, other ancillary data, medications required for treatment, and clinical judgment. Because hypersensitivity and anaphylaxis occur on a continuum, with considerable overlap, their categorization is often challenging and partly open to interpretation on the part of the on-site investigator and during subsequent evaluation

The details of the other 9 subjects with serious hypersensitivity in the three main clinical studies are provided in Table 8.34, followed by their narratives..

Table 8.34 Subjects in the FDA ESP in whom Infusion was Discontinued due To Adverse Event, or Who Were Discontinued from the Study Due to an AE – all in the Obiltoxaximab arm

Subject	DPH*	Arm/Sequence	Time to Withdrawal of Drug Relative to Start of Infusion (mins)	Symptoms	Treatment
104-002-350	+	obiltoxaximab	66m	Urticaria, pruritus	PO/IV DHP
104-002-053	-	obiltoxaximab	34m	Cough, headache, dysphonia, pruritus (severe), urticaria (severe), throat irritation	PO/IV DHP
104-002-068	+	obiltoxaximab	34m	Urticaria, hives, pruritus, dizziness, chills	PO/IV DHP
104-003-101	-	obiltoxaximab	58m	Rash, throat irritation, cough, hypoaesthesia	IV DHP, IV famotidine
104-003-107	-	obiltoxaximab	64m	Headache, cough, pruritus, rash	IV DHP, IV famotidine
104-003-258	+	obiltoxaximab	55m	Anaphylaxis	PO/IV DHP, IV famotidine, IM epinephrine, IV methylprednisone, salbutamol
109-002-204	-	B (obiltoxaximab)	Completed infusion but was withdrawn from study	Back pain, flushing, chills, dyspnea, cyanosis, pallor, restlessness, myalgias, rash	Acetaminophen, IV DHP, saline, 0_2
109-002-205	+	A (obiltoxaximab)	Completed infusion but was withdrawn from study	Urticaria	IV DHP
110-001-103	+	obiltoxaximab plus Cipro	48 mins (Cipro not given)	Urticaria, jaw pain, chest discomfort, postural dizziness (no change in bp recorded)	IV DHP, IV famotidine, IV methylprednisolone
110-001-133	+	obiltoxaximab plus Cipro	50 mins (Cipro not given)	Urticaria	None

Source: Adapted from CSRs of AH104, AH109 and AH110; *DPH: diphenhydramine

Narratives of Subjects Identified in Table 8.34.

1. Subject AH104-002-053 was a 43 year old healthy white male. He did not receive diphenhydramine premedication. The infusion was started at 0940h on (b) (6), and stopped at 0959h apparently due to air in the line. It was started again at 1002h, but stopped at 1014h due to pruritus, urticaria, throat irritation (mild), cough (mild), headache and muscle twitching (mild). He was treated with 50 mg diphenhydramine both PO and IV. The pruritus and urticaria were rated as severe by the investigator and lasted about 2.5 hours, after which they resolved to moderate, then mild in 6 hours. Both resolved on Day 2, however, the throat irritation lasted until Day 11 and the cough until Day 24. The dysphonia started 7 hours and 20 minutes after the start of the infusion and resolved on Day 23. His systolic bp started at 107 mm Hg predose with a pulse rate of 74, and reached a high of 186 mmHg with a HR of 105 bpm at 36 minutes post start of infusion. The systolic BP then gradually fell to 109 at 4 hours post start of infusion; his heart rate went to a high of 121 bpm 44 mins after start of infusion, and gradually returned to 69 at 4 hours. He was mildly tachypneic at 24 breaths/minute at 39 mins; his respiratory rate fell to 18 breaths/min at 90 mins.

2. Subject 104-002-068 was a 54 year old white female with a history of urinary tract infections. She received diphenhydramine prior to the dose of obiltoxaximab. The infusion started at 0940h (b) (6), and was stopped at 1024h due to AE's consisting of moderate urticaria and pruritus, mild ear discomfort and moderate dizziness and chills which started 48 and 53 minutes after the start of the infusion respectively, and resolved after 1 hour. Rash was present on her legs, arms, head and stomach. She was treated with 50 mg diphenhydramine both PO and IV. The urticaria resolved on Day 2, the pruritus resolved on Day 1. Her predose BP was 131/87 with a pulse rate of 58. Her systolic BP rose to 166 at 30 minutes, and a high of 181 64 mins after start of infusion. She was tachycardic to 105 bpm at 48 min; the HR gradually fell to 68 bpm at 4 hours. The rash was still present on Day 2, but there was no record of a skin exam in the eCRF on Day 7 or Day 15. She completed the study.

3. Subject 104-003-101 was a 28 year old healthy white male; he did not receive premedication with diphenhydramine. At 58 minutes after the start of the infusion of obiltoxaximab, he experienced a moderate rash, throat irritation and cough and the infusion was stopped. The eCRF describes an urticarial rash over chest, back, face, neck, both arms, and the left foot. He also experienced hypoaesthesia in both hands but there were no changes in his vital signs. He received 25 mg IV diphenhydramine and IV famotidine (20 mg). The AEs were judged to be of moderate severity, but necessitated withdrawal of medication. The rash resolved after 7 hours; the cough at 5 days and the throat irritation at 20 hours. The subject completed the study on Day 71.

Subject 104-003-107 was a 49 year old healthy white female with a history of tubal ligation. She was not pretreated with diphenhydramine. According to the eCRF, the infusion of

obiltoxaximab was started at 1104h, paused at 1149h for 15 secs, restarted at 1149h, paused for 10 seconds at 1152h, started again at 1152, and stopped at 1204h at the MD's request. The reason for stoppage was not specified in the eCRF, but she appears to have had headache, papules, itching on trunk and arms, and rash. Pruritus was reported at 23 minutes after start of IV obiltoxaximab, with a moderate rash at 63 minutes. There were no significant changes in her vital signs. She received 25 mg IV diphenhydramine, 20 mg IV famotidine and acetaminophen and obiltoxaximab was withdrawn. The subject further experienced mild cough starting at 3.5 hours after the start of infusion which resolved 30 minutes later, as well as a headache starting 90 minutes after start of infusion, and resolving at 17h 45 mins. Rash was still noted on her Day 2 assessment. She redeveloped pruritus of the trunk and arms on Day 8 which continued to Day 18.

Subject 104-002-350 was a 29 year old healthy white female who received 50 mg diphenhydramine premedication. The infusion of obiltoxaximab started at 1040h on (b) (6), and stopped at 1145h. She developed pruritus and hives on the abdomen and back 64 minutes after the start of the infusion, both of which resolved in 54 minutes and 8 hours respectively. She was treated with 50 mg IV diphenhydramine. There was no change in her vital signs during the infusion, but her blood pressure at 1410 was 96/54, then 96/60 at 18:33 (after infusion). She also developed rash, phlebitis, and swelling at the infusion site. These adverse events were judged by the investigator to be of moderate severity.

Subject 109-002-204 was a 66 year old female of American Indian/Alaska native descent who was randomized to sequence B (obiltoxaximab on Days 1 and 120, placebo on Day 14). She had a history of dyslipidemia, myopia, presbyopia, left knee arthritis and a remote history of a coccygeal fracture, but was on no prior medications. She did not receive diphenhydramine pre-medication. Starting 1.5 hours after the start of obiltoxaximab infusion, she experienced severe back pain, flushing, moderate chills, moderate dyspnea (duration 28 mins), moderate cyanosis (duration 40 minutes), moderate pallor (40 minutes duration) and moderate restlessness (duration 1.5 hours). She also experienced moderate myalgias, mild rash on the trunk and mild erythema at the infusion site; this latter event began about 23 hours after the start of the infusion and lasted about 4 days. This subject required diphenhydramine, acetaminophen, normal saline infusion and oxygen by nasal prongs as treatment. Her predose BP was 119/73 with a pulse rate of 60 bpm. About 90 minutes into the infusion, her systolic BP increased to a high of 152, and she was tachycardic. She was noted to have a BP of 111/48 on Day 28. Blood work done on Day 2 revealed a decreased white cell count, lymphocyte count and neutrophil count. She completed study assessments through Day 85, but was withdrawn from the study on Day 106 to avoid a second infusion of obiltoxaximab which was due on Day 120.

Reviewer comment: Given her dyspnea, cyanosis, severe back pain, rash and chills as well as the need for significant concomitant medication including IV normal saline and oxygen by nasal cannula constituting a highly suggestive picture for anaphylaxis, it is concerning that her

infusion of obiltoxaximab was not discontinued. Cyanosis was recorded as an AE occurring during this reaction; this was identified in the study protocol as a significant criterion for hypersensitivity, and one that should potentially trigger a pause in the study.

Subject 109-002-205 was a 70 year old white male with a prior history of bilateral hearing loss, presbyopia, cataracts, mild lactose intolerance, low back pain, nephrolithiasis, tendon repair in an arm, insomnia, hives and a right ankle fracture; he was on no prior medications, and was randomized to sequence A. He experienced moderate urticaria 4 hours after the start of the infusion which resolved after 4 days, and mild urticaria which started 22 days after the start of the infusion and resolved after 38 days. He did not receive any further infusions and was withdrawn from the study early due to hypersensitivity and the concern for administration of a second dose of obiltoxaximab.

Subject 110-001-103 was a 59 year old white male with a medical history of astigmatism, myopia and presbyopia who was randomized to the obiltoxaximab plus ciprofloxacin treatment group. He was given premedication with diphenhydramine. Twenty-eight minutes after the start of the infusion of obiltoxaximab, he had a generalized urticarial rash (chest, back and face) of moderate intensity. He was given 50 mg IV diphenhydramine, but 8 minutes later, the infusion was stopped due to a worsening rash (spread to the abdomen). The rash then progressed to his legs, and 125 mg methylprednisolone IV was given. He then reported mild jaw pain, mild chest discomfort and moderate postural lightheadedness and was given 20 mg IV famotidine. He improved with this. He also reported palpitations, fatigue and diarrhea on Days 1 and 2. The investigator did not feel these latter AEs were related to obiltoxaximab but this clinical reviewer differs with this assessment. He did not appear to have a significant change in his vital signs (other than mild tachycardia with a HR to 102 bpm at 7.5 hours), laboratory parameters or ECG. He did not receive ciprofloxacin.

Subject 110-001-133 was a 58 year old healthy male with myopia. He was randomized to the obiltoxaximab plus ciprofloxacin group. He did receive premedication with diphenhydramine. Fifty minutes after the start of infusion, the subject experienced moderate urticaria on the trunk and palms and his infusion was stopped due to increasing erythema of the trunk. He did not require medications for the rash, and it resolved about 1.5 hours after onset. There were no significant changes in vital signs, laboratory parameters, or ECG.

Reviewer comment: Each of the adverse events described in these 10 subjects were described as of mild or moderate severity by the investigators, with the exception of pruritus and hives in subject AH104-002-053 which were described as initially severe. However, when taken together, the clinical complex was concerning enough to warrant discontinuation of the infusion of obiltoxaximab in 8 subjects, discontinuation from the study in 2 subjects, and/or administration of concomitant medications. Further, in this circumstance, it is this reviewer's view that stopping the infusion in and of itself, constitutes an intervention that would prevent a more serious

outcome.Indeed, the study protocols of the main human studies state that the 90 minute infusion time was chosen such that exposure to obiltoxaximab could be limited by stopping the infusion in the event of hypersensitivity (see Section 8.1.1).

In such clinical situations, the severity of each individual symptom or sign at a particular time point is less relevant than the potentially greater clinical consequence of their occurring together. Therefore, the overall adverse event complex in the subjects in whom the obiltoxaximab infusion was interrupted due to hypersensitivity or who were discontinued from the study due to hypersensitivity, should be considered together as serious occurrences. Thus, in the FDA ESP, a total of 10 subjects or 3.1% had serious hypersensitivity.

Further, of these 10 subjects, this clinical reviewer felt that the narratives and clinical presentations of Subjects AH104-002-053, 104-002-068, 104-003-101, 104-003-107, 109-002-204, and 110-001-103 are compatible with anaphylaxis of varying severity. Taken together with Subject AH104-003-258 whose AE was labeled Anaphylactic Reaction by the Applicant, the incidence of anaphylaxis in the FDA ESP was 2.1% (7/320).

8.5.1.2 Diphenhydramine Premedication

In July 2013, after 5 generalized urticarial reactions had occurred in the major human studies, the protocol of all ongoing clinical studies was amended to add premedication with 50 mg oral diphenhydramine (DPH) approximately 30 minutes prior to infusion of study drug. Table 8.35 provides a summary of the number of subjects in each arm of each study in the FDA PSP who did or did not receive diphenhydramine .

Table 8.35 FDA Analysis of Subjects Who Received DPH in the FDA PSP

	Obiltoxaximab, N=300		**Placebo, N=70**	
Study ID	**DPH+ (n=226) (75.3%)**	**DPH- (n=73)* (24.3%)**	**DPH+ (n=48) (68.6%)**	**DPH- (n=22) (31.4%)**
AH104	144	66	48	22
AH109	62	8	0	0
AH110	20	0	0	0

*Subject 104-001-026 had a missing treatment record and did not receive DPH. Thus, there are 73 subjects in DPH- group in the obiltoxaximab arm.

All 40 subjects in study AH110 received diphenhydramine (though only the 20 subjects who received obiltoxaximab alone in the FDA PSP are depicted in Table 8.35).

Out of 370 total subjects in the FDA PSP, 165 subjects or 44.5% experienced 329 TEAE's – 138 of these were in the obiltoxaximab arm (138/300 or 46%), and 27 were in the placebo arm (27/70 or 38.6%). Of the 138 subjects with TEAE's in the obiltoxaximab group, 95 subjects received

diphenhydramine, and 43 did not. Of the 27 subjects with TEAE's in the placebo arm, 18 subjects received diphenhydramine, and 9 did not.

Table 8.36 FDA Analysis of Occurrence of TEAE's Correlated with Diphenhydramine Use in the FDA PSP

Number of subjects in FDA PSP N=370	**Obiltoxaximab, N=300**		**Placebo, N=70**	
	DPH+ (n=226) (75.3%)	DPH- (n=73) (24.3%)	DPH+ (n=48) (68.6%)	DPH- (n=22) (31.4%)
Number of subjects with TEAE's N=165 (44.5%)	**Obiltoxaximab, N=138**		**Placebo, N=27**	
	95 (95/226=42%)	43 (43/73=58.9%)	18 (18/48=37.5%)	9 (9/22=40.9%)

Overall in the FDA PSP, there were fewer TEAE's in subjects who received obiltoxaximab when they were premedicated with DPH (42%) vs. without DPH (58.9%). In the placebo arm, this difference was minor (37.5% with DPH vs. 40.9% without DPH).

Table 8.37 FDA Analysis of Occurrence of TEAE's Correlated with Diphenhydramine Use in the FDA ESP

Number of subjects in FDA ESP N=390	**Obiltoxaximab, N=320**		**Placebo, N=70**	
	DPH+ (n=246) (76.9%)	DPH- (n=73) (24.3%)	DPH+ (n=48) (68.6%)	DPH- (n=22) (31.4%)
Number of subjects with TEAE's N=203 (63.4%)	**Obiltoxaximab, N=176**		**Placebo, N=27**	
	133 (133/246=54%)	43 (43/73=58.9%)	18 (18/48=37.5%)	9 (9/22=40.9%)
Subjects in whom infusion was discontinued due to serious hypersensitivity	5 (2.0%)	3 (4.1%)	0	0
Subjects who were discontinued from study AH109 due to serious hypersensitivity	1 (0.4%)	1 (1.4%)	0	0
Total subjects with serious hypersensitivity	6 (2.4%)	4 (5.5%)	0	0
FDA analysis of subjects with anaphylaxis*	3 (1.2%)	4 (5.5%)		

*Based on the clinical reviewer's evaluation of the clinical narratives, time of occurrence, relatedness, use of concomitant medications and laboratory data gleaned from the Applicant's submission. The Applicant identified a single subject with anaphylaxis.

Reviewer comment: In the FDA ESP, the effect of diphenhydramine on occurrence of TEAE's in either subjects who received obiltoxaximab or placebo was not obvious – the inclusion of

subjects who received a repeat dose may account for some of this, as by contrast, a clear effect was seen in the FDA PSP. The FDA PSP may be a more accurate representation of the effect of diphenhydramine on immediate hypersensitivity since it included only subjects who received a single dose of obiltoxaximab.

Of the 10 subjects in the FDA ESP (3.1%) in whom the infusion of obiltoxaximab was interrupted, or who were discontinued from the study due to hypersensitivity, 6 received DPH premedication, and 4 subjects did not. When considered according to administration of DPH, **2.4% of subjects who received DPH vs. 5.5% of subjects who did not receive DPH, had significant hypersensitivity**. **Of the 2.4% with serious hypersensitivity who received DPH, 1.2% had anaphylaxis.**

Table 8.38 FDA Analysis of Use of DPH in Subjects in Whom Infusion was Discontinued due to Hypersensitivity

	DPH+	DPH-
Study/Subject ID	104-002-068*	104-002-053*
	104-002-350	104-003-101*
	109-002-205	104-003-107*
	110-001-103*	109-002-204*
	110-001-133	
	104-003-258*	

*Clinical constellation compatible with anaphylaxis; DPH: diphenhydramine

Occurrences of TEAE's within the SOC's of interest were explored in Table 8.39 below. TEAEs that occurred in ≥ 2 subjects are included in the tables.

Table 8.39 FDA Analysis of Diphenhydramine Premedication Correlated with Occurrence of TEAE's and Their Severity in the FDA PSP

Preferred Term	Severity	Placebo		Obiltoxaximab	
		DPH		DPH	
		No, n=9 N (%)	Yes, n=18 N (%)	No, n=43 N (%)	Yes, n=95 N (%)
General Disorders and Administration Site Conditions					
Application site erythema	MILD	0	0	1 (2.3%)	1 (1.1%)
Chills	MILD	1 (11.1%)	0	0	0
	MODERATE	0	0	1 (2.3%)	1 (1.1%)
Influenza like illness	MILD	0	0	0	1 (1.1%)
Infusion site discolouration	MILD	0	0	0	3 (3.6%)
Infusion site erythema	MILD	1	1 (5.6%)	3 (7.0%)	1 (1.1%)
Infusion site pain	MILD	0	0	2 (4.7%)	5 (5.3%)
Infusion site swelling	MILD	0	0	1 (2.3%)	7 (7.4%)
Pain	MILD	2 (22.2%)	0	1 (2.3%)	2 (2.1%)
Vessel puncture site bruise	MILD	0	1 (5.6%)	1 (2.3%)	7 (7.4%)
Vessel puncture site pain	MILD	0	0	1 (2.3%)	1 (1.1%)
Infections and Infestations					
Upper respiratory tract infection	MILD	0	1 (5.6%)	2 (4.7%)	9 (9.5%)
	MODERATE	1 (11.1%)	0	0	0
Urinary tract infection	MILD	1 (11.1%)	1 (5.6%)	0	0
Nervous System Disorders					
Dizziness	MILD	0	0	0	2 (2.1%)
	MODERATE	0	0	0	1 (1.1%)
Headache	MILD	3 (33.3%)	1 (5.6%)	12 (27.9%)	11 (11.6%)
	MODERATE	0	0	1 (2.3%)	0
Migraine with aura	MODERATE	0	0	1 (2.3%)	0
Somnolence	MILD	0	0	0	17 (17.9%)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	MILD	0	0	6 (13.9%)	3 (3.2%)
Dry throat	MILD	0	0	2 (4.7%)	0
Dysphonia	MILD	0	0	1 (2.3%)	0
Dyspnoea	MODERATE	0	0	1 (2.3%)	0
Nasal congestion	MILD	0	1 (5.6%)	2 (4.7%)	3 (3.2%)
Oropharyngeal pain	MILD	0	0	0	3 (3.2%)
Rhinorrhoea	MILD	0	0	2 (4.7%)	0
Throat irritation	MILD	0	1 (5.6%)	2 (4.7%)	0
Gastrointestinal Disorders					
Abdominal pain	MILD	1 (11.1%)	0	0	1 (1.1%)
Diarrhoea	MILD	1 (11.1%)	1 (5.6%)	0	0
Nausea	MILD	1 (11.1%)	1 (5.6%)	0	5 (5.3%)

Preferred Term	Severity	Placebo		Obiltoxaximab	
		DPH		DPH	
		No, n=9 N (%)	Yes, n=18 N (%)	No, n=43 N (%)	Yes, n=95 N (%)
	MODERATE	0	0	0	1 (1.1%)
Vomiting	MILD	0	0	0	2 (2.1%)
	MODERATE	0	0	0	1 (1.1%)
Skin and Subcutaneous Tissue Disorders					
Dermatitis contact	MILD	0	1 (5.6%)	2 (4.7%)	4 (4.2%)
Papule	MILD	0	0	1 (2.3%)	0
Pruritus	MILD	0	1 (5.6%)	3 (7.0%)	7 (7.4%)
	MODERATE	0	0	1 (2.3%)	1 (1.1%)
	SEVERE	0	0	1 (2.3%)	0
Rash	MILD	0	2 (11.1%)	1 (2.3%)	2 (2.1%)
	MODERATE	0	0	2 (4.7%)	1 (1.1%)
Rash erythematous	MILD	0	0	0	1 (1.1%)
Rash generalised	MILD	0	0	1 (2.3%)	1 (1.1%)
Rash papular	MILD	0	0	1 (2.3%)	0
Skin exfoliation	MILD	0	0	0	1 (1.1%)
Skin irritation	MILD	0	0	0	1 (1.1%)
Urticaria	MILD	0	0	1 (2.3%)	2 (2.1%)
	MODERATE	0	0	1 (2.3%)	3 (3.2%)
	SEVERE	0	0	1 (2.3%)	0

DPH – diphenhydramine group
Highlighted cells denote variations of interest

Reviewer comment: In the FDA PSP, there was a decline in occurrence of infusion site erythema, headache, cough, rhinorrhea, and throat irritation after the protocols were amended to premedicate subjects with diphenhydramine (Table 8.39). The most striking decrease was in the occurrence of headache, but this occurred in both the placebo and obiltoxaximab arms. Incidence of headache in the placebo arm declined from 33.3 without, to 5.6% with, diphenhydramine; in the obiltoxaximab arm, headache incidence dropped from 27.9% to 11.6% respectively. The mechanistic explanation for this is unclear as headache is not usually considered a classic manifestation of hypersensitivity. Cough incidence declined from 13.9 to 3.2%, while rhinorrhea and throat irritation declined from 4.7% to 0 without and with diphenhydramine respectively; cough, especially, seemed to occur with some frequency in the context of hypersensitivity in this Application. Dyspnea and dysphonia occurred only in 1 subject with hypersensitivity, but was shown in this table as related information.

There was a slight decline in the incidence of rash generalized (2.3% to 1.1%), rash of moderate severity (4.7% to 1.1%), rash papular (2.3% to 0), moderate (2.3% to 1.1%) and severe pruritus (2.3% to 0), and severe urticaria (2.3% to 0) without and with premedication with

diphenhydramine respectively. The numbers are small, so this reviewer only noted the trend; data from more subjects would be needed in order to clarify the issue.

The severity of these TEAEs was examined in order to see if diphenhydramine had any effect in abrogating the severity of TEAEs. As noted above, there is an intriguing and minor trend noted in occurrence of types of rash, severe pruritus and severe urticaria, but the numbers are too small to comment. Some negative results are also included in the table to set a frame of reference. Thus, there was no difference in occurrence of TEAEs in the gastrointestinal or musculoskeletal SOCs with DHP premedication.

There were more infections in the group that received obiltoxaximab and were premedicated with DPH, compared with the group that did not receive DPH. Infusion site swelling and vessel puncture site bruise were also increased in the group that received both diphenhydramine and obiltoxaximab.

Some AE's occurred more than once in the same subject with different severities, e.g., subject 104-002-053 had mild, moderate and severe pruritus, and mild, moderate and severe urticaria. Similarly, 104-002-068 had moderate and mild urticaria.

Table 8.40 FDA Analysis: Correlation of Pre-Medication with Diphenhydramine with Occurrence of Hypersensitivity Symptoms in the FDA PSP and FDA ESP

Preferred Term	Placebo		Obiltoxaximab (PSP)		Obiltoxaximab (ESP)	
	DPH		DPH		DPH	
	No, n=9 N (%)	Yes, n=18 N (%)	No, n=43 N (%)	Yes, n=95 N (%)	No, n=43 N (%)	Yes, n=133 N (%)
Rash	0	2 (11.1%)	3 (7.0%)	3 (3.2%)	3 (7.0%)	3 (2.3%)
Cough	0	0	6 (14%)	3 (3.2%)	6 (14%)	4 (3.0%)
Urticaria	0	0	1 (2.3%)	3 (3.2%)	1 (2.3%)	7 (5.3%)
Pruritus	0	1 (5.6%)	4 (9.3%)	8 (8.4%)	4 (9.3%)	9 (6.8%)
Rash Papular	0	0	1 (2.3%)	0	1 (2.3%)	0
Rash erythematous	0	0	0	1 (1.1%)	0	1 (0.8%)
Dermatitis allergic	0	0	0	1 (1.1%)	0	1 (0.8%)
Rash generalised	0	0	0	1 (1.1%)	1 (2.3%)	1 (0.8%)
Hypersensitivity	0	0	0	1 (1.1%)	0	1 (0.8%)
Anaphylactic Reaction	0	0	0	1 (1.1%)	0	1 (0.8%)
Flushing	1 (11.1%)	0	1 (2.3%)	0	1 (2.3%)	0
Cyanosis	0	0	1 (2.3%)	0	1 (2.3%)	0
Dyspnea	0	0	1 (2.3%)	0	1 (2.3%)	0
Throat Irritation	0	1 (5.6%)	0	0	2 (4.7%)	0

In the PTs that were included in analysis of hypersensitivity, cough and rash were again the only two TEAEs that were less frequent in the obiltoxaximab group with diphenhydramine premedication vs. the group that did not receive diphenhydramine. There were also minor decreases, as noted in Table 8.40, in the incidence of cyanosis, dyspnea, throat irritation and flushing, all of which occurred in 2 subjects with severe hypersensitivity.

Reviewer comment: *Interestingly, although the numbers of subjects are relatively small, the administration of diphenhydramine did not appear to have a noticeable impact on the incidence of both pruritus and urticaria, suggesting that histamine release may not play a big role in the causation of these AEs. Also, the 2 subjects with hypersensitivity and anaphylaxis did receive diphenhydramine prior to obiltoxaximab, which underscores the fact that blocking histamine release does not prevent hypersensitivity but may decrease its incidence. The dose of diphenhydramine and its route and timing of administration may also be variables that affect prevention of hypersensitivity – these factors were not addressed in this Application, but may be considerations for post-marketing studies.*

There was 1 subject with the PT of hypersensitivity. Although obiltoxaximab infusion was not discontinued when she developed a hypersensitivity reaction, her narrative is provided here because of the designation

AH104-002-351 – Hypersensitivity – This was a 27 year old Hispanic female with a normal physical examination on Day -1, and no pre-existing medical conditions. She received diphenhydramine premedication prior to the start of her infusion of obiltoxaximab at 1000h on (b) (6); this was completed at 1130h without interruption. The clinical narrative provided by the Applicant mentions that the subject "experienced a mild infusion reaction/hypersensitivity which was reported as an AE related to study treatment" but does not specify what the clinical manifestations were. The eCRF recorded variation in BP as noted below, though there was no tachycardia. BP at 1015h was 115/65, HR=59, RR=12. At 1030h, BP was 108/65, HR=55, RR=18. At 1100h, BP was 100/56, HR=58, RR=14. At 1137h, BP was 126/78, HR=88, RR=18. AT 1158h, BP was120/74, HR=69, RR=12. ECGs up to then had been normal. At 1248h, her ECG was noted to have sinus arrythmia. At 1401h, her BP was 108/62, HR=72, RR=12, and at 1753h, her BP was 100/52, HR=64, RR=18. The eCRF also notes the presence of a red raised rash on her neck initially noted at 1115h and resolved at 1400h. It is unclear whether the rash was equated with hypersensitivity. The subject received 50 mg diphenhydramine again IV for treatment of her reaction. The subject's histamine levels rose from 2.2 nmol/L predose to 9.8 nmol/L postdose, although her IgE levels did not change.

Reviewer comment: This information was culled from the eCRF and the subject narrative provided, but because the physical examination is not very complete, it was difficult to develop a clear picture of the event or its importance.

8.5.1.3 Hypersensitivity in Individual Studies

AH104

After the first 88 subjects were enrolled and treated, the CTSC amended the protocol to specify that diphenhydramine (DPH) should be given prior to infusion of either study drug or placebo. Diphenhydramine was administered prior to infusion in 192 of 280 subjects - 48 subjects were in the placebo arm, and 144 subjects were in the obiltoxaximab arm The following table highlights the numbers of subjects with TEAEs with and without premedication in the most frequently occurring SOCs.

TEAEs occurred in 115 (41.1%) of the 280 subjects – of these, 88 of 115 (76.5%) of the population with TEAEs or 88/280 (31.4%) of the total population received obiltoxaximab , while 27 of 115 (23.4%) of the TEAE population, or 27/280 (9.6%) of the total population received placebo. In the 88 subjects who had TEAEs with obiltoxaximab infusion, 53 received diphenhydramine, and 35 subjects did not. Of the 27 subjects who had TEAEs with placebo infusion, 18 received diphenhydramine, and 9 did not.

Table 8.41 shows the incidence of TEAEs in the most frequently occurring SOCs in AH104 by study arm and premedication with diphenhydramine.

Table 8.41 FDA analysis*: Numbers and percentages of subjects with TEAE's with and without diphenhydramine premedication by most frequently occurring SOC's

	Obiltoxaximab		Placebo	
Total	**DPH+ n=144**	**DPH- n=66**	**DPH+ n=48**	**DPH- n=22**
Subjects with TEAE's	53 (36.8%)	35 (53%)	18 (37.5%)	9 (40.9%)
Skin/subcutaneous disorders	15 (10.4%)	6 (9.1%)	4 (8.3%)	1 (4.5%)
General disorders and administration site conditions	15 (10.4%)	9 (13.6%)	2 (4.1%)	5 (22.7%)
Nervous system disorders	11 (7.6%)	14 (21.2%)	1 (2.0%)	3 (13.6%)
Respiratory, thoracic and mediastinal disorders	6 (4.1%)	8 (12.1%)	2 (4.1%)	0 (0%)
Gastrointestinal disorders	11 (7.6%)	0 (0%)	1 (2.0%)	1 (4.5%)
Infections and Infestations	7 (4.8%)	2 (3.0%)	2 (4.1%)	2 (9.0%)

*FDA conducted an independent analysis of these data which agrees with that conducted by the Applicant. DPH: diphenhydramine

As seen in table 8.41, 71 of the 192 subjects (36.9%) who received diphenhydramine had TEAEs - 53 in the obiltoxaximab arm and 18 in the placebo arm; while 44 of 88 (50%) subjects who did not receive diphenhydramine experienced TEAEs. In the obiltoxaximab arm, there were higher percentages of general disorders and administration site conditions in those who did not receive diphenhydramine compared to those who did: 13.6 % vs. 10.2%. Similarly greater percentages of TEAEs were seen in the group that did not receive diphenhydramine in the Nervous System Disorder SOC (21.2% vs. 7.6%), and in the Respiratory, Thoracic and Mediastinal SOC (12.1% vs. 4.1%), though the numbers are small. Conversely, there was a greater percentage of TEAEs in the Skin and Subcutaneous Tissue Disorders SOC in subjects who received DPH compared with those who did not (10.4 vs. 9.1%); similarly in the Gastrointestinal Disorder SOC (7.5% vs. 0%).

Individual PTs were also analyzed under each SOC by the Applicant. For example, 9 subjects (6.2%) in the obiltoxaximab arm who were pretreated with DPH had headache, while 12

(18.5%) subjects in the obiltoxaximab arm who did not receive DPH had headache. In the placebo arm, 1 subject who received DPH had headache, while 3 subjects (13.6%) who did not receive DPH , had headache. The occurrence of pruritus and urticaria was similar in the subjects in the obiltoxaximab group who received premedication with DPH vs. not: 7 (4.8%) vs. 3 (4.6%) and 2 (1.4%) vs. 1 (1.5%) respectively. Cough occurred more often in the obiltoxaximab arm subjects who did not receive DPH, vs. those who did: 5 subjects (7.7%) vs. 1 subject (0.7%). In contrast, nausea and vomiting, taken together, occurred more frequently in the obiltoxaximab subjects who received DPH vs. those who did not: 8 subjects (5.5%) vs. 0 (0.0%).

AH109

The occurrence of hypersensitivity in the repeat dose study, AH109, was analyzed. Because hypersensitivity was clearly triggered by administration of obiltoxaximab in a proportion of subjects, it may be expected that the incidence of hypersensitivity would be higher when the frequency of obiltoxaximab administration and overall exposure were increased.

TEAE's related to hypersensitivity per treatment period were shown in Table 8.42.

Table 8.42 Hypersensitivity in AH109 by Treatment Period*

Hypersensitivity PT	Sequence A				Sequence B			
	Obmab N=35 n (%)	Obmab N=34 n (%)	Placebo N=30 n (%)	Total N=35 n (%)	Obmab N=35 n (%)	Placebo N=33 n (%)	Obmab N=31 n (%)	Total N=35 n (%)
Hypersensitivity	3 (8.6)	2 (5.9)	0	5 (14.3)	2 (5.7)	0	1 (3.2)	3 (8.6)
Cough	1 (2.9)	0	0	1 (2.9)	1 (2.9)	0	0	1 (2.9)
Cyanosis	0	0	0	0	1 (2.9)	0	0	1 (2.9)
Dermatitis acneiform	0	1 (2.9)	0	1 (2.9)	0	0	0	0
Dyspnea	0	0	0	0	1 (2.9)	0	0	1 (2.9)
Flushing	0	0	0	0	1 (2.9)	0	0	1 (2.9)
Pneumonitis	0	1 (2.9)	0	1 (2.9)	0	0	0	0
Pruritus	1 (2.9)	0	0	1 (2.9)	0	0	0	0
Rash	0	0	0	0	1 (2.9)	0	0	1 (2.9)
Rash macular	0	1 (2.9)	0	1 (2.9)	0	0	0	0
Rash maculopapular	0	0	0	0	0	0	1 (3.2)	1 (2.9)
urticaria	1 (2.9)	0	0	1 (2.9)	0	0	0	0

*Adapted from Applicant's submission (Table 35 – ISS) along with independent FDA analysis; Obmab: Obiltoxaximab

There was a slightly higher incidence of AEs related to hypersensitivity in sequence A (5/34 or 14.7%) compared with sequence B (3/35 or 8.6%), always in relation to obiltoxaximab infusion; none occurred with placebo administration. However, the numbers of subjects reporting any of these AEs with their second dose of obiltoxaximab are small.
Reviewer comment: The higher incidence of hypersensitivity-related AEs in sequence A compared with sequence B suggests that increasing dose or frequency of obiltoxaximab administration may be associated with more hypersensitivity. As noted previously, high serum levels of obiltoxaximab circulate for about 20 days; therefore, when re-administered at 14 days, there is likely a higher C_{max} which may correspond with greater hypersensitivity. Again, a table such as this can be misleading if not interpreted in a clinical light; other PTs such as rash, pruritus, cough and urticaria are also associated with hypersensitivity and may not be adequately represented by the numbers of subjects under the heading of hypersensitivity. For example, subject 109-002-204 in sequence B had cough, cyanosis, dyspnea and flushing as well as rash, and was withdrawn from the study. Subject 109-002-205 in sequence A had urticaria both immediately and on Day 22 – he was withdrawn from the study as well. These narratives were provided earlier in this Section.

AH110

There appeared to be a difference between the obiltoxaximab alone arm and the obiltoxaximab plus ciprofloxacin arm in occurrence of TEAEs (e.g., gastrointestinal disorders occurred in 7 subjects - 1 with toothache, 2 with nausea, 3 with diarrhea and 1 with an anal fissure - in the obiltoxaximab plus ciprofloxacin arm, but not at all in the obiltoxaximab alone arm). Therefore, the population who received ciprofloxacin in addition to obiltoxaximab (n=20) was excluded from the FDA PSP.

Table 8.43 Hypersensitivity in AH110

PT	Obiltoxaximab	%	Obiltoxaximab + Ciprofloxacin	%
Cough	1	5%	0	0
Dizziness postural	0	0	1	5% (1/20)
Urticaria	0	0	3	15%

Source: AH110 CSR and FDA analysis

AH106 – Dose Escalation Study of Obiltoxaximab used Intramuscularly.

(b) (4)

8.5.1.4 Possible Mechanism of Hypersensitivity

As part of the Applicant's exploratory analyses, predose samples of blood for IgE and histamine levels were drawn from all subjects who received either placebo or obiltoxaximab, but postdose levels were done only in subjects who developed hypersensitivity. The findings for those subjects with serious hypersensitivity are tabulated below.

Table 8.44 FDA Analysis: Histamine and IgE Levels in Subjects in the FDA ESP in whom Obiltoxaximab was Discontinued Due to Hypersensitivity, or Who were Discontinued from the Study* Due to Hypersensitivity

Subject Identifier [n/gender/age(yr)]	Premedication with Diphenhydramine	Histamine level (nmol/L) Ref range: 0-8.1		IgE level (mg/L) Ref range: 0-0.24	
AH104		Pre-dose	Post-dose	Pre-dose	Post-dose
002-053/M/43	No	2.7	8.2	1.75	1.86
002-068/F/54	Yes	NA	NA	1.5	1.5
002-350/F/29	Yes	3.8	3.7	0.54	0.54
003-101/M/28	No	<8	11	0.34	0.36
003-107/F/49	No	<8	22	0.1	0.1
003-258/M/62	Yes	<8	15	1.45	1.44
AH110					
001-103/M/39	Yes	11.9	NA	0.057 (0.007-0.117)	0.056
001-133/M/58	Yes	3.4	7.6 d1 35.5 d2	0.12 (0.007-0.117)	0.12 d1 0.14 d2
AH109					
002-204/F/66*	No	2.9	3.2	0.13	0.14
002-205/M/70*	Yes	6.6	6.0	0.24	0.22

NA – not available; FDA tabulation adapted from data in individual study CSR's

As seen in Table 8.44, some of the data was incomplete. However, in some subjects, there was an increase in histamine levels post-dose compared with pre-dose levels; this was not universal even in this population of subjects with significant hypersensitivity. Of the 6 subjects who received premedication with diphenhydramine, 2 had incomplete data (subjects 104-002-068, 110-001-103), 2 experienced no change in histamine levels pre- and post-dose (subjects 104-002-350, and 109-002-205) and 2 subjects had elevations post-dose (subject 104-003-258 immediately post-obiltoxaximab, and subject 110-001-133 on Day 2). Of the 4 subjects who did not receive diphenhydramine, 1 subject had no change pre- to postdose (subject 109-002-204), 1 subject had a moderate increase (104-002-053), and 2 subjects had significant postdose increases in histamine (subjects 104-003-101 and 104-003-107). Except in subject 104-002-053,

who had elevated IgE levels both pre- and postdose samples, all IgE levels were within normal limits.

There were other subjects who were identified by the Applicant as experiencing hypersensitivity with administration of obiltoxaximab but were able to complete their infusions. There is limited information provided about them; available details are tabulated below.

Table 8.45 Subjects with Hypersensitivity which did not Result in Discontinuation of Infusion

Subject/Sex/Age (yrs)	Arm	Study Day/DPH	Onset time relative to start of infusion: d/hr/m	Signs and symptoms	Action taken with study treatment
104-001-173/F/67	Obmab	1/Y	0:00:30	Pruritus thighs	none
104-002-236/F/58	Obmab	1/Y	0:04:30	Rash left thigh	none
104002-239/M/70	Obmab	2/Y	0:22:00	rash	none
104-002-351/F/27	Obmab	1/Y	0:01:15	Hypersensitivity[5]	None, add'l DPH given[1]
104003-111/M/58	Obmab	1/Y	0:01:01	Pruritus, rash	None, IV DPH/famotidine[2]
110-001-104/M/39	Obmab + cipro	1/Y	0:01:03	urticaria	None[3]
110-001-136/F/27	obmab	1/Y	0:00:40	cough	none
109-001-101/F/21	Seq B	120/Obmab/Y	0:04:05	Maculopapular rash	None[4]
109-001-103/F/44	Seq A	120/placebo/Y	0:01:00; 0:09:40	Pruritus, skin lesion	
109-002-226/F/23	Seq A	1/Obmab/Y	0:00:46/0:00:15	Pruritus, dizziness	None, tolerated 2nd dose

Adapted and tabulated from the Applicant's Submission
Obmab: obiltoxaximab; DPH: diphenhydramine
[1]Plasma histamine levels increased from 2.2 nmol/L predose to 9.8 nmol/L postdose. IgE levels did not change.
[2]Plasma histamine 8 to 9 nmol/L pre- and postdose. No change in IgE.
[3]Paired histamine samples NA, IgE levels elevated pre- and postdose (0.56 mg/L and 0.55 mg/L)
[4]Histamine and IgE levels were normal pre and postdose.
[5]No details of hypersensitivity were provided

Reviewer comment: There was a spectrum of hypersensitivity seen in the three main human volunteer studies – AH104, AH109 and AH110 - in this Application, ranging from a single manifestation such as localized rash or pruritus not requiring concomitant medication all the way to anaphylaxis. If the ten subjects in Table 8.45 are combined with the ten subjects with serious hypersensitivity in Table 8.34, twenty subjects were described with hypersensitivity – an incidence of 6.3% (20/320). Hypersensitivity occurring at this frequency with administration of obiltoxaximab mandates close clinical supervision during infusion and could influence the circumstances under which this product is used.

Exploratory Analysis: Cytokine levels did not show a clinically significant change with obiltoxaximab in AH104; all but TNF-α were at levels below the lower limit of quantitation in both the obiltoxaximab and placebo groups before, and at the end of study drug infusion.

Clinical Reviewer Comment: The mechanism of the hypersensitivity seen with obiltoxaximab is not clear from the data, though in this small group of subjects with incomplete data, histamine release does seem to occur in some after infusion of obiltoxaximab. Analysis of TEAEs before and after the protocols were amended to include premedication with diphenhydramine (as noted earlier) do suggest that there is some effect of diphenhydramine in reducing selected TEAEs, including some of those associated with hypersensitivity. Diphenhydramine does not appear to be fully protective, nor does it appear to act universally against all manifestations of hypersensitivity. It is possible that variations in dosage of diphenhydramine, or the timing and route of its administration would produce a more marked effect, but these factors were not evaluated in this Application. In the 2 subjects in whom elevations in histamine level postdose were seen, it is possible that the extent of the elevation was abrogated to a certain extent by administration of diphenhydramine prior to obiltoxaximab, but the numbers are far too small to allow a definitive conclusion.

Further, interpretation of these results is further complicated by the fact that, to this reviewer's knowledge, there are no studies correlating serum levels of histamine with clinical manifestations and hypersensitivity. Thus, even though some changes are seen in histamine concentrations, it is difficult to assign causality.

Finally, FDA analysis did show that the incidence of anaphylaxis was reduced from 5.5% in subjects who received obiltoxaximab without diphenhydramine to 1.2% in subjects who received obiltoxaximab with diphenhydramine premedication.

Thus, even though the reduction in hypersensitivity-related TEAEs is limited and not fully protective, this reviewer agrees with the Applicant that diphenhydramine should be required prior to administration of obiltoxaximab.

Based on this reviewer's analysis, the incidence of hypersensitivity seen in this Application may adversely influence the recommendation for use of obiltoxaximab for prophylaxis, and this will be reflected in labeling.

Exploratory analysis of cytokine levels in 80 subjects in AH104, did not reveal any particular patterns suggestive of relatedness or causality.

8.5.2 Infections

Reviewer comment: as the review progressed, it became apparent that upper respiratory tract infections seemed to be occurring with some frequency. With monoclonal antibodies as a class, increased infections could be a possibility as a result of immunomodulation, although variations in effect are likely depending on the target of the monoclonal. For example, monoclonal antibodies against TNF-α, useful in chronic inflammatory conditions such as inflammatory bowel

disease or rheumatoid arthritis, have a profound effect on cell-mediated immunity with consequent increased risks of infections such as tuberculosis and fungal infections. Since the target of obiltoxaximab is protective antigen of the B. anthracis exotoxins, obviously not an innate human protein, and with no known cross-reactivity with other human proteins, a significant decline in immune function would not be expected with its administration. A slight increase in infections was also seen in the human volunteer studies with raxibacumab although the mechanism was unknown.

This reviewer therefore analyzed occurrence of infections more closely in the main human studies in this Application.

Table 8.46 FDA Analysis: Occurrence of Infections in AH104, FDA PSP and FDA ESP

Preferred Term	Placebo	Obiltoxaximab		
	N=70, n(%)	AH104 N=210 n (%)	FDA PSP N=300 n (%)	FDA ESP N=320 n (%)
Upper respiratory tract infection	2 (2.9%)	5 (2.4%)	11 (3.7%)	29 (9.1%)
Bronchitis	0	1 (0.5%)	1 (0.3%)	1 (0.3%)
Pharyngitis Streptococcal	0	1 (0.5%)	1 (0.3%)	2 (0.6%)
Pharyngitis	0	0	0	2 (0.6%)
Viral infection	0	1 (0.5%)	1 (0.3%)	1 (0.3%)
Viral upper respiratory tract infection		0	0	1 (0.3%)
Laryngitis	0	0	0	1 (0.3%)
Sinusitis	0	0	0	2 (0.6%)
Rhinitis	0	0	0	1 (0.3%)
Pneumonia	0	0	1 (0.3%)	1 (0.3%)
Vulvovaginal mycotic infection	0	1 (0.5%)	1 (0.3%)	3 (0.9%)
Urinary tract infection	2 (2.9%)	0	0	0
Cystitis	0	0	1 (0.3%)	1 (0.3%)
Asymptomatic bacteriuria	0	0	1 (0.3%)	1 (0.3%)
Folliculitis	0	0	1 (0.3%)	1 (0.3%)
Gastroenteritis	0	0	0	2 (0.6%)
Gastroenteritis viral	0	0	0	1 (0.3%)
Gingivitis	0	0	0	1 (0.3%)
Labyrinthitis	0	0	0	1 (0.3%)
Vaginitis bacterial	0	0	1 (0.3%)	2 (0.6%)
Postoperative wound infection	0	0	0	1 (0.3%)
Acarodermatitis	0	0	0	1 (0.3%)

Table 8.46 shows that upper respiratory infections (URTI) occurred at frequencies of ≥ 2.4% in the main populations analyzed. While this frequency was similar in the placebo and single-dose

administrations of obiltoxaximab (i.e, in AH104 and the FDA PSP), there was a sharp increase in occurrence of upper respiratory infections in the FDA ESP (9.1%). The incidence of every other infection listed was not unusual. Overall however, there were multiple infections relating to various parts of the upper respiratory tree, such as bronchitis, pharyngitis Streptococcal, pharyngitis, viral infection, viral upper respiratory tract infection, laryngitis, sinusitis, and rhinitis. This reviewer combined these terms for analysis in order to explore this possible safety signal.

Reviewer comment: The difference in occurrence of URTIs between the FDA ESP and the other populations was striking; this reviewer considered 3 possibilities to account for it: a) the repeat dose of obiltoxaximab in AH109 somehow led to an increase in incidence of upper respiratory tract infections, b) the longer study period of 191 days in AH109 allowed for the capture of increased numbers of URTI, or c) this was an expected occurrence based on the seasonal timing of these studies. AH104 was carried out between July 9, 2013 and November 29, 2013, AH109 between July 23, 2013 and April 19, 2014, and AH110 between October 29, 2013 and April 9, 2014. Indeed, a significant portion of AH109 and AH110 was carried out over the winter influenza season; this may have contributed to the incidence of upper respiratory infections for reasons unrelated to the infusion of obiltoxaximab.

The occurrence and distribution of other infections was considered by this reviewer to be reflective of baseline incidence in a given population; thus, infections involving a body system other than respiratory, were not considered further.

For exploratory analysis, this reviewer combined any term that could refer to infection of the upper respiratory tree; therefore, URTI, bronchitis, sinusitis, pharyngitis, pharyngitis Streptococcal, viral infection, viral upper respiratory infection, laryngitis, viral infection were all combined for analysis. The verbatim term, dictionary-derived term, high-level term, low-level term were all examined for each respiratory infection to characterize them as specifically as possible, but no further details were available.

In general, the verbatim term matched well with the preferred term but full clinical details were not available for these subjects to allow for truly specific characterization of these infections.

Occurrence of Infections of the Upper Respiratory Tract in AH104

There were 5 subjects with URTIs, 1 subject with bronchitis, 1 subject with pharyngitis Streptococcal and 1 subject with viral infection in the obiltoxaximab arm for a total of 8/210 (3.8%), vs. 2/70 (2.9%) in the placebo arm. The only other infection in the obiltoxaximab arm was a single occurrence of vulvovaginal mycotic infection; there were two occurrences of urinary tract infection in the placebo arm.

Reviewer comment: Although the percentages of infections of the upper respiratory tract did not differ significantly between the obiltoxaximab and placebo arms, there were numerically more of them in the obiltoxaximab arm. As detailed above, the significance of this observation is unclear.

Occurrence of Infections in FDA PSP

The terms referrable to infections of the upper respiratory tract were as follows: URTI (n=11), bronchitis (n=1), pharyngitis Streptococcal (n=1), viral infection (n=1), for a total of 14 in the obiltoxaximab arm, with an incidence of 6.7%. Two URTI's occurred in the placebo arm, with an incidence of 2.9%.

Occurrence of Infections in FDA ESP

In the FDA ESP, there were 61 occurrences of infection overall; again, relevant preferred terms that could refer to infections of the upper respiratory tract were identified and combined. The following counts were obtained: upper respiratory tract infection (n=29), viral upper respiratory tract infection (n=1), viral infection (n=1), sinusitis (n=2), pharyngitis (n=2), pharyngitis Streptococcal (n=2), rhinitis (n=1), bronchitis (n=1), and laryngitis (n=1). The 1 subject with rhinitis was excluded from this analysis since it could have been due to allergies. **Thus combined, there were 39 infections referable to the upper respiratory tract in subjects who received obiltoxaximab, for an incidence of 12.2%.** One other subject was listed as having had pneumonia (110-001-102); since this is a lower respiratory tract infection, it was also excluded from consideration.

Occurrence of Infections of the Upper Respiratory Tract in AH109 and AH110

Thirty-six (51.4%) of subjects in AH109 had infections, of which 24 (34.3%) had URTIs and related terms. Of these, 10 subjects in Sequence A had URTI/related terms (28.6%), while 14 (40%) in sequence B had URTI/related terms. In AH110, 5 subjects in the obiltoxaximab only arm (25%) had URTIs, and another subject (5%) had pneumonia. Three of 4 infections in the obiltoxaximab plus ciprofloxacin arm, were URTIs/related disorders (15%).

Reviewer comment: Taken together, these data suggest that infections of the upper respiratory tract occur with higher frequency after administration of obiltoxaximab compared with placebo, and highest in the double-dose population compared with the single dose. Discussion with the toxicology reviewer, Dr. Amy Norstrandt, did not offer any clues from pre-clinical studies for a possible mechanism to explain this observation, i.e., there were no specific concerns regarding preferential staining of lung or bronchial tissue, and no gross pathological pulmonary changes were seen in animals exposed to obiltoxaximab. Interestingly, upper respiratory tract infections were identified as frequent TEAEs in AH101 (16.7% with ETI-204 vs. 0 with placebo), AH102

(11.1% in both groups), and AH105 (11.1% with ETI-204 vs. 5.6% with placebo). After a literature search, this reviewer was unable to find reports of monoclonal antibodies against toxins associated with specific respiratory effects. In the future, this reviewer recommends further attention to this potential signal, along with measurement of relevant laboratory parameters, such as serum IgA levels and complement levels, as well as evaluation of T helper cell number and function.

8.6 Specific Safety Studies/Clinical Trials

Six studies are discussed in this section – AH109, AH110, AH105, AH106, AH101 and AH102. Because AH109 and AH110 are part of the pooled safety populations, FDA PSP and FDA ESP, their study designs were reviewed along with AH104 in Sections 8.1.1, 8.1.2 and 8.1.3. Thus, only safety results and discussion for AH109 and AH110 are presented here for evaluation of the safety of repeat doses of obiltoxaximab and safety of its administration with ciprofloxacin. AH105 is summarized briefly as is AH106, the only study evaluating intramuscular administration of obiltoxaximab. Brief summaries of relevant information from AH101 and AH102 are included for completeness.

8.6.1 AH109 – Safety Analysis

Of 35 subjects each in Sequences A and B of AH109, 85.7% or 30 subjects each completed the study. Their disposition is summarized in Table 8.47. The arms are identified as Sequences A and B for these analyses - Sequence A: 16 mg/kg obiltoxaximab on Day 1,16 mg/kg obiltoxaximab on Day 14 and placebo on Day 120; Sequence B is 16 mg/kg obiltoxaximab on Day 1, placebo on Day 14 and 16 mg/kg obiltoxaximab on Day 120.

Table 8.47 Disposition of Subjects in AH109

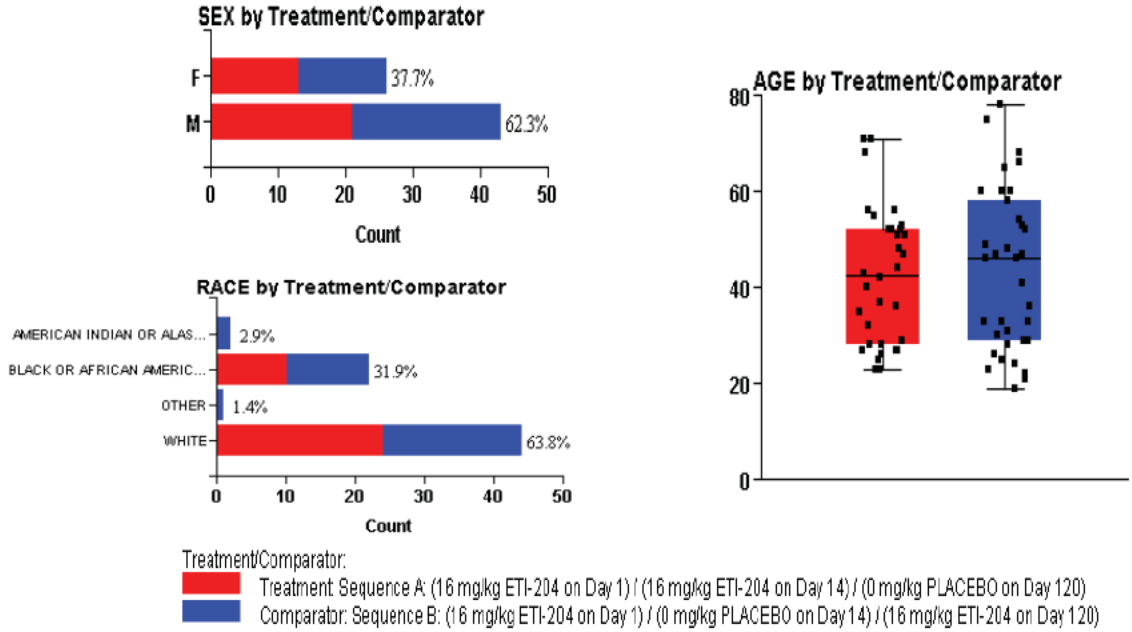
		Sequence A, N=35 n(%)	Sequence B, N=35 n(%)	Total, N=70 n(%)
Dosed		35 (100%)	35 (100%)	
Completed Study		30 (85.7%)	30 (85.7)	60 (85.7)
Study discontinuation		5 (14.3)	5 (14.3)	10 (14.3)
	Adverse event	1 (2.9)	1 (2.9)	2 (2.9)
	Consent withdrawal	1 (2.9)	1 (2.9)	2 (2.9)
	Death	0	0	0
	Lost to followup	2 (5.7)	2 (5.7)	4 (5.7)
	Protocol violation	1 (2.9)	1 (2.9)	2 (2.9)

Source: AH109 CSR, Table 14.1-1.1

Protocol Violations: These occurred in 2 subjects. Both subjects 109-001-119 in Sequence A and 109-001-127 in Sequence B had a positive drug screen after receiving their first dose of study drug – both were subsequently withdrawn from the study.

Demographics: The demographic characteristics between the two groups were similar

Figure 8.6 FDA Analysis of Demographics in AH109



The mean body weight, height and BMI of subjects in the two groups were also very similar. A previous medical diagnosis or procedure at baseline was reported in 58 (82.9%) subjects (88.6% in sequence A, 94.3% in sequence B). The most common concurrent conditions were presbyopia, myopia, headache and seasonal allergies; with the exception of myopia (20% in Sequence A vs. 37.1% in Sequence B) and seasonal allergies (20% vs. 8.6% respectively), the other conditions occurred equally in both groups. The most common previous procedures were open reduction of fracture, Caesarean section, and tonsillectomy/adenoidectomy.

Previous and Concomitant Medications

The most common previous medications were multivitamins, dietary supplements and analgesics for pain management. All subjects in this study, with the exception of the first 8 subjects enrolled, received premedication with 50 mg PO diphenhydramine ½ hour prior to study drug infusion. Other commonly used medications were paracetamol, ibuprofen,

amoxicillin, azithromycin and hydrocortisone. A total of 31 subjects (51.4%) received concomitant medications for AEs during the study – just 4 subjects were treated for rash or hypersensitivity.

Table 8.48 Extent of Exposure in AH109

	Sequence A N=35	Sequence B, N=35	All subjects, N=70
Subjects who completed all infusions	30 (85.7%)	30 (85.7%)	61 (87.1%)
Subjects who completed 2 infusions	4 (11.4%)	2 (5.7%)	6 (8.6%)
Subjects who completed 1 infusion	1 (2.9%)	2 (5.7%)	3 (4.3%)
Subjects with infusion interrupted on Day 1	7 (20%)	7 (20%)	14 (20%)
Subjects with infusion interrupted on Day 14	4 (11.4%)	0	4 (5.7%)
Subjects with infusion interrupted on Day 120	2 (5.7%)	6 (17.1%)	8 (11.4%)

Source: Adapted from AH109 CSR, p.61 and from the ISS, p.88. *NB. The number of subjects who completed the study in sequence B is noted as 31 in the AH109 CSR and 30 in the ISS – this reviewer has followed the ISS)*

All of the subjects in whom infusion was interrupted, were able to resume and complete their infusions; none were permanently discontinued. Interruptions of study drug infusion were reported for 14 subjects on Day 1 (7 each for Sequences A and B), 4 subjects on Day 14 (all for Sequence A), and 8 subjects on Day 120 (2 for Sequence A and 6 for Sequence B). None of the infusion interruptions were due to the development of AEs; the primary reason for the interruptions was equipment related.

Adverse Events

Table 8.49 Overview of Adverse Events in AH109

	Sequence A			Sequence B		
	Obmab* N=35 n (%)	Obmab N=34 n (%)	Placebo N=30 n (%)	Obmab N=35 n (%)	Placebo N=33 n (%)	Obmab N=31 n (%)
AE's	17 (48.6%)	22 (64.7%)	16 (53.3%)	20 (57.1%)	24 (72.7%)	13 (41.9%)
Death	0	0	0	0	0	0
SAE's	0	0	0	0	0	1 (3.2%)
AE's leading to study drug D/C	1 (2.9%)	0	0	1 (2.9%)	0	0

Source: AH109 CSR, Section 14.5.2 Table 14.3.5-1; *Obmab: Obiltoxaximab

Reviewer comment: TEAEs occurred in significant proportions of subjects at each time period in the two Sequences, and were more frequent at Day 14, regardless of whether obiltoxaximab or placebo was administered. Incidence of TEAEs at the last time point, Day 120, appeared lower than at Day 14.

In AH109, AEs most frequently occurred in the SOCs of Infections and Infestations, Nervous System Disorders, General Disorders and Administration Site Conditions, Skin and Subcutaneous Disorders, and Gastrointestinal Disorders; this mirrors what was found in AH104, the FDA PSP and the FDA ESP. The incidence of TEAEs by SOC and treatment period in Sequences A and B was examined; in addition, the incidence of PTs within the major SOCs of interest by Sequence was also analyzed.

Table 8.50 Adverse Events by System Organ Class in AH109

	Sequence A			Sequence B			
System Organ Class	Obmab N=35 n (%)	Obmab N=34 n (%)	Placebo N=30 n (%)	Obmab N=35 n (%)	Placebo N=33 n (%)	Obmab N=31 n (%)	Total
Subjects with TEAEs	17 (48.6)	22 (64.7)	16 (53.3)	20 (57.1)	24 (72.7)	13 (41.9)	61 (87.1)
Infections and infestations	1 (2.9)	7 (20.6)	2 (6.7)	4 (11.4)	11 (33.3)	5 (16.1)	27 (38.6)
Nervous system disorders	7 (20.0)	10 (29.4)	8 (26.7)	8 (22.9)	10 (30.3)	1 (3.2)	25 (35.7)
General disorders and administration site conditions	6 (17.1)	4 (11.8)	4 (13.3)	7 (20.0)	3 (9.1)	3 (9.7)	22 (31.4)
Skin and subcutaneous tissue disorders	3 (8.6)	4 (11.8)	5 (16.7)	5 (14.3)	5 (15.2)	2 (6.5)	20 (28.6)
Gastrointestinal disorders	1 (2.9)	3 (8.8)	1 (3.3)	2 (5.7)	4 (12.1)	0	11 (15.7)
Injury, poisoning, procedural disorders	1 (2.9)	3 (8.8)	1 (3.3)	1 (2.9)	2 (6.1)	2 (6.5)	10 (14.3)
Musculoskeletal and connective tissue disorders	2 (5.7)	2 (5.9)	0	2 (5.7)	1 (3.0)	2 (6.5)	8 (11.4)
Respiratory, thoracic and mediastinal disorders	2 (5.7)	1 (2.9)	0	2 (5.7)	1 (3.0)	2 (6.5)	8 (11.4)
Vascular disorders	1 (2.9)	1 (2.9)	1 (3.3)	1 (2.9)	1 (3.0)	1 (3.2)	6 (8.6)
Investigations	0	0	0	1 (2.9)	2 (6.1)	0	3 (4.3)
Cardiac disorders	0	0	0	1 (2.9)	0	0	1 (1.4)
Eye disorders	1 (2.9)	0	0	0	0	0	1 (1.4)
Psychiatric disorders	0	0	0	1 (2.9)	0	0	1 (1.4)
Renal and urinary disorders	1 (2.9)	0	0	0	0	0	1 (1.4)

Source: AH109 CSR

Preferred Terms within each SOC were examined – those that occurred in ≥ 2 subjects are included in the following tables.

Table 8.51 FDA Analysis of Occurrence of Treatment-Emergent Infections in AH109

Dictionary-Derived Term	Sequence B	Sequence A	Total
Upper respiratory tract infection	11 (31.4%)	6 (17.1%)	17 (24.2%)
Gastroenteritis	0	2 (5.7%)	2 (2.9%)
Pharyngitis	0	2 (5.7%)	2 (2.9%)
Sinusitis	2 (5.7%)	0	2 (2.9%)
Labyrinthitis	1 (2.9%)	0	1 (1.4%)
Pharyngitis streptococcal	0	1 (2.9%)	1 (1.4%)
Rhinitis	1 (2.9%)	0	1 (1.4%)
Viral upper respiratory tract infection	0	1 (2.9%)	1 (1.4%)

The incidence of URTIs was striking in AH109, with an incidence of 31.4% in Sequence B, almost double the incidence of infection in Sequence A (17.1%). This is in contrast to the 2.4% incidence of URTI in AH104. This difference may have been related to the repeat dose of obiltoxaximab and may also reflect the time of year in which the study took place.

Further, if similar terms are added together - URTI, viral upper respiratory tract infection, pharyngitis Streptococcal, rhinitis, sinusitis and pharyngitis - there were 15 subjects (42.9%) with some form of upper respiratory tract infection in Sequence B, and 10 subjects (28.6%) with the same in Sequence A. In addition, there were 2 individuals with a PT of influenza-like illness in sequence A for a total of 12 (34.3%).

Reviewer comment: See Section 8.5.2 for a full discussion of infections in this Application. Briefly however, the reason for the increased incidence of infections in both arms of AH109 was unclear, but may have been related to the longer study duration (191 days) compared with the study duration for AH104 and AH110 (71 days). However, a specific effect of increased exposure to obiltoxaximab cannot be ruled out.

Table 8.52 FDA Analysis of Occurrence of Treatment-Emergent Nervous System Disorders (≥ 2 subjects) in AH109

Preferred Term	B	A	Total
Somnolence	10 (28.6%)	10 (28.6%)	20 (28.5%)
Headache	3 (8.6%)	3 (8.6%)	6 (8.6%)
Dizziness	2 (5.7%)	2 (5.7%)	4 (5.7%)

Somnolence occurred in 28.6% of subjects in each arm. This likely reflects the use of diphenhydramine premedication in all but 8 subjects in AH109; as discussed in section 8.4.5, there was a stark discrepancy in the recording of somnolence as an AE among studies, as none

were recorded in AH104. Headaches occurred in 8.6% of the population, and dizziness in 5.7% - the incidence of these AE's was equivalent in both arms. Migraine occurred in one individual in Sequence B, and syncope in one individual.

Table 8.53 FDA Analysis of Occurrence of Treatment-Emergent General Disorders and Administration Site Conditions in AH109

Preferred Term	Sequence A	Sequence B	Total
Infusion site swelling	3 (8.6%)	4 (11.4%)	7 (10%)
Infusion site erythema	4 (11.4%)	1 (2.9%)	5 (7.1%)
Infusion site pain	3 (8.6%)	2 (5.7%)	5 (7.1%)
Vessel puncture site haemorrhage	2 (5.7%)	1 (2.9%)	3 (4.3%)
Vessel puncture site pain	2 (5.7%)	1 (2.9%)	3 (4.3%)
Influenza like illness	2 (5.7%)	0	2(2.9%)
Infusion site extravasation	1 (2.9%)	1 (2.9%)	2(2.9%)
Vessel puncture site swelling	1 (2.9%)	0	1 (1.4%)

Chills, fatigue, feeling cold, injection site extravasation, and injury associated with a device all occurred in single individuals in Sequence B.

Table 8.54 FDA Analysis of Occurrence of Treatment-Emergent Respiratory, Thoracic and Mediastinal Disorders in AH109

Dictionary-Derived Term	Sequence B	Sequence A	Total
Cough	2 (5.7%)	1 (2.9%)	3 (4.3%)
Nasal congestion	1 (2.9%)	1 (2.9%)	2 (2.9%)
Dry throat	0	1 (2.9%)	1 (1.4%)
Dyspnoea	1 (2.9%)	0	1 (1.4%)
Oropharyngeal pain	1 (2.9%)	0	1 (1.4%)
Pneumonitis	0	1 (2.9%)	1 (1.4%)

Dry throat, and pneumonitis occurred in one subject each in sequence A, while dyspnea and oropharyngeal pain had one occurrence in sequence B.

Table 8.55 FDA Analysis of Occurrence of Treatment-Emergent Skin and Subcutaneous Tissue Disorders in AH109

Dictionary-Derived Term	Sequence A	Sequence B	Total
Dermatitis contact	6 (17.1%)	4 (11.4%)	10 (14.3%)
Pruritus	2 (5.7%)	1 (2.9%)	3 (4.3%)
Rash maculo-papular	1 (2.9%)	1 (2.9%)	2 (2.9%)
Urticaria	1 (2.9%)	1 (2.9%)	2 (2.9%)
Dermatitis acneiform	1 (2.9%)	0	1 (1.4%)
Ecchymosis	0	1 (2.9%)	1 (1.4%)
Eczema	1 (2.9%)	0	1 (1.4%)
Petechiae	0	1 (2.9%)	1 (1.4%)
Rash	0	1 (2.9%)	1 (1.4%)
Rash macular	1 (2.9%)	0	1 (1.4%)
Skin lesion	1 (2.9%)	0	1 (1.4%)

Pruritus occurred more commonly in Sequence A (5.7%) than in Sequence B (2.9%). When all rash terms were combined – rash maculopapular, urticaria, dermatitis acneiform (judged to be related to infusion), rash, rash macular, and skin lesion, there were a total of 7 or 20% in Sequence A, vs. 4 or 11.4% in Sequence B.

Reviewer comment: This may suggest that 2 doses of obiltoxaximab 2 weeks apart may be associated with more rash-related adverse events i.e. hypersensitivity, compared with 2 doses 4 months apart.

The two subjects who had hypersensitivity severe enough to be discontinued from the study, both completed the infusion of obiltoxaximab, 1 subject was in Sequence A and 1 subject was in Sequence B. Neither subject received a second dose of obiltoxaximab. Their narratives are included in the Section on Hypersensitivity, 8.5.1.

AEs by Severity

Moderate AE's occurred in 14.3% and 31.4% of Sequences A and B respectively. All moderate AEs were reported only for one subject each. In Sequence A, one subject each had urticaria, pneumonitis, Streptococcal pharyngitis, gastroenteritis, dyspepsia while in Sequence B, 11 subjects had ankle fracture, back pain, chills, cough, cyanosis, dizziness, gastroenteritis viral, inguinal hernia, labyrinthitis, migraine with aura, muscle contracture, myalgia, nausea, pallor, decreased neutrophil count, restlessness, syncope, toothache, urticarial, bacterial vaginitis, vulvovaginal mycotic infection and sinusitis. Several of these PT's – back pain, chills, cough, cyanosis, dizziness, restlessness, pallor and myalgia – were part of a significant hypersensitivity reaction which resulted in discontinuation of subject 109-002-204 from the study.
Four subjects had severe AEs – 1 in sequence A, 3 in sequence B:

Table 8.56 FDA Tabulation of Severe AEs in AH109

Sequence/Subject ID/Gender/Age	Verbatim Term	Study Day	Relationship to Study Treatment	Additional details
A/109-002-218/M/51y	Gingivitis	15	Not related	None
B/109-002-204/F/66y	Back pain	1	Related	Section 8.5.1
B/109-002-232/M/46y	Ankle fracture	166	Not related	Section 8.4.2
B/109-001-129/M/29y	Increase in serum CK	28	Not related	Section 8.4.6

Reviewer comment: All symptoms/signs should ideally be considered in relation to the clinical context in which they occurred. For example, severe back pain and the moderate AE's outlined above, when considered separately, obscure the safety signal in subjects who had some of these manifestations in combination. For example, these symptoms taken together, though mostly designated as moderate, made up a clinical syndrome which was clinically severe (109-002-204) and resulted in the subject being withdrawn from the study rather than receive a second dose of obiltoxaximab.

No deaths occurred in either group. There was one SAE, in the subject with an ankle fracture (109-002-232) – details are provided in Section 8.4.2.

Infusion site assessments showed a small proportion of subjects in both arms with infusion site tenderness (11.4% in sequence A; 5.7% in sequence B), erythema (11.4% and 2.9% respectively), and swelling (8.6% vs. 11.4% respectively).

Laboratory evaluation

No subjects fulfilled Hy's Law in this study. There was little mean change from baseline in ALT, ALP, AST, and bilirubin. As in the Applicant's Single-Dose Pool, increased cholesterol levels (sequence A: 25.7%; sequence B: 22.9%), increased creatinine kinase (22.9% in each group), and increased potassium (sequence A: 2.9%; sequence B 20%), were the most frequent ≥2-grade shifts in this study. Electrolyte levels and calcium levels, BUN and creatinine appeared comparable between the two groups. Baseline hematology parameters also appeared comparable between the two groups. There were 3 subjects who had ≥ 2-grade decrease in neutrophil count – 1 in sequence A, 3 in sequence B. One other subject in sequence A had a ≥ 2-grade decrease in hemoglobin postbaseline, while one subject each in sequence B had a ≥ 2-grade increase in aPTT, increase in WBC and decrease in WBC. Subject 109-002-204 accounted for the findings of decreased WBC, mild lymphocyte decrease and mild neutrophil decrease in the context of hypersensitivity. Subject 109-001-114 had a mild increase in WBC.

There were no differences between the two groups in thyroid function values at baseline, changes over time or percentage with a value outside the reference range.

Vital signs

Mean changes from baseline for each vital sign parameter were similar between the two groups; a small number of individuals in each group had potentially clinically significant changes, but none were classified as an AE.

8.6.2 AH110 – Safety Analysis

AH110 is also included in the FDA PSP and FDA ESP; therefore, the study design and details of this study are included in Section 8.1.3. It was the largest DDI study in this Application, with 20 subjects in the obiltoxaximab alone arm, and 20 subjects in the obiltoxaximab + ciprofloxacin arm. In this study, Group 1 received obiltoxaximab IV + 400 mg ciprofloxacin, followed by 750 mg PO ciprofloxacin for 15 doses and group 2 received obiltoxaximab IV alone. Disposition and duration of exposure are both summarized in Table 8.57.

Table 8.57 Disposition and Duration of Exposure in AH110

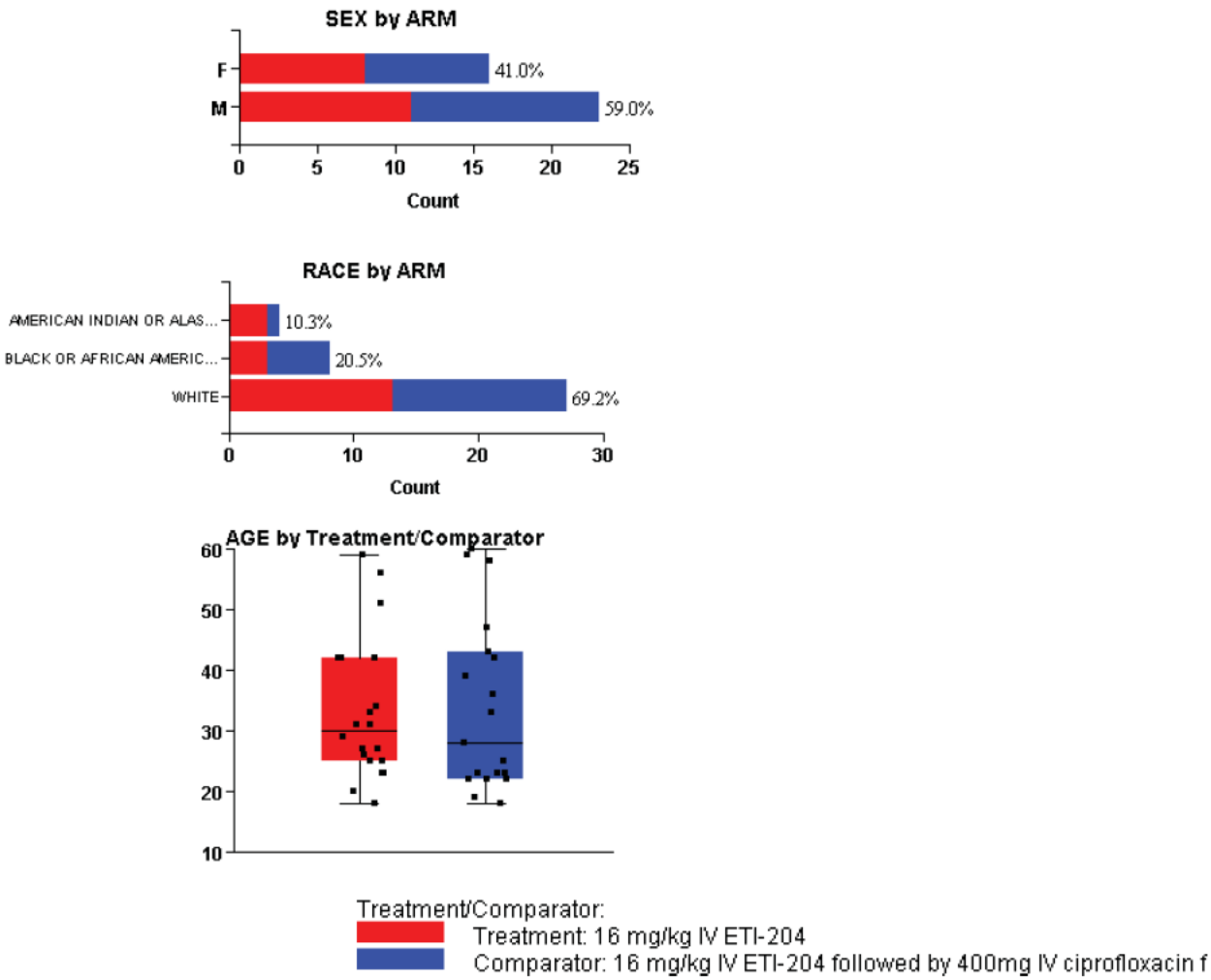
	Group 1	Group 2	Total
Subjects in study	20	20	40
Subjects completing study	19	20	38
Subjects completing infusion	18 (90%)	20 (100%)	39 (97.5%)
Subjects with interrupted infusion	2 (10%)	2 (10%)	4 (10.2%)
Number resumed/completed	0	2 (10%)	2 (5.1%)
Number permanently discontinued	2 (10%)	0	2 (5.1%)
Reason for Interruption			
Adverse Event	2 (10%)	0	2 (5.1%)
Equipment	0	2 (10%)	2 (5.1%)

Adapted from AH110 CSR

Group 1: Eighteen subjects (90%) completed the infusion of obiltoxaximab. Two subjects in this group (110-001-103 and 110-001-133) had their infusion of obiltoxaximab stopped permanently due to an AE, and did not receive ciprofloxacin; however, both completed the study. Seventeen of 20 subjects in Group 1 completed the obiltoxaximab infusion on Day 1 followed by 400 mg IV ciprofloxacin followed by 750 mg oral ciprofloxacin twice a day from Day 2 through the morning of Day 9. Subject 110-001-113 withdrew consent on Day 1 for personal reasons after the infusion of obiltoxaximab and IV ciprofloxacin; subjects 110-001-103 and 110-001-133, as mentioned previously, had obiltoxaximab withdrawn due to hypersensitivity. Narratives of the latter two subjects are provided in Section 8.5.1.

Group 2: All 20 subjects in the obiltoxaximab alone group completed the planned dose of study drug.

Figure 8.7 FDA Analysis: Demographics in AH110



Fifty-nine percent of the study population was male, and 41% were female, with each being roughly half of each study arm. Almost 70% were white, about 20.5% were black. The age distribution between the groups was very similar.

Fourteen subjects in Group 1 and 13 subjects in Group 2 had a total of 53 TEAEs. These are summarized in the table below.

Table 8.58 FDA Analysis of Occurrence of TEAEs by SOC in AH110

System Order Class	Preferred Term	Group 1, N=19 n (%)	Group 2, N=20 n (%)	Total, N=39 n (%)

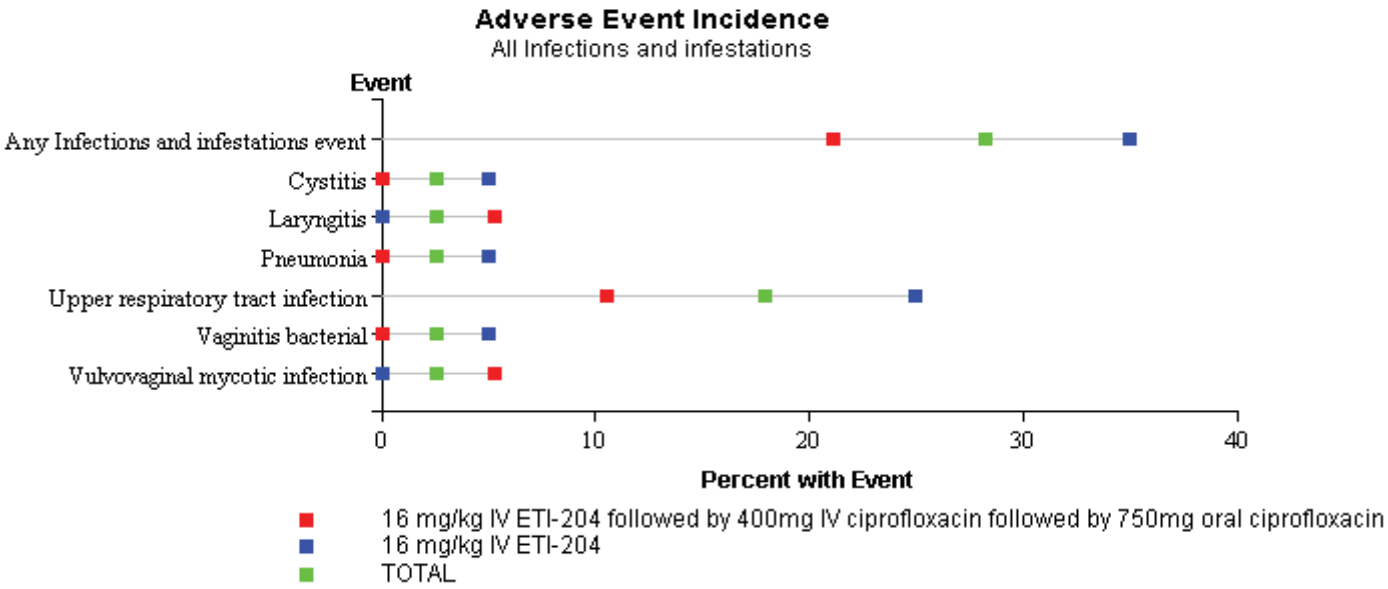
System Order Class	Preferred Term	Group 1, N=19 n (%)	Group 2, N=20 n (%)	Total, N=39 n (%)
Any body system		13 (68.4%)	14 (70%)	27 (69.2%)
Nervous System Disorders		6 (31.6%)	7 (35%)	13 (33.3%)
	Dizziness Postural	1 (5.3%)	0	1 (2.6%)
	Dysarthria	1 (5.3%)	0	1 (2.6%)
	Dysgeusia	1 (5.3%)	0	1 (2.6%)
	Headache	1 (5.3%)	1 (5%)	2 (5.1%)
	Somnolence	5 (26.3%)	6 (30%)	11 (28.2%)
Skin and Subcutaneous Disorders		4 (21.1%)	1 (5%)	5 (12.8%)
	Dermatitis contact	1 (5.3%)	1 (5%)	2 (5.1%)
	Urticaria	3 (15.8%)	0	3 (7.7%)
Gastrointestinal Disorders		5 (26.3%)	0	5 (12.8%)
	Diarrhea	2 (10.5%)	0	2 (5.1%)
	Nausea	2 (10.5%)	0	2 (5.1%)
	Toothache	1 (5.3%)	0	1 (2.6%)
	Anal fissure	1 (5.3%)	0	1 (2.6%)
Cardiac Disorders		1 (5.3%)	0	1 (2.6%)
	Palpitations	1 (5.3%)	0	1 (2.6%)
General Disorders and Administration Site Conditions		1 (5.3%)	1 (5%)	2 (5.1%)
	Chest discomfort	1 (5.3%)	0	1 (2.6%)
	Fatigue	1 (5.3%)	0	1 (2.6%)
	Vessel Puncture Site Bruise	0	1 (5%)	1 (2.6%)
Infections and Infestations		4 (21.1%)	7 (35%)	11 (28.2%)
	Cystitis	0	1 (5%)	1 (2.6%)
	Laryngitis	1 (5.3%)	0	1 (2.6%)
	Pneumonia	0	1 (5%)	1 (2.6%)
	Upper respiratory tract infection	2 (10.5%)	5 (25%)	7 (17.9%)
	Vaginitis bacterial	0	1 (5%)	1 (2.6%)
	Vulvovaginal mycotic infection	1 (5.3%)	0	1 (2.6%)
Musculoskeletal and Connective Tissue Disorders		3 (15.8%)	2 (10%)	5 (12.8%)
	Arthralgia	0	1 (5%)	1 (2.6%)
	Back pain	1 (5.3%)	1 (5%)	2 (5.1%)
	Muscle twitching	1 (5.3%)	0	1 (2.6%)
	Pain in extremity	0	1 (5%)	1 (2.6%)
	Pain in jaw	1 (5.3%)	0	1 (2.6%)

System Order Class	Preferred Term	Group 1, N=19 n (%)	Group 2, N=20 n (%)	Total, N=39 n (%)
Respiratory, Thoracic and Mediastinal Disorders		0	1 (5%)	1 (2.6%)

Reviewer Comment: Though this study was small, there was a trend to more gastrointestinal system disorders (26.3% vs. 0) and urticaria (15.8% vs. 0) in the combined obiltoxaximab + ciprofloxacin group (group 1) compared with obiltoxaximab alone (group 2). The GI disorders, particularly diarrhea and nausea are likely related to ciprofloxacin, though no subject developed C. difficile colitis. Again, there was a significant incidence of upper respiratory infections, with 17.9% of the total study population developing URTIs; there were more in group 2 (25%) compared with group 1 (10.5%). These differences partly drove this reviewer's decision to pool the data differently from the Applicant in the FDA PSP, in which only the obiltoxaximab alone arm of AH110 is combined with populations from AH104 and AH109. Headache occurred less frequently in AH110 than in AH109 or AH104, and may just reflect smaller numbers in this study. Somnolence was reported equally frequently in both study arms, and in 28.2% of all 39 subjects who completed AH110. This incidence is similar to that reported in AH109, but very different from that reported in AH104. Somnolence is most likely related to diphenhydramine, but the different rate between studies likely reflects inconsistency in reporting by the study investigators, rather than any intrinsic difference between the populations or their clinical course.

Subject 110-001-103 had diarrhea starting Day 6, and lasting for 5 days, while 110-001-131 had 2 episodes of diarrhea, one on Day 2 lasting for 3 days, and one on Day 56 for 11 hours. The diarrhea was not considered by the Applicant to be related to study drug, but this reviewer differs. The diarrhea occurring in these two subjects on Days 6 and 2 respectively, were probably related to study drug, especially since subject 110-001-103 clinically had anaphylaxis

Figure 8.8 FDA Analysis of Occurrence of Infections in AH110



No AE was identified as severe in AH110, but there were 4 moderate AEs – 2 of generalized urticarial rash, one each of postural dizziness and upper respiratory tract infection. AEs were reported in 27 of 40 subjects; AEs were judged by the investigator to be related to study drug in 5/40 subjects (12.5%).

Table 8.59 FDA Analysis of Related TEAEs in AH110

Subject ID	Group	Preferred Term	Severity
AH110-001-103	1	Chest discomfort	Mild
AH110-001-103	1	Dizziness postural	Moderate
AH110-001-103	1	Pain in jaw	Mild
AH110-001-103	1	Urticaria	Moderate
AH110-001-104	1	Urticaria	Mild
AH110-001-121	1	Headache	Mild
AH110-001-133	1	Urticaria	Moderate
AH110-001-136	2	Cough	Mild

Reviewer comment: Subject AH110-001-103 had several TEAEs rated as mild or moderate, but had obiltoxaximab infusion discontinued early due to hypersensitivity; this reviewer feels that the clinical syndrome was compatible with anaphylaxis (see Section 8.5.1) Although the Applicant stated that no pre-specified hypersensitivity reactions were reported, the evaluation of individual TEAEs has limited clinical relevance to identify hypersensitivity. Subject 110-001-133 also had infusion stopped early due to urticaria, another hypersensitivity reaction. The narratives of these subjects are provided in Section 8.5.1.

In the first 3 hours after start of infusion, 8 (40%) subjects in Group 1 and 7 (35%) subjects in Group 2 had TEAEs – somnolence was reported most frequently as noted above. Four subjects had hypersensitivity in the first 3 hours – 110-001-104, 110-001-133 and 110-001-103 had urticaria, which occurred in the latter subject along with other symptoms of hypersensitivity; all were in Group 1. Subject 110-001-136 in the obiltoxaximab alone arm reported cough within 40 minutes of the start of the infusion, though it was not associated with other symptoms. There were no infusion-related AEs with onset between 3 and 24 hours of obiltoxaximab infusion.

Anti-therapeutic Antibodies

A positive post-dose ATA value (1:80) was observed in subject 110-001-135 (obiltoxaximab alone) at Day 71 after multiple negative values on prior visits, but there did not appear to be an effect on obiltoxaximab disposition. Two other subjects, 110-001-103 in group 1, and 110-001-114 in group 2 were positive for a low level of ATA at Screening only.

Reviewer Comment: Several subjects across each of the main human studies were noted to have positive anti-therapeutic antibodies on assay even prior to administration of obiltoxaximab. The

Applicant explained it by the fact that the assay captures all isotypes of IgG in ATA positive serum samples, rather than just antibodies to obiltoxaximab. After review, the Clinical Pharmacology team noted that the positive samples had very small amounts of antibody, and were unlikely to be significant. Bioanalytical inspections of the (b) (4) *facility was partially triggered by this, but no concerns were identified.*

Laboratory evaluation

No major abnormalities were noted in AH110.

8.6.3 AH105

As part of the development program, study AH105 was designed to evaluate the safety of the affinity-enhanced, humanized, deimmunized anti-PA mAb, ETI-204, generated from murine MAb 14B7 and manufactured by Baxter Biologics. The dose range evaluated in this study was chosen based on previous human studies of ETI-204 which evaluated the safety and PK of fixed single doses of 19-360 mg (approximately 0.25-5 mg/kg).

Study Initiation date: September 14 2011; Study completion date: June 29 2012. It was conducted at Quintiles Phase I Services in Overland Park, KS.
Study Objectives:

1) Primary: To evaluate the safety of increasing doses of ETI-204 in healthy subjects

2) Secondary: a) To evaluate the PK of increasing single doses of ETI-204 in healthy subjects, b) to evaluate the immunogenicity of ETI-204 following IV administration in healthy subjects.

Ethics and Administrative Structure

The study protocol, amendments, and other study-related documents were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB). The study was conducted in full accordance with the Good Clinical Practice guideline by the International Conference on Harmonization (ICH), the Declaration of Helsinki, and GCP outlined in 21 CFR. The study was monitored by Quintiles Global Phase I Services in Overland Park, Kansas. Routine laboratory safety assessments were performed according to standard laboratory procedures at (b) (4) Data management was performed by Quintiles Global Phase I Services. Analysis of the pharmacokinetics (PK) of ETI-204 was done by the clinical pharmacokineticist at (b) (4) The PK and immunogenicity data summaries and listings as well as the statistical analysis of the PK variables were performed by the study biostatistician the same facility, who also performed the statistical analysis of safety variables.

Cardiac assessment during the study was provided by (b) (4)

Study Design

AH105 was a randomized, double-blind, placebo-controlled, sequential, single-dose, dose-escalation, single-center, Phase 1 study using 4mg/kg, 8 mg/kg, 16 mg/kg IV ETI-204 vs. placebo. Following a screening period of 21 days, eligible subjects were admitted to the study center for predose assessment; on Day 1, study drug was administered and postdose safety and PK assessments were performed over 48 hours prior to discharge. Subsequent clinic visits were scheduled for Days 8, 15, 29, 43, and 71. The 70-day postdose follow-up was selected to allow characterization of the PK profile of ETI-204 and the potential development of anti-treatment antibodies. The schedule of assessments is provided in the Appendix, Section 12.3.1. There was a 48-hour washout period for caffeine and alcohol prior to the administration of study drug.

Selection of Study Population: Healthy adult male and female subjects were recruited from the general population and had to participate in the informed consent process and sign and date the ICF before any study procedures were performed.

Inclusion Criteria: The same as for AH104 (outlined in Section 8.1.1.3) with the following additions: subjects had to have a BMI of 18.5 kg/m^2 or greater and less than 30 kg/m^2; subjects who smoked 3 or less cigarettes daily were permitted in the study provided their cotinine level was ≤400 ng/mL. Subjects with a positive cotinine had to properly document their smoking habits. Further, subjects had to have no clinically significant abnormalities on clinical laboratory tests at screening, although elevated bilirubin was permitted as long as the ALT and AST were within normal limits.

Exclusion Criteria: These were the same as for AH104 (see Section 8.1.1.3) with the following additions - subjects were excluded if a) the subject required regular use of a medication for a chronic condition with the exception of acetaminophen (as needed); b) the subject had current suspected drug or alcohol abuse as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association 2000), or c) the subject donated plasma within 7 days of Day 1 of the study.

Completion/Discontinuation of Subjects: Subjects who discontinued from the study early were to be discontinued for 1 of the following reasons: adverse event, lost to follow-up, subject request, administrative/other. Any subject who stopped returning for visits was followed up by phone, mail, or other means in order to gather information such as the reason for failure to return, presence or absence of AEs and signs and symptoms.
Treatments: Study infusions were prepared by an unblinded pharmacist in a similar fashion as in AH104 (Section 8.1.1.3), diluted to a final concentration of 10 mg/mL and administered at a

rate not to exceed 2 mL/min over 90 minutes. The study preparation of ETI-204 (Lot (b) (4)-0031-001) was manufactured and labeled in accordance with GMP at Baxter Biologics, Hayward, CA and (b) (4) respectively. The study preparation had the same excipients as the subsequent Lonza preparation (Section 8.1.1.3), and matching placebo was also prepared with the same inactive ingredients.

Dose Selection: Doses were chosen based on previous human studies of ETI-204 which evaluated the safety of fixed single doses of 19 to 360 mg (~ 0.25 to 5 mg/kg).

Blinding: The investigator, study center staff, the subject and the Data Safety Monitoring Committee (DSMC) were blinded; only the study pharmacist was unblinded.

Method of Assigning Subjects to Treatment: Subjects were randomly assigned to receive either single doses of ETI-204 or a matching volume of placebo in 3 sequential cohorts. Within each cohort (dose level), subjects were randomly assigned to receive ETI-204 or placebo in a ratio of 5:1, using a block size of 6. Enrollment was controlled so that at least 4 female subjects were enrolled in each cohort. Cohorts were also split approximately equally into 2 BMI groups: 18.5 to 24.25 kg/m^2 (inclusive), and 24.26 to 29.99 kg/m^2 (inclusive). However, treatments were not stratified by sex or BMI category.

Safety Variables: A detailed schedule of study assessments is presented in the Appendix (Section 12.3.1). The safety of ETI-204 was evaluated based on the occurrence of TEAEs and changes in the subjects' clinical laboratory results, vital signs, ECGs and physical examinations. Since ETI-204 is a monoclonal antibody, hypersensitivity reactions were anticipated. Definitions of adverse events were standard. On study Days -1, 1, 2, 3, 8, 15, 29, 43, and 71, the investigator obtained information on AEs by specific questioning and, as appropriate, by examination. All observed or volunteered AEs reported, regardless of treatment group and suspected causal relationship to study drug, were recorded on the Adverse Event Form of the eCRF. Subjects fasted for 12 hours prior to collection of laboratory samples; they were to abstain from physical activity for 72 hours prior to admission to the clinic and for 72 hours prior to each follow-up visit.

Any SAE had to be reported within 24 hours of knowledge of the event to the Sponsor Medical Monitor. This included a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. All SAEs had to be followed to resolution, stabilization, death or loss to follow-up.

Data Safety Monitoring Committee: The primary objective of the DSMC was to review the accumulating safety data on an ongoing basis and make recommendations as to the future of the study. Dose escalation from 8 mg/kg to 16 mg/kg was not initiated until safety and

tolerability of the previous dose groups were determined through at least the first 14 days after dosing.

Clinical Evaluations: Laboratory testing, vital signs, physical examinations and ECGs were done in accordance with Schedule of Assessments, and with the method of evaluations outlined in Section 8.1.1.3.

The Statistical Analysis Plan used quantitative and descriptive statistics as outlined in Section 8.1.1.4.

Analysis Variables: PK variables and anti-treatment antibodies (ATA) were determined similarly to AH104, and analyzed at (b) (4). Positive immunogenicity was defined as serum binding activity (i.e., anti-therapeutic antibody) against ETI-204 during the study exceeding threshold, and was categorized as either positive or negative. Within each dosing group (both active and placebo), threshold was defined as the mean of the predose samples obtained on Day 1 plus 2 standard deviations.
The total number and percentage of subjects with TEAEs were presented by SOC and PT. All AEs were coded to the body system and preferred term using MEDDra version 14.0.

Determination of Sample Size: The study was designed to detect at least a 20% difference in PK parameters (C_{max} and AUC) with 80% power based on the variability observed in previous studies. The Applicant's analysis showed that a sample size of 30 per group would yield a power of greater than 80%.

Changes in Study Conduct:

1. Protocol Amendment 1 (August 24, 2011): the upper limit of BMI was changed from 35 to 30 mg kg/m^2, 90 minutes infusion time was assured , and blood was to be drawn for PK analysis from 4 hours after start of infusion, instead of during the infusion.

2. Protocol Amendment 2 (October 4, 2011): addressed the allowance of acetaminophen at various study time points.

3. Protocol Amendment 3 (June 12, 2012): new inclusion and exclusion criteria were added, and various study parameters were altered, added, removed or clarified. (AH105 CSR, Section 9.7.1, p. 46).

Safety Results

Disposition of Subjects

A total of 108 subjects were enrolled and randomly assigned to receive study treatment.

Table 8.60 Extent of Exposure

Category	Placebo	ETI-204			Total
		(4 mg/kg)	(8 mg/kg)	(16 mg/kg)	
Subjects enrolled	18	30	30	30	108
Subjects completed infusion	18	30	30	29	107
Subjects completed study	18 (100%)	29 (96.7%)	27 (90%)	29 (96.7%)	103 (95.4%)
Infusion permanently discontinued	0	0	0	1 (3.3%)	1 (0.9%)
Prematurely withdrawn from study	0	1 (3.3%)	3 (10%)	0	5 (4.6%)
Adverse event	0	0	0	0	0
Withdrew consent	0	1 (3.3%)	0	0	1 (0.9%)
Lost to follow-up	0	0	3 (10%)	0	3 (2.8%)

Source: AH105 CSR, Table 10, p. 48

In 10 subjects, infusion was briefly interrupted due to technical reasons with the IV apparatus; all were restarted and completed without difficulty. One subject, 3031, in the 16 mg/kg ETI-204 arm, had infusion stopped prematurely due to urticaria. He completed all study procedures.

Demographics

The mean age was 30 ±10 years for all subjects (range: 18-58). There were 30 women (27.8%) and 78 men (72.2%). The groups were comparable with regard to race, mean weight and mean BMI. Ten subjects (9.3%) had infusion interrupted for technical reasons and 1 (0.9%) had infusion stopped after 1 hour due to urticaria. Forty-three subjects received previous or concomitant medications. Twenty-eight subjects received concomitant medication for TEAEs.

Pharmacokinetic parameters

A 4-fold increase in dose from 4 mg/kg to 16 mg/kg resulted in an approximate 4-foldincrease in mean $AUC_{(0\text{-inf})}$ and $AUC_{(0\text{-last})}$. Mean C_{max} increased approximately 3.5-fold across this same range of doses. Please see the Clinical Pharmacology review by Dr. Zhixia Yan for complete discussion.

Immunogenicity

Six subjects randomized to receive ETI-204 tested positive for anti-therapeutic antibodies prior to receiving study medication. Of these, only one (subject 1011) was positive for ATA after receiving ETI-204.

Six of 87 subjects (6.9%) tested following exposure to ETI-204 developed ATA. One of 18 placebo subjects (5.6%) also tested positive for ATA. The development of ATA did not appear to be dose-related as the number of subjects testing positive for ATA following exposure to ETI-204 did not increase with increasing dose. The development of ATA did not alter the PK of ETI-204. On Day 71, 1, 3, 2, and 1 subject(s) were positive for ATA in the placebo, ETI-204 4 mg/kg, ETI-204 8 mg/kg, and ETI-204 16 mg/kg groups, respectively.

Adverse Events: There were no deaths or severe AEs in AH105. TEAEs occurred in 72 subjects (66.7%) overall and were judged to be related in 36.1% of subjects. The only SAE was in subject 1023 (4 mg/kg) and was unrelated to study drug.

Table 8.61 Summary of TEAEs in AH105

Category	Placebo N=18	ETI-204			
		4 mg/kg N=30	8 mg/kg N=30	16 mg/kg N=30	Overall N=108
TEAEs	14 (77.8%)	22 (73.3%)	17 (56.7%)	19 (63.3%)	72 (66.7%)
Death	0	0	0	0	0
Severe TEAEs	0	0	0	0	0
Serious TEAEs	0	1 (3.3%)	0	0	1 (0.9%)
TEAEs leading to study drug discontinuation	0	0	0	1 (3.3%)	1 (0.9%)

Source: AH105 CSR, Table 12.1, p.67

Three TEAEs were categorized as moderate in severity – pharyngitis (8 mg/kg ETI-204 arm, increased creatine kinase (4 mg/kg ETI-204 arm) and urticaria (16 mg/kg ETI-204); the latter occurred in the subject whose infusion was discontinued due to urticaria. All other TEAEs were classified as mild.

Subject 1023 - SAE: This 20 year old white male had nonserious pain on Day 1 due to a herniated intervertebral disc, and was given Flexeril and ibuprofen on Day 7. Due to ongoing pain in the left leg, he underwent epidural injections on Days 14 and 26. However, the pain continued, and on Day 67, the subject was hospitalized and underwent surgery. He was released the next day, but since he was hospitalized, the event was reported as an SAE. He completed the infusion and study requirements.

Infusion of ETI-204 was discontinued in one subject due to hypersensitivity. His narrative is provided below:

Subject 3031 - Hypersensitivity: This was a 21 year old white male, healthy at baseline. He developed moderate urticaria over his body, and pruritus 36 minutes after the infusion of ETI-204 (16 mg/kg) started; the infusion was stopped at 1 hour. He had no other symptoms, and vital signs remained stable, but according to the Applicant's narrative, "the infusion was stopped as a precaution to avoid additional hypersensitivity". When the subject was re-examined 5 minutes after the infusion was stopped, the lesions were receding. The rash resolved after about 2.5 hours. This subject later admitted to having received a single dose of anthrax vaccine during military service in 2010. He subsequently completed all study procedures.

Ten subjects had AEs that were assessed as ongoing at the end of the study: 3 with Chlamydia urethritis, 1 with a finger contusion, 1 with elevated CK, 1 with ankle sprain, 1 with oropharyngeal pain and nasal congestion, 2 with URTI, and 1 with nephrolithiasis.

Analysis of Adverse Events

TEAEs were reported in 58 of 90 (64.4%) of subjects who received ETI-204 and 14 of 18 (77.8%) who received placebo. There was no increase in overall incidence of TEAEs with increasing doses of ETI-204, and all were assessed by the investigator as mild or moderate. The most frequently occurring TEAEs (more than 3 subjects) with ETI-204 infusion are shown in Table 8.62.

Table 8.62 Frequent TEAEs in AH105 by Study Arm and SOC/PT

SOC/Preferred Term [a, b]	Placebo N=18	ETI-204			
		4 mg/kg N=30	8 mg/kg N=30	16 mg/kg N=30	All N=90
Number of subjects with TEAEs	14 (77.8%)	22 (73.3%)	17 (56.7%)	19 (63.3%)	58 (64.4%)
Gastrointestinal disorders	1 (5.6%)	6 (20.0%)	2 (6.7%)	4 (13.3%)	12 (13.3%)
Nausea	1 (5.6%)	3 (10.0%)	2 (6.7%)	4 (13.3%)	9 (10.0%)
General disorders and administration site conditions	4 (22.2%)	7 (23.3%)	4 (13.3%)	3 (10.0%)	14 (15.6%)
Infusion site erythema	0	1 (3.3%)	2 (6.7%)	0	3 (3.3%)
Oedema peripheral	1 (5.6%)	2 (6.7%)	1 (3.3%)	0	3 (3.3%)
Infections and infestations	4 (22.2%)	6 (20.0%)	8 (26.7%)	7 (23.3%)	21 (23.3%)
Upper respiratory tract infection	1 (5.6%)	2 (6.7%)	5 (16.7%)	3 (10.0%)	10 (11.1%)
Investigations	0	1 (3.3%)	1 (3.3%)	2 (6.7%)	4 (4.4%)
Blood creatine kinase increased	0	1 (3.3%)	1 (3.3%)	1 (3.3%)	3 (3.3%)
Metabolism and nutrition disorders	0	1 (3.3%)	1 (3.3%)	2 (6.7%)	4 (4.4%)
Decreased appetite	0	1 (3.3%)	1 (3.3%)	2 (6.7%)	4 (4.4%)
Nervous system disorders	5 (27.8%)	6 (20.0%)	3 (10.0%)	3 (10.0%)	12 (13.3%)
Headache	3 (16.7%)	5 (16.7%)	3 (10.0%)	3 (10.0%)	11 (12.2%)
Respiratory, thoracic and mediastinal disorders	1 (5.6%)	6 (20.0%)	3 (10.0%)	6 (20.0%)	15 (16.7%)
Cough	1 (5.6%)	1 (3.3%)	0	2 (6.7%)	3 (3.3%)
Nasal congestion	0	2 (6.7%)	1 (3.3%)	3 (10.0%)	6 (6.7%)
Oropharyngeal pain	0	3 (10.0%)	1 (3.3%)	1 (3.3%)	5 (5.6%)
Rhinorrhea	0	1 (3.3%)	2 (6.7%)	0	3 (3.3%)
Skin and subcutaneous tissue disorders	4 (22.2%)	5 (16.7%)	3 (10.0%)	7 (23.3%)	15 (16.7%)
Erythema	1 (5.6%)	5 (16.7%)	1 (3.3%)	1 (3.3%)	7 (7.8%)
Pruritus	0	2 (6.7%)	2 (6.7%)	0	4 (4.4%)
Ecchymosis	2 (11.1%)	0	0	3 (10.0%)	3 (3.3%)

Source: AH105 CSR, Table 12.2, p70

[a] The SOC subject totals can be higher than the preferred term subject totals because the SOC total can contain TEAEs that were experienced by fewer than 3 subjects; whereas the TEAEs listed by preferred term occurred in 3 or more ETI-204-treated subjects. If a subject experienced more than 1 episode of the same AE, the event was counted only once within a preferred term. If a subject experienced more than 1 AE within an SOC, the subject was counted once for each preferred term and once for the SOC.

[b] System organ class and preferred term are from the Medical Dictionary for Regulatory Affairs, version 14.0.

Reviewer comment: There did not seem to be a dose-response relationship for TEAEs - indeed, more TEAEs occurred in the 4 mg/kg dose as compared to the 16 mg/kg dose – 22 (73%) vs. 19 (63.3%). PTs such as headache occurred more frequently in the 4 mg/kg group compared with the 16 mg/kg group (16.7% vs 10% respectively), and even had the same occurrence in the placebo group (16.7%). PTs in the skin and subcutaneous tissue disorders SOC occurred more frequently in the 16 mg/kg group compared to the 4 mg/kg group (23.3% vs. 16.7%) although only PTs which occurred in more than 3 subjects are listed in Table 8.62.

Laboratory Evaluation

Overall, there were no trends or clinically meaningful changes in laboratory values, though small variations were seen.

Table 8.63 Subjects with most frequently occurring shifts (≥ 3 subjects) in clinical laboratory values from baseline to end of study (day 71 ± 4 days)

		Placebo N=18	4 mg/kg N=30	8 mg/kg N=30	16 mg/kg N=30
Red blood cell count	Nl to low	-	-	3 (10%)	-
	NL to high	-	-	-	-
Hematocrit	Nl to low	-	-	4 (13.3%)	3 (10%)
	NL to high	-	-	-	-
Hemoglobin	Nl to low	-	3 (10%)	3 (10%)	4 (13.3%)
	NL to high	-	-	1 (3.3%)	-
White blood cell count	Nl to low	-	-	-	4 (13.3%)
	NL to high	-	-	-	-
Eosinophils	Nl to low	-	-	-	-
	NL to high	3 (16.7%)	4 (13.3%)	-	3 (10%)
Creatine kinase	Nl to low	-	-	-	-
	NL to high	3 (16.7%)	5 (16.7%)	-	-
BUN	NL to low	3 (16.7%)	-	5 (16.7%)	1 (3.3%)
	NL to high	2 (11.1%)	-	1 (3.3%)	4 (13.3%)
Glucose	Nl to low	-	3 (10%)	-	-
	NL to high	-	-	-	-

Source: Adapted from AH105 CSR, Table 12.4, p.76

AEs related to laboratory values were reported for 4 subjects; none were thought to be serious.

1. Subject 1031 (4 mg/kg ETI-204) – a 22 year old African American male, had an elevated CK on day 33 (day 29 value was 2024 U/L, with normal 32-294 U/L); this was ongoing at the end of the study. Values were above normal at screening (404 U/L), at most of the time points throughout

the study, and at the follow-up visit (358 U/L). AST was also above normal at day 29 (105 U/L). Troponin I and MB mass remained normal throughout the study. The subject had no other complaints and admitted to increased physical activity throughout the study, including prior to dosing. Other laboratory parameters were normal.

2. Subject 2009 (8 mg/kg ETI-204) - a 20yearold, African American male, experienced an AE of elevated CK that was reported on Day 43 (1516 U/L, normal range=32 to 294 U/L) and resolved 7 days later. Values were above the normal range at screening (366 U/L), Day -1 (358 U/L), periodically throughout the study, as well as at the follow-up visit (451 U/L). The investigator assessed the AE as mild in severity and unrelated to study drug. Aspartate aminotransferase was also above normal limits on Day 43 (57 U/L) (normal range=0 to 45 U/L). Creatine kinase-MB Mass was monitored for this subject periodically throughout the study and remained normal with the exception of a slight elevation on Day 43 (3.6 µg/L, normal range < 3.0 µg/L). The subject admitted to increased physical activity prior to his follow-up visit (walking 4 to 5 hours prior to the visit). Other laboratory parameters for the subject were within normal limits.

3. Subject 3004 (16 mg/kg ETI-204) - a 25-year-old, white male, experienced an AE of decreased lymphocyte count that was reported on Day 1 and resolved 2 days later. Lymphocytes were reported as 0.4×10^9/L on Day 1; and 0.5×10^9/L and 0.9×10^9/L on Day 2 (normal range=1.0 to 4.8 × 109/L). The investigator assessed the AE as mild in severity and probably related to study drug. White blood cell counts were above normal limits on Day 1 (14.9 × 109/L) and Day 2 (11.8 × 109/L) (normal limits=4.0 to 11.0 × 109/L). Adverse events of nausea, generalized weakness, loose stool, emesis, and induration of infusion site were also reported on Day 1. Other laboratory parameters for the subject were not clinically significant.

Reviewer comment: It is unclear from the data provided if the total white cell count was above normal on the same blood sample that revealed lymphopenia. This might be a different circumstance than if the white cell count and lymphocyte count both became low on Day 1 after infusion of study drug. In the latter circumstance, and along with the other clinical manifestations listed, it may represent an atypical form of hypersensitivity. If only the lymphocyte count was low, it could be a transient phenomenon or may raise the question of some form of immunosuppression.

4. Subject 3019 (16 mg/kg ETI-204), a 38-year-old, American Indian or Alaska Native female, experienced AEs of elevated CK (8366 U/L) and AST (156 U/L) that were reported on Day 29 (CK normal range=21 to 215 U/L, and AST normal range=0 to 45 U/L), and resolved 14 days later. Values were also above the normal range on Day 31 (CK=1731 U/L, AST=76 U/L), but were normal on the Day 43 assessment (CK=79 U/L, and AST=24 U/L). Alanine aminotransferase was also slightly above normal limits on Day 29 (63 U/L, normal range=0 to 38 U/L) and on Day 31 (51 U/L). Creatine kinase-MB Mass testing on

Day 29 indicated a slightly elevated CK-MB Mass (3.5 µg/L, normal range <3.0 µg/L) but Troponin I was normal. The subject admitted to increased physical activity prior to her follow-up visit (moved some items into a second floor storage unit). Other laboratory parameters for the subject were within normal limits. The investigator assessed the AEs mild in severity and unrelated to study drug.

Vital signs did not show any clinically relevant changes following dosing with ETI-204 and there were no dose-related changes with increasing doses.

There were no safety signals identified through cardiac monitoring or ECG data. None of the subjects had uncorrected QT interval values that were > 500 ms.

Reviewer comment: Given the small numbers of subjects in each arm, no major safety signals arose out of this study, except for some findings consistent with hypersensitivity (see summary table). There did not seem to be an increased risk of TEAEs with increasing dose of ETI-204, and several were similar to rates of occurrence in the placebo group. No major laboratory concerns were identified.

The single subject in whom infusion was stopped due to hypersensitivity was not premedicated with diphenhydramine (not required at that time per protocol) and eventually admitted that he had previously received the anthrax vaccine. In this single subject, this occurrence is both reassuring and somewhat concerning. While it may seem that there was a reason for hypersensitivity to occur given his prior vaccination with AVA, it also raises the question of whether hypersensitivity would be increased in individuals with pre-existing anti-PA antibodies. This is not a concern during well-controlled clinical trials, but may be a potential concern if ETI-204, now obiltoxaximab, was utilized widely in a bioterrorism event. If there were mass casualties, panic and chaos, it would be even more challenging to accurately identify past exposures to other products on an individual basis. Strong consideration should be given to evaluating the safety of obiltoxaximab in previously-vaccinated personnel.

The development of anti-treatment antibodies was not related to dose and did not appear to alter the PK of ETI-204.

8.6.4 AH106

This was the only human study evaluating the intramuscular route of administration for obiltoxaximab. This was a phase I, double-blind, randomized, placebo-controlled single-ascending-dose study to evaluate the safety, tolerability and PK of obiltoxaximab administered by IM injection in adult subjects. (b) (4)

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(b) (4)

[redacted]

8.6.5 AH101

Reviewer comment: AH101 and AH102 were the earliest human studies. The dose of the then-investigational product, ETI-204, was much lower than now used. These studies are therefore, not the focus of the review as explained earlier, but presented to complete the account of the clinical development of obiltoxaximab.

Study AH101 was a Phase 1, randomized, double-blind, placebo-controlled, dose-escalation study that was conducted between November 14 2005 and March 27 2006. There were two parts: Part 1 evaluated the safety, tolerability, and PK of a single dose of placebo or 19 mg, 57 mg, and 114 mg ETI-204 IV; part 2 evaluated the safety, tolerability, and PK of a single 114 mg dose of IV ETI-204 or placebo administered on Day 1 plus oral ciprofloxacin (500 mg every 12 hours for 14 days). The control group for Part 2 was the 114 mg ETI-204 group from Part 1.

Key differences between the entry criteria for AH101 compared to the criteria for the 3 main human safety studies included the following:

• An upper age limit of 50 years for inclusion

• BMI of ≥18.5 kg/m2 or <30 kg/m2 for inclusion

• Non-smoker or ex-smoker for at least 6 months for inclusion

• No prescription or over-the counter medication required during or for 1 week before the study for inclusion, with the exception of hormonal contraceptives, hormone replacement therapy, and thyroid replacement therapy.

Safety parameters included AEs, AEs leading to permanent discontinuation of study treatment, SAEs, standard laboratory tests and vital signs monitoring, ECGs, and ATA. Thyroid function tests, and cytokine, IgE, and histamine levels were not assessed in AH101. Infusion site assessments were also not conducted. Subjects were followed for safety for 42 days in AH101, including a 3-day stay (Days 0-2) in the investigational unit. Subjects who were positive for ATA at the end of the follow-up period in AH101 were followed for an additional 6 months.

Treatment: ETI-204 at the doses above, diluted in normal saline, was administered IV over 90 minutes. Diphenhydramine premedication was not given.

Subject Disposition and Demographics
Overall, 24 subjects were randomized to Part 1 (6 subjects per group) and 12 subjects to Part 2 (6 subjects each in the 114 mg ETI-204 plus ciprofloxacin group and the placebo plus ciprofloxacin groups). All subjects completed the study. More male subjects (62.5%) than female subjects (37.5%) were enrolled in Part 1. Most subjects were white (70.8%); age ranged from 18 to 50 years.

Safety Results

The AE profile of the ETI-204 and placebo groups in AH101 were similar and a dose relationship was not seen for any individual AE or AE severity. The most frequent AEs in Part 1 of AH101 were upper respiratory tract infection (ETI-204, 16.7%; placebo, 0) and nasopharyngitis (ETI-204, 11.1%; placebo, 33.3%). There was no occurrence of rash or hypersensitivity events. No severe AEs, deaths, SAEs, or permanent discontinuations of study drug due to an AE occurred in Part 1 of AH101.

No clinically significant laboratory abnormalities were seen and no subjects had laboratory values suggestive of hepatic or renal toxicity. A dose relationship was not seen for any

laboratory parameter in the percentage of subjects with a shift from normal to outside of the reference range following study drug administration. Changes in vital signs and ECG parameters following study drug administration were small, similar between the ETI-204 and placebo and judged by the investigator to be non-significant.

8.6.6 AH102

AH102 was a Phase 1, single-center, randomized, double-blind, dose-escalation study to evaluate the safety, tolerability, and PK of a single ETI-204 IV dose of 120, 240, and 360 mg compared to placebo. It was conducted from February 23, 2009 to September 26, 2009.

The differences in entry criteria from AH104/109/110, and safety parameters were identical to those used in AH101, (Section 8.6.5). The various doses of ETI-204 were prepared in the standard way. Diphenhydramine premedication was not given.

Subject Disposition and Demographics
Overall, 45 subjects were randomized: 9 to the placebo group and 12 subjects each to 120, 240, or 360 mg of ETI-204. All subjects completed the study. More subjects were male (73.3%) than female (26.7%) and most subjects were white (95.6%); ages ranged from 19 to 50 years.

Safety Results
The overall AE profile of the ETI-204 and placebo groups in AH102 were similar and a dose relationship was not seen for any AE. The most frequently reported AEs in AH102 were headache (ETI-204, 28%; placebo, 22%), upper respiratory tract infection (ETI-204, 11.1%; placebo, 11.1%), and urinary tract infection (ETI-204, 8.3%; placebo, 11.1%). No hypersensitivity reactions, including rash, were reported.

One SAE of toothache was reported in the 240 mg ETI-204 group. No deaths, SAEs, or permanent discontinuations of study drug due to an AE occurred. No clinically significant laboratory abnormalities were seen and no subjects had laboratory values suggestive of hepatic or renal toxicity. A dose relationship was not seen for any laboratory parameter in the percentage of subjects with a shift from normal to outside of the reference range following study drug administration. Changes in vital signs were similar between the ETI-204 and placebo groups and were not significant.

8.7 Additional Safety Explorations

8.7.1 Human Carcinogenicity or Tumor Development

There are no anticipated issues related to human carcinogenicity or tumor development with single-dose obiltoxaximab.

8.7.2 Human Reproduction and Pregnancy

Pregnancy and lactation were exclusion criteria for all the human studies. One subject in the safety database of the 3 main human studies became pregnant during the study period: Subject 104-002-230 was a 25 year old African-American woman who received a single infusion of obiltoxaximab on Day 1. Pregnancy tests at Screening, Day -1 and Day 29 were negative, but the qualitative βHCG at study completion (Day 71) was positive. A subsequent quantitative β-HCG was consistent with a 4-6 week gestation. On Day 83, the subject was contacted by study personnel by phone and she informed them that she might be experiencing signs of miscarriage. The investigator reported a possible spontaneous abortion as an AE – this was judged by the investigator to be unrelated to study drug. Several subsequent attempts were made to contact this individual by phone and by certified letter, but she was lost to follow-up. There was no further medical information available.

(b) (4)

There were no drug exposures in pregnant or lactating women.

<u>Reviewer comment</u>: *In an outbreak or bioterrorism situation, obiltoxaximab would potentially be an important part of the arsenal for treatment and post-exposure prophylaxis by the IV route. Its applicability to an entire population is therefore vital, especially in a scenario where large numbers of people are potentially affected and emergency and health care resources may be stretched enough to make it challenging to carefully evaluate each individual's clinical situation for risks and benefits of therapy. The emphasis in such a situation may be more on providing post-exposure prophylaxis to the largest number of people as possible in a short period, and pregnant women would likely form a significant portion of an affected population.*

The pre-clinical studies in pregnant animals were reassuring as they did not show associated teratogenicity or toxicity. While it would be ideal to obtain some data in pregnant women, it would likely not be ethical unless obiltoxaximab were being used to treat inhalational anthrax infection in a pregnant woman.

8.7.3 Pediatrics and Assessment of Effects on Growth

This application was submitted under the Animal Rule, and with Orphan Drug Designation; therefore, the requirements for PREA do not apply. Pediatric subjects under the age of 18 were not included in the safety human database, and therefore there are no data available.

Reviewer comment: The same concerns outlined in Section 8.7.2 apply here as well, for the pediatric population. The Applicant has submitted their recommended dosing schedule for pediatric subjects; please refer to the Clinical Pharmacology review by Dr. Zhixia Yan for a discussion of their modeling and evaluation of pediatric dosing.

8.7.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no concern for overdose or drug abuse potential with obiltoxaximab.

8.8 Safety in the Postmarket Setting

8.8.1 Safety Concerns Identified Through Postmarket Experience

This product has never been marketed; thus there is no postmarket experience either in the US or in foreign markets. Given the low occurrence of inhalational anthrax in this country, and the fortunate lack of an outbreak situation since 2001, a similar FDA-approved monoclonal antibody against the PA antigen, raxibacumab, has also never been used clinically, so no postmarket information is available even with a similar product.

8.8.2 Expectations on Safety in the Postmarket Setting

The major potential concern with the use of obiltoxaximab for treatment and prophylaxis of inhalational anthrax arises from the 3.1% incidence of serious hypersensitivity observed in the healthy human volunteer studies submitted in this Application. In this reviewer's opinion, the benefit of obiltoxaximab for treatment of this potentially fatal infection outweighs the risk of hypersensitivity. Any person who is clinically ill with anthrax is likely to be in a monitored situation and the most critical goal in that situation would be to control the infection before irreversible sepsis and multi-organ failure develop.

However, the use of obiltoxaximab for prophylaxis may be more problematic. The subjects who developed hypersensitivity after infusion of obiltoxaximab in these studies, especially the ones with anaphylaxis, did not have more serious outcomes since they were monitored closely, the infusion was stopped as soon as there was concern for an allergic reaction, and concomitant medications were administered to treat the condition. **Serious hypersensitivity reactions including anaphylaxis, occurred in 3.1% of subjects in the 3 main safety studies. Less serious reactions (not requiring discontinuation of obiltoxaximab) occurred in at least 10 other subjects out of 320 (also 3.1% - see Section 8.5.1) who were specifically identified, and PTs associated with hypersensitivity occurred in 10.6% of the FDA ESP.**

In an outbreak situation where there is likely to be widespread confusion, and resources may be overwhelmed, the need to educate and observe subjects who receive obiltoxaximab as

post-exposure prophylaxis may impose an added responsibility on already-burdened responders. Further, the recommendation to administer diphenhydramine 30 minutes prior to the infusion of obiltoxaximab, and to administer the mAb itself over 90 minutes, would slow down and complicate its prophylactic administration to hundreds or thousands of people.

Various other concerns have not been explored due to the fact that human studies were confined to healthy adult volunteers. As addressed in previous sections, the efficacy and safety of obiltoxaximab has not been evaluated in children, pregnant women or even people with significant co-morbidies, including immunosuppression. One possible way to address this is to make this therapy available to the CDC such that obiltoxaximab can be dispensed for treatment in the few naturally-occurring cases that occur in the U.S. Not only would this presumably benefit the patients, but though numbers would be low, experience with obiltoxaximab in the treatment of real infections would provide the best opportunity to study efficacy in humans and thereby guide governmental and healthcare decision-making regarding the most effective ways to maximize the biologic weapons against anthrax – AIGIV, raxibacumab, AVA and obiltoxaximab – in the Strategic National Stockpile.

Because of the questions raised by the multidisciplinary review of obiltoxaximab by FDA regarding the utility and safety of an even higher IV dose, the question of a PMR to address this issue should be considered. An important part of that decision is the ethics of such an undertaking in view of the known incidence of hypersensitivity.

Finally, the efficacy and safety of obiltoxaximab when used in the presence of the anthrax vaccine, has not been addressed even in pre-clinical studies. In a setting where large numbers of people are infected, the use of multiple products in the same patient may occur. It would be important to make sure there is no interference from these products with the efficacy of obiltoxaximab, and that the incidence of adverse events, especially hypersensitivity, is not even higher than that observed in the human studies in this Application.

Because of the severity of clinical disease in inhalational anthrax, and the situation for which this product has been developed, it would be almost impossible to design a REMS; this is therefore not considered

8.9 **Additional Safety Issues from Other Disciplines**

The Clinical Pharmacology review has raised the possibility of added efficacy with a higher dose of obiltoxaximab as noted above (please see the Clinical Pharmacology review by Dr. Zhixia Yan); the concerns for added hypersensitivity were also discussed. No additional safety issues have been identified from other disciplines.

8.10 **Integrated Assessment of Safety**

Obiltoxaximab is a monoclonal antibody intended for use in the treatment of inhalational anthrax in combination with antibacterial medications. Given its development under the Animal Rule, the safety of obiltoxaximab was evaluated in 7 safety studies conducted in healthy adult volunteers. This review focused on the 3 main human studies which use the 16 mg/kg dose and the Lonza formulation of obiltoxaximab intended for commercial use. In this safety database of 320 subjects exposed to obiltoxaximab IV and 70 subjects exposed to placebo, the major safety concern was hypersensitivity. This adverse clinical complex led to discontinuation of the study drug, or discontinuation of the subject from the study, in 10 (3.1%) healthy human subjects, all in the obiltoxaximab arm, vs. 0 in the placebo arm. Seven (7) subjects (2.2%) were judged to have had anaphylaxis by the clinical reviewer, although only 1 of these was identified by the Applicant. Less serious hypersensitivity (not requiring discontinuation of obiltoxaximab) was noted in another 10 subjects (3.1%), while PTs associated with hypersensitivity were noted in 10.6% of subjects treated with obiltoxaximab in the FDA ESP.

In July 2013, after more than 5 occurrences of urticaria/hypersensitivity were noted, the Clinical Trials Steering Committee amended the clinical protocols to mandate premedication with diphenhydramine (DPH), resulting in a database in which a proportion of subjects did not receive premedication, and some did. The incidence of hypersensitivity and other TEAEs was examined closely with a focus on the effect of diphenhydramine. In the obiltoxaximab arm, 5.5% of subjects who did not receive DPH had significant hypersensitivity compared with 2.4% of subjects who did receive DPH. The incidence of anaphylaxis in the group that received obiltoxaximab but no DPH was 5.5%; this incidence fell to 1.2% in subjects who did receive DPH.

In an effort to elucidate a mechanism for the observed hypersensitivity, IgE and histamine levels were measured in subjects who developed hypersensitivity. Although collection of pre-dose samples in all subjects and post-dose samples in those who manifested symptoms/signs of hypersensitivity was part of the clinical protocol, 2 subjects with serious hypersensitivity lacked one or both of these samples; thus the database was incomplete. Histamine levels did increase postdose in 6 of 10 subjects with hypersensitivity, although IgE levels did not (see Section 8.5.1.4 for full discussion). However, histamine and IgE measurements were not done in subjects without hypersensitivity; therefore, there is no context to judge causality in subjects with hypersensitivity. Although the mechanism of hypersensitivity is unclear, this reviewer's analysis supports the utility of diphenhydramine in decreasing incidence of hypersensitivity; thus, premedication with this product is recommended.

In the initial submission of this BLA, the Applicant identified 16 mg/kg as the human equivalent of the fully effective IV dose in animals for treatment of inhalational anthrax, (b) (4)

Other prominent treatment-emergent adverse events with administration of obiltoxaximab included headache, somnolence, rash, upper respiratory tract infections. Headache occurred in 9.1% of subjects with obiltoxaximab. Most of the headaches reported in this Application, were characterized as mild; however, headaches were clearly related to the administration of obiltoxaximab with the majority of them occurring in the first 10 days or so after infusion, though not in the first 24 hours.

Somnolence was predominantly noted in studies AH109 and AH110 but not in AH104, and was thought to be primarily related to diphenhydramine. However, there appeared to be inconsistent reporting of this AE, i.e., it was not identified at all in AH104. Since it is biologically implausible that somnolence due to diphenhydramine could occur in one set of healthy humans, but not at all in another, this reviewer felt that the highlighting of somnolence as an AE is somewhat misleading, as it is unlikely to be related to administration ofobiltoxaximab.

The incidence of infection of the upper respiratory tract was intriguing. When the occurrence of the preferred term, upper respiratory tract infection (URTI) alone, was utilized, there was an incidence of 2.9% in the placebo group, 2.4% in the obiltoxaximab arm of AH104, and 3.7% in the obiltoxaximab arm of the FDA PSP (pooled single-dose group); the incidence of URTI rose to 9.1% in the recipients of obiltoxaximab in the ESP (combined single- and double-dose group). However, the occurrence of other TEAEs indicative of infections of the upper respiratory tract (bronchitis, pharyngitis, pharyngitis Streptococcal, viral infection, viral upper respiratory tract infection, laryngitis, sinusitis, influenza-like illness) was noted. When all of these PTs from the single-dose pool of the 3 major safety studies (FDA PSP) were combined, their incidence was about 6.7% vs. 2.9% in the obiltoxaximab and placebo groups respectively; but increased to 12.2% in the obiltoxaximab group when all the repeat-dose data from AH109 were included. When the repeat-dose administration of obiltoxaximab was compared between the 2 weeks apart arm (Sequence A) and the 4 months apart arm (Sequence B) in AH109, there were many more infections of the upper respiratory tract in the 4 month apart group (40%) vs. 28.6% in the

other. However, no correlation was found with the different treatment periods in AH109. The effect of the season was also considered, and indeed the 191 days of follow-up in AH109 ran through fall and winter.
The apparent increased incidence of URTIs was however, supported by data from the earlier studies. In AH101, there was a 16.7% incidence of URTI in the ETI-204 group vs. 0 in the placebo group, an 11.1% incidence of URTI in both the ETI-204 and placebo groups in AH102, and an 11.1% incidence in the ETI-204 group vs. 5.6% in the placebo group in AH105. Interestingly, there were a higher number of URTI's found with raxibacumab as well (11.6% in the double-dose group vs. 3.9% in the single dose, and 5% in the placebo subjects), raising the possibility of a product-related effect. In this Application, the incidence of other infections was not increased, so this effect seemingly appears to be confined to the respiratory tract, and bears further investigation.

The potential mechanism of such an effect, if truly present, is unclear. Pre-clinical data did not highlight particular concerns related to the respiratory tract. A literature search conducted by this reviewer did not reveal reports of monoclonal antibodies particularly associated with specific respiratory effects. However, taken together, the data from this Application raise the question of whether the use of obiltoxaximab could increase the incidence of infections in immunocompromised hosts or those with pre-existing pulmonary disease, with consequent concern for safety in these populations. Measurements of FEV_1 or other parameters including immunoglobulin levels, particularly IgA, and T helper cell number and function, may be of use to investigate a mechanism.

All of the dose-escalation information in the early human studies (AH101 and AH102), and in AH105 or AH106 (though the route of administration is different) does not support an increase in incidence of TEAEs with increasing doses of obiltoxaximab. However, the incidence of hypersensitivity is definitely more pronounced with a 16 mg/kg dose (as seen in AH104, AH109 and AH110) compared with lower doses, and this may have implications for future work with obiltoxaximab. Although 16 mg/kg IV is identified through animal studies as the equivalent fully effective dose for humans, pharmacokinetic modeling by the Clinical Pharmacology team indicates that there may be a small increase in efficacy with an even higher dose. A PMR to test this may be considered in another human study, but must be weighed carefully against the possibility of increased hypersensitivity with a higher dose.

Safety data for obiltoxaximab obtained exclusively through studies in healthy adult volunteers presents a concern regarding its applicability to the wider U.S. population. Studies in animals have not identified specific concerns for a developing fetus, but its use in human pregnancy or childhood has not been studied. Similarly, as noted above, there are potential questions about the effect of administration of obiltoxaximab on immunocompromised patients, or those with severe lung disease. Since it is a monoclonal antibody, elimination pathways through the liver and kidney are not expected to be significant, and indeed no concerns for liver or kidney

function were raised in these human studies. Further, the applicability of the current dosing recommendation to obese subjects or those with significant peripheral edema (especially as edema is significant in inhalational anthrax) is unknown.

Assuming that obiltoxaximab IV for treatment of inhalational anthrax is approved, strong consideration should be given to making it available to treat any patient ill with naturally-acquired inhalational anthrax. Because obiltoxaximab has shown efficacy in animal studies, it would be the right course of action to make it available to sick patients in combination with ABT and other therapies. A secondary advantage would be to gain experience with the use of these products in sick individuals. Studies in animals show that the level of pre-treatment bacteremia correlates with PA levels and severity of clinical illness, and that if obiltoxaximab is given after a certain level of bacteremia is attained, its benefit is significantly abrogated. These considerations would presumably apply in humans as well and any opportunity to elucidate these effects further should be taken. For example, would the effect of obiltoxaximab be diminished if there are overwhelming levels of PA in the blood or would there be benefit at any level of bacteremia? Would there be interference with development of immunity if obiltoxaximab was given concomitantly with anthrax vaccine?

Finally, any discussion of risk-benefit must take place against the background of the condition in question. Inhalational anthrax is a life-threatening, easily acquired, devastating disease. Although the issues raised in the paragraphs above should ideally be answered, individual willingness to be treated with this product and governmental willingness to use it on a large population scale will be driven by the immediate threat to life posed by a bioterrorism event. In this situation, the potential benefits of administration of obiltoxaximab along with ABT for treatment could be life-saving and should not be denied to a sick patient. The issue of obiltoxaximab for prophylaxis is more problematic but it too, will depend on the situation. A bioterrorism event such as occurred in 2001 may provide an opportunity to offer different modes of prophylaxis to individuals based on their previous exposures or risks with one product or the other. However, in the event of a large disaster with hundreds or thousands of casualties, unavailability of raxibacumab, or dispersal of an antibiotic-resistant strain of *B. anthracis*, there would likely be a clear advantage to utilizing obiltoxaximab for post-exposure prophylaxis as well.

In conclusion, this reviewer recommends approval of obiltoxaximab for the treatment of inhalational anthrax in combination with appropriate antimicrobial therapy, and for prophylaxis of inhalational anthrax with caveats pertaining to the risk of hypersensitivity, to be included in labeling. Raxibacumab, the only currently FDA-approved monoclonal antibody against the PA of *B. anthracis*, in contrast to obiltoxaximab, had an incidence of significant hypersensitivity of 0.6%, with only 2 subjects requiring discontinuation of study drug due to urticaria. With the current availability of several products for treatment and prophylaxis of inhalational anthrax - raxibacumab, anthrax immune globulin (AIGIV) and anthrax vaccine (AVA), in addition to

antibacterial drugs - a logical hierarchy of use should be constructed with the addition of obiltoxaximab to the armamentarium. For example, AVA would continue to be used routinely for pre-exposure prophylaxis, but in the immediate aftermath of a bioterrorism event, raxibacumab may be recommended for post-exposure prophylaxis along with antibacterial drugs and AVA for long-term immunity due to its lower incidence of hypersensitivity. AIGIV would be an alternative to raxibacumab in this situation. In patients with inhalational anthrax, either obiltoxaximab or raxibacumab could be administered along with antibacterial drugs ± AVA. In all situations, strong direction from governmental agencies will be critical.

9 Advisory Committee Meeting and Other External Consultations

There are currently no issues with obiltoxaximab that would need to be addressed through an Advisory Committee. This conclusion is in large part based on the fact that an Advisory Committee meeting was held in connection with the raxibacumab application in November 2012; its conclusions were reviewed and presented in the Appendix. Given the similar nature of obiltoxaximab and raxibacumab and their similar purpose, an Advisory Committee meeting to discuss this product was considered unnecessary. However, it would be important to ascertain what, if any, steps have been taken to address the concerns and suggestions that arose out of that meeting, as that information would inform recommendations regarding further development of obiltoxaximab.

10 Labeling Recommendations

10.1 Prescribing Information

The prescribing information and labeling recommendations are under review. Substantive changes are being made to the Warnings and Precautions and Adverse Events Section to reflect the findings and concerns regarding serious hypersensitivity and anaphylaxis.

10.2 Patient Labeling

Patient labeling is still under review

10.3 Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

Given the life-threatening nature of inhalational anthrax, the development of obiltoxaximab occurred under the Animal Rule. It is neither ethical nor feasible to study this monoclonal antibody in infected humans. Further obiltoxaximab is intended for single use primarily in critical situations, such as after large-scale population exposure following a bioterrorism event, so a REMS would not be applicable

11.1 Safety Issue(s) that Warrant Consideration of a REMS

A REMS is not required. See section 1.3.

11.2 Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3 Recommendations on REMS

Not applicable.

12 Postmarketing Requirements and Commitments

Discussions about postmarket requirements and commitments are ongoing. However, a PMR may be considered to evaluate the following:

(b) (4)

(b) (4)

(b) (4)

[24] Emanuel EJ et al. What Makes Clinical Research Ethical? JAMA 2000 May 24/31: 2701-11

(b) (4)

13 Appendices

13.1 References

Please refer to the references in footnotes.

13.2 Financial Disclosure

The Applicant certified that there are no financial arrangements with the study investigators and that none of the investigators disclosed any proprietary interest in the product or significant equity in the Applicant as defined in 21 CFR 54.2(b). None of the investigators were the recipients of significant payments as defined in 21 CFR 54.2(f).

The following summarizes specifics from each of the main human studies:

1. AH104 – A list of clinical investigators was provided. There were 4 Principal Investigators (PI) and 22 Sub-Investigators (SI).

2. AH109 – There were 2 PIs and 13 Sis

3. AH110 – There was 1 PI and 9 SIs

4. AH106 – (b) (4)

13.3 Schedules of Assessment

13.3.1 Study AH105

Table 13.1 AH105 Schedule of Assessments

	Visit 1		Visit 2			Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Procedures and Assessments	Day -21 to -2	Day -1	Day 1	Day 2	Day 3	Day 8	Day 15	Day 29	Day 43	Day 71
Informed Consent	X									
Medical History	X	X								
Prior Medication History	X	X								
Inclusion and Exclusion Criteria	X	X								
Clinical Laboratory Tests	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen	X	X								
Physical Examination [a]	X [a]	X [a]	X [a]	X [a]	X	X	X	X	X	X
Vital Signs Measurement [b]	X	X[b]	X	X	X	X	X	X	X	X
Electrocardiography [c]	X		X [c]							
Urine Pregnancy Test	X	X	X							
Admit to Inpatient Facility		X								
Discharge From Inpatient Study [d]					X [d]					
Administer Study Medication			X							
Blood Samples for PK [e]			X [e]	X [e]	X [e]	X	X	X	X	X
Blood Samples for anti-treatment antibodies [f]			X [f]			X [f]			X	X
Concomitant Medication review		X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; PK = pharmacokinetic.
When PK blood draws, vital sign assessments, and ECG recordings were scheduled to take place at the same time, the following sequence and timing were followed: 1) ECG recording, 2) vital sign measurement, and 3) PK sample collection.

[a] A general physical examination was required at screening (Day -21 to Day -2) and baseline (Day -1). The following were assessed: head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, neurological, and skin. (At baseline, 12, and 24 hours postdose, an assessment for skin rashes was performed. The development of any new skin rashes postdose was to be noted, with a description of any abnormalities as well as their distribution and extent). Clinically significant abnormalities that developed postdose were recorded as adverse events, and any concomitant medications used for their treatment recorded appropriately. A general or targeted physical examination was performed as appropriate post-baseline.

[b] Vital signs included temperature, heart rate, respiratory rate, and blood pressure at all visits. Height was measured as screening only. Body weight was measured at screening, Day -1 (while wearing surgical scrub attire), and on the final visit. On Day 1, temperature, heart rate, respiratory rate, and blood pressure were measured predose and 15 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, and 8 hours post-infusion.

[c] On Day 1 ECGs were performed predose and 2 hours post-infusion.

[d] On Day 3 subjects could be discharged after collection of the 48-hour PK sample.

[e] Blood samples for PK were obtained predose and at 4, 8, 24, 36, and 48 hours after the end of the infusion.

[f] The anti-treatment antibody sample taken on Day 1 was taken at predose; the Day 8 sample was not analyzed, but held in reserve.

13.3.2 Study AH106

(b) (4)

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13.4 Conclusions from Advisory Committee Meeting on Raxibacumab

The conclusions from the AC meeting for raxibacumab are as follows:

1. By a vote of 16 (yes) to 1(no) with 1 abstention, the committee agreed that the therapeutic studies of raxibacumab with and without antimicrobials in two animal models of inhalational anthrax is reasonably likely to produce clinical benefit in the treatment of humans with this disease. Though the combination studies (raxibacumab + antibiotic vs. antibiotic alone) were not statistically different, the committee felt that these results were clinically significant.

2. The committee recommended several additions to the labeling, including:

a) clear guidance and protocols on which patients should receive this product;

b) guidance on the logistical use of this product during a large-scale emergency event; and

c) labeling emphasizing that this product will not protect against central nervous system infections such as meningitis due to its inability to penetrate the blood-brain barrier. The committee suggested additional trials be conducted to study the following: 1) potential interactions with anthrax vaccinations; 2) shorter infusion times or more concentrated infusions;

d) dosing in obese patients or those with large amounts of edema/ fluid retention (dosing based on actual body weight vs. ideal body weight); 4) efficacy of doses greater than 40 mg/kg and

e) effective dosing during different stages of disease progression

3. By an unanimous vote, the committee agreed that the results from the raxibacumab safety trials in healthy volunteers and studies in animals support an acceptable risk benefit profile given its potential benefits for treatment of a disease with high fatality.

4. The majority of the committee agreed with the proposed dosing of 40 mg/kg for adults, but some felt that this dose may not be the maximum effective dose. They therefore recommended additional studies to evaluate the efficacy and safety of doses >40 mg/kg. They also suggested evaluating alternative body surface area (BSA) or lean body weight (LBW) based dosing for pediatric patients.

Since the conclusions, potential concerns, and areas identified for future work in the AC meeting held in connection with the raxibacumab approval closely mirror the same

conclusions, potential concerns and recommendations with regard to obiltoxaximab, this reviewer feels that another AC meeting is not warranted.

However, it would be important to ascertain what, if any, steps have been taken to address the concerns and suggestions that arose out of that meeting, as that information would inform recommendations regarding further development of obiltoxaximab.

APPEARS THIS WAY ON ORIGINAL

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