CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125509Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM FOR THE CLINICAL PHARMACOLOGY REVIEW

BLA:	125509
Submission Date(s):	03/20/2015
Brand Name:	Anthim®
Generic Name:	Obiltoxaximab
Primary Reviewer:	Zhixia (Grace) Yan, Ph.D.
Team Leader:	Kimberly L. Bergman, Pharm.D.
PM Reviewer:	Fang Li, Ph.D.
PM Team Leader:	Jeff Florian, Ph.D.
OCP Division:	DCP4
OND Division:	DAIP
Applicant:	Elusys Therapeutics, Inc.
Submission Type; Code:	Original BLA submitted under 21 CFR 601.90
Formulation; Strength(s):	Injection for intravenous use; 600 mg/6 mL (100 mg/mL) solution in single-dose vial
Indication	Anthim is indicated in adult and pediatric patients for: • Treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs. • Prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

BACKGROUND

Elusys Therapeutics, Inc. submitted a biologic license application (BLA) for Anthim® (obiltoxaximab) for the treatment of 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 current BLA for obiltoxaximab seeks approval under the "Animal Efficacy Rule" (21 CFR 601.90 "Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible"). The effectiveness of Anthim is based solely on efficacy studies in animal models of inhalational anthrax. The recommended dose of Anthim in adult patients is a single dose of 16 mg/kg administered intravenously over 90 minutes and pre-medicated with diphenhydramine prior to dosing. There have been no studies of safety or PK of Anthim in the pediatric population. A population PK approach was used to derive intravenous infusion dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults. The recommended dose for pediatric patients is based on weight as shown in Table 1 below.

Table 1. Recommended Pediatric Dose of Anthim (weight based dosing)

Pediatric Body Weight	Pediatric Dose
Greater than 40 kg	16 mg/kg
Greater than 15 kg to 40 kg	24 mg/kg
Less than or equal to15 kg	32 mg/kg

The following analytical inspection summary and labeling recommendations are provided as an addendum to the Clinical Pharmacology Review (DARRTS dated 12/07/2015).

ANALYTICAL INSPECTION SUMMARY

At the request of the review team, analytical inspections of 12 nonclinical and clinical studies were conducted by the Division of New Drug Bioequivalence Evaluation (DNDBE) in the Office of Study Integrity and Surveillance (OSIS). A Form FDA 483 was not issued at the close-out of the inspections for the clinical studies (see the Review of establishment inspection reports (EIRs), covering BLA 125509 dated 2/14/16 in DARRTS). However, a five-item Form FDA 483 was issued at the close-out for the nonclinical studies. The final classification for this inspection is voluntary action indicated (VAI). Following the evaluation of the inspectional findings and the firm's response to the Form FDA 483, the analytical data from the audited studies were found to be reliable. Therefore, it was recommended that the analytical data from the nonclinical and clinical studies be accepted for review by the Agency with certain limitations, as follows (see the Analytical Inspection Report for details in DARRTS dated 1/15/2016):

Nonclinical Studies (AP116, AP202, AP203, AP204, and AP301):
1. Reassessing validation and study data without background subtraction in the confirmatory assay may provide a more specific assay.
2. Reassessing validation and study data with a statistically calculated confirmatory cut point may provide a more specific method.
3. Pre-dose samples that test positive for anti-drug antibodies should be evaluated for the presence of interfering anthrax molecules that may skew assay results.

The Clinical Pharmacology Review Team reviewed the Analytical Inspection Report and concluded that the limitations described in this report are not expected to affect obiltoxaximab pharmacokinetics observed in nonclinical and clinical studies.

LABELING RECOMMENDATIONS

Sponsor's draft label version: 03/20/2015

The following proposed package insert has been marked by revisions made by the Reviewer, indicated with ~~red strikethrough font~~ for deleted text and underlined blue font for inserted text. Affected sections include **Highlights, Indications and Usage (1**), **Dosage and administration (2), Drug Interactions (7), Use in Specific Populations (8), and Clinical Pharmacology (12).**

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ZHIXIA YAN
03/02/2016

KIMBERLY L BERGMAN
03/02/2016

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA:	125509
Submission Date(s):	03/20/2015
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1. EXECUTIVE SUMMARY

Obiltoxaximab (ETI-204 or Anthim®) is a deimmunized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) produced via cultures of (b) (4) GS-NS0 myeloma cells that specifically binds the Protective Antigen (PA) of *Bacillus anthracis*, thereby preventing its association with the anthrax toxin receptor on host cells. The indication currently being sought for obiltoxaximab is the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis (B. anthracis)* in combination with antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. The proposed dose for obiltoxaximab is a single intravenous (IV) infusion of 16 mg/kg over 90 minutes and pre-medicated with diphenhydramine (b) (4) prior to dosing.

The current BLA for obiltoxaximab seeks approval under the "Animal Efficacy Rule" (21 CFR 601.90 "Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible"). In accordance with the Animal Rule and because evaluation of new treatment options for inhalational anthrax is not possible in controlled clinical trials in humans for ethical reasons, the efficacy of obiltoxaximab was evaluated in two animal species, specifically New Zealand white rabbits and cynomolgus monkeys, with symptomatic anthrax disease. These pivotal efficacy studies were placebo-controlled, parallel-group randomized studies. Obiltoxaximab doses evaluated in pivotal animal model efficacy studies (AR021, AR033, AP201, AP202, AP203, and AP204) ranged from 1 to 32 mg/kg single-dose administered intravenously. The efficacy of antibiotics administered concomitantly with obiltoxaximab in the setting of therapeutic treatment also was evaluated in rabbits and monkeys with symptomatic anthrax disease. To allow selection of an effective dose in humans for therapeutic treatment of anthrax, the applicant has submitted clinical pharmacology data for obiltoxaximab in healthy humans and in the two pivotal animal species, rabbits and cynomolgus monkeys. The pharmacokinetics (PK) and safety of obiltoxaximab administered as 16 mg/kg over 90-min IV infusion have been evaluated in a Phase 1 single-dose PK/safety study (AH104), a repeat-dose PK/safety study (AH109) and a Phase 1 antibiotic interaction study with ciprofloxacin (AH110). Overall, the safety of obiltoxaximab has been evaluated in over 400 healthy human volunteers, including 320 subjects treated with the proposed dose of 16 mg/kg with product manufactured and formulated by the same process proposed for licensure.

1.1. Recommendation

Based on a cross-species comparison of obiltoxaximab exposure and dose-response information for obiltoxaximab, PA concentration, and survival, the clinical pharmacology information provided by the applicant is acceptable and supports the use of the 16 mg/kg dose of obiltoxaximab.

Simulations show humans (healthy and infected) achieve similar obiltoxaximab median C_{max} and 2-fold greater median AUC_{inf} following a single 16 mg/kg IV dose compared to infected rabbits and monkeys receiving the fully effective dose (14.5 mg/kg). However, there is partial overlap in the range of AUC_{inf} between humans and monkeys at the respective dose. Simulations of obiltoxaximab concentrations in humans demonstrate potential to minimize overlap in exposure with the fully effective dose in animals and decrease uncertainty surrounding the dose-response relationship for survival by administering a higher dose (e.g., 24 mg/kg). Nevertheless, based on the relationships of dose vs. survival and exposure vs. PA concentrations, an increase from 16 mg/kg to 24 mg/kg would be expected to achieve minimal improvement in survival in humans, suggesting 16 mg/kg is an acceptable dose in humans. If future trials are conducted, higher doses (e.g., 24 mg/kg) could be explored provided that such trial is considered ethical to conduct in healthy human subjects.

The Clinical Pharmacology Recommendations based on the data provided by the Sponsor are dependent on the results of clinical and analytical site inspections.

1.2. Phase 4 Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

Obiltoxaximab is a deimmunized IgG1mAb that binds the PA of *Bacillus anthracis* with high affinity and inhibits its biological activity. The clinical pharmacology characteristics of obiltoxaximab have been defined in rabbits, monkeys 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 obiltoxaximab demonstrates the following clinical pharmacology characteristics:

- The disposition of IV obiltoxaximab 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. 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 C_{max}, AUC_{inf}, CL, or half-life of obiltoxaximab between the 2 doses administered ≥4 months apart were observed.
- In the treatment of a *Bacillus anthracis* infection and in response to an anthrax-related emergency, obiltoxaximab will likely be administered concurrently with a fluoroquinolone antibiotic active against *B. anthracis*. Therefore, the drug-drug interaction potential between obiltoxaximab and a fluoroquinolone antibacterial (ciprofloxacin) was evaluated in humans. Serum obiltoxaximab concentration-time profiles were similar following administration of obiltoxaximab alone and with both PO and IV ciprofloxacin. Overall, exposure to ciprofloxacin appears to have no consistent or meaningful impact on obiltoxaximab PK. Likewise, obiltoxaximab did not alter the PK of ciprofloxacin administered PO and/or IV. Thus, there is no significant interaction between obiltoxaximab and ciprofloxacin.
- Based on the dose-response relationship with the endpoint of survival derived from the combined infected rabbit and monkey monotherapy survival data, a dose of 14.5 mg/kg (ED_{90}) was identified by the Clinical Pharmacology Review Team as the fully effective dose in infected animals according to the Animal Rule guidance.
- Simulations show humans (healthy and infected) achieve similar or greater exposure to obiltoxaximab following a single 16 mg/kg IV dose compared to infected rabbits and monkeys receiving the fully effective dose (14.5 mg/kg). Following a single 16 mg/kg IV dose, median obiltoxaximab C_{max} in humans is similar to that in rabbits and monkeys; median obiltoxaximab AUC_{inf} in humans is at least 2-fold higher than that in rabbits and monkeys.
- Although humans achieve greater median AUC_{inf} following a 16 mg/kg obiltoxaximab dose compared to monkeys receiving the fully effective dose (14.5 mg/kg), there is partial overlap in the range of AUC_{inf} between humans and monkeys at the respective dose. Simulations 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 monkeys with the fully effective dose (14.5 mg/kg).
- Based on predicted human PK profiles, the proposed dose of 16 mg/kg in humans would be expected to achieve maximum obiltoxaximab serum concentrations of 1 and 2 orders of magnitude greater than the concentrations required for 99.9% (48 μg/mL) and 99% (4.8 μg/mL)

PA neutralization, respectively. Moreover, a molar excess of obiltoxaximab is maintained in serum for 2 to 3 weeks. More than 95% of humans administered a 16 mg/kg IV dose can be expected to achieve serum obiltoxaximab concentrations that are equimolar to or in excess of the highest observed serum PA concentration across all infected rabbits and monkeys (9.67 µg/mL or 153 nM) for more than 3 weeks, which is expected to be sufficient to allow development of endogenous adaptive immunity in humans.

- Simulations of obiltoxaximab concentrations in humans demonstrate potential to minimize overlap in exposure with the fully effective dose in animals and decrease uncertainty surrounding the dose-response relationship for survival at higher doses (e.g., 24 mg/kg). However, based on the relationships of dose vs. survival and exposure vs. PA concentrations, an increase from 16 mg/kg to 24 mg/kg would be expected to achieve minimal improvement in survival in humans.
- Obiltoxaximab administered as either pre- or post-exposure prophylaxis resulted in higher survival outcomes compared to placebo in multiple animal studies where obiltoxaximab was given at various IV doses (up to 16 mg/kg) and treatment times.
- Taken together, from a Clinical Pharmacology perspective, the proposed dose of 16 mg/kg for obiltoxaximab is acceptable for the treatment and prophylaxis of inhalational anthrax.

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Obiltoxaximab is an affinity enhanced deimmunized mAb of the IgG1κ isotype (~148 kDa) produced via cultures of [redacted] (b) (4) GS-NS0 myeloma cells. The target for obiltoxaximab is *B. anthracis* PA, the cell-binding component of the anthrax tripartite toxin. Anthrax exotoxins are binary A2/B-type bacterial toxins comprising the enzyme (A) moiety lethal factor (LF) or edema factor (EF), each associated with the common binding (B) component PA. Obiltoxaximab contains human constant region sequences and deimmunized murine variable region sequences generated from the murine mAb clone 14B7.

Structural Formula: The primary amino acid sequence of obiltoxaximab [redacted] (b) (4) is:

[redacted] (b) (4)

Source: Section 2.3.S

Obiltoxaximab drug product (DP) is a clear to opalescent, colorless to pale yellow-pale brownish-yellow solution. The obiltoxaximab DP is manufactured by [redacted] (b) (4) No additional excipients are added in the production of obiltoxaximab DP. It is provided in sterile, [redacted] (b) (4) glass, single-use vials with [redacted] (b) (4) rubber stoppers. The nominal fill volume of obiltoxaximab DP is 6 mL per vial at a concentration of 100 mg/mL (600 mg obiltoxaximab). The target fill volume per vial is [redacted] (b) (4) mL to ensure that 6.0 mL can be withdrawn from the vial.

The proposed commercial obiltoxaximab DP, manufactured at [redacted] (b) (4), is formulated by [redacted] (b) (4)

[redacted]. The inactive components of the DP solution formulation include histidine, sorbitol and polysorbate 80 [redacted]. The 40mM histidine (pH[redacted]) was selected [redacted]

Source: Section 2.3.P

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Obiltoxaximab is a deimmunized IgG1κ monoclonal antibody that binds PA with high affinity and inhibits its biological activity. Thus, the principal mechanism of action is to neutralize the effects of anthrax toxins.

Obiltoxaximab is indicated in adult and pediatric patients for:

- Treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.
- Prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration of obiltoxaximab is a single dose of 16 mg/kg administered as an intravenous (IV) infusion over 90 min.

Patients should be premedicated with oral diphenhydramine [redacted] prior to the infusion of obiltoxaximab, due to the possibility of infusion-related and hypersensitivity reactions.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To allow selection of an effective dose in humans for therapeutic treatment of anthrax, the applicant has submitted clinical pharmacology data for obiltoxaximab in humans and in the two pivotal animal species, rabbits and non-human primates. The pharmacokinetics (PK) and safety of obiltoxaximab administered as 16 mg/kg over 90-min IV infusion as the to-be-marketed formulation have been evaluated in a Phase 1 single-dose PK/safety study (AH104), a repeat-dose PK/safety study (AH109) and a Phase 1 antibiotic interaction study with ciprofloxacin (AH110). Single-dose PK and safety of obiltoxaximab as the investigational material were also assessed across doses from 19 mg (~0.23 mg/kg) to 16 mg/kg in Study AH101, AH102, and AH105. The study design of all human PK and safety studies is presented in Table 2.2.1-1.

Table 2.2.1-1. Study Design of Human PK and Safety Studies of Obiltoxaximab

Study Number	Design	Treatment Arms (Number of Subjects)
Single-dose		
AH101 (Part 1)	Single center, randomized, double-blind, placebo-controlled, sequential, dose-escalation study in healthy adult subjects. Samples collected over 42 days for determination of ETI-204 PK.	• 19 mg ETI-204 (6) • 57 mg ETI-204 (6) • 114 mg ETI-204 (6) • Placebo (6) ETI-204/placebo administered by IV infusion over 90 min.
AH102	Single center, randomized, double-blind, placebo-controlled, sequential, dose-escalation study in healthy adult subjects. Samples collected over 70 days for determination of ETI-204 PK.	• 120 mg ETI-204 (12) • 240 mg ETI-204 (12) • 360 mg ETI-204 (12) • Placebo (9) ETI-204/placebo administered by IV infusion over 60 min.
AH105	Single center, randomized, double-blind, placebo-controlled, sequential, dose-escalation study in healthy adult subjects. Samples collected over 71 days for determination of ETI-204 PK.	• 4 mg/kg ETI-204 (30) • 8 mg/kg ETI-204 (30) • 16 mg/kg ETI-204 (30) • Placebo (18) ETI-204/placebo administered by IV infusion over 90 min.
AH104	Multi-center, double-blind, randomized, placebo-controlled study in healthy adult subjects. Samples collected over 71 days for determination of ETI-204 PK.	• 16 mg/kg ETI-204 (210) • Placebo (70) ETI-204/placebo administered by IV infusion over 90 min.
Multiple-dose		
AH109	Multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, PK, and potential immunogenicity of repeat administration (two doses) of IV ETI-204, either 14 or 120 days following the initial dose in healthy adult subjects. Samples collected over 191 days for determination of ETI-204 PK.	Sequence A: • 16 mg/kg ETI-204 Days 1 and 14; Placebo on Day 120 (35) Sequence B: • 16 mg/kg ETI-204 Days 1 and 120; Placebo on Day 14 (35) ETI-204/placebo administered by IV infusion over 90 min.
Study Number	**Design**	**Treatment Arms (Number of Subjects)**
Drug-drug interaction		
AH101 (Part 2)	Single center, randomized, double-blind, placebo-controlled study in healthy adult subjects to evaluate the interaction between ETI-204 and ciprofloxacin. Samples collected over 42 days for determination of ETI-204 PK. Samples collected for 12 hours after the first ciprofloxacin dose and at sequential pre-dose times through Day 14 for determination of ciprofloxacin PK.	• 114 mg ETI-204 with ciprofloxacin (6) • ETI-204 placebo with ciprofloxacin (6) ETI-204/placebo administered by IV infusion over 90 min. Ciprofloxacin administered orally 500 mg every 12 hours for 14 days starting on the day of ETI-204 administration.
AH110	Single center, randomized, open-label, parallel group study in healthy adult subjects. Samples collected over 71 days for determination of ETI-204 PK. Samples collected for 24 hours after the first IV ciprofloxacin dose and last oral ciprofloxacin dose (Day 9) for determination of ciprofloxacin PK.	• 16 mg/kg ETI-204 with ciprofloxacin (20) • 16 mg/kg ETI-204 without ciprofloxacin (20) ETI-204 administered by IV infusion over 90 min. Ciprofloxacin administered 400 mg IV immediately after ETI-204 dose on Day 1, followed by 750 mg orally every 12 hours from Days 2-8, with a final dose in the morning of Day 9.

In accordance with the Animal Rule and because evaluation of new treatment options for inhalational anthrax is not possible in controlled clinical trials in humans for ethical reasons, the efficacy of obiltoxaximab was evaluated in two animal species, specifically New Zealand white rabbits and cynomolgus monkeys, with symptomatic anthrax disease. These pivotal efficacy studies were placebo-controlled, parallel-group randomized studies. Obiltoxaximab doses evaluated in pivotal animal model monotherapy efficacy studies (AR021, AR033, AP201, AP202, AP203, and AP204) ranged from 1 to 32 mg/kg single-dose administered intravenously. The efficacy of antibiotics administered concomitantly with obiltoxaximab in the setting of therapeutic treatment also was evaluated in rabbits and monkeys with symptomatic anthrax disease. To allow selection of an effective dose in humans for therapeutic treatment of anthrax, the applicant has submitted clinical pharmacology data for obiltoxaximab in healthy humans and in the two pivotal animal species, rabbits and cynomolgus monkeys.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint of the animal efficacy studies is survival, which is the desired benefit in humans.

2.2.3. Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety obiltoxaximab was appropriately identified and measured in serum from rabbits, monkeys and humans by validated Meso-Scale Discovery electrochemiluminescence assays (MSD-ECL) and enzyme-linked immunosorbent assays (ELISA).

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics for exposure-response relationships (dose-response, concentration-response) for efficacy?

The dose-response relationship for obiltoxaximab has been evaluated based on monotherapy in animal models of inhalation anthrax infection. All of the obiltoxaximab monotherapy treatment studies were randomized, placebo-controlled, parallel-group studies in which obiltoxaximab alone was administered IV New Zealand white rabbits or cynomolgus monkeys who were exhibiting clinical signs or symptoms of systemic anthrax infection. Animals were aerosol challenged with an approximate *B. anthracis* (Ames strain) spore dose 200 times the median lethal dose (200x LD_{50}). Treatment was initiated based on the appearance of one of the following clinical signs or symptoms of systemic anthrax (whichever occurred first): a significant increase in body temperature (rabbits only) or a positive serum PA level using an electrochemiluminescence (ECL) assay. Monkeys were treated at the time of a positive serum PA level at a mean time of approximately 40 hours post-challenge with *B. anthracis*. In most rabbit treatment studies, animals were treated after sustained elevation of body temperature above baseline, at a mean time of approximately 30 hours post-challenge. Most study animals were bacteremic and had a positive serum PA level prior to treatment. Survival was assessed at 28 days post-challenge with *B. anthracis* in most studies. The efficacy of antibiotics administered concomitantly with obiltoxaximab in the setting of therapeutic treatment also was evaluated in rabbits and monkeys with symptomatic anthrax disease. Obiltoxaximab administered in combination with antibacterial drugs (levofloxacin, ciprofloxacin, and doxycycline) did not interfere with the efficacy of antibacterial drugs and resulted in higher survival outcomes than antibacterial therapy alone in multiple studies where obiltoxaximab and antibacterial therapy was given at various doses and treatment times.

Dose-Survival Relationship

A summary of survival results from these studies is provided in Table 2.2.4.1-1. Survival rates in both species exhibited a dose-response relationship (i.e., higher doses associated with higher overall survival) within studies, although overall survival rates were inconsistent across all studies (e.g., AP203 survival rate of 6% at 8 mg/kg compared to AP201 survival rate of 73% for 8 mg/kg). A contributing factor to these observations was the prior-to-treatment (PTT) bacteremia levels, where higher PTT bacteremia levels were associated with a decreased likelihood of survival. Those studies with the lowest overall survival rates (AP202 and AP203) also had a substantially greater proportion of individual PTT bacteremia values in the top quartile of the overall bacteremia distribution compared to other studies such as AP204 (Figure 2.2.4.1-1).

Survival data from the studies in Table 2.2.4.1-1 were pooled together and plotted by dose and PTT bacteremia quartile in Figure 2.2.4.1-2. When separated by PTT quartile, the dose-response relationship is maintained, but the percentage of animals surviving is reduced, regardless of obiltoxaximab dose, in animals with higher PTT bacteremia levels. This is further illustrated in Figure 2.2.4.1-3, where survival outcomes versus PTT were analyzed for all animals administered 16 mg/kg. These analyses suggest an influence of both obiltoxaximab and PTT in the overall dose-survival relationship.

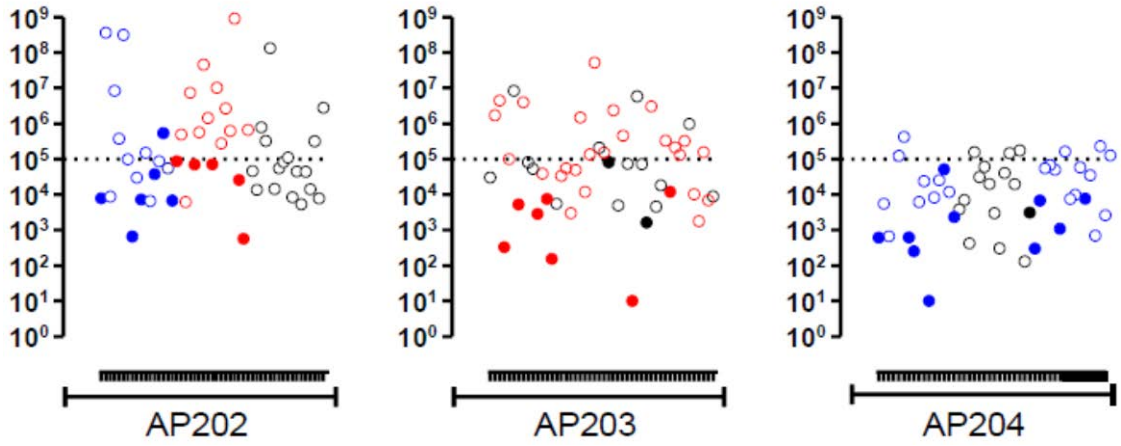
Table 2.2.4.1-1 Survival Data of Obiltoxaximab in Rabbit and Monkey Efficacy Studies

Study Number	Dose (mg/kg)[a]	Survival %[b] (# Survived/ #Treated)	Difference in Survival Rate Compared to Control	95% CI[c]	Statistical Assessment (p-values)[d]	
					Fisher Exact Test	Boschloo Test
New Zealand White Rabbits:						
AR021	0	0% (0/9)	NA	NA	-	-
	1	38% (3/8)	0.375	(-0.022 , 0.755)	NS	NS
	4	73% (11/15)	0.733	(0.298, 0.925)	0.0005*	0.0012*
	16	93% (13/14)	0.929	(0.593, 0.998)	<0.0001*	0.0010*
	Levofloxacin[e]	89% (8/9)	0.889	(0.454, 0.997)	0.0002*	0.0011*
AR033	0	0% (0/13)	NA	NA	-	-
	1	17% (2/12)	0.167	(-0.098, 0.484)	NS	NS
	4	33% (4/12)	0.333	(0.035, 0.651)	NS	0.0232*
	8	69% (9/13)	0.692	(0.367, 0.909)	0.0002*	0.0011*
	16	62% (8/13)	0.615	(0.290, 0.861)	0.0008*	0.0013*
Cynomolgus Monkeys:						
AP201	0	14% (2/14)	NA	NA	-	-
	4	79% (11/14)	0.643	(0.260, 0.879)	0.0009*	0.0015*
	8	73% (11/15)	0.591	(0.207, 0.841)	0.0019*	0.0017*
AP203	0	13% (2/16)	NA	NA	-	-
	8	6% (1/16)	-0.063	(-0.319, 0.194)	NS	NS
	32	38% (6/16)	0.250	(-0.065, 0.541)	NS	NS
AP204	0	6% (1/16)	NA	NA	-	-
	4	25% (4/16)	0.188	(-0.090, 0.473)	NS	NS
	16	47% (7/15)	0.404	(0.089, 0.681)	0.0139*	0.0068*
AP202	0	0% (0/17)	NA	NA	-	-
	16 (Lonza)	31% (5/16)	0.313	(0.079, 0.587)	0.0184*	0.0085*
	16 (Baxter)	35% (6/17)	0.353	(0.113, 0.617)	0.0092*	0.0055*

NA – not applicable
[a] *Doses were administered by IV bolus unless otherwise noted; vehicle without ETI-204 was administered to animals receiving placebo treatments*
[b] *Only animals that were bacteremic prior to treatment were included in the analysis*
[c] *Exact 95% confidence interval based on the score statistic of difference in survival rates*
[d] *Statistical assessment based on 1-sided Fisher's Exact Test and 1-sided Boschloo Test (with Berger-Boos modification of gamma=0.001), compared to control. Values represent p values; * - statistically significant difference from control (p <0.025); NS – not statistically significant (p >0.025)*
[e] *Levofloxacin was included as a positive control at a dose of 50 mg/kg/day x 3 days orally*

Source: Section 2.7.2

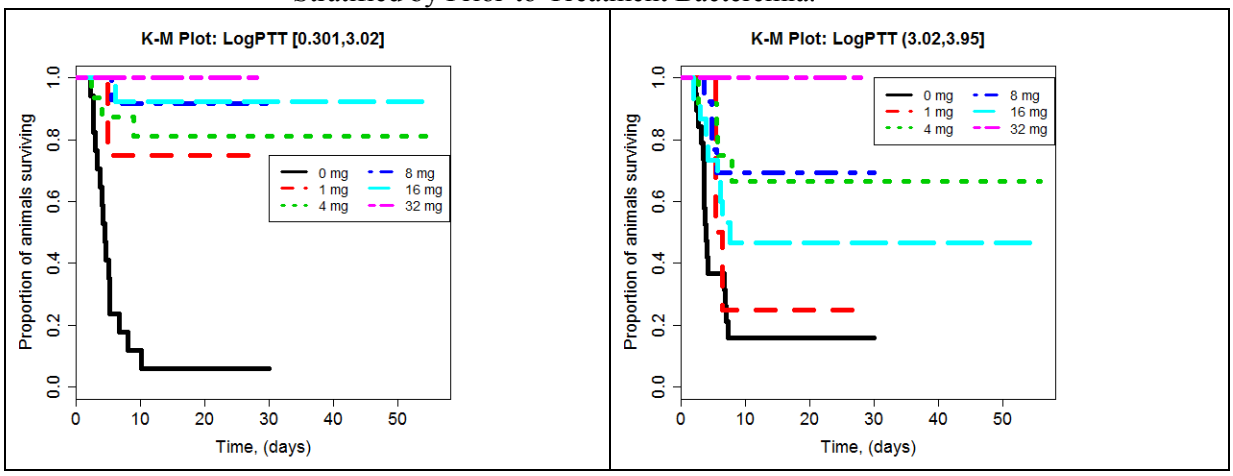
Figure 2.2.4.1-1 Prior-to-Treatment Bacteremia Values in Individual Monkeys in Studies AP202, AP203, and AP204.

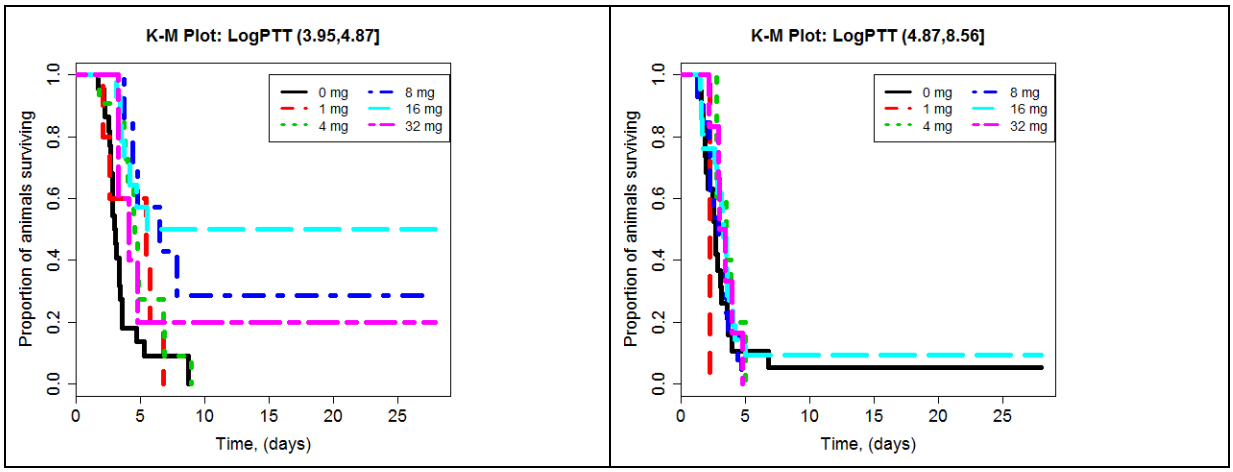


Open circles = non-survivors; Closed circles = survivors. Y-axis is colony forming units/mL (CFU/mL).
Blue = ETI-204 supplied by Baxter; Red = ETI-204 supplied by Lonza; Black = vehicle control.
Dashed line at 10^5 CFU/mL approximates the demarcation between the 3rd and 4th quartiles of the distribution of PTT bacteremia values across all studies.

Source: Adapted from Module 2.7.2 Summary of Clinical Pharmacology, Figure 52

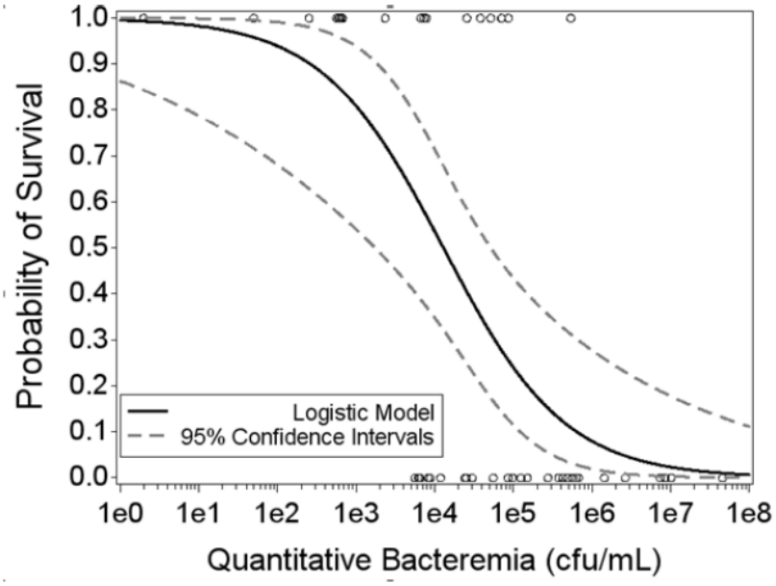
Figure 2.2.4.1-2 Kaplan-Meier Survival Curves of Obiltoxaximab in Rabbits and Monkeys, Stratified by Prior-to-Treatment Bacteremia.





Source: Reviewer's Analysis

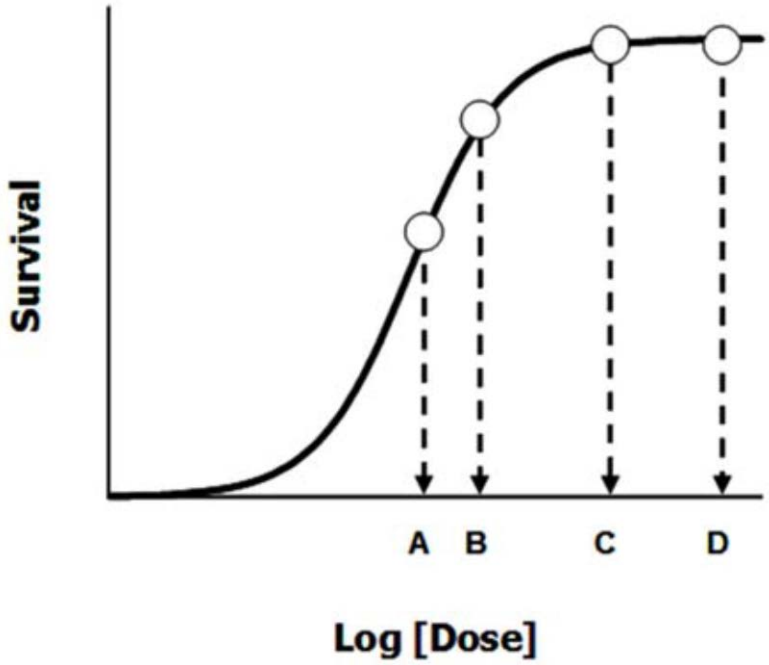
Figure 2.2.4.1-3 Relationship between Survival and Prior-to-Treatment Bacteremia in Monkeys in 16 mg/kg Dose Groups in Studies AP204 and AP202



Source: Module 2.7.2 Summary of Clinical Pharmacology, Figure 49

A population dose-survival analysis was performed by the Applicant and the Clinical Pharmacology Reviewer based on survival data from the trigger-to-treat studies in rabbits (AR033) and monkeys (AP201, AP204, AP203, and AP202). This analysis had several objectives, including the development of a survival model to describe obiltoxaximab dose-response in infected rabbits and cynomolgus monkeys, to identify factors (e.g., dose, PTT, species [rabbit versus monkey]) influencing treatment outcome, and to identify a fully effective dose in animals for treatment of inhalational anthrax. Per the Animal Rule guidance, the definition of a fully effective dose is depicted in Figure 2.2.4.1-4, where survival is increased (compared to placebo) following administration of Doses A, B, C, and D of the investigational drug. The results of the testing of Dose D confirm that Dose C is a fully effective dose, because increasing the dose from C to D did not further increase survival.

Figure 2.2.4.1-4 A Representative Dose-Response Curve for Survival Based on Four Doses of an Investigational Drug Studied in a Well-Characterized Animal Model



Source: Product Development Under the Animal Rule Guidance for Industry, October 2015, Figure 1.

A Weibull cure-rate model was implemented to describe time course survival for the combined infected rabbit and monkey survival data. The survival model included an E_{max} dose-response effect and an exponential $\log_{10}$(PTT bacteremia) effect on the proportion of animals surviving (effectively 'cured') at the end of treatment. Log-transformed PTT was also a covariate on the survival time course, where animals with a higher baseline PTT were more likely to expire at earlier times. The Weibull cure-rate model was fit to the survival data. The survival function for this model is given by:

$$P(T > t) = p_{surv} + (1 - p_{surv}) \exp\{-(\lambda t)^{\alpha}\}$$

Where T is the time-to-death. The parameter p_{surv} is the probability that an animal survives to the end of the study (Day 28), and λ is the rate at which animals die. The shape of the survival curve is determined by the parameter α. Based on the survival function of the Weibull cure-rate model shown above, Sponsor's model on the survival function was modified by the Clinical Pharmacology Team, where the α power was corrected to be associated with the quantity of λ (LAM) times T (modified model) instead of T alone (Sponsor's model):

Sponsor's Model:

SURV = CURE + (1-CURE)*EXP(-(LAM)*(T)**ALPH)

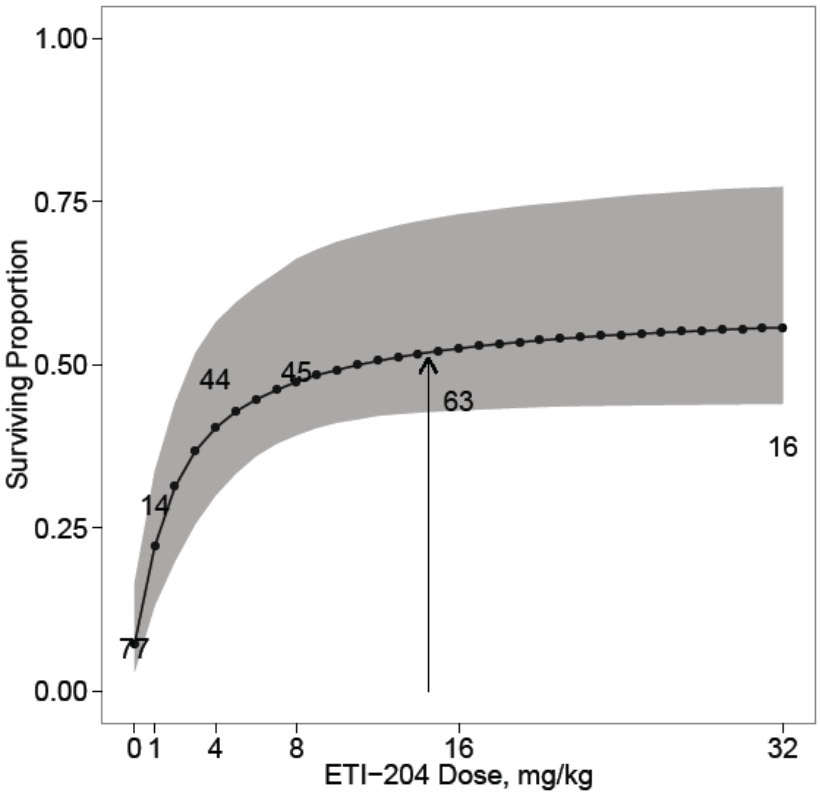
Modified Survival Model by the Clinical Pharmacology Team:

SURV = CURE + (1-CURE)*EXP(-(LAM*T)**ALPH)

Animal species was not identified as a significant stand-alone factor or as a factor on ED_{50}. As such, it is considered appropriate to combine data from both animal species in the final analysis. Simulations were performed using the final model to determine the proportion of surviving animals over a range of

obiltoxaximab doses. The final model fit of survival versus dose demonstrated an early linear increase in response that gradually reached a plateau above which additional increases in dose did not improve the efficacy outcome (Figure 2.2.4.1-5).

Figure 2.2.4.1-5 Estimated Obiltoxaximab Dose-Response in Monkeys (Studies AP201, AP204, AP203, AP202) and Rabbits (Study AR033) Based on the Final Survival Model.



Markers indicate the total number of animals (monkeys + rabbits) comprising each observed mean data point; the prediction (solid line), with 90% confidence interval (shaded region), based on modeling of survival data and dose, is overlaid.

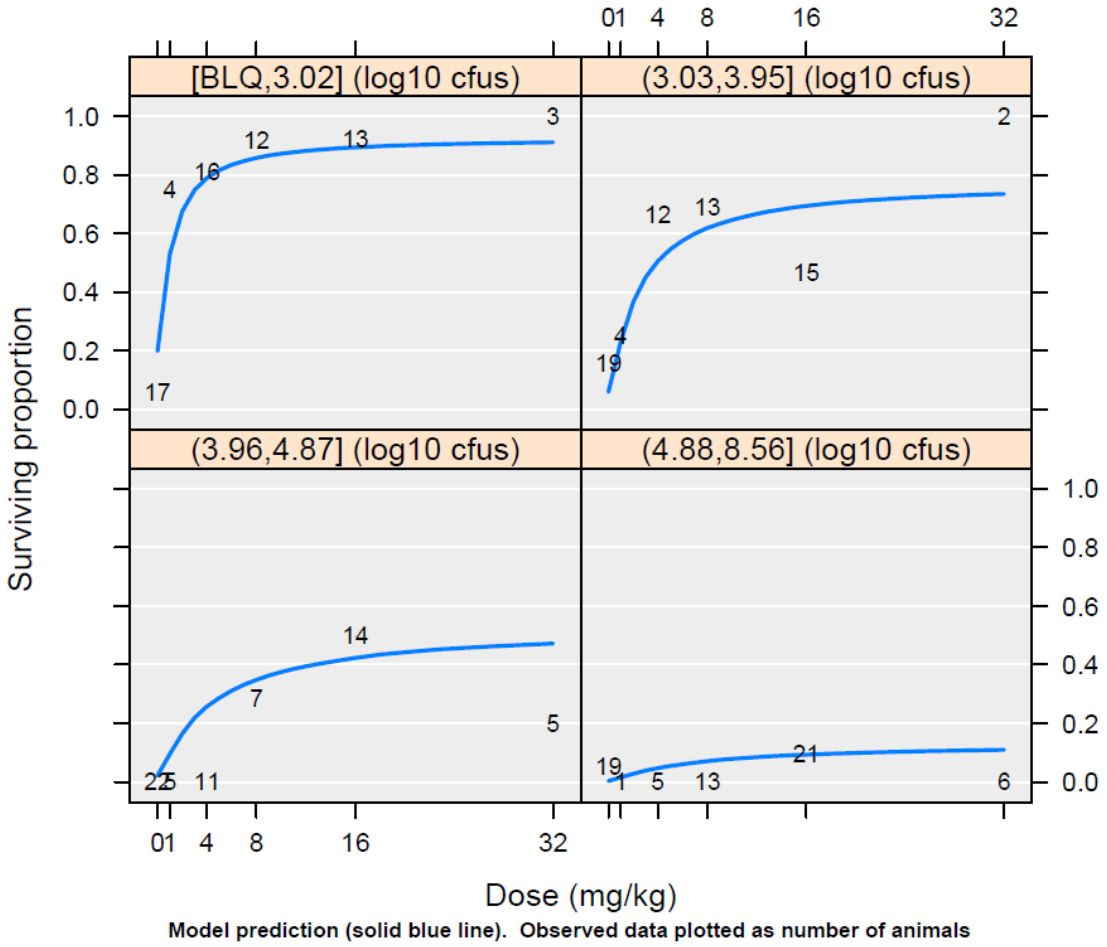
Source: Module 2.7.2 Summary of Clinical Pharmacology, Figure 50

FDA's analysis showed that the estimated dose associated with 50% of the maximal effect (ED_{50}) for the endpoint of survival is 1.6 mg/kg (95% confidence interval: 0.6 – 4.4 mg/kg); the estimated dose to achieve 90% of the maximal effect (ED_{90}) is 14.5 mg/kg (95% confidence interval: 5.4 – 39.3 mg/kg); the estimated dose to achieve 95% of the maximal effect (ED_{95}) is 30.5 mg/kg (95% confidence interval: 11.4 – 83.1 mg/kg);. Doubling the dose from ED_{90} to ED_{95} (14.5 to 30.5 mg/kg) is predicted to only marginally increase the probability of survival by 2.8% (from 49.5% to 52.3%). Therefore, ***a dose of 14.5 mg /kg (ED_{90}) was determined by the clinically pharmacology review team to be the fully effective dose for obiltoxaximab because further increasing the dose does not appear to appreciably improve survival.*** Of note, the Applicant concluded that 16 mg/kg (a dose explicitly studied in animals) is the maximum effective dose in rabbits and monkeys with anthrax infection.

As noted above, PTT bacteremia was identified as a covariate with a significant effect on response to obiltoxaximab treatment. Dose-response relationships, stratified by PTT bacteremia quartile, are shown in Figure 2.2.4.1-6. A higher PTT bacteremia is associated with a lower maximum cure rate; in other words, with increasing bacteremia, the response plateau decreases. At the lowest PTT bacteremia (BLQ-3.02 log_{10} cfus), it appears that the maximum survival was achieved at doses as low as 8 mg/kg. At higher PTT bacteremia levels, a higher dose is required to reach the response plateau, although doses of 14.5 mg/kg

and greater (i.e., 16 and 32 mg/kg) remain on the response plateau in all cases. While the dose-response relationships at low PTT bacteremia levels (represented by the upper 2 quadrants in Figure 2.2.4.1-6) indicate the maximum survival could be achieved at a lower dose (i.e., 8 mg/kg), the expected level of bacteremia in human anthrax infection is unknown. As such, the dose-response relationships at high PTT bacteremia levels (represented by the lower 2 quadrants in Figure 2.2.4.1-6) should be considered as the worse-case scenario in determining the fully effect dose, and these results continue to support the identified fully effective dose of 14.5 mg/kg (ED_{90}) in infected animals.

Figure 2.2.4.1-6 Estimated Obiltoxaximab Dose-Response in Monkeys (AP201, AP204, AP203, AP202) and Rabbits (AR033), Stratified by Prior-to-Treatment Bacteremia Based on the Final Survival Model.

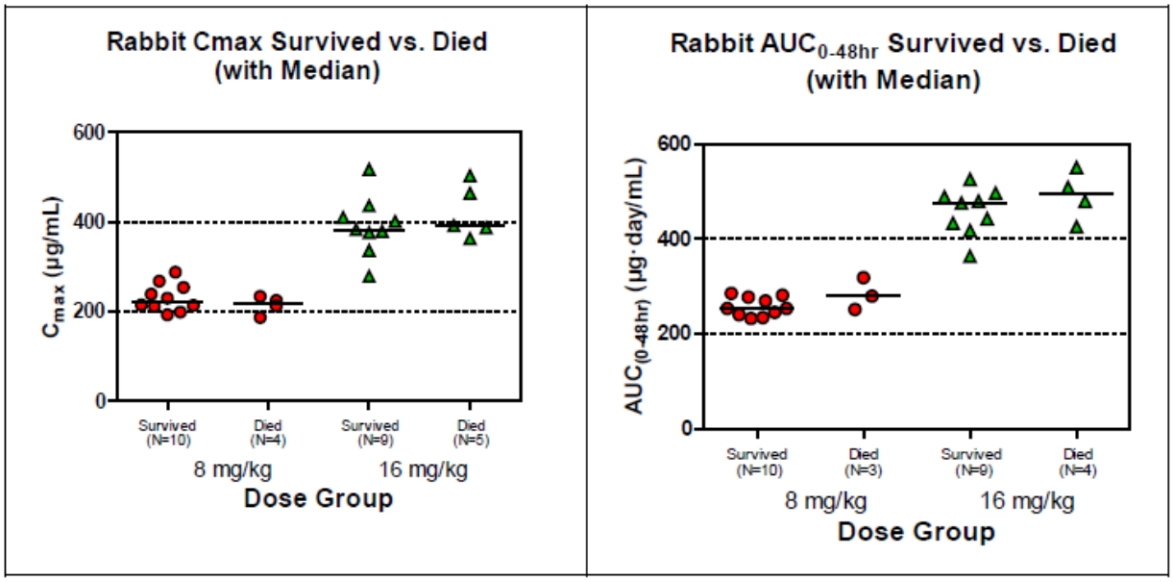


The four quadrants represent quartiles of the PTT bacteremia distribution across all 5 studies. Markers indicate the total number of animals (monkeys + rabbits) comprising each observed mean data point; the prediction based on modeling of survival data and dose (solid blue line) is overlaid. cfus = colony forming units/mL.
Source: Module 2.7.2 Summary of Clinical Pharmacology, Figure 51

Comparisons of obiltoxaximab exposure (C_{max}, or $AUC_{0\text{-}48h}$) between animals that survived and animals that died following *B anthracis* spore challenge and treatment with single intravenous administration of 8 and 16 mg/kg in rabbits and cynomolgus monkeys are displayed in Figure 2.2.4.1-7 and Figure 2.2.4.1-8, respectively. AUC over the first 48 hours ($AUC_{0\text{-}48h}$), instead of AUC_{inf} was chosen for this assessment in animals because there were too few animals with a valid estimate of AUC from time 0 extrapolated to infinity (AUC_{inf}), particularly in nonsurviving infected animals, to make a useful comparison with this

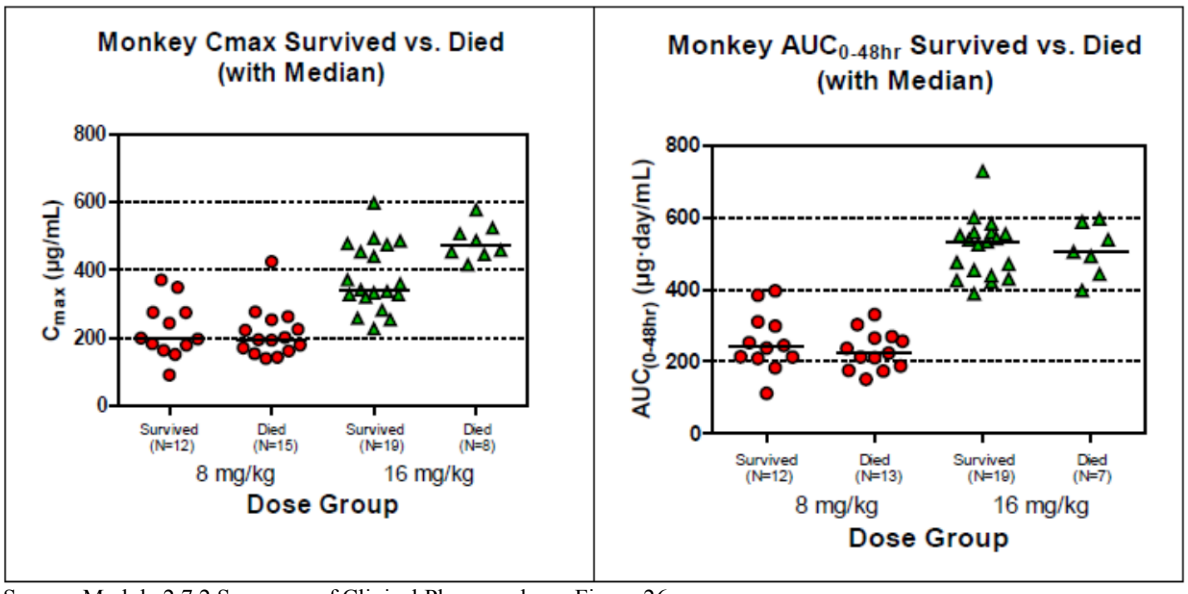
parameter. In addition, AUC values from time 0 through the time of the last measurable serum concentration ($AUC_{0\text{-last}}$) were skewed in animals that died prior to scheduled termination since the time of the last measurable concentration in this group occurred earlier than in animals that survived for a longer period of time, whether healthy or infected. Exposure over the first 48 hours post dose was considered a relevant time frame over which to assess AUC as animals that did not survive in the obiltoxaximab trigger-to-treat studies died after 48 hours and before 10 days post treatment. As shown in Figure 2.2.4.1-7 and Figure 2.2.4.1-8, no distinct differences in obiltoxaximab C_{max}, or $AUC_{0\text{-48h}}$ were observed between animals that died and animals that survived.

Figure 2.2.4.1-7 Individual and Median Obiltoxaximab C_{max} and $AUC_{0\text{-48h}}$ in Infected Rabbits that Survived Compared to Non-Survivors at 8 mg/kg and 16 mg/kg



Source: Module 2.7.2 Summary of Clinical Pharmacology, Figure 25

Figure 2.2.4.1-8 Individual and Median Obiltoxaximab C_{max} and $AUC_{0\text{-48h}}$ in Infected Monkeys that Survived Compared to Non-Survivors at 8 mg/kg and 16 mg/kg

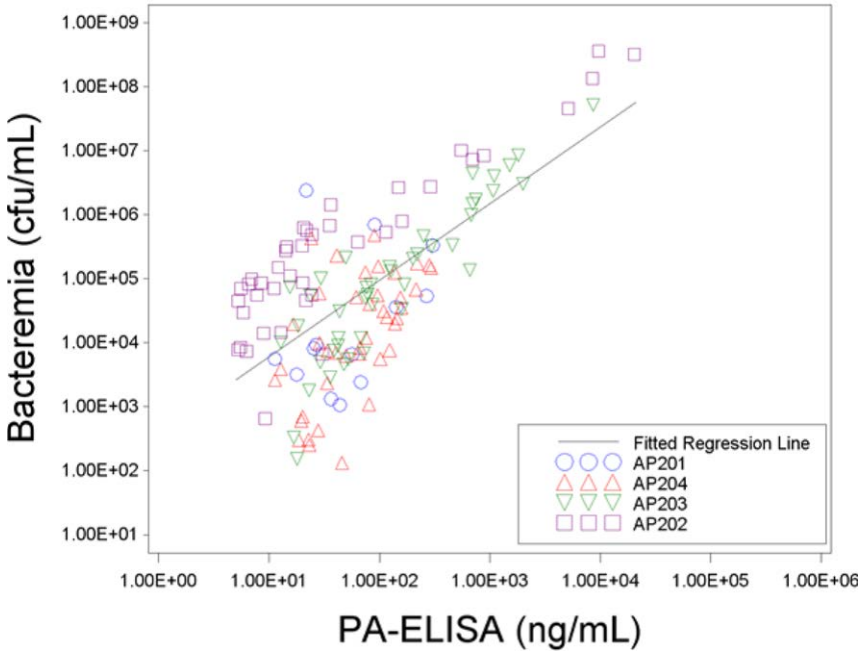


Source: Module 2.7.2 Summary of Clinical Pharmacology, Figure 26

Exposure-PA Relationship

The following two characteristics of an "effective human obiltoxaximab dose" were proposed by the applicant: 1) a sufficiently high C_{max}, and 2) at least 2-3 weeks duration of protective serum obiltoxaximab levels. A correlation between PTT bacteremia and PTT PA concentrations has been demonstrated in cynomolgus monkeys (r = 0.685; Figure 2.2.4.1-9). This provides experimental support for the use of PTT PA concentrations as a biomarker for PTT bacteremia. In infected animals, PA concentrations rise rapidly, generally within 1 to 3 days, after spore challenge. This was particularly consistent in monkeys, for which PA toxemia was the primary trigger for treatment. Within minutes, the administration of obiltoxaximab fostered a reduction in serum PA concentrations to below the limit of quantification (BLQ) levels (Figure 2.2.4.1-10). In addition, the peak PA levels in animals that died are orders of magnitude higher than the peak levels in the animals that survived. As proposed by the applicant, the data suggest that an efficacious human obiltoxaximab dose needs to be large enough to rapidly attain serum levels equal to or in excess of those needed to bind systemic PA concentrations, to prevent the mortality associated with PA toxemia. In other words, ***a human obiltoxaximab dose should attain a sufficiently high C_{max} to optimize the likelihood of achieving efficacy***.

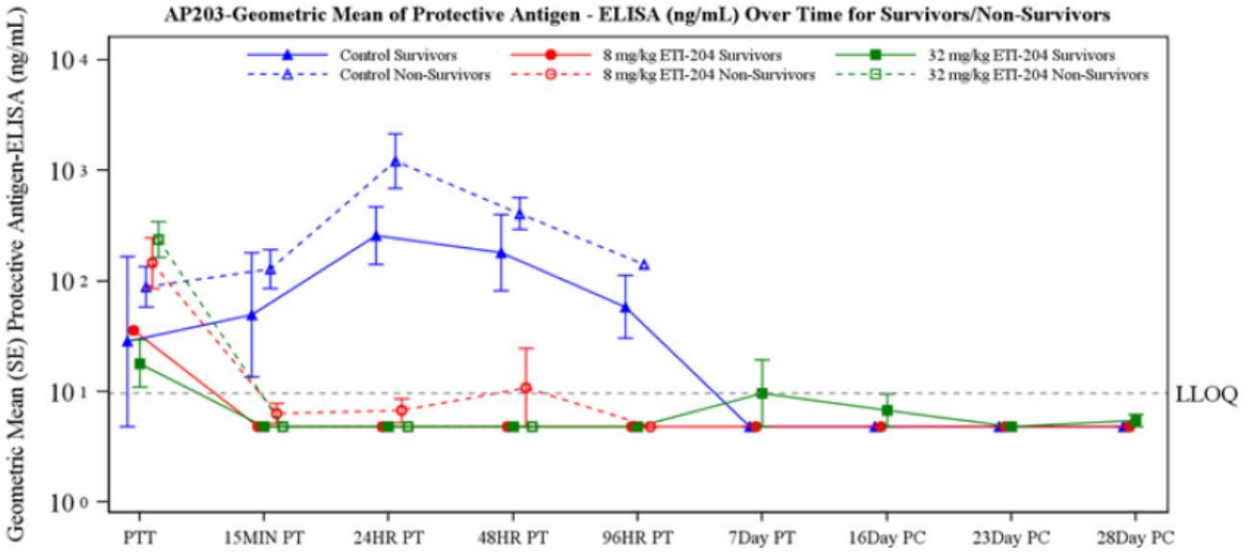
Figure 2.2.4.1-9 Individual Animal PTT Bacteremia vs. PTT Free PA in Monkeys (Studies AP201, AP204, AP203, and AP202 Combined)



Fitted regression line is overlaid ($p < 0.0001$); N = 138; r = 0.685

Source: Section 2.7.2

Figure 2.2.4.1-10 Serum PA Concentrations in Monkeys Following IV Administration of Obiltoxaximab at 0, 8, and 32 mg/kg (Study AP203)



PTT = Prior-to-Treatment; PT = Post-Treatment; PC = Post-Challenge

Terminal samples are not included

Dotted line represents the lower limit of assay quantification (LLOQ) of 9.68 ng/mL; for computational purposes, values below the LLOQ were given a value of ½ the LLOQ (4.84 ng/mL)

Source: Section 2.7.2

In rabbit and monkey efficacy studies, animals died before 10 days post challenge, and anti-PA IgG was detected in rabbits within 10 to 14 days post challenge. This same time frame would allow for the development of endogenous adaptive immunity in humans; anti-PA IgG was detected in 16 of 17 patients with confirmed or suspected clinical anthrax within 11 days after the onset of symptoms (15 days after likely exposure) (Quinn et al, 2004), and within 5 to 7 days after onset of symptoms in a patient with naturally acquired inhalational anthrax (Walsh et al, 2007). Thus, the applicant proposes an efficacious human obiltoxaximab dose ***should maintain protective systemic obiltoxaximab exposure for at least 10 days after administration, to allow the innate immune response to PA to develop***.

As shown in Figure 2.2.4.1-11 and Figure 2.2.4.1-12, maximum obiltoxaximab serum concentrations in simulated human populations are 1 and 2 orders of magnitude greater than the concentrations required for 99.9% (48 µg/mL) and 99% (4.8 µg/mL) PA neutralization, respectively. Moreover, a molar excess of obiltoxaximab is maintained in serum for 2 to 3 weeks. Specifically, the time at which the lower end of the 90% prediction interval declines to the 99.9% PA binding concentration is approximately Day 20 and Day 16 for healthy and infected subjects, respectively.

Figure 2.2.4.1-11 Obiltoxaximab Concentration vs. Time Curves (Mean and 90% Prediction Interval) for a Simulated Population of Healthy Human Subjects (N=500) in Comparison to Obiltoxaximab Levels Required for 99% and 99.9% Neutralization of PA. (semilogarithmic scale)

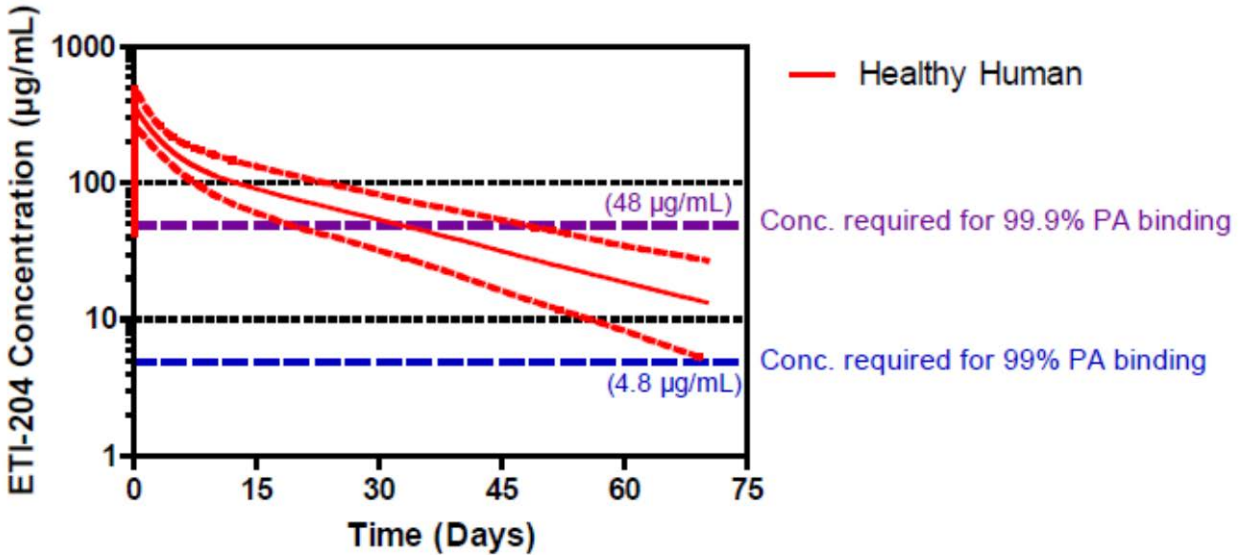
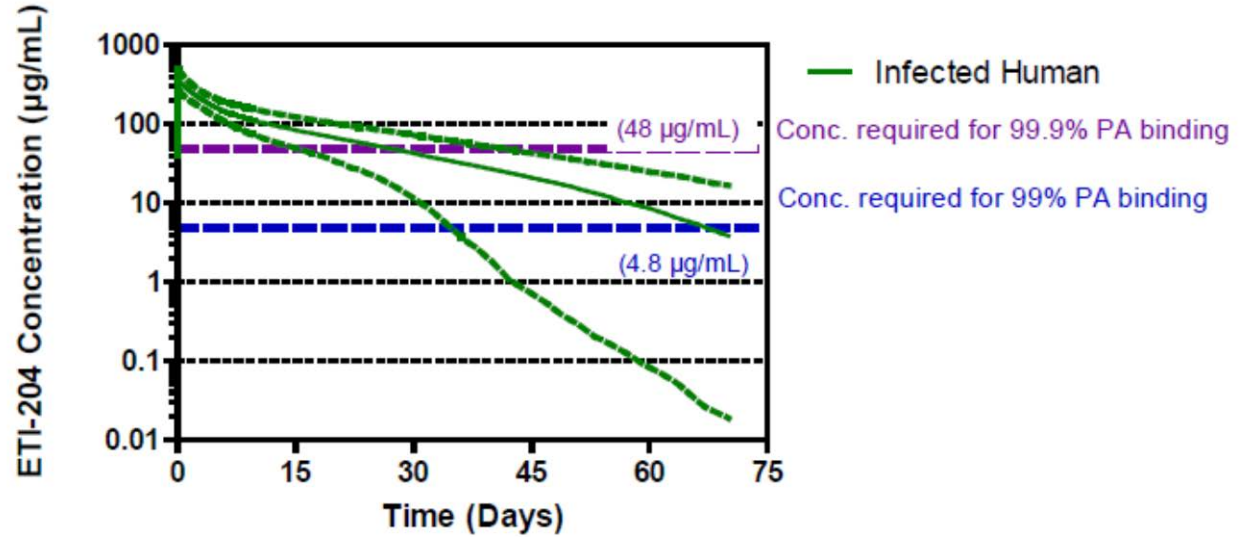


Figure 2.2.4.1-12 Obiltoxaximab Concentration vs. Time Curves (Mean and 90% Prediction Interval) for a Simulated Population of Infected Human Subjects (N=500) in Comparison to Obiltoxaximab Levels Required for 99% and 99.9% Neutralization of PA (semilogarithmic scale)



Source: Section 2.7.2

In addition, obiltoxaximab Cmax in humans following 16 mg/kg IV dose (approximately 390 µg/mL or 2600 nM) is two orders of magnitude greater than putative point-of-no-return PA concentrations that are associated with overwhelming infection in animals (1.4 to 1.7 µg/mL, or 22 to 27 nM), and is an order of magnitude greater than the maximum individual PTT PA concentration observed across all infected rabbits and monkeys (9.67 µg/mL or 153 nM). In addition, obiltoxaximab concentrations persist above

the maximum PTT PA concentrations observed in animals for more than 3 weeks (Figure 2.2.4.1-13 and Figure 2.2.4.1-14).

Figure 2.2.4.1-13 Obiltoxaximab Concentration vs. Time Curves (Mean and 90% Prediction Interval) for a Simulated Population of Healthy Human Subjects (N=500) in Comparison to Maximum Individual PTT PA Concentrations Observed in Monkeys and Rabbits. (semilogarithmic scale)

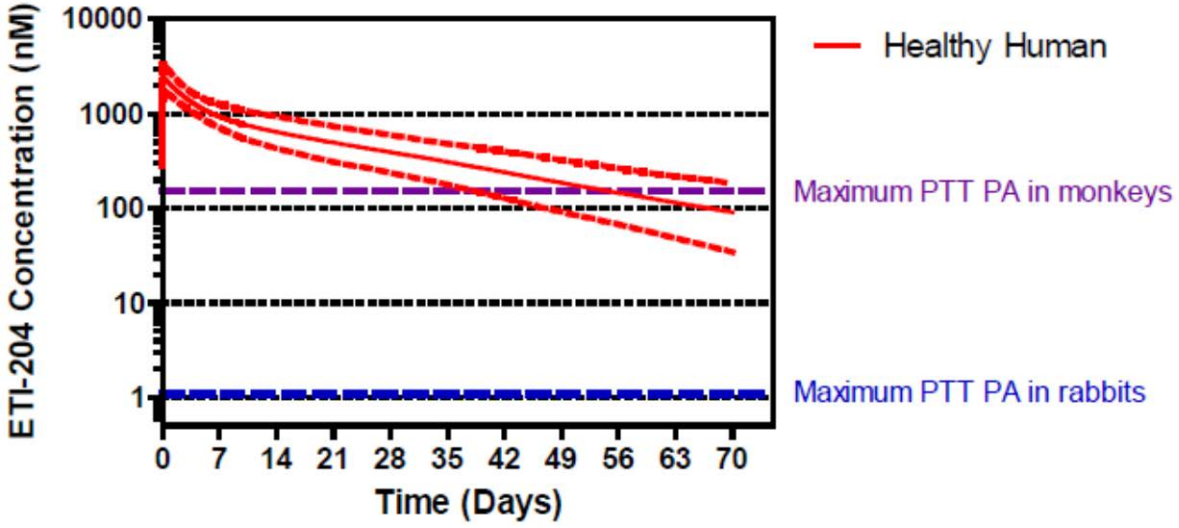
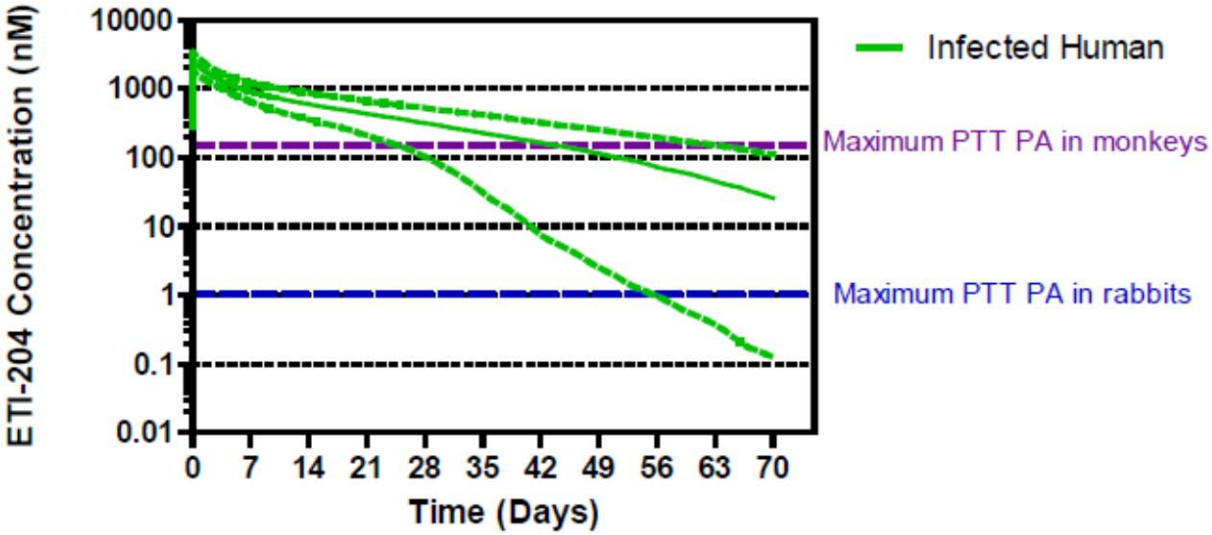


Figure 2.2.4.1-14 Obiltoxaximab Concentration vs. Time Curves (Mean and 90% Prediction Interval) for a Simulated Population of Infected Human Subjects (N=500) in Comparison to Maximum Individual PTT PA Concentrations Observed in Monkeys and Rabbits. (semilogarithmic scale)



Source: Section 2.7.2

In summary, an evaluation of the relationship between obiltoxaximab dose/concentrations, PA concentrations, and outcome (survival or death) based on monotherapy in monkeys and rabbits suggests the following:

1. The dose-response data in rabbits and monkeys suggest a dose of 14.5 mg/kg (ED_{90}) as the fully effective dose in animals with inhalational anthrax infection.
2. No distinct differences in obiltoxaximab C_{max}, or AUC_{0-48h} were observed between animals that died and animals that survived.
3. Based on in vitro binding kinetics studies, the proposed dose of 16 mg/kg in humans would be expected to maintain obiltoxaximab concentrations required for virtually complete binding (99.9%) of PA for 2-3 weeks.
4. Based on predicted human PK profiles, more than 95% of humans administered a 16 mg/kg IV obiltoxaximab dose can be expected to have serum obiltoxaximab concentrations that are equimolar to or in excess of the highest observed serum PA concentration in any animal for at least 3 weeks.
5. As stated by the applicant and supported by literature, the duration of time when obiltoxaximab concentrations are in molar excess of PA concentrations following 16 mg/kg IV dose (2-3 weeks) appears sufficient to allow development of innate immunity in humans.

The efficacy of antibiotics administered concomitantly with obiltoxaximab in the setting of therapeutic treatment also was evaluated in rabbits and monkeys with symptomatic anthrax disease. Please refer to reviews from the Statistical (Dr. Ling Lan), Microbiology (Dr. Shukal Bala), and Clinical (Dr. Elizabeth O'Shaughnessy) Reviewers for more details.

2.2.4.2. What are the characteristics for exposure-response relationships (dose-response, concentration-response) for safety?

Adverse Events in Humans

The safety of obiltoxaximab was evaluated in 320 healthy subjects treated with a 16 mg/kg IV dose in 3 clinical trials: a placebo-controlled study evaluating single doses (AH104) of obiltoxaximab (210 subjects received obiltoxaximab, 70 received placebo), a repeat-dose study of 70 subjects, 35 subjects receiving a second obiltoxaximab dose either 2 weeks or ≥4 months after the first dose (AH109), and a drug interaction study with ciprofloxacin in 40 subjects, 20 subjects receiving obiltoxaximab alone, 20 subjects receiving obiltoxaximab+ciprofloxacin (AH110).

Because obiltoxaximab is intended for single-dose use, the overall safety of obiltoxaximab was evaluated as an integrated summary in 300 subjects who received a single dose in these 3 clinical trials – 210 subjects from study AH104, 70 subjects from the initial treatment period of Study AH109, and 20 subjects who received obiltoxaximab alone in study AH110. The subjects were 18 to 79 years of age, 54% male, 70.0% Caucasian, 27% Black/African American, 1% American Indian/Alaska Native, 1% Asian and 8.3% Hispanic.

The most frequently reported adverse reactions were headache, pruritus, cough and urticaria (Table 2.2.4.2-1).

Table 2.2.4.2-1 Adverse Reactions Reported in ≥ 1.5%* of Healthy Adult Subjects Exposed to Single Dose Obiltoxaximab 16 mg/kg IV

Adverse Reactions	**Placebo N =70 (%)**	**Single Dose Obiltoxaximab N = 300 (%)**
Headache	4 (6%)	24 (8%)
Pruritus	1 (1%)	11 (4%)
Upper Respiratory Infection	3 %	4%
Rash/Rash generalized/Rash papular/ Rash erythematous	2 (3%)	10 (3%)

Cough	0	9 (3%)
Vessel puncture site bruise	1 (1%)	8 (3%)
Infusion site swelling	1 (1%)	8 (3%)
Nasal congestion	1 (1%)	5 (2%)
Infusion site pain	0	7 (2%)

**Somnolence was seen in 6% of subjects in the obiltoxaximab arm, likely due to diphenhydramine administration.*

Ten (10) subjects (3.1%) either had their infusion of obiltoxaximab discontinued due to significant hypersensitivity reactions occurring within 64 minutes after the infusion was started (8 subjects), or were discontinued from the study due to hypersensitivity (2 subjects). These reactions included urticaria, rash, pruritus, cough, throat irritation, dyspnea and dizziness. Seven (7) subjects (2.2%) fit FDA's Clinical Reviewer's criteria for anaphylaxis. Subjects who received premedication with diphenhydramine were less likely to experience hypersensitivity reactions with administration of obiltoxaximab compared to those who did not receive diphenhydramine. Specifically, the incidence of cough and rash were lower in subjects who received diphenhydramine, but there was no change in the incidence of pruritus or urticaria. Diphenhydramine premedication did not prevent anaphylaxis, but its incidence of 4 of 73 (6%) in the group that did not receive diphenhydramine was greater than in the group that did (3 of 246, 1%). Premedication with diphenhydramine (b) (4) prior to administering obiltoxaximab is recommended. Overall, no discernable differences in obiltoxaximab exposure were observed in the subjects who experienced hypersensitivity reactions relative to those who did not.

Please refer to Dr. Ramya Gopinath's Clinical Safety Review for more details.

2.2.5. What are the PK characteristics of Obiltoxaximab?

2.2.5.1. What are the single dose and multiple dose PK parameters?

Single Dose Pharmacokinetics of Obiltoxaximab

In rabbits, obiltoxaximab exposure, as indicated by C_{max} and $AUC_{(0\text{-}inf)}$ values, increased approximately proportionally from 3 to 30 mg/kg in healthy animals (AR010), from 16 to 32 mg/kg in pregnant rabbits (EFT001), and from 1 to 16 mg/kg in infected animals (AR033) (Table 2.2.5.1-1).

In monkeys, obiltoxaximab C_{max} and $AUC_{(0\text{-}inf)}$ values increased approximately dose proportionally from 3 to 30 mg/kg in healthy animals (Study AP116) and from 4 to 8 mg/kg in infected animals (Study AP201). C_{max} increased approximately proportionally, while $AUC_{(0\text{-}inf)}$ increased greater than dose proportionally from 8 to 32 mg/kg (Study AP203) and from 4 to 16 mg/kg (Study AP204) in infected monkeys (Table 2.2.5.1-1).

Obiltoxaximab PK data in humans after an IV dose are summarized in Table 2.2.5.1-2. In humans, obiltoxaximab C_{max} and AUC values increased approximately proportionally from 19 mg (~0.23 mg/kg) to 114 mg (~1.55 mg/kg) in Study AH101, and from 120 mg (~1.49 mg/kg) to 360 mg (~4.69 mg/kg) in Study AH102. A statistical assessment (ANOVA) was performed in the latter study and, although strict dose proportionality could not be demonstrated unequivocally, there were no statistically significant differences between the groups in dose-normalized PK parameters. In AH105, dose proportionality was established across the 4 mg/kg to 16 mg/kg dose groups, based on linear regression analysis.

In animals and humans, obiltoxaximab serum concentrations declined in a bi- or multi-exponential fashion after IV administration. The $t_{1/2}$ in healthy rabbits, monkeys, and humans was as follows: 3 to 4 days, 5 to 12 days, and 15 to 23 days, respectively. The V_{ss} is 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.

Table 2.2.5.1-1. Obiltoxaximab PK Parameters following Single IV Administration to Healthy and Infected Rabbits and Monkeys via Extensive PK sampling

Species	Status	Study No.	Dose (mg/kg)	PC Dosing Schedule	C_{max} (µg/mL)	T_{max} (d)	$AUC_{(0-inf)}$ (µg·d/mL)	t½ (d)	CL (mL/d/kg)	V_z (mL/kg)	V_{ss} (mL/kg)
Rabbit	Healthy	AR002[a]	4[b]	NA	-	-	243	4.0	16.6[c]	-	97.6[c]
		AR008[a]	8[b]	NA	-	-	558	3.1	14.4[c]	-	79.6[c]
		AR010	3	NA	102	-	368	4.34	8.41	48.7	53.0
			10	NA	342	-	1200	4.17	8.72	46.5	53.9
			30	NA	1030	-	3320	4.23	9.22	53.2	58.2
		EFT001[d]	16	NA	588	0.00207	1710	4.08	9.74	54.4	-
			32	NA	1180	0.00207	3220	3.60	10.3	50.3	-
	Infected	AR033[e,f]	1	48 h PC[g]	22.3	0.0104	54.9	2.12	18.2	-	55.5
			4	48 h PC[g]	109	0.0104	222	0.831	18.0	-	29.9
			8	48 h PC[g]	221	0.0104	470	1.23	17.0	28.5	28.5
			16	48 h PC[g]	401	0.0104	926	1.04	17.3	36.6	36.6
		AR028[e]	16[h]	72 h PC	378	0.217	940	1.74	18.0	43.0	44.0
		AR034[e]	16	30 h PC	413	0.0416	-	-	-	-	-
			16[h]	30 h PC	375	0.0416	-	-	-	-	-
Monkey	Healthy	AP106[a]	5	NA	108	0.125	510	5.48	10.3	81.6	-
		AP116	3	NA	80.9	0.0503	497	9.36	6.36	80.0	72.9
			10	NA	292	0.0104	2510	12.4	4.18	71.3	67.0
			30	NA	783	0.0104	5540	10.4	5.49	81.7	79.4
		AP115[i]	10	NA	258	0.0445	1270	6.20	6.62	58.7	-
			30	NA	781	0.0445	2030	7.22	6.94	68.5	-
	Infected	AP201[e,f]	4	48 h PC[g]	94.6	-	451	7.58	8.87	-	66.7
			8	48 h PC[g]	225	-	954	5.95	8.39	-	61.2
		AP204[e,f]	4	48 h PC[g]	87.8	0.0104	286	6.73	14.0	-	92.1
			16	48 h PC[g]	429	0.0800	1870	4.05	8.55	-	55.7
		AP203[e,f]	8	48 h PC[g]	171	0.0800	608	5.44	13.2	-	63.2
			32	48 h PC[g]	890	0.0104	5010	9.48	6.38	-	76.2
		AP202[e,f]	16[j]	48 h PC[g]	324	-	1790	5.66	8.96	-	47.7
			16[k]	48 h PC[g]	298	-	2050	7.37	7.82	-	59.0

- No data reported
Values are combined-sex means unless otherwise indicated
AUC(0–inf) – Area under the concentration vs. time curve from time 0 extrapolated to infinity; CL – clearance; Cmax – maximum concentration; d – day; h – hours; IV – intravenous; NA – not applicable; PC – post-challenge with B. anthracis; t½ – half-life; Tmax – time of Cmax; Vss – volume of distribution at steady-state; Vz – volume of distribution in the terminal phase
a: ETI-204 samples analyzed via a non-validated method
b: Calculated from nominal (mg/animal) dose using mean body weight.
c: Per-kg value calculated from uncorrected value provided in the study report and assuming a 2.5 kg rabbit body weight.
d: After first dose of a repeat-dose regimen in pregnant rabbits (Days 1, 4, and 7); t1/2, AUC(0-inf), CL, and Vz should be interpreted cautiously as samples were collected over approximately one $t_{1/2}$

e: Animals challenged with a target dose of 200 LD50 equivalents of B. anthracis (Ames strain) spores.
f: Due to mortality observed post-challenge, PK parameters based on composite mean of concentrations from all animals per timepoint per dose group (male and female values combined) analyzed as one profile.
g: Treatment (trigger-to-treat) study; for convenience in determining PK parameters, it was assumed that dose was administered 48 hours post-challenge.
h: Animals co-administered oral levofloxacin at 6.5 mg/kg (AR028) or 50 mg/kg (AR034) for 3 days.
i: After first dose of a repeat-dose regimen [Days 1 and 9 (30 mg/kg) or Days 9 and 17 (10 mg/kg)]; $t_{1/2}$, AUC(0-inf), CL, and Vz should be interpreted cautiously as samples were collected over approximately one t1/2
j: Lonza ETI-204
k: Baxter ETI-204

Table 2.2.5.1-2. Obiltoxaximab PK Parameters following a Single IV Administration to Healthy Humans

Study	Dose (mg/kg)	N	C_{max} (µg/mL)	T_{max} (d)	$AUC_{(0\text{-inf})}$ (µg·d/mL)	$t_{1/2}$ (d)	CL (L/d)	Vd (L)	V_{ss} (L)
AH101[a]	0.23[b]	6	6.1 (16)	NR	49.9 (28)	10.9 (63)	0.404 (25)	5.77 (47)	NR
	0.75[b]	6	19.7 (19)	NR	273 (41)	16.9 (34)	0.228 (25)	5.18 (9.0)	NR
	1.55[b]	6	34.9 (18)	NR	448 (26)	15.3 (22)	0.270 (27)	5.71 (14)	NR
	1.55[b,c]	6	37.9 (18)	0.104 (73)	504 (26)	15.5 (22)	0.252 (27)	5.08 (14)	NR
AH102	1.49[d]	12	39.3 (19)	NR	507 (28)	21.9 (41)	0.252 (24)	7.47 (24)	NR
	3.04[d]	12	89.5 (36)	NR	1090 (21)	20.9 (18)	0.229 (21)	6.95 (32)	NR
	4.69[d]	12	154 (37)	NR	1680 (23)	16.8 (14)	0.225 (23)	5.43 (26)	NR
AH105	4	30	94.0 (21)	0.283 (NR)	1080 (23)	18.2 (4.3)	0.279 (23)	7.08 (18)	NR
	8	30	210 (41)	0.267 (NR)	2390 (22)	20.8 (4.4)	0.270 (24)	7.89 (20)	NR
	16	29	330 (19)	0.259 (NR)	4410 (23)	20.4 (5.0)	0.287 (28)	8.05 (18)	NR
AH104	16	202	400 (23)	0.178 (NR)	5170 (26)	20.2 (26)	0.270 (33)	7.41 (26)	6.34 (24)
AH109	16[e]	35	384 (27)	0.134 (122)	4690 (29)	21.5 (31)	0.300 (35)	8.75 (24)	7.20 (21)
	16[f]	31	402 (33)	0.122 (136)	4400 (18)	18.6 (19)	0.313 (24)	8.33 (29)	7.01 (33)
	32[g]	32	NA[h]	NA[h]	10,300 (25)	22.8 (26)	0.274 (31)	8.69 (31)	NA[h]
AH110	16	20	402 (23)	0.206 (134)	4891 (18)	19.5 (21)	0.268 (22)	7.57 (34)	6.28 (27)
	16[c]	18	397 (16)	0.161 (133)	4990 (19)	19.0 (16)	0.247 (30)	6.59 (20)	5.68 (17)

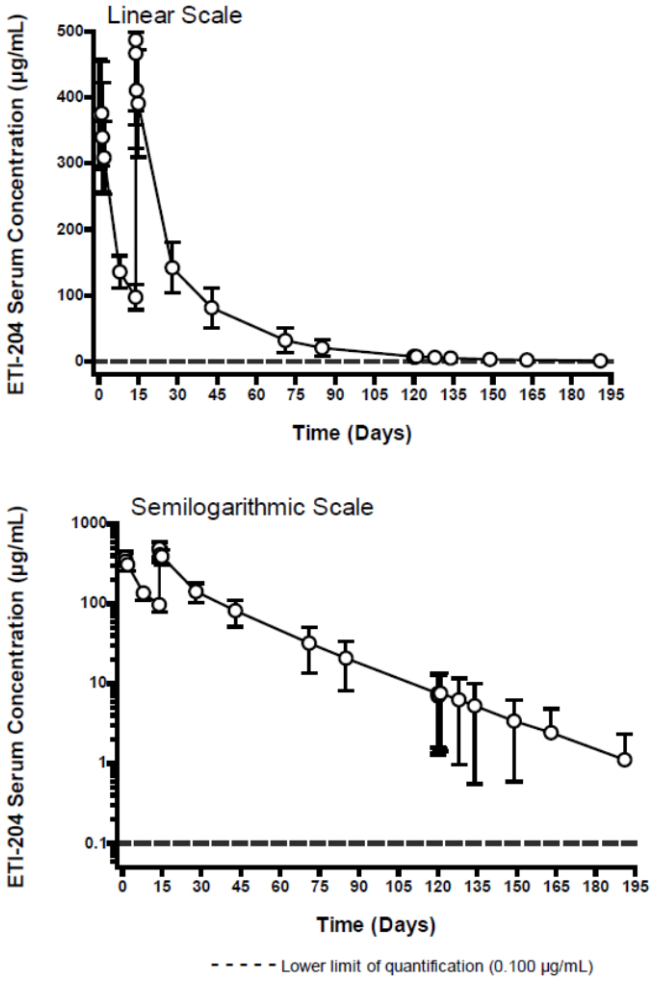
a: Samples analyzed with a non-validated assay
b: Nominal doses were 19, 57, and 114 mg; mg/kg dose estimated using mean body weight in each group
c: Coadministered with ciprofloxacin (500 mg orally twice daily for 14 days in AH101; 400 mg IV single dose followed by 750 mg orally twice daily for 8 days in AH110)
d: Nominal doses were 120, 240, and 360 mg; mg/kg dose estimated using mean body weight in each group
e: Day 1 dose in Sequence B
f: Day 120 dose in Sequence B (not considered definitive)
g: Two 16 mg/kg doses in Sequence A (Day 1 and Day 14)
h: Not valid for comparison (split dose)

Source: Section 2.7.2

Multiple Dose Pharmacokinetics of Obiltoxaximab

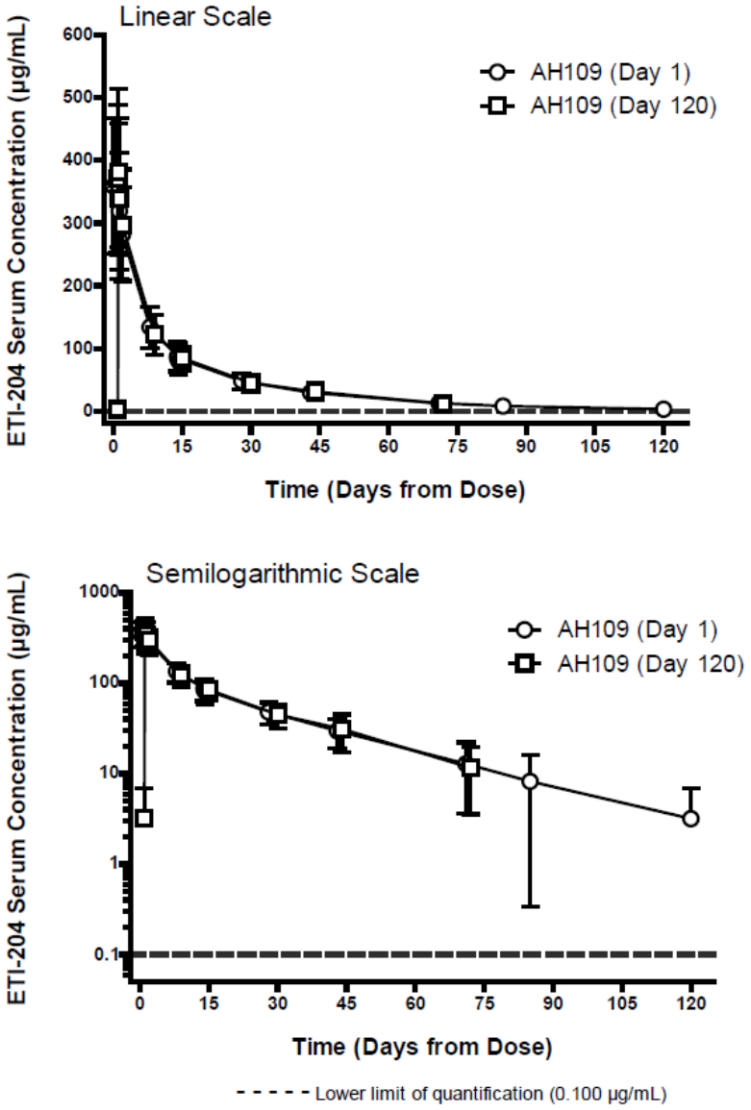
Although obiltoxaximab is intended for single dose administration, Study AH109 was designed to evaluate the safety and tolerability of repeat-dose administration of obiltoxaximab, and multiple dose pharmacokinetics of obiltoxaximab were assessed as a secondary objective. Obiltoxaximab multiple-dose PK was evaluated in humans by administration of two successive doses either 2 weeks or ≥ 4 months apart. A 16 mg/kg IV dose was administered on Day 1 and a subsequent 16 mg/kg IV dose was administered either on Day 14 (Sequence A) or on Day 120 (Sequence B). The PK in Sequence A was treated as one 32 mg/kg dose that was split into two 16 mg/kg administrations (Figure 2.2.5.1-1). The PK in Sequence B was treated as 2 separate 16 mg/kg doses. The disposition of obiltoxaximab after the Day 1 dose was virtually indistinguishable from that after the Day 120 dose (Figure 2.2.5.1-2). The obiltoxaximab $AUC_{(0\text{-inf})}$ from Sequence A, following two 16 mg/kg doses in relatively short succession, was approximately twice that after a single 16 mg/kg dose on Day 1 or Day 120 in Sequence B (Table 2.2.5.1-1). In addition, $t_{1/2}$, CL, and Vd values for the Day 1 and Day 120 doses in Sequence B were quite similar to those observed in Sequence A (Table 2.2.5.1-2).

Figure 2.2.5.1-1. Mean (± SD) Serum Concentration-Time Profiles for Obiltoxaximab for Sequence A (16 mg/kg Obiltoxaximab on Day 1 / 16 mg/kg Obiltoxaximab on Day 14 / Placebo on Day 120) in Healthy Subjects



Source: Study Report AH109

Figure 2.2.5.1-2. Mean (± SD) Serum Concentration-Time Profiles for Obiltoxaximab for Sequence B (16 mg/kg Obiltoxaximab on Day 1 / Placebo on Day 14 / 16 mg/kg Obiltoxaximab on Day 120) in Healthy Subjects



Source: Study Report AH109

Table 2.2.5.1-1 Summary of Obiltoxaximab Pharmacokinetic Parameters for Sequence A (16 mg/kg Obiltoxaximab on Day 1 / 16 mg/kg Obiltoxaximab on Day 14 / Placebo on Day 120) in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$AUC_{(0\text{-191 days})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)
N	34	34	32	32	32	32	32	32
Mean	506	12.8	10,200	10,300	10,300	22.8	0.274	8.69
SD	102	2.27	2500	2530	2480	5.82	0.0862	2.65
CV%	20.2	17.6	24.4	24.5	24.2	25.6	31.4	30.5
Min	315	0.125	6290	6300	6300	12.0	0.134	4.62
Median	520	13.1	10,200	10,200	10,200	22.8	0.260	8.52
Max	739	14.0	17,200	17,400	17,200	34.1	0.499	16.6
Geometric mean	496	NC	9970	10,000	9990	22.0	0.262	8.32

NC: not calculated

Table 2.2.5.1-2 Summary of Obiltoxaximab Pharmacokinetic Parameters for Sequence B, Day 1 (16 mg/kg Obiltoxaximab on Day 1 / Placebo on Day 14 / 16 mg/kg Obiltoxaximab on Day 120) in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$AUC_{(0\text{-120 days})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)	Vss (L)
N	35	35	34	34	34	34	34	34	34
Mean	384	0.134	4550	4690	4560	21.5	0.300	8.75	7.20
SD	103	0.164	1220	1370	1220	6.73	0.104	2.09	1.49
CV%	26.7	122.4	26.7	29.3	26.7	31.2	34.7	24.0	20.8
Min	200	0.0625	1950	1980	1970	14.4	0.106	4.39	3.73
Median	360	0.125	4320	4440	4300	20.1	0.302	8.56	7.17
Max	577	1.00	8890	9580	8890	49.4	0.699	15.6	10.0
Geometric mean	371	NC	4410	4520	4420	20.8	0.284	8.51	7.04

NC: not calculated

Source: Study Report AH109

2.2.5.2. How does the PK of drug and its major active metabolites in healthy volunteers compare to that in patients?

Due to the nature and incidence of the indication (inhalational anthrax) and since evaluation of treatment for inhalational anthrax is not possible in controlled clinical trials in humans, the PK of obiltoxaximab has not been evaluated in patients.

In animals, anthrax infection was associated with increased clearance. Infected animals had comparable Cmax values, but ~20% lower AUC_{inf} relative to uninfected animals based on population PK simulation results in animals (Figure 2.2.5.2-1). This difference was characterized in the cynomolgus monkey population PK analysis by including a parallel nonlinear elimination term to describe target-mediated drug disposition (TMDD) for obiltoxaximab during an ongoing infection. The analogous parameter for infected humans cannot be estimated; instead, the parameterization identified from cynomolgus monkey was scaled and included in the human population PK model to obtain obiltoxaximab AUC_{inf} and C_{max} predictions for infected humans. The simulated PK profiles and calculated PK parameters for obiltoxaximab in healthy and infected humans are shown in Figure 2.2.5.2-1 and Table 2.2.5.2-1. Obiltoxaximab concentrations are predicted to be almost identical over the first 7 days with no difference in C_{max}. AUC_{inf} is predicted to be 17% lower in infected humans compared to healthy humans following a 16 mg/kg IVdose. This difference in exposure is not expected to require any dose adjustments, but it is relevant for the purposes of comparing human exposures to exposures with the fully effective dose in animals.

Figure 2.2.5.2-1 Population PK Simulation Results: Comparison of Healthy and Infected Rabbit (Top) and Monkey (Bottom) Obiltoxaximab (ETI-204) Concentrations after a 16 mg/kg IV Dose. Results are Shown as the Median Concentration (solid lines) and 90% Prediction Interval (dashed lines) from 500 Simulated Rabbits and Monkeys Administered 16 mg/kg IV Obiltoxaximab.

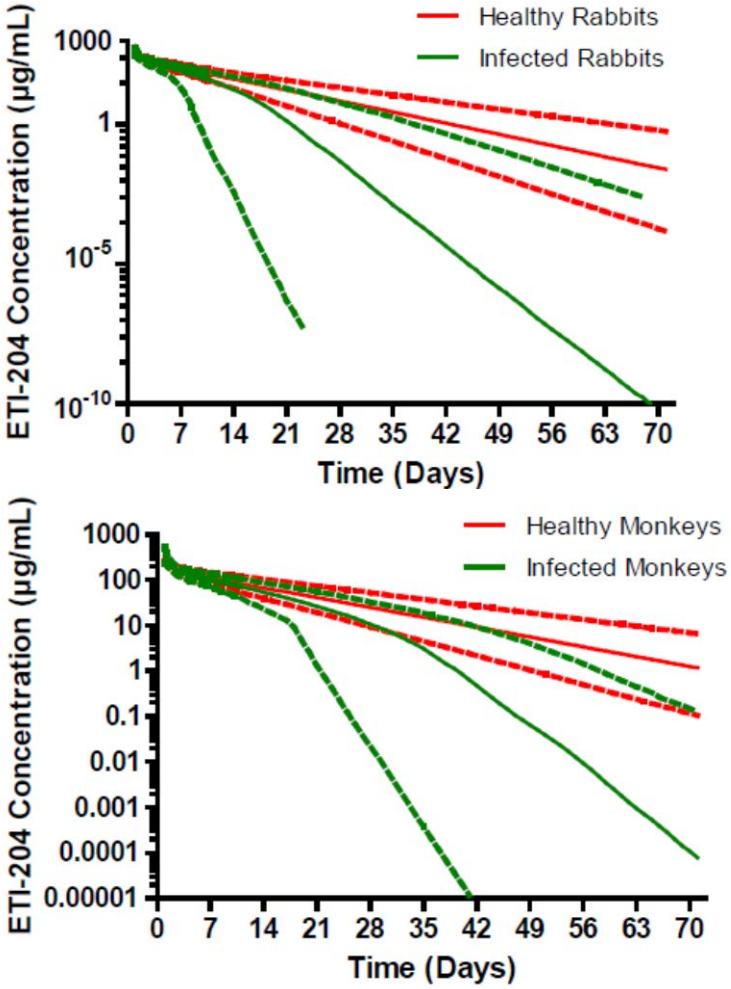
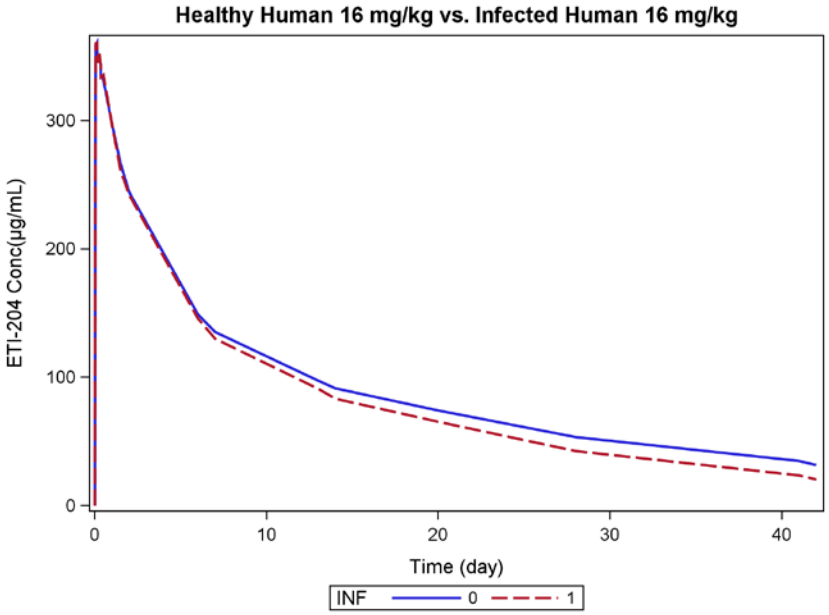


Figure 2.2.5.2-2 Simulated Obiltoxaximab PK profile in Healthy and Infected Humans Administered 16 mg/kg IV dose



Source: Figure generated by the reviewer using simulated data from the sponsor's final model
Note: Healthy human (INF=0); Infected human(INF=1), the lines are median concentrations

Table 2.2.5.2-1 Simulated Obiltoxaximab Exposure in Healthy and Infected Humans

	AUC_{inf} (µg.day/mL)			**C_{max} (µg/mL)**		
	Median	5^{th} Perc.	95^{th} Perc.	Median	5^{th} Perc.	95^{th} Perc.
Healthy Humans 16 mg/kg	4893	3119	7528	359	240	536
Infected Humans 16 mg/kg	4068	2393	6507	360	239	535

Please see Dr. Fang Li's Pharmacometric Review for more details.

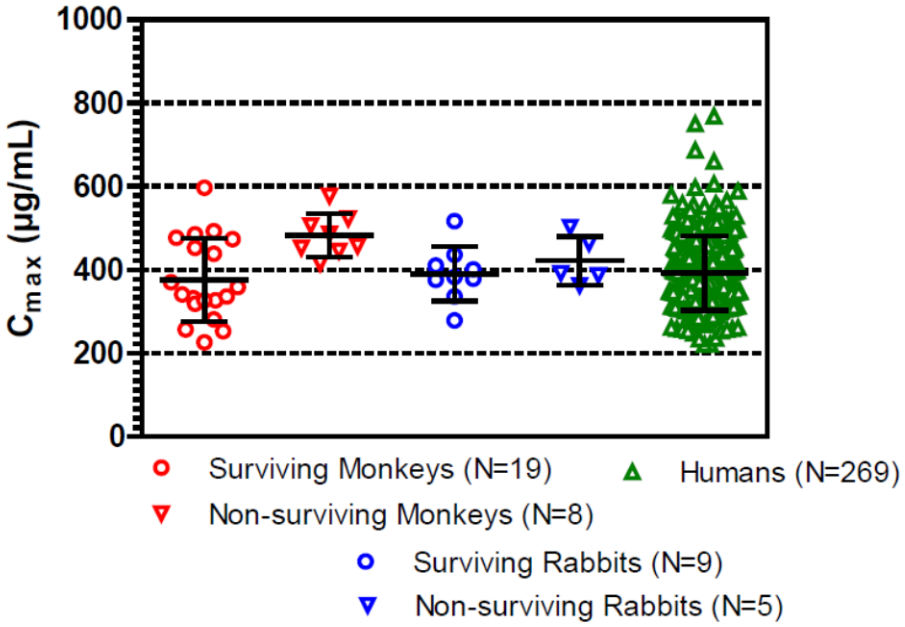
2.2.5.3. How does obiltoxaximab exposure in humans following single 16 mg/kg IV dosing compare to animals with the fully effective dose?

To addresses the sufficiency of the clinical pharmacology data to support the use of a 16 mg/kg obiltoxaximab dose for therapeutic treatment of inhalation anthrax, observed and simulated exposures (serum concentrations, Cmax, and AUC) in humans following a 16 mg/kg dose were compared with rabbits and monkeys following a 16 mg/kg dose (observed data) and following the fully effective dose, 14.5 mg/kg (simulated data).

Comparison of Observed Exposures in Humans (16 mg/kg) versus Animals (16 mg/kg)
A comparison of key human obiltoxaximab exposure parameters to those in rabbits and monkeys following 16 mg/kg single IV dosing is provided in 2.2.5.3-1 and 2.2.5.3-2. Observed obiltoxaximab C_{max} values in humans were comparable to those in both rabbits and monkeys, with overlapping individual values and standard deviation estimates among infected monkeys that survived, infected monkeys that died, infected rabbits that survived, infected rabbits that died, and healthy human subjects. $AUC_{0\text{-}inf}$ values were notably greater in humans than in infected rabbits and monkeys; two individual human $AUC_{0\text{-}inf}$ values fell within the range of individual animal values (Table 2.2.5.3-1). Obiltoxaximab serum

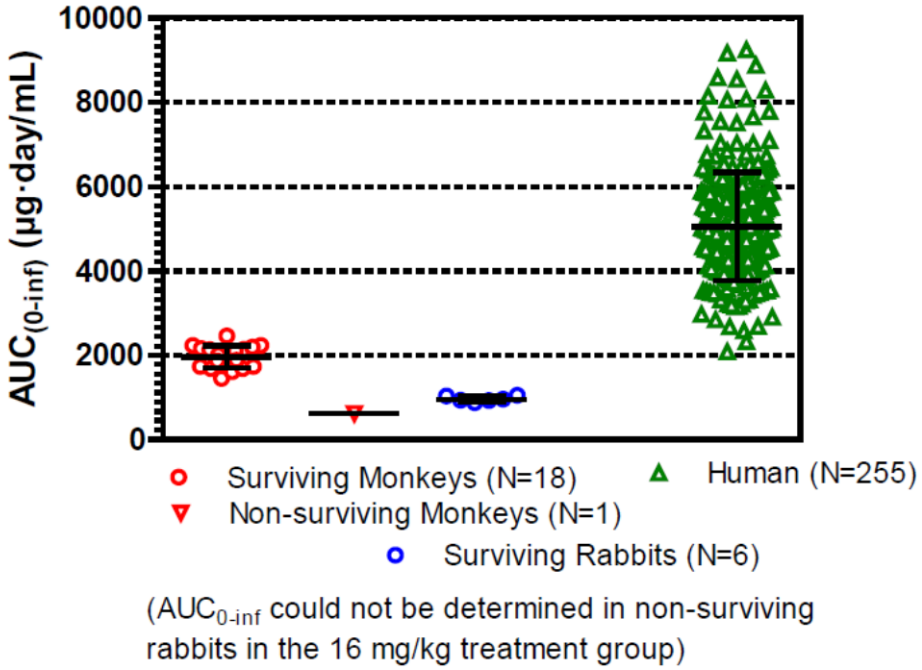
concentrations are sustained at higher levels over a longer period of time in humans than in animals, which is consistent with the longer terminal half-life in humans (~ 20 days) compared to rabbits (~ 2 days) and monkeys (~ 6 days).

Figure 2.2.5.3-1 Obiltoxaximab Cmax Values after a 16 mg/kg IV Dose in Healthy Human Subjects (Studies AH105, AH104, and AH110), Infected Monkeys (Studies AP204 and AP202), and Infected Rabbits (Study AR033)



Source: Section 2.7.2

Figure 2.2.5.3-2 Obiltoxaximab $AUC_{0\text{-inf}}$ Values after a 16 mg/kg IV Dose in Healthy Human Subjects (Studies AH105, AH104, and AH110), Infected Monkeys (Studies AP204 and AP202), and Infected Rabbits (Study AR033)



Source: Section 2.7.2

Table 2.2.5.3-1. Comparison of Observed Obiltoxaximab PK Parameters in Humans (Studies AH105, AH104, AH110), Infected Monkeys (Studies AP204 and AP202), and Infected Rabbits (Study AR033) after a 16 mg/kg IV Dose

		C_{max} (µg/mL)		$AUC_{(0\text{-inf})}$ (µg·day/mL)	
		N	**Mean (SD)**	**N**	**Mean (SD)**
Monkeys	- Survived	19	376 (99.5)	18	1937 (269)
	- Died	8	483 (51.6)	1	613 (NA)
Rabbits	- Survived	9	391 (65.5)	6	958 (66.5)
	- Died	5	422 (52.0)	0	ND
Healthy Humans		269	392 (89.3)	255	5049 (1286)

NA = not applicable; ND = no data

Source: Section 2.7.2

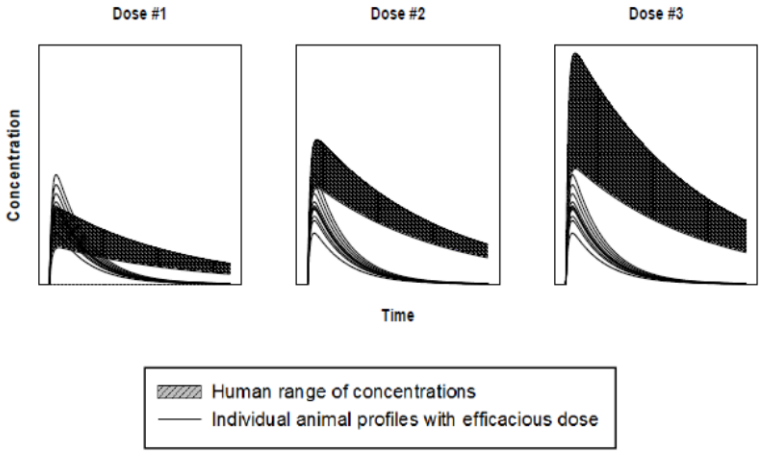
In summary, the observed data show that mean exposures to obiltoxaximab in humans following a single 16 mg/kg IV dose were similar (for Cmax) or greater (for AUCinf) compared to rabbits and monkeys receiving the same dose.

Comparison of Simulated Exposures in Humans (16 mg/kg) versus Animals (14.5mg/kg)

According to the Agency's 'Product Development Under the Animal Rule' Guidance, the exposures in animals resulting from the administration of the fully effective dose should serve as the reference point for choosing the appropriate human dose. Due to the uncertainty as to whether the E/R relationship in humans is similar to the E/R relationship in animals, doses should be selected for humans that provide exposures that exceed those associated with the fully effective dose in animals, ideally by several-fold, if the drug's safety profile allows such dosing. To further minimize the possibility of sub-therapeutic exposures, human dose selection should also take into account the variability of exposure parameters in humans and healthy and affected animals so that any low values of exposure in humans will be greater than those associated with efficacy in animals.

The Guidance includes a set of three PK comparisons between humans and animals to assist in the interpretation of the appropriateness of human dosing when using PK criteria (Figure 2.2.5.3-3). An ideal dose situation is when the full range of human exposure (both Cmax and overall exposure) exceeds the exposures of each animal administered the fully effective dose (Dose #3, right). In contrast, if neither Cmax or AUC in humans exceeds that observed in animals (Dose #1, left), then the proposed human dosing would be considered unacceptable (in the absence of scientific justification). If efficacy is not associated with the drug's Cmax, Dose 2 also represents an acceptable situation.

Figure 2.2.5.3-3. Comparisons of Animal and Human PK Data to Support the Selection of an Effective Dose in Humans



Source: FDA Guidance for Industry: Product Development Under the Animal Rule

The fully effective dose of obiltoxaximab in infected animals was identified via D/R analysis as 14.5 mg/kg based on the independent assessment by the clinical pharmacology review team (See Section 2.2.4.1). Because rabbits achieve similar C_{max} but lower AUC_{inf} than monkeys when the same dose was administered (Table 2.2.5.1-1), simulations were conducted to compare obiltoxaximab concentration-time profiles (Figure 2.2.5.3-4) and to estimate AUC_{inf} and Cmax (Table 2.2.5.3-2) in healthy and infected humans administered single 16 mg/kg IV dose compared to infected cynomolgus monkeys administered the fully effective dose of 14.5 mg/kg. Obiltoxaximab C_{max} in humans (healthy or infected) administered16 mg/kg is comparable to that in infected monkeys administered 14.5 mg/kg. The AUC_{inf} in humans (healthy or infected) administered 16 mg/kg is predicted to exceed that in infected monkeys administered 14.5 mg/kg; however, there is partial overlap of the 5^{th} percentile of human AUC_{inf} with the 95^{th} percentile in

monkey AUC_{inf}. This situation with the proposed obiltoxaximab dose is similar to 'Dose #2' as described in the Guidance (Figure 2.2.5.3-3).

Figure 2.2.5.3-4 Simulated Obiltoxaximab Concentration-Time Profiles in Healthy (Right) and Infected (Left) Humans Administered IV 16 mg/kg Compared to Infected Cynomolgus Monkeys Administered the Fully Effective Dose of 14.5 mg/kg

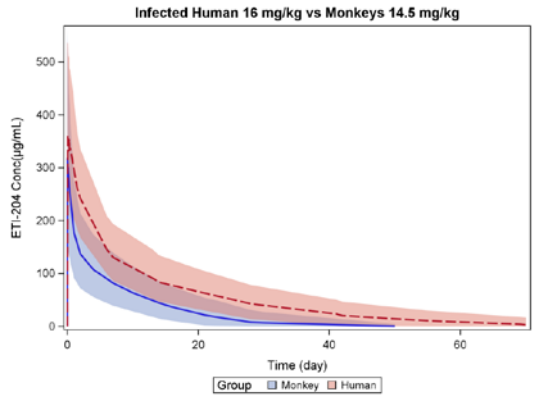
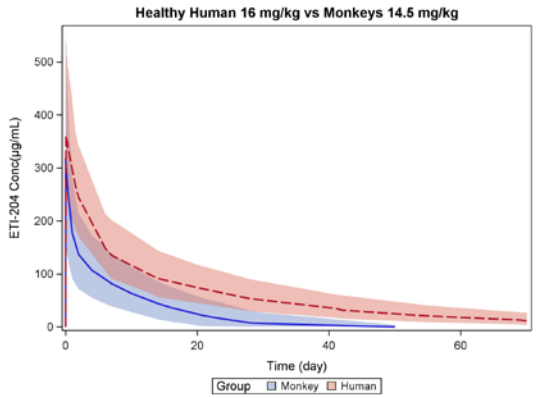
Infected Humans vs. Infected Monkeys	**Healthy Humans vs. Infected Monkeys**
	

Table 2.2.5.3-2. Simulated Obiltoxaximab Exposure in Healthy and Infected Humans Administered 16 mg/kg Compared to Infected Monkeys Administered 14.5 mg/kg

Population	AUC_{inf} (µg.day/mL)			C_{max} (µg/mL)		
	Median	5^{th} percentile	95^{th} percentile	Median	5^{th} percentile	95^{th} percentile
Healthy Humans 16 mg/kg	4893	3119	7528	359	240	536
Infected Humans 16 mg/kg	4068	2393	6507	360	239	535
Infected Monkeys 14.5 mg/kg	2228	1214	3721	318	157	553

As there is partial overlap of AUC_{inf} and C_{max} with 16 mg/kg in humans to those with 14.5 mg/kg in monkeys, further simulations were conducted to compare human exposures with a theoretical dose of 24 mg/kg to monkey exposures with 14.5 mg/kg. As shown in Figure 2.2.5.3-5 and Table 2.2.5.3-3, the full-range of human AUC_{inf} is predicted to exceed that in monkeys. At the 24 mg/kg human dose, the median C_{max} also exceeds that with the fully effective dose in monkeys by ~50%.

Figure 2.2.5.3-5. Simulated Obiltoxaximab Concentration-Time Profiles in Healthy (Right) and Infected (Left) Humans Administered IV 24 mg/kg Compared to Infected Cynomolgus Monkeys Administered the Fully Effective Dose of 14.5 mg/kg

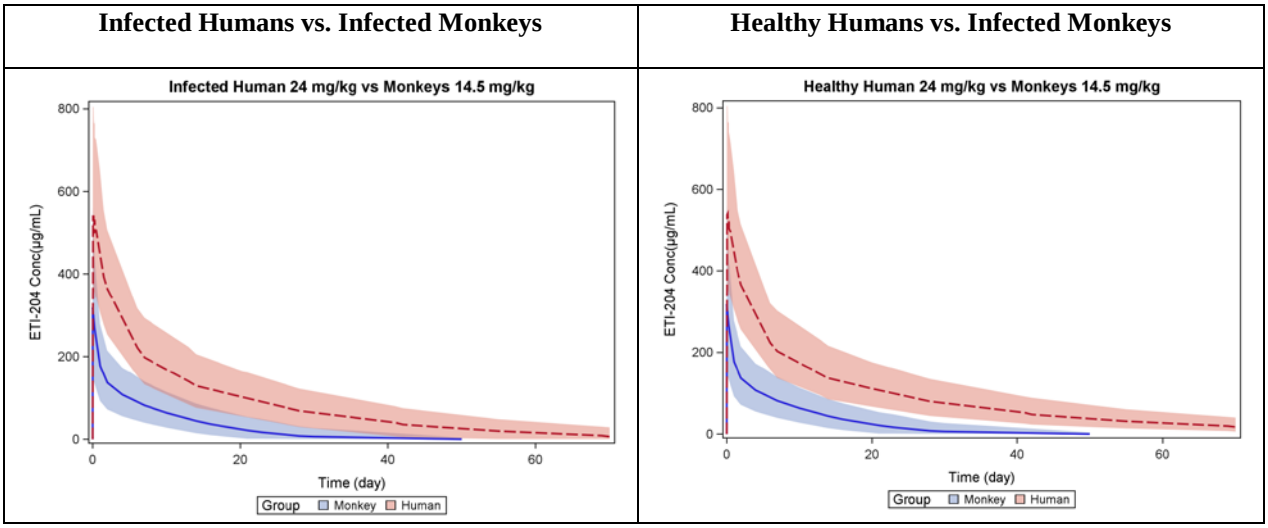


Table 2.2.5.3-3. Simulated Obiltoxaximab Exposure in Healthy and Infected Humans Administered 24 mg/kg Compared to Infected Monkeys Administered 14.5 mg/kg.

Population	AUCinf (µg.day/mL)			Cmax (µg/mL)		
	Median	5th percentile	95th percentile	Median	5th percentile	95th percentile
Healthy Humans 24 mg/kg	7339	4679	11292	538	359	804
Infected Humans 24 mg/kg	6393	3878	10142	540	358	803
Infected Monkeys 14.5 mg/kg	2228	1214	3721	318	157	553

Please refer to Dr. Fang Li's Pharmacometric Review for more details.

2.2.5.4. What are the characteristics of drug absorption?

Description of absorption characteristics is not applicable, as obiltoxaximab is formulated for intravenous administration.

2.2.5.5. What are the characteristics of drug distribution?

The steady state volume of distribution (Vss) for obiltoxaximab in humans is approximately 5.68-7.2 L. Accounting for the differences in body size, the Vss in rabbits, monkeys and humans is similar across species. These values are greater than plasma volume (3 L), but lower than extracellular fluid volume (18 L) in a 70 kg human. This suggests that, across species, obiltoxaximab distributes outside of the vascular compartment, but not extensively, which is consistent with the general distribution pattern of other mAbs.

2.2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not conducted for Obiltoxaximab.

2.2.5.7. What are the characteristics of drug metabolism?

As a monoclonal antibody, obiltoxaximab is expected to be catabolized by proteases to small peptides and amino acids which are subsequently incorporated into the endogenous pool or excreted. No biotransformation studies have been conducted with obiltoxaximab.

2.2.5.8. What are the characteristics of drug excretion?

Obiltoxaximab clearance in humans ranges from 0.225 to 0.313 L/day, which is much smaller than the glomerular filtration rate. Therefore, there is virtually no renal clearance of this monoclonal antibody.

2.2.5.9. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

A linear increase in obiltoxaximab exposures was observed across studies in humans using both investigational and commercial formutions (Studies AH101, AH102, AH105, AH104, AH109, and AH110) (Figures 2.2.5.9-1 and 2.2.5.9-2). The slopes and 90% CIs of the dose and exposure relationship for C_{max} and $AUC_{(0\text{-}inf)}$ (after log transformation) were 0.981 (0.935, 1.027) and 1.01 (0.960, 1.067), respectively.

Figure 2.2.5.9-1 Effect of Increasing Dose of Obiltoxaximab on Obiltoxaximab Cmax

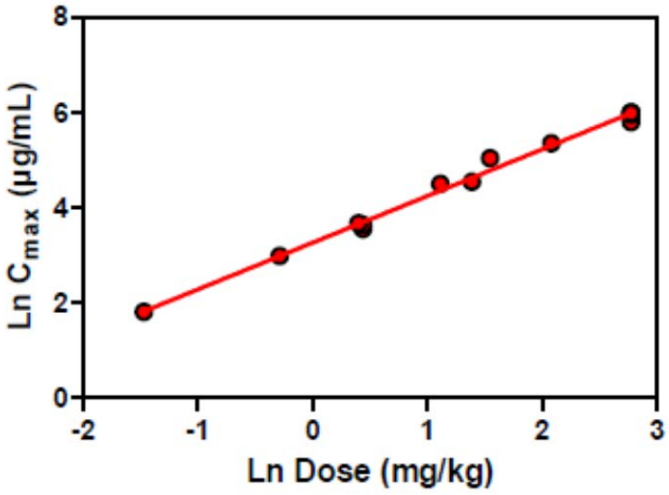
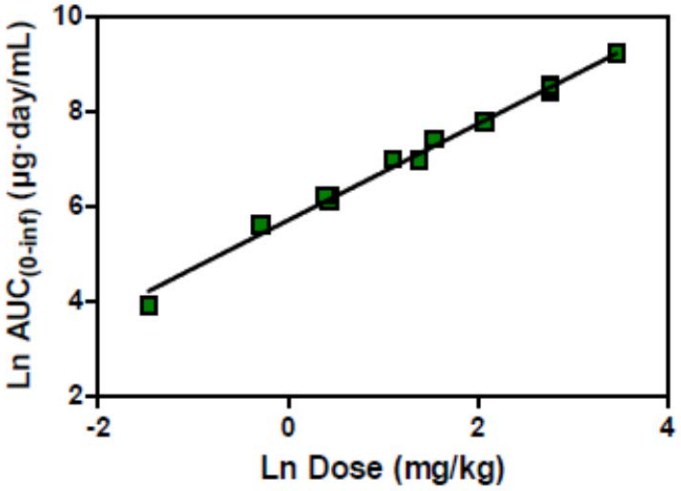


Figure 2.2.5.9-2 Effect of Increasing Dose of Obiltoxaximab on Obiltoxaximab AUCinf



2.2.5.10. How do the PK parameters change with time following chronic dosing?

Obiltoxaximab is intended for single dose administration; therefore the PK of obiltoxaximab following chronic dosing was not evaluated.

2.2.5.11. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Obiltoxaximab exhibited low degree of intersubject variability (22-33% CV) in PK parameters in healthy volunteers. In the population PK analysis, the variability in CL, Vc, and Vp was estimated as approximately 30.2%, 22.7%, and 29.5%, respectively. Evaluation of subject covariates demonstrated that body weight is the most significant covariate contributing to variability in obiltoxaximab PK. Obiltoxaximab clearance increases with increasing body weight such that the clearance for humans with mean body weight of 60 kg was 32% lower than humans with mean body weight of 100 kg. Besides body weight, Caucasians were associated with an 18%

lower clearance compared to non-Caucasians, female subjects had a 14% lower clearance than males, and subjects of age 65 years and older had an 11% lower clearance than subject less than 65 years of age. However, these differences in clearance were not considered to necessitate any dosing adjustments.

2.2.5.12. Does the clinical pharmacology information presented by the applicant support the use of a 16 mg/kg Obiltoxaximab dose for therapeutic treatment of inhalation anthrax?

Simulations show humans (healthy and infected) achieve similar to or greater exposure to obiltoxaximab following a single 16 mg/kg IV dose compared to infected rabbits and monkeys receiving the fully effective dose (14.5 mg/kg). Following a single 16 mg/kg IV dose, median obiltoxaximab C_{max} in humans is similar to that in rabbits and monkeys; median obiltoxaximab AUC_{inf} in humans is at least 2-fold higher than that in rabbits and monkeys. However, there is partial overlap in the range of AUC_{inf} between humans administered 16 mg/kg and monkeys administered 14.5 mg/kg. Simulations 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 monkeys with the fully effective dose (14.5 mg/kg). The situation with the proposed obiltoxaximab dose (16 mg/kg) is similar to 'Dose #2' as described in the Animal Rule Guidance (Figure 2.2.5.3-3) provided that C_{max} is not associated with efficacy.

Based on predicted human PK profiles, the proposed dose of 16 mg/kg in humans would be expected to achieve maximum obiltoxaximab serum concentrations of 1 and 2 orders of magnitude greater than the concentrations required for 99.9% (48 μg/mL) and 99% (4.8 μg/mL) PA neutralization, respectively. Moreover, a molar excess of obiltoxaximab is maintained in serum for 2 to 3 weeks. In addition, more than 95% of humans administered a 16 mg/kg IV obiltoxaximab dose can be expected to achieve serum obiltoxaximab concentrations that are equimolar to or in excess of the highest observed serum PA concentration across all infected rabbits and monkeys (9.67 μg/mL or 153 nM) for more than 3 weeks. The duration of time over which concentrations of obiltoxaximab persist in molar excess relative to PA is critical as it ensures continued neutralization of newly generated or redistributed PA and disrupts disease progression, and allows development of endogenous adaptive immunity. A higher dose would increase the C_{max}; however, once a molar excess is achieved, further increasing C_{max} would not be expected to accrue additional therapeutic benefit.

A risk/benefit assessment was conducted between 16 mg/kg and 24 mg/kg to further evaluate whether the proposed 16 mg/kg is the appropriate dose for obiltoxaximab in humans (Table 2.2.5.12-1). Simulations of obiltoxaximab concentrations in humans indicate a higher dose (i.e., 24 mg/kg) has potential to minimize overlap in exposure with the fully effective dose in animals and decrease uncertainty surrounding the dose-response relationship for survival. However, based on the relationships of dose vs. survival and exposure vs. PA concentrations observed in infected animals, an increase from 16 mg/kg to 24 mg/kg would be expected to achieve minimal improvement in survival in humans. It is worth noting that in the treatment of inhalational anthrax and in response to an anthrax-related emergency, obiltoxaximab will likely be administered concurrently with an antibiotic active against *B. anthracis*; thus, a substantial difference between 16 and 24 mg/kg on obiltoxaximab efficacy against anthrax (if any) is not likely to be evident when coadministered with antibiotics. In addition, hypersensitivity to obiltoxaximab was the greatest safety concern in humans that received 16 mg/kg, and occurred in 3.1% of the safety population; 2.2% had anaphylaxis. Although limited clinical data did not show a correlation between obiltoxaximab dose/exposure and the risk of hypersensitivity, increasing the dose from 16 to 24 mg/kg could potentially increase the risk for hypersensitivity, which may be further

exacerbated in a mass casualty setting (i.e., large number of people; reduced medical supervision). Given the uncertainty of translating animal dose-response data to humans, the partial overlap in the range of AUC_{inf} between humans administered 16 mg/kg and monkeys administered 14.5 mg/kg, together with the unknown typical bacteremia level in humans presenting with clinical anthrax disease, the benefit of administering higher doses in humans is unknown. To support a higher dose (e.g., 24 mg/kg), a pharmacokinetic and safety study in healthy volunteers needs to be conducted at this dose. Given hypersensitivity adverse events observed with the 16 mg/kg dose, such study at a higher dose raises ethical concerns about the safety of study participants.

Taken together, based on risk/benefit considerations, the proposed human dose of 16 mg/kg is acceptable for both treatment and prophylaxis of inhalational anthrax from a Clinical Pharmacology perspective. If future clinical trials are conducted, higher dose (e.g., 24 mg/kg) could be explored provided that such trial is considered ethical to conduct in healthy human subjects.

Table 2.2.5.12-1. Risk/Benefit Assessment of the 16 mg/kg and 24 mg/kg Dose for Obiltoxaximab in Humans

Human Dose (mg/kg)	**RISK**	**BENEFIT**	**ADDITIONAL DATA REQUIRED**
16	Overlapping exposure (5^{th} percentile AUC not exceeding monkey 95^{th} percentile with the fully effective dose)	• Known safety and PK profiles • Based on animal data, minimal increase in survival with higher doses (i.e., plateau of D/R curve)	N/A
24	• Potential increased incidence of hypersensitivity • Hypersensitivity risk may further increase in a mass casualty setting (i.e., large number of people exposed; reduced medical supervision; increased need for emergency management)	• Minimizes overlap in exposure with the fully effective dose in animals • Addresses uncertainty surrounding extrapolation of E/R in animals to humans	Healthy volunteer safety and PK study evaluating 24 mg/kg

2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of intrinsic factors on the pharmacokinetics of obiltoxaximab was explored in the population PK analysis. As anticipated based on experience with other monoclonal antibodies, weight is a significant covariate for obiltoxaximab PK. The applicant has proposed weight-based dosing for obiltoxaximab, thus the impact of this covariate on efficacy and safety responses should be minimal.

2.3.1.1. Elderly

Of the 320 subjects in clinical studies of obiltoxaximab, 9.4% (30/320) were 65 years and over, while 2% (6/320) were 75 years and over. Population PK analysis based on limited data in elderly subjects showed that age was not a significant covariate for obiltoxaximab PK. Thus, no dosage regimen adjustments based on age are recommended.

2.3.1.2. Pediatric patients

Obiltoxaximab has not been studied in children (individuals under 18 years of age). As exposure of healthy children to obiltoxaximab is not ethical, a simulation approach was used to derive IV dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 16 mg/kg. As obiltoxaximab is eliminated by non-specific proteolysis, and a minimal effect of maturation on obiltoxaximab clearance was expected, no maturation effect was included in the simulation model. To perform the pediatric simulations, the adult model was translated to pediatric subjects using the estimated adult weight effect exponents rather than allometric scaling. The Applicant's proposed dose for pediatric patients is based on weight (Table 2.3.1.2-1).

Table 2.3.1.2-1 Applicant Proposed Pediatric Dosing

Pediatric Body Weight	Pediatric Dose
Greater than (b) (4) kg	16 mg/kg
Greater than 15 kg to (b) (4) kg	24 mg/kg
15 kg or less	32 mg/kg

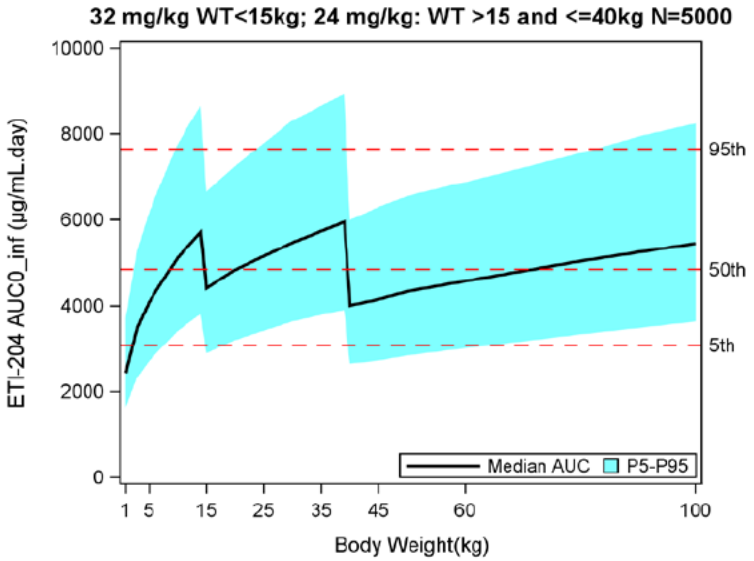
FDA's analysis showed that with the applicant's proposed dosing of (b) (4) mg/kg, median AUC_{inf} in pediatric subjects with body weight (b) (4) kg would be 29% greater than the median AUC_{inf} in adults receiving 16 mg/kg (Figure 2.3.1.2-1). Therefore, it is recommended that pediatrics (and adults) with body weight between (b) (4) kg should be administered 16 mg/kg rather than the applicant's proposed dosing of (b) (4) mg/kg (Table 2.3.1.2-2). Simulations based on FDA's proposed pediatric dose, obiltoxaximab AUC_{inf} in pediatrics would fall within the range of exposures observed and predicted in healthy adults (Figure 2.3.1.2-2).

Figure 2.3.1.2-1

Table 2.3.1.2-2 FDA Recommended Pediatric Dosing

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

Figure 2.3.1.2-2 Simulated Obiltoxaximab $AUC_{0\text{-}inf}$ vs. Body Weight in Healthy Pediatric Subjects (N=5000) Administered Adjusted Dosing Regimen with Comparisons to Healthy Adult Exposures from 16 mg/kg



Please refer to the Dr. Fang Li's Pharmacometric review for details on pediatric dosing.

2.3.1.3. Gender

Population analysis shows that sex does not have a clinically meaningful impact on obiltoxaximab PK and no dosage regimen adjustments based on sex are recommended.

2.3.1.4. Race

Population analysis shows that race (non-Caucasian versus Caucasian) does not have a clinically meaningful impact on obiltoxaximab PK and no dosage regimen adjustments based on race are recommended.

2.3.1.5. Renal impairment

The effect of renal impairment on obiltoxaximab PK has not been investigated. Obiltoxaximab clearance in humans ranges from 0.225 to 0.313 L/day, which is much smaller than the glomerular filtration rate. Therefore, there is virtually no renal clearance of this monoclonal antibody.

2.3.1.6. Hepatic impairment

The effect of hepatic impairment on obiltoxaximab PK has not been investigated. As a monoclonal antibody, obiltoxaximab is expected to be catabolized by proteases to small peptides and amino acids which are subsequently incorporated into the endogenous pool or excreted. As obiltoxaximab disposition is not mediated by hepatic elimination, it is considered unlikely that alterations in hepatic function would have a meaningful impact on obiltoxaximab PK.

2.3.2. Immunogenicity

Approximately 3% (14/470) of subjects were positive for treatment-emergent antitherapeutic antibodies (ATA) after a single obiltoxaximab IV dose. A total of 6% (4/65) human subjects were positive for treatment-emergent ATA in those who received two IV obiltoxaximab doses. Titers ranged from 1:20 to 1:320 and from 1:20 to 1:80 after single and repeat doses, respectively.

In Study AH104 (16 mg/kg single dose) and Study 109 (2 repeated doses administered at 2-week and 4-month intervals), the presence of ATA did not appear to have an impact on obiltoxaximab PK (i.e., CL and $t_{1/2}$) in the individuals who had detectable ATA. The shapes of obiltoxaximab concentration-time profiles in these subjects were not noticeably different from the rest of the subject population. In addition, PK parameters for these subjects were similar with those of the other subjects in the studies, falling within the range of values observed in the PK population.

Overall, the presence of ATA had no discernable effect on obiltoxaximab PK following IV administration in animals or humans. There were no AEs coincident with the development of ATA in human subjects.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response? Based upon what is known about exposure-response relationships

and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors?

Since obiltoxaximab is a mAb, it is not expected that extrinsic factors (such as drugs, herbal products, diet, smoking, and alcohol use) would influence obiltoxaximab exposure-response. Therefore, no dosage adjustments for extrinsic factors are recommended.

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

There is no in vitro basis to suspect in vivo drug-drug interactions with obiltoxaximab.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

As a monoclonal antibody, obiltoxaximab is expected to be degraded into small peptides and individual amino acids. Therefore, it is not expected to be a substrate of CYP enzymes nor have metabolism influenced by genetics.

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

As a monoclonal antibody, obiltoxaximab is not expected to be an inhibitor and/or an inducer of CYP enzymes.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

As a monoclonal antibody, obiltoxaximab is not expected to be a substrate and/or an inhibitor of P-glycoprotein transport processes.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

Since obiltoxaximab is a monoclonal antibody, other metabolic/transporter pathways are not expected to be of importance.

2.4.2.6. Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The DOSAGE AND ADMINISTRATION section of the proposed labeling suggests premedication with (b) (4) diphenhydramine administered (b) (4) prior to obiltoxaximab infusion, due to the possibility of infusion and hypersensitivity reactions. The effect of 50 mg oral diphenyhydramine on obiltoxaximab disposition was evaluated in Study AH104 (Table 2.4.2.6-1). Results showed that no clinically meaningful effect of diphenhydramine pre-treatment on mean obiltoxaximab PK parameter values was observed.

Table 2.4.2.6-1. PK Parameters for Obiltoxaximab following a 16 mg/kg Dose, with or without Diphenhydramine Pretreatment (Study AH104)

Treatment/ Statistic	C_{max} (µg/mL)	T_{max} (d)	$AUC_{(0\text{-last})}$ (µg·d/mL)	$AUC_{(0\text{-inf})}$ (µg·d/mL)	$t_{1/2}$ (d)	CL (L/d)	Vd (L)	Vss (L)
No Pretreatment with Diphenhydramine								
n	60	60	60	58	59	58	58	58
Mean SD[a]	395 (90.5)	0.125 (0.0681-1.00)	4840 (1220)	5300 (1460)	21.0 (4.86)	0.263 (0.0797)	7.56 (1.86)	6.54 (1.64)
Pretreated with Diphenhydramine[b]								
n	142	142	139	133	134	133	133	133
Mean SD[a]	402 (91.8)	0.0750 (0.0674-1.01)	4740 (1130)	5110 (1310)	19.8 (5.41)	0.273 (0.0923)	7.34 (1.92)	6.25 (1.50)

[a]: Median and range are reported for T_{max}
[b]: 50 mg diphenhydramine orally, 30 minutes prior to initiation of ETI-204 infusion

Source: Summary of Clinical Pharmacology Studies, Section 2.7.2

Subjects who received premedication with diphenhydramine were less likely to experience hypersensitivity reactions with administration of obiltoxaximab compared to those who did not receive diphenhydramine. Specifically, the incidence of cough and rash were lower in subjects who received diphenhydramine, but there was no change in the incidence of pruritus or urticaria. Diphenhydramine premedication did not prevent anaphylaxis, but decreased its incidence from 6% in the group that did not receive diphenhydramine, to 1% in the group that did. Premedication with diphenhydramine (b) (4) prior to administering obiltoxaximab is recommended.

Please refer to Dr. Ramya Gopinath's Clinical Safety Review for detailed information regarding the use of diphenhydramine with obiltoxaximab infusion.

2.4.2.7. What co-medications are likely to be administered to the target patient population?

In the course of treatment of a *Bacillus anthracis* infection and in response to an anthrax-related emergency, obiltoxaximab will likely be administered concurrently with a fluoroquinolone antibiotic active against *Bacillus anthracis*. To assess the effect of co-administration of the fluoroquinolone antibiotic on obiltoxaximab pharmacokinetics, the applicant conducted a Phase 1 drug interaction study with ciprofloxacin in healthy subjects (AH110).

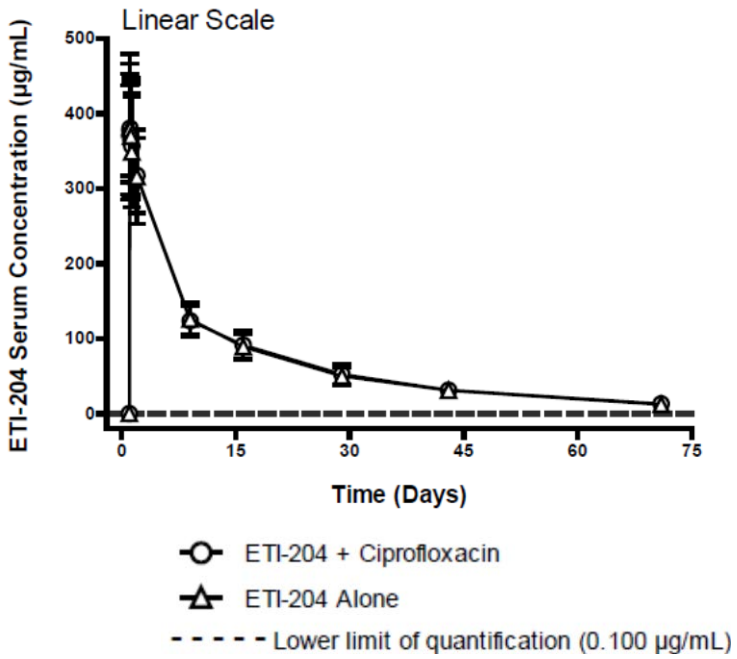
AH110 is a Phase 1, single center, randomized, open-label, parallel group study conducted in healthy adult subjects. A 16 mg/kg IV dose of obiltoxaximab was administered alone and in the presence of IV and oral ciprofloxacin in 40 adult volunteers randomized in a 1:1 ratio to either:

• Group 1: IV obiltoxaximab (16 mg/kg) followed by IV ciprofloxacin (400 mg) on Day 1, followed by oral ciprofloxacin (750 mg BID) on Days 2-8, with the final 750 mg dose administered on the morning of Day 9
• Group 2: IV obiltoxaximab alone (16 mg/kg)

The mean obiltoxaximab serum concentration vs time profiles were biexponential in appearance in both groups, and were virtually superimposable in the presence and absence of ciprofloxacin PO or IV in healthy humans (Figure 2.4.2.7-1). The disposition of obiltoxaximab was similar in

subjects who received obiltoxaximab alone and those who received obiltoxaximab with ciprofloxacin. Co-administration of ciprofloxacin did not have a meaningful impact on the disposition of obiltoxaximab.

Figure 2.4.2.7-1. Mean (± SD) Serum Concentration-Time Profiles for Obiltoxaximab Following Single Intravenous Administration of 16 mg/kg with and without Ciprofloxacin PO or IV in Healthy, Male and Female Subjects



Source: AH110 Study Report, Section 11.2.1

The disposition of ciprofloxacin after a single 400 mg IV dose in Study AH110 was generally similar to that described in the literature. Mean $t_{1/2}$, CL, and Vss values reported by one group following a single 300 mg or 400 mg IV ciprofloxacin dose (Lettieri, et al, 1992) were within the range of values observed in the present study. The mean $AUC_{(0\text{-inf})}$ reported in the literature after a 400 mg IV dose was also within the range of values observed in Study AH110. Following multiple oral dosing, ciprofloxacin appeared to be at steady-state by Day 9 in Study AH110. Ciprofloxacin PK after multiple, twice-daily 750 mg oral doses in Study AH110 was generally comparable to that described in literature.

In summary, co-administered ciprofloxacin had no meaningful impact on obiltoxaximab disposition; a 16 mg/kg IV infusion dose of obiltoxaximab did not appear to have an significant effect on the PK of ciprofloxacin given as a single-dose IV infusion or given orally twice daily to steady-state.

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

There are no in vivo drug interaction studies that indicate exposure or E/R relationships are different when the drugs are co-administered.

2.4.2.9. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for pharmacodynamic drug-drug interactions.

2.4.2.9.1. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved issues related to metabolism, active metabolites, metabolic drug interactions or protein binding for this monoclonal antibody.

2.4.3. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Simulations of obiltoxaximab concentrations in humans indicate a higher dose (i.e., 24 mg/kg) may have the potential to minimize overlap in exposure with the fully effective dose in animals and decrease uncertainty surrounding the dose-response relationship for survival. If future clinical trials are conducted, higher doses (e.g., 24 mg/kg) could be explored provided that such trial is considered ethical to conduct in healthy human subjects.

2.5. General Biopharmaceutics

Not applicable.

2.6. Analytical Section

This section summarizes the bioanalytical method utilized to assess therapeutic protein concentrations. Details for the bioanalytical methodology used to determine ciprofloxacin plasma concentrations in Study AH110 are presented in the individual study review in Section 4.1.

2.6.1. What bioanalytical methods are used to assess the therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

Obiltoxaximab concentrations in serum of rabbits were quantified by validated Meso-Scale Discovery electrochemiluminescence assays (MSD-ECL). Obiltoxaximab concentrations in serum of monkeys and humans were quantified by validated enzyme-linked immunosorbent assays (ELISA). Primary analysis was conducted by comparing obiltoxaximab exposures in humans to monkeys, both using ELISA as the bioanalytical method. Therefore, cross-validation of MSD-ECL and ELISA is not considered to be necessary. Obiltoxaximab is a monoclonal antibody and is expected to be degraded into small peptides and individual amino acids. Therefore, no metabolites were measured.

Assay specifics and performance are summarized in Table 2.6.1-1.

Table 2.6.1-1. Qualification and Performance of Bioanalytical Assays Used to Quantify Obiltoxaximab Concentrations

Method (Studies)	(b) (4) 12-093 (Study AR033)	11-035 (Study AP 201, 202, 203, and 204)	11-094 and 11-069 (Studies AH104,109, and 110)
Description	Rabbit PK assay (MSD-ECL)	Monkey PK assay (ELISA)	Human PK assay (ELISA)
LLOQ (ng/mL)	50	100	100
ULOQ (ng/mL)	6000	5000	5000

Linearity Range (ng/mL)	50 – 6000	100 – 5000	100 – 5000
Dilutional linearity	-	1:8000	1:500
Intra-assay Accuracy (%bias)	-20.7 to 6.7	-1.7 to 6.8	-2.4 – 4.7
Inter-assay Accuracy (%bias)	-6.8 to -2.3	-1.6 to 6.7	-2.4 – 4.7
Intra-assay precision (%CV)	1.4 to 16.3	6.5 to 10.9	4.1 – 15.2
Inter-assay precision (%CV)	6.2 to 9.6	6.8 to 12.2	4.4 – 15.2

LLOQ, lower limit of quantitation
ULOQ, upper limit of quantitation

2.6.1.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The range of the standard curve was determined using accuracy and precision data from all obiltoxaximab concentrations. The highest and lowest values that met the acceptable total error were assigned as the ULOQ and LLOQ and thus define the range (see Table 2.6.1-1). The fitted standard curve was used to interpolate obiltoxaximab concentrations of all validation samples using a fixed weighted 5-parameter logistic algorithm.

The ranges of standard curves and dilution linearity for the rabbit, monkey and human assays are adequate for purposes of determining serum concentrations of obiltoxaximab in the pivotal animal and clinical studies.

2.6.1.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Refer to Table 2.6.1-1 for the LLOQ and ULOQ for each obiltoxaximab assay.

2.6.1.3. What are the accuracy, precision, and selectivity at these limits?

Refer to Table 2.6.1-1 for the accuracy and precision for each obiltoxaximab assay.
Matrix components can potentially interfere with the antibody binding. Therefore, the potential for variable matrix-related interferences was evaluated in eight independent sources of Normal Human Serum at 300 and 3,000 ng/mL for three reportable results per concentration for each lot of matrix. For all eight lots of Normal Human Serum tested, lot precision for each concentration, 300 and 3,000 ng/mL, was within the acceptance criteria of ≤ 20%, and ranged from 1.5% to 14.6%. The accuracy for all eight lots for each concentration was within the acceptance criteria of ± 20% of the nominal, ranging from -12.1% to 6.4%.

2.6.1.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Obiltoxaximab was stable for 24 hours at ambient temperature and at 2° to 8°C, over 8 freeze/thaw cycles at -20°C, -60°C and -85°C, and for 24 months at -70°C.

2.6.1.5. What is the QC sample plan?

Three positive controls were included, as follows: 150, 2400, and 4800 ng/mL for rabbits; 200, 1000, and 4000 ng/mL for monkeys; 300, 1500, and 4000 ng/mL for humans.

2.6.2. What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and summarize the assay performance, including sensitivity, specificity, precision, cut point, interference and matrix, etc.

To detect antitherapeutic antibodies (ATA), a binding antibody tiered approach is used that included an initial screening assay followed by confirmatory assay. For ATA detection, an ECL-based bridging ELISA assay was used. An acid dissociation step is used to enhance the sensitivity of the assay prior to the ELISA. The sensitivity of the screening assay was determined to be 27 ng/mL. A sample containing 500 ng/mL ATA (affinity purified rabbit anti- obiltoxaximab) is shown to detect antibodies to obiltoxaximab in the presence of obiltoxaximab levels of up to 50 μg/mL. Overall, the ADA screening assay is considered to be suitable for the intended use.

The sponsor also developed a cell-based assay to detect neutralizing antibody (NAb assay) response to obiltoxaximab. However, this assay was found to be very sensitive to the presence of drug in the patients' samples. The tolerance of the NAb assay for obiltoxaximab was shown to be approximately 1000 ng/mL and 500 ng/mL for high ATA and low ATA positive controls. These levels are below obiltoxaximab serum concentration that is expected to be present in the patients' immunogenicity samples. Therefore this assay is not considered suitable for the intended use.

Please refer to Dr. Tao Xie's review (Office of Biotechnology Products [OBP]) for more details.

Treatment-emergent antitherapeutic antibodies (ATA), defined as ATA observed at any time from the start of study drug infusion through the last visit, were observed in 3% (14/470) of subjects following a single obiltoxaximab IV dose. The presence of ATA does not appear to have discernable effect on obiltoxaximab PK following IV administration humans. Therefore, the lack of suitability of Nab assay is not considered to affect the obiltoxaximab PK results or interpretations.

3. REFERENCES

John T. Lettieri, et al., *Pharmacokinetic Profiles of Ciprofloxacin after Single Intravenous and Oral Doses.* Antimicrobial Agents and Chemotherapy, May 1992, p. 993-996.

Conrad P. Quinn, et al., *Immune Responses to Bacillus anthracis Protective Antigen in Patients with Bioterrorism-Related Cutaneous or Inhalation Anthrax.* The Journal of Infectious Diseases 2004; 190:1228–36.

James J. Walsh, et al., *A Case of Naturally Acquired Inhalation Anthrax: Clinical Care and Analyses of Anti–Protective Antigen Immunoglobulin G and Lethal Factor*. Clinical Infectious Diseases 2007; 44:968–71.

4. APPENDICES

4.1. Individual Study Reviews

AH104:
A Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Dose of ETI-204 in Adult Volunteers

Date(s): July 9, 2013– November 29, 2013
Sponsor: Elusys Therapeutics, Inc.
Clinical Site: 4 Covance study centers in Florida, Texas, Indiana, and Wisconsin
Analytical Site: (b) (4)

OBJECTIVES:
The primary objective of the study was to evaluate the safety and tolerability of a single IV dose of ETI-204.

Secondary objectives of the study were:
• To evaluate the PK of a single IV dose of ETI-204
• To evaluate the immunogenicity of a single IV dose of ETI-204

STUDY DESIGN:
This was a Phase 1, double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety, tolerability, PK, and immunogenicity of ETI-204 in adult subjects. Approximately 280 females or males ≥ 18 years of age were to be randomized in a randomized block design in a 3:1 ratio to receive one of the following treatments:

• A single 16 mg/kg IV dose of ETI-204 (~210 subjects)
• Matching placebo (~70 subjects)

Following completion of a Screening visit during the Screening period (Day -28 to Day -2), subjects arrived at the clinical research unit on Day -1 (note: there was no Day 0 in this study). On Day 1, eligible subjects were randomized to receive either ETI-204 or matching placebo (3:1) and study treatment was administered. Subjects were discharged from the clinical research unit on Day 2 following completion of study assessments and returned to the clinical research unit for five additional visits on Days 8 (±2 days), 15 (±3 days), 29 (±3 days), 43 (±3 days), and 71 (±4 days). The total duration of each subject's participation in the study was approximately 100 days.

FORMULATIONS:
ETI-204 was supplied in sterile, (b) (4)-mL, clear, (b) (4) glass vials with gray stoppers that contained (b) (4) mL of clear, colorless to pale yellow solution consisting of 100 mg/mL ETI-204, 40 mM histidine, 200 mM sorbitol, and 0.01% polysorbate 80 with a pH of 5.5. Translucent particles may have been present. Matching placebo contained the same inactive components as ETI-204 and was provided in the same type vials as ETI-204.

ETI-204 bulk drug substance was manufactured, packaged, and labeled in accordance with current Good Manufacturing Practices at Lonza Biologics, Portsmouth, NH. Final drug product and placebo were manufactured, packaged, and labeled in accordance with current Good Manufacturing Practices at (b) (4). The ETI-204 and placebo lots used for this study were 3-FIN-1513 and 3-FIN-1491, respectively.

INCLUSION/EXCLUSION CRITERIA:
Healthy males and females of non-childbearing potential of ≥18 years of age without restrictions for body weight, body mass index, and smoking were enrolled.

DOSE AND ADMINISTRATION
Single doses of 16 mg/kg ETI-204 were administered via IV infusion (total volume of 250 mL) over 90 minutes (± 5 minutes) at a rate of approximately 3 mL/min using a Primary PlumSet™ infusion set with a 0.2 micron in-line filter and an appropriate infusion pump. 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 Day 1.

PHARMACOKINETIC ASSESSMENTS:
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.

IMMUNOGENICITY ASSESSMENTS:
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.

BIOANALYTICAL ANALYSIS:
Serum samples were analyzed for ETI-204 at (b) (4) , using a validated enzyme-linked immunosorbent assay method with an assay range of 100 ng/mL to 5000 ng/mL (Table 1). Recombinant anthrax protective antigen (rPA83) was used as the capture reagent; sheep anti-human IgG(Fc) HRP (monkey adsorbed) peroxidase conjugate was used as the detection reagent.

Table 1. Bioanalytical results of ETI-204 in serum (Bioanalytical study report 13-180)

Criterion	ETI-204	Comments
Calibration Range	100-5000 ng/mL	Satisfactory
LLOQ	100 ng/mL	Satisfactory
ULOQ	5000 ng/mL	Satisfactory
Linearity, mean R^2	Not reported	N/A
Accuracy	Within ±1.8%	Satisfactory
Precision, CV	≤7.2%	Satisfactory
Quality Control	300, 1500, 4000 ng/mL	Satisfactory
Accuracy (%RE)	Within ±8%	Satisfactory
Precision, CV	≤13 %	Satisfactory
Stability	• Samples were analyzed within 288 days of collection • Stability: 24 month at -70 ºC	Satisfactory

PHARMACOKINETIC/PHARMACODYNAMIC/STATISTICAL ANALYSIS:
PK parameters included maximum concentration (C_{max}); time to reach C_{max} (T_{max}); area under the concentration-time curve (AUC) from time 0 to 10 days ($AUC_{0\text{-}10\ days}$); AUC from time 0 to the

time of last measurable concentration ($AUC_{0\text{-last}}$); AUC from time 0 extrapolated to infinite time ($AUC_{0\text{-inf}}$); mean residence time from time 0 extrapolated to infinite time ($MRT_{0\text{-inf}}$); terminal half-life ($t_{½}$); systemic clearance (CL); CL divided by weight (CL/kg); volume of distribution (Vd); Vd divided by weight (Vd/kg), volume of distribution at steady state (Vss), and Vss divided by weight (Vss/kg).

The PD parameter was anti-therapeutic antibodies (ATA); exploratory PD parameters included cytokines (interleukin [IL]-β, IL-2, IL-6, tumor necrosis factor-alpha [TNF-α], and interferon gamma [IFNγ]) and IgE and plasma histamine levels.

PK parameters were summarized descriptively (mean, arithmetic standard deviation, arithmetic coefficient of variation, median, minimum, maximum, geometric mean, and number). PD and safety data were also summarized descriptively using the summary statistics noted above for PK parameters (except for geometric mean) or frequency counts and percentages. PK parameters and AEs were analyzed for the overall population and for the following subgroups: age (≤ 65 years of age, > 65 years of age), gender, race, body mass index [BMI] (above and below the median), renal function (above or below median CrCl; PK parameters only), and diphenhydramine pretreatment (with or without).

RESULTS:

Study Population

Overall, 280 subjects were randomized: 210 to the ETI-204 group and 70 to the placebo group. All subjects received study drug and were included in the Safety Population. Overall, 202 subjects in the ETI-204 group were included in the PK population. One subject was excluded from the PK population because the dosing record was missing and 7 subjects were excluded because they received a partial dose of ETI-204.

Demographics

A summary of demographic and baseline characteristics for the study population is presented in Table 2. There were no substantial differences in demographic characteristics between the study groups. After protocol amendment 1, 50 mg oral diphenhydramine was a required premedication before study drug infusion. The majority of subjects (ETI-204, 70.0% and placebo, 68.6%) in both groups were premedicated with diphenhydramine before study drug infusion.

Table 2. Demographics and Baseline Characteristics – Study AH104

	16 mg/kg ETI-204 N=210	Placebo N=70	Overall N=280
Age (years)			
n	210	70	280
Mean	42.4	41.5	42.2
SD	15.59	13.90	15.17
Median	43.0	40.0	42.0
Min	18	20	18
Max	79	78	79
Gender, n (%)			
Male	106 (50.5%)	38 (54.3%)	144 (51.4%)
Female	104 (49.5%)	32 (45.7%)	136 (48.6%)
Race, n (%)			
White	151 (71.9%)	44 (62.9%)	195 (69.6%)
Black or African American	53 (25.2%)	23 (32.9%)	76 (27.1%)
Asian	3 (1.4%)	2 (2.9%)	5 (1.8%)
Other	3 (1.4%)	1 (1.4%)	4 (1.4%)
Ethnicity, n (%)			
Hispanic or Latino	20 (9.5%)	9 (12.9%)	29 (10.4%)
Not Hispanic or Latino	189 (90.0%)	61 (87.1%)	250 (89.3%)
Unknown	1 (0.5%)	0 (0%)	1 (0.4%)
Body Weight (kg)			
n	210	70	280
Mean	81.15	77.62	80.27
SD	17.853	13.554	16.927
Median	79.20	75.90	78.70
Min	48.4	55.4	48.4
Max	149.5	110.6	149.5
Height (cm)			
n	210	70	280
Mean	170.95	169.18	170.50
SD	8.997	8.657	8.931
Median	170.40	169.85	170.25
Min	149.5	153.0	149.5
Max	194.8	187.0	194.8
BMI (kg/m2)			
n	210	70	280
Mean	27.73	27.11	27.57
SD	5.643	4.343	5.347
Median	26.90	26.30	26.85
Min	18.1	19.4	18.1
Max	52.3	43.8	52.3
Percent Body Fat (%)			
n	210	70	280
Mean	28.75	27.39	28.41
SD	8.617	8.805	8.668
Median	30.00	28.40	29.75
Min	8.1	11.2	8.1
Max	45.1	42.0	45.1

Note: Values for height are from Screening; weight, BMI, and % body fat are from Day -1.
N = number of subjects randomized; n = number of subjects in a given category.

Source: AH104 Pharmacokinetic Report, Section 10.3

ETI-204 Serum Pharmacokinetics

Data Excluded From Analysis

Of the 210 subjects who received ETI-204, 202 were included in the PK population. The dosing record for Subject 001-026 was missing, which prevented accurate determination of PK parameters. Concentration data for Subject 001-026 were reported, but were excluded from summary statistics; PK parameters were not calculated for this individual. Seven subjects received partial doses of ETI-204 (Subjects 002-053, 002-068, 002-350, 003-101, 003-107, and 003-258 discontinued study drug due to an AE and Subject 002-062 received a partial dose because of mechanical issues with the infusion pump) and were excluded from the PK population. Concentration data and PK parameters for subjects who received a partial dose of ETI-204 were reported, but were excluded from summary statistics.

ETI-204 Serum Concentrations and PK Parameters
Of 70 individuals in the placebo group, three had measurable ETI-204 in their predose sample (001-032, 001-166, and 003-266), two of whom (001-032 and 003-266) also had measurable ETI-204 in the end-of-infusion sample. Reported concentrations in placebo subjects (0.101 to 0.695 μg/mL) were near the assay LLOQ (0.1 μg/mL). All other samples from subjects that received placebo were BLQ.

In subjects who received ETI-204, measurable ETI-204 concentrations were observed in the predose serum sample in 13 subjects from the PK population (001-170, 002-054, 002-064, 002-208, 002-226, 002-229, 003-086, 003-104, 003-261, 004-148, 004-156, 004-304, and 004-316) and 1 subject who received a partial ETI-204 dose (002-350). In these subjects, predose ETI-204 concentrations ranged from 0.102 to 0.399 μg/mL in 13 subjects, which was within 4 times the assay LLOQ and was 4.85 μg/mL in Subject 003-104.

The sponsor stated that the measurable predose concentrations in the PK population were considered to have had a negligible effect on calculated PK parameter values as the reported concentrations were only 0.024% to 0.090% of the concentration at the subsequent time point (end of infusion) in 12 subjects and was only 1.17% of the end-of-infusion value in Subject 003-104. The Sponsor also stated that measurable levels in the predose and placebo samples could not be attributed to an issue with the bioanalytical method. The 17 ETI-204-positive predose samples represent approximately 6% of all predose serum samples collected, which is within the acceptable range that was established during assay validation. For the ETI-204 assay, selectivity was observed in 9 of 10 samples (10% nonselectivity). The Sponsor concluded that 6% positive predose incidence is within the 10% nonselectivity rate observed during ETI-204 method validation and within the acceptable industry standard nonselectivity rate (20%).

Reviewer Comment: There is no information regarding the specific selectivity criteria of a ligand-binding assay provided in the FDA draft Guidance for Industry-Bioanalytical Method Validation. Per the European Medicines Agency (EMA) Guideline on bioanalytical method validation, Selectivity is tested by spiking at least 10 sources of sample matrix at or near the LLOQ. Selectivity should be evaluated at the low end of an assay where problems occur in most cases. It may be prudent also to evaluate selectivity at higher analyte concentrations. The accuracy should be within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated.

In the Sponsor's bioanalytical assay validation report (09-004), the potential for variable matrix-related interferences was evaluated in eight independent sources of Normal Human Serum at the targeted LQC (300 ng/mL) and HQC (3,000 ng/mL) concentrations. For all eight lots of Normal Human Serum tested, lot precision for each concentration, LQC (300 ng/mL) and HQC (3,000 ng/mL), was within the acceptance criteria of ⩽20%, and ranged from 1.5% to 14.6%. The accuracy for all eight lots for each concentration was within the acceptance criteria of ± 20% of the nominal, ranging from -12.1% to 6.4%. In the Sponsor's bioanalytical assay validation report (11-069), the validation acceptance criteria for selectivity were set by the Sponsor as follows: ± 20% relative error (RE) of Nominal Value for at least 80% of samples; unspiked sample < LLOQ. The potential for variable matrix-related interferences was evaluated in 10 lots of Normal Human Serum at 0 ng/mL (unspiked) and low QC (300 ng/mL) concentrations. Results showed that 8 out of 10 (80%) of the matrix lots initially evaluated were within the acceptance criteria for %RE<20%; 9 of 10 (90%) of the unspiked samples were < LLOQ.

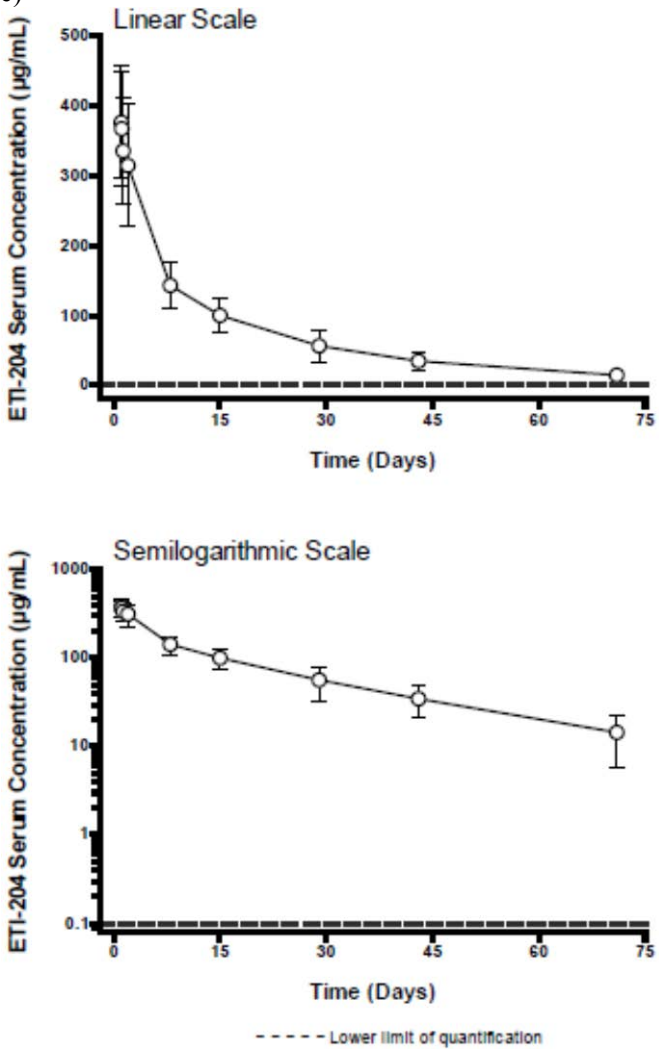
The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH104 was 6%, which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, in the placebo group, the positive predose concentrations ranged from 0.101 to 0.695 μg/mL, which were near the assay LLOQ (0.1 μg/mL); in the ETI-204 group, the positive predose concentrations ranged from 0.102 to 0.399 μg/mL in 12 subjects, and was 4.85 μg/mL in Subject 003-104, representing 0.024% to 0.090% of the concentration at the subsequent time point (end of infusion) in 12 subjects and 1.17% of the end-of-infusion value in Subject 003-104. From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204. The adequacy of the ELISA assay of ETI-204 will be further assessed pending results of inspection of the corresponding bioanalytical site (b) (4) .

Mean (± SD) ETI-204 concentration versus time data are presented for the PK population across the sampling time course in Figure 1. Pharmacokinetic parameters for ETI-204 following single intravenous administration of 16 mg/kg in healthy subjects are summarized in Table 3.

The mean ETI-204 serum concentration versus time profile was biexponential in appearance, with the terminal phase beginning between Days 7 and 14. Mean ETI-204 C_{max} was 400 μg/mL and mean AUC_{0-10} days was 2020 μg*day/mL. ETI-204 attained maximum serum concentrations at or after the end of the 1.5-hour infusion. In the great majority of subjects (92.6%, n=187), T_{max} occurred at no later than 0.340 days (8.16 hours) and in the remaining subjects (7.4%, n=15), T_{max} was approximately 1 day. Overall,
Tmax ranged from 0.0674 to 1.01 days (1.62 to 24.2 hours) after the beginning of ETI-204 infusion. Median Tmax was 0.0782 days (1.88 hours), which approximated the end of the infusion time. CL ranged from 0.107 to 0.731 L/day, with a mean of 0.270 L/day. This is less than 0.02% of hepatic or renal blood flow (2100 and 1800 L/day, respectively) and less than 0.2% of the glomerular filtration rate (180 L/day) in a 70 kg human, which suggests that the fraction of administered ETI-204 eliminated by the liver or unchanged via the kidney is negligible. Mean Vss was 6.34 L, ranging from 3.16 to 12.7 L. This is greater than human plasma volume (3 L), but lower than extracellular fluid volume (18 L), suggesting that ETI-204 may distribute out of the vascular compartment, but not extensively.

Intersubject variability in PK was moderate, with CV values across parameters ranging from approximately 22% to 33%. Based on subgroup comparisons, there was no notable effect on ETI-204 disposition conferred by age (≤ 65 years of age vs > 65 years of age), gender, race (White versus Asian vs black or African American vs other), BMI (<26.90 kg/m^2 versus ≥ 26.90 kg/m^2), renal function (< 122.9 mL/min versus ≥ 122.9 mL/min), or diphenhydramine pretreatment (yes vs no).

Figure 1. Mean (± SD) Serum Concentration-Time Profiles for ETI-204 Following Single Intravenous Administration of 16 mg/kg in Healthy Subjects (Linear and Log Scale)



Source: AH104 Pharmacokinetic Report, Section 11.2

Table 3. Summary of ETI-204 Pharmacokinetic Parameters Following Single Intravenous Administration of 16 mg/kg IV in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg-day/mL)	$AUC_{(0\text{-inf})}$ (µg-day/mL)	$AUC_{(0\text{-10 days})}$ (µg*day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)	Vss (L)
N	202	202	199	191	202	193	191	191	191
Mean	400	0.178	4770	5170	2020	20.2	0.270	7.41	6.34
SD	91.2	0.243	1160	1360	448	5.26	0.0886	1.90	1.55
CV%	22.8	NC	24.3	26.2	22.1	26.1	32.8	25.6	24.4
Min	221	0.0674	2070	2080	1160	6.60	0.107	2.30	3.16
Median	390	0.0782	4690	5050	2000	19.9	0.256	7.30	6.19
Max	769	1.01	8230	9240	4470	34.3	0.731	14.0	12.7
Geometric mean	390	NC	4630	4990	1980	19.5	0.257	7.16	6.15

NC: not calculated

Source: AH104 Pharmacokinetic Report, Section 11.3

Pharmacodynamics

Two subjects (1.0%) in the ETI-204 group and no subjects in the placebo group had treatment-emergent antitherapeutic antibody (ATA). The presence of ATA did not appear to have an impact on ETI-204 disposition in these individuals. The shapes of the ETI-204 concentration-time profiles in these subjects were not noticeably different from the rest of the subject population and did not display evidence of nonlinearity. In addition, PK parameters for both subjects were consistent with those of the other subjects in the study, falling within the range of values observed in the PK population. Both subjects reported AEs before the development of ATA (rash, papule, and mood disorder in Subject 001-160; dermatitis in Subject 003-271); no AEs were associated with the development of ATA. IL-6 and TNF-α levels were similar in the ETI-204 and placebo groups before study drug infusion, at the end of study drug infusion, and on Day 8. In the ETI-204 group, levels of IFN-γ, IL-1B, and IL-2 were also similar before and following study drug infusion; these cytokines were below the limit of quantification in the placebo group.

Reviewer Comment: Please refer to the OBP review for the assessment of ETI-204 immunogenicity following a single IV dose of 16 mg/kg.

SAFETY RESULTS

No deaths were reported during the study. One subject in the placebo group had an SAE of moderate ovarian cyst. Six subjects (2.9%) in the ETI-204 group and no subjects in the placebo group permanently discontinued study drug before infusion completion because of an AE. The most frequent AEs leading to discontinuation of study drug included cough (3 subjects), urticaria (3 subjects), pruritus (3 subjects), rash (2 subjects), and throat irritation (2 subjects). The percentage of subjects with at least one AE was similar in the ETI-204 (41.9%) and placebo (38.6%) groups. The most frequently reported AEs in the ETI-204 group were headache (ETI-204, 10.0%; placebo, 5.7%), pruritus (ETI-204, 4.8%; placebo, 1.4%), and vessel puncture site bruise (ETI-204, 3.3%; placebo, 1.4%). Most AEs were mild or moderate. Two severe AEs occurred. Subject 002-053 in the ETI-204 group had severe pruritus and severe urticaria.

Reviewer Comment: Please refer to the Clinical Review by Dr. Gopinath, Ramya for safety assessment of ETI-204 following a single IV dose of 16 mg/kg.

APPLICANT'S DISCUSSION
Study AH104 was a double-blind, randomized, placebo-controlled, multicenter study designed to evaluate the safety, tolerability, PK, and immunogenicity of a 16 mg/kg dose of ETI-204 administered as a 90 minute IV infusion to male and female adult subjects.

PK results were consistent with expectations based upon previous studies and were not impacted by age, gender, race, BMI, renal function, or diphenhydramine premedication. All samples collected from subjects in the PK population (n=202 subjects) from the end of study drug infusion through Day 71 had quantifiable ETI-204 concentrations, except the Day 71 sample in one subject (BLQ). Having measurable ETI-204 concentrations at the terminal sampling point didn't compromise the determination of PK parameters since only 4% of subjects had an extrapolated AUC portion > 20% of the total $AUC_{(0\text{-inf})}$. Mean ETI-204 Cmax was 400 µg/mL and mean AUC0-10 days was was 2020 µg*day/mL. Median Tmax was 0.0782 days (1.88 hours). ETI-204 concentrations declined in a biexponential fashion with a mean terminal $t_{1/2}$ of 20.2 days. Mean CL was 0.270 L/day, which was a negligible fraction of hepatic and renal blood flow, as well as glomerular filtration rate. Mean Vss was 6.34 L, which suggests that ETI-204 may distribute out of the vascular compartment, but not extensively.

ETI-204 was safe and well tolerated with a safety profile similar to placebo. The percentage of subjects with AEs was similar in the ETI-204 and placebo groups. Headache (ETI-204, 10.0%; placebo, 5.7%) and pruritus (ETI-204, 4.8%; placebo, 1.4%) were the most frequently reported AEs in the ETI-204 group. The vast majority of AEs were of mild severity; there were no related treatment-emergent serious adverse events. Local tolerability was acceptable. Approximately 5% of subjects treated with ETI-204 experienced transient reactions consistent with hypersensitivity during the infusion, including pruritus, rash, and urticaria. These reactions were generally mild in severity although one subject did develop anaphylaxis. All infusion reactions were managed medically on an outpatient basis, including the subject who developed anaphylaxis. Hypersensitivity reactions were seen with ETI-204 administration both with and without diphenhydramine premedication. There was no evidence of cytokine release syndrome. Only about 3% of subjects treated with ETI-204 required permanent infusion discontinuation prior to completion. Cough (3 subjects), urticaria (3 subjects), pruritus (3 subjects), rash (2 subjects), and throat irritation (2 subjects) were the most frequently reported AEs leading to study drug discontinuation in the ETI-204 group. All patients who discontinued the infusion permanently were White, but there were no apparent predisposing factors identified. Four of these 6 subjects received more than 50% of the intended dose. Changes from baseline in laboratory, ECG, and vital signs parameters were isolated, generally minor, not consistent across the study population, and not considered clinically meaningful. Immunogenicity was low with only 2 subjects meeting the criteria for a positive ATA response. There were no apparent, associated effects on safety or drug disposition in these subjects.

APPLICANT'S CONCLUSIONS:
This study suggests that ETI-204 can be administered safely and completely within 90 minutes to patients being treated for an anthrax infection. Additionally, in the event of an anthrax event when alternative therapies are not available or appropriate, therapeutic interventions may need to be urgently administered to substantial populations of patients by limited healthcare resources. The results of this study suggest that ETI-204 doses can be safely and completely administered within 90 minutes on an outpatient basis to patients exposed to anthrax, with the need for only routine medical monitoring of symptoms and vital signs during and immediately following the infusion.

REVIEWER ASSESSMENT:

Results from Study AH104 adequately determined the pharmacokinetics of ETI-204 after a single IV dose of 16 mg/kg. The applicant's pharmacokinetic conclusions based on these findings are valid. The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH104 was 6%, which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, in the placebo group, the positive predose concentrations ranged from 0.101 to 0.695 μg/mL, which were near the assay LLOQ (0.1 μg/mL); in the ETI-204 group, the positive predose concentrations ranged from 0.102 to 0.399 μg/mL in 12 subjects, and was 4.85 μg/mL in Subject 003-104, representing 0.024% to 0.090% of the concentration at the subsequent time point (end of infusion) in 12 subjects and 1.17% of the end-of-infusion value in Subject 003-104. Thus, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204. In addition, the presence of ATA did not appear to have an impact on ETI-204 disposition.

AH105:
A Randomized, Double-blind, Placebo-controlled, Sequential Group, Single Dose, Dose-escalation Study to Evaluate the Safety and Pharmacokinetics of ETI-204 in Healthy Subjects

Date(s): September 14, 2011– June 29, 2012
Sponsor: Elusys Therapeutics, Inc.
Clinical Site: Quintiles Phase I Services, 6700 W. 115th Street, Overland Park, KS 66211
Analytical Site: (b) (4)

OBJECTIVES:

Primary Objective:

- To evaluate the safety of increasing doses of ETI-204 in healthy subjects

Secondary Objective:

- To evaluate the pharmacokinetics of increasing single doses of ETI-204 in healthy subjects
- To evaluate the immunogenicity of ETI-204 following intravenous administration in healthy subjects

STUDY DESIGN:
This was a single-center, randomized, double-blind, placebo-controlled, sequential, dose-escalation study. It evaluated the safety and pharmacokinetics of single intravenous doses of 4 mg/kg, 8 mg/kg, or 16 mg/kg ETI-204 administered to 108 healthy male and female subjects. Eligible subjects were enrolled in the study in 3 sequential cohorts of 36 subjects each (30 subjects received ETI-204 and 6 subjects received placebo in each cohort).

Enrollment was controlled by sex so that at least 4 female subjects were in each cohort and by body mass index to ensure an equal distribution of low and high body mass indexes in each cohort. Only subjects with a body mass index of 18.5 kg/m^2 or greater and less than 30 kg/m^2 were included in the study. Cohorts were split equally into 2 body mass index groups: 18.5 to 24.25 kg/m^2 (inclusive), and 24.26 to 29.99 kg/m^2 (inclusive).

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. A Data Safety Monitoring Committee reviewed blinded safety data for the first 2 cohorts before the final cohort was randomized and dosed.

Safety and pharmacokinetic assessments were performed during the first 48 hours after the start of the intravenous infusion, after which subjects were discharged from the study center. They returned for follow-up evaluation (safety and pharmacokinetic) visits on Days 8, 15, 29, 43, and a final visit on Day 71, at which time they were discharged from the study. The 70-day postdose follow-up in this study was selected to allow characterization of the pharmacokinetic profile of ETI-204 and the potential development of anti-treatment antibodies.

FORMULATIONS:
The Sponsor supplied ETI-204 to the unblinded pharmacist in sterile, single-use, (b) (4) mL clear (b) (4) glass vials with gray stoppers. Vials of ETI-204 contained (b) (4) mL of clear colorless solution containing (b) (4) mg/mL of ETI-204, 40 mM histidine, 200 mM sorbitol, and 0.01% polysorbate 80, pH 5.5.

ETI-204 (Lot Number PBR-0031-001) was manufactured and labeled in accordance with Good Manufacturing Practices at Baxter Biologics (Hayward, California, United States) and (b) (4)), respectively. Study drug was supplied to the study center as bulk kits/cartons. Matching placebo (Lot Number PBR-0076-001) was provided in the same type vials as ETI-204. It contained the same inactive components as ETI-204 and was stored under the same conditions as ETI-204.

Reviewer Comment: Of note, the test product, ETI-204, used in Study 105 was manufactured at Baxter Biologics; whereas, the commercial formulation of ETI-204 was manufactured at Lonza Biologics, which was used in Studies 104, 106, 109, and 110.

INCLUSION/EXCLUSION CRITERIA:
Healthy males and females of non-childbearing potential of ≥18 years of age with a body mass index of 18.5 kg/m^2 or greater and less than 30 kg/m^2 were enrolled.

DOSE AND ADMINISTRATION
Active study drug (single doses of 4, 8, or 16 mg/kg of ETI-204) was prepared by diluting a volume of ETI-204 into a sufficient volume of 0.9% sterile sodium chloride for infusion to a final concentration of 10 mg/mL and administered intravenously at a controlled rate over 90 minutes. Placebo solution was prepared in an identical fashion in sterile 0.9% sodium chloride to match the volume of the active study drug to be administered for a subject at the same dose level and weight and was administered in the same manner as ETI-204.

Reviewer Comment: Of note, subjects in this study were not premedicated with 50 mg oral diphenhydramine approximately 30 minutes prior to the start of the infusion of ETI-204 on Day 1.

PHARMACOKINETIC ASSESSMENTS:
Pharmacokinetic blood samples were collected prior to dosing (0 h) and at 4, 8, 24, 36, and 48 hours following the end of infusion. Additional pharmacokinetic blood samples were obtained on Days 8, 15, 29, 43, and Day 71.

IMMUNOGENICITY ASSESSMENTS:
Blood samples for evaluation of anti-treatment antibodies were obtained on Day 1 prior to dosing, Day 8, Day 43, and Day 71. Samples were tested using a validated electrochemiluminescence method. Samples testing positive (above the population cut point) were confirmed using immune-inhibition and titered. Testing of confirmed positive samples for ETI-204 neutralizing activity is planned and positive samples will be isotyped for class (Immunoglobulins G, M, A, and E) for further characterization. Results of neutralization and isotyping will be reported separately from this clinical study report.

BIOANALYTICAL ANALYSIS:
Serum concentrations of ETI-204 were determined by means of a validated enzyme-linked immunosorbent assay (ELISA) method (GCL-160). (Table 1).

Table 1. Bioanalytical results of ETI-204 in serum (Bioanalytical study report 13-180)

Criterion	ETI-204	Comments
Calibration Range	100-5000 ng/mL	Satisfactory

LLOQ	100 ng/mL	Satisfactory
ULOQ	5000 ng/mL	Satisfactory
Linearity, mean R^2	Not reported	N/A
Accuracy	Within ±7.0%	Satisfactory
Precision, CV	≤11.2%	Satisfactory
Quality Control	300, 1500, 4000 ng/mL	Satisfactory
Accuracy (%RE)	Within ±2.3%	Satisfactory
Precision, CV	≤8.3 %	Satisfactory
Stability	• Samples were analyzed within 71 days of collection • Stability: 24 month at -70 ºC	Satisfactory

PHARMACOKINETIC/PHARMACODYNAMIC/STATISTICAL ANALYSIS:
Pharmacokinetic parameters, determined using a noncompartmental approach, included maximum concentration in serum (Cmax), time of maximum concentration (tmax), area under the concentration-time curve in serum from zero (predose) to time of last quantifiable concentration [AUC(0-last)], area under the concentration-time curve in serum from zero (predose) extrapolated to infinite time [AUC(0-inf)], mean residence time in serum from zero (predose) extrapolated to infinite time [MRT(0-inf)], apparent terminal rate constant (λz), apparent terminal half-life (t1/2), systemic clearance (CL), and volume of distribution (Vd).

Pharmacokinetic parameters were summarized by treatment using descriptive statistics. The dose proportionality of the pharmacokinetic parameters, AUC(0-inf), AUC(0-last), and Cmax, over the administered dose range was investigated using a power model. The effect of sex and body mass index on the pharmacokinetics of ETI-204 was also examined.

RESULTS:
Study Population
Of the 90 subjects who received ETI-204, 89 subjects were included in the PK analysis dataset. The PK analysis dataset consisted of all 30 subjects dosed with 4 mg/kg and 8 mg/kg of ETI-204 and 29 of the 30 subjects dosed with 16 mg/kg of ETI-204.

Demographics
A summary of demographic and baseline characteristics for the study population is presented in Table 2. Demographics and baseline characteristics were similar among the treatment groups in general except that the mean ages for the 2 highest ETI-204 dose groups (8 mg/kg and 16 mg/kg) were slightly higher than those for the other treatment groups ($p<0.05$).

Table 2. Demographics and Baseline Characteristics – Study AH104

Variable/ Category	Placebo N=18	ETI-204 4 mg/kg N=30	ETI-204 8 mg/kg N=30	ETI-204 16 mg/kg N=30	All Subjects N=108
Sex					
Male	16 (88.9%)	18 (60.0%)	25 (83.3%)	19 (63.3%)	78 (72.2%)
Female	2 (11.1%)	12 (40.0%)	5 (16.7%)	11 (36.7%)	30 (27.8%)
Race					
White	11 (61.1%)	20 (66.7%)	19 (63.3%)	18 (60.0%)	68 (63.0%)
Black/African American	6 (33.3%)	10 (33.3%)	10 (33.3%)	9 (30.0%)	35 (32.4%)
American Indian or Alaska Native	1 (5.6%)	0	1 (3.3%)	2 (6.7%)	4 (3.7%)
Asian	0	0	0	1 (3.3%)	1 (0.9%)
Ethnicity					
Not Hispanic	14 (77.8%)	29 (96.7%)	26 (86.7%)	28 (93.3%)	97 (89.8%)
Hispanic	4 (22.2%)	1 (3.3%)	4 (13.3%)	2 (6.7%)	11 (10.2%)
Age (years)					
Mean	27	26	34	32	30
SD	9	8	11	11	10
Range	18-45	18-54	20-58	19-58	18-58
Screening Height (cm)					
Mean	175.9	174.6	175.4	172.6	174.5
SD	8.7	9.2	7.7	6.6	8.0
Range	163.4 – 190.2	160.1 – 199.4	158.6 – 188.1	157.9 – 185.4	157.9 – 199.4
Screening Weight (kg)					
Mean	75.3	72.5	78.6	75.4	75.5
SD	10.6	10.2	12.6	11.3	11.3
Range	57.9 – 91.8	56.1 – 95.9	53.4 – 102.0	49.8 – 98.2	49.8 – 102.0
BMI (kg/m^2)					
Mean	24.2	23.8	25.4	25.4	24.8
SD	3.0	2.7	2.9	3.1	3.0
Range	19.5 – 29.2	19.4 – 29.7	19.4 – 29.9	19.3 – 29.6	19.3 – 29.9

Note(s): BMI = body mass index; SD = standard deviation.

Source: AH105 Pharmacokinetic Report, Section 11.2

ETI-204 Serum Pharmacokinetics

Data Excluded From Analysis

The ETI-204 infusion for Subject 3031 (16 mg/kg) was stopped 30 minutes early due to an AE. This subject's concentration data and PK parameters are included in listings but have been excluded from all summaries and analyses. There were 3 subjects with missing PK samples. Subject 2018 was missing all samples after 672 hours (Day 28), Subject 2029 was missing all samples after 48 hours, and Subject 2036 was missing all samples after 48 hours with the exception of the sample at 336 hours. No half-life related parameters (ie AUC(0-inf), MRT, λz, t1/2, CL, and Vd) were calculated for these subjects as the sample collection period was not adequate to accurately estimate the elimination rate for ETI-204 and the percent of AUC extrapolated exceeded 20% (Subject 2018, 25%; Subject 2029, 52.8%; and Subject 2036, 34.2%). In addition, these missing samples resulted in an underestimation of AUC(0-last) and although calculated, this parameter was excluded from all summaries and analyses.

ETI-204 Serum Concentrations and PK Parameters

Five subjects had quantifiable predose concentrations (Subjects 1022, 1027, 2007, 2012, and 3036). These values were equal to or below 0.164 µg/mL for 4 of these subjects which were near the limits of the assay (0.100 µg/mL). For subject 2012, the predose value was 0.664 µg/mL which was equivalent to less than 0.2% of this subject's C_{max}. These quantifiable predose values were included in all summaries and analyses.

Reviewer Comment: There is no information regarding the specific selectivity criteria of a ligand-binding assay provided in the FDA draft Guidance for Industry-Bioanalytical Method Validation. Per the European Medicines Agency (EMA) Guideline on bioanalytical method

validation, Selectivity is tested by spiking at least 10 sources of sample matrix at or near the LLOQ. Selectivity should be evaluated at the low end of an assay where problems occur in most cases. It may be prudent also to evaluate selectivity at higher analyte concentrations. The accuracy should be within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated.

In the Sponsor's bioanalytical assay validation report (09-004), the potential for variable matrix-related interferences was evaluated in eight independent sources of Normal Human Serum at the targeted LQC (300 ng/mL) and HQC (3,000 ng/mL) concentrations. For all eight lots of Normal Human Serum tested, lot precision for each concentration, LQC (300 ng/mL) and HQC (3,000 ng/mL), was within the acceptance criteria of ≤ 20%, and ranged from 1.5% to 14.6%. The accuracy for all eight lots for each concentration was within the acceptance criteria of ± 20% of the nominal, ranging from -12.1% to 6.4%. In the Sponsor's bioanalytical assay validation report (11-069), the validation acceptance criteria for selectivity were set by the Sponsor as follows: ± 20% relative error (RE) of Nominal Value for at least 80% of samples; unspiked sample < LLOQ. The potential for variable matrix-related interferences was evaluated in 10 lots of Normal Human Serum at 0 ng/mL (unspiked) and low QC (300 ng/mL) concentrations. Results showed that 8 out of 10 (80%) of the matrix lots initially evaluated were within the acceptance criteria for %RE<20%; 9 of 10 (90%) of the unspiked samples were < LLOQ.

The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH105 was estimated to be 5.6% (5 out of 89 subjects), which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, in the placebo group, the positive predose concentrations were equal to or below 0.164 μg/mL for 4 of these subjects which were near the limits of the assay (0.100 μg/mL). For subject 2012, the predose value was 0.664 μg/mL which was equivalent to less than 0.2% of this subject's C_{max}. From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204. The adequacy of the ELISA assay of ETI-204 will be further assessed pending results of inspection of the corresponding bioanalytical site ((b) (4)

Mean (SD) ETI-204 concentration-time profiles are shown by treatment throughout the entire 71-day sampling period in Figure 1. ETI-204 serum concentrations were quantifiable in all subjects (with samples) for the 71-day sampling period following each dose level. ETI-204 appears to have a bi-exponential profile with the terminal phase commencing around Day 8. In the semi-logarithmic presentation, the terminal portions of the concentration-time profiles appear to be parallel providing evidence the rate of elimination was similar across the dose groups.

Pharmacokinetic parameters for ETI-204 following single intravenous administration of 16 mg/kg in healthy subjects are summarized in Table 3. Figure 2 through Figure 6 display individual, mean and geometric mean values for $AUC_{(0\text{-inf})}$, $AUC_{(0\text{-last})}$, C_{max}, $t_{1/2}$, and CL.

A 4-fold increase in dose from 4 mg/kg to 16 mg/kg resulted in an approximate 4-fold increase 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. Dose proportionality was assessed based on whether the 90% CI constructed for the estimate of the slope of the linear relationship between exposure and dose was contained within the interval (0.84, 1.16). For $AUC_{(0\text{-inf})}$ and $AUC_{(0\text{-last})}$, this criterion was met, thus demonstrating these parameters increased in a dose-proportional manner across this range of doses. The 90% CIs for the slopes for $AUC_{(0\text{-inf})}$ and $AUC_{(0\text{-last})}$ were (0.945, 1.09) and (0.935,

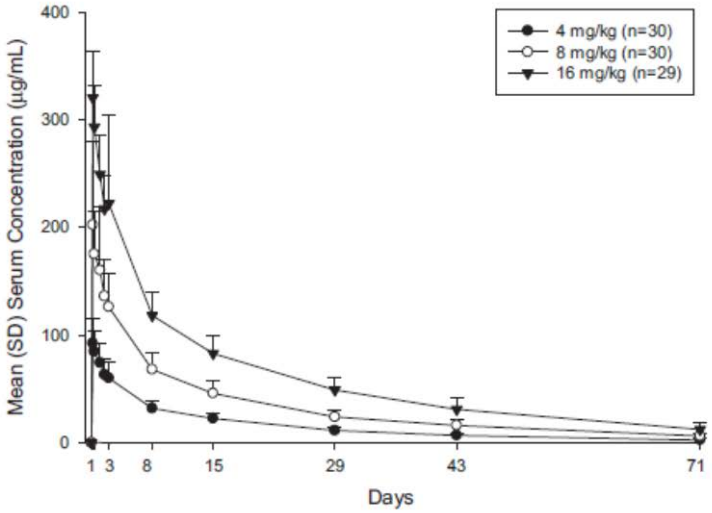
1.07), respectively. The 90% CI for this slope for C_{max} (0.83, 1.01) fell just below the lower limit of this interval showing this parameter appeared to increase in a general dose-proportional manner as well.

Median Tmax occurred at the time of the first PK sample obtained after the start of the 90-minute infusion (4 hours). Five subjects had delayed Tmax values ranging from 24 to 48 hours, 2 of these subjects (Subjects 1008 and 1013) received the 4 mg/kg dose, 2 subjects (Subjects 2012 and 2028) received the 8 mg/kg dose and 1 subject (Subject 3007) received the 16 mg/kg dose. For 2 of these subjects (Subjects 2012 and 3007), Cmax exceeded the population mean. For 2 of these subjects (Subjects 1013 and 2028), Cmax was lower than the population mean but within 1 SD of the mean while the Cmax value for the remaining subject (Subject 1008) was more than 3 SDs below the mean. Half-life ranged from approximately 18 to 21 days across the 3 treatment groups and was independent of dose. Mean Vd ranged from approximately 7 to 8 L across the 3 treatments.

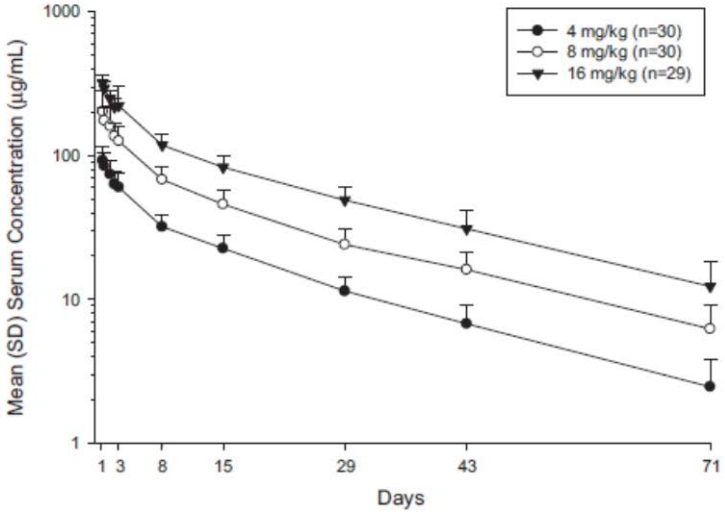
The PK parameters of $AUC_{(0\text{-inf})}$/DN, C_{max}/DN, and Vd were compared between males and females and between low and high BMI categories ($\geq$18.5 to 24.25 kg/m^2 or >24.25 to <30.0 kg/m^2). The 90% CI for the ratios of the LS means comparing $AUC_{(0\text{-inf})}$/DN, C_{max}/DN, and Vd between females and males and the 2 BMI categories were contained with the limits of 80% to 125%. These results demonstrate there was no difference in the PK of ETI-204 based on sex or BMI category. These comparisons are presented in Table 4 and Table 5 for sex and BMI, respectively. In addition, the relationship between BMI and the PK parameters of $AUC_{(0\text{-inf})}$/DN, C_{max}/DN, and Vd were also examined using linear regression. For these 3 regression analyses, only the slope of the relationship between Vd and BMI was statistically different from zero ($p<0.10$). The coefficient of determination for these relationships shows BMI accounts for less than 4% of the variability for any of these 3 PK parameters.

Figure 1. Mean (± SD) Serum Concentration-Time Profiles for ETI-204 Following Single Intravenous Administration of 4, 8, and 16 mg/kg in Healthy Subjects (Linear and Log Scale)

Linear



Semi-logarithmic



Source: AH105 Pharmacokinetic Report, Section 11.4

Table 3. Summary of ETI-204 Pharmacokinetic Parameters Following Single Intravenous Administration of 16 mg/kg IV in Healthy Subjects

	$AUC_{(0\text{-}inf)}$ (µg*d/mL)	$AUC_{(0\text{-}last)}$ (µg*d/mL)	MRT (d)	C_{max} (µg/mL)	t_{max}[a] (h)	$t_{1/2}$ (d)	CL (L/d)	CL/kg (L/d/kg)	V_d (L)
ETI-204 4 mg/kg									
N	30	30	30	30	30	30	30	30	30
Mean	1080	1010	22.3	94.0	--	18.2	0.279	0.00393	7.08
SD	250	213	5.5	19.3	--	4.29	0.0629	0.00105	1.28
CV%	23.2	21.1	24.6	20.6	--	23.6	22.5	26.6	18.1
Minimum	588	546	13.1	23.4	4.00	10.5	0.197	0.00241	5.08
Median	1130	1050	21.4	96.8	4.00	17.5	0.277	0.00356	6.94
Maximum	1660	1390	37.5	122	48.00	28.9	0.471	0.00680	10.3
Geo.Mean	1050	984	21.7	91.0	--	17.7	0.273	0.00381	6.97
ETI-204 8 mg/kg									
N	27	27	27	30	30	27	27	27	27
Mean	2390	2190	25.3	210	--	20.8	0.270	0.00349	7.89
SD	521	432	5.73	85.5	--	4.43	0.0655	0.000736	1.60
CV%	21.8	19.7	22.6	40.7	--	21.3	24.3	21.0	20.3
Minimum	1610	1530	14.9	120	4.00	14.1	0.184	0.00223	5.48
Median	2250	2130	25.3	190	4.00	20.6	0.244	0.00355	7.71
Maximum	3590	3150	37.8	506	36.00	29.1	0.416	0.00498	12.0
Geo.Mean	2340	2150	24.7	197	--	20.4	0.263	0.00342	7.74
ETI-204 16 mg/kg									
N	29	29	29	29	29	29	29	29	29
Mean	4410	4010	26.3	330	--	20.4	0.287	0.00382	8.05
SD	1000	774	6.29	63.5	--	4.95	0.0802	0.000943	1.45
CV%	22.7	19.3	23.9	19.2	--	24.3	28.0	24.7	18.0
Minimum	2320	2270	15.0	253	3.98	12.2	0.175	0.00246	5.82
Median	4330	4040	26.0	321	4.00	20.0	0.268	0.00369	7.77
Maximum	6520	5470	38.7	589	47.98	30.9	0.527	0.00690	11.9
Geo.Mean	4300	3940	25.5	325	--	19.8	0.278	0.00372	7.94

[a] only minimum, median, and maximum are presented for t_{max}.

N = number of subjects; SD = standard deviation; CV% = coefficient of variation; Geo = geometric.

Source: AH105 Pharmacokinetic Report, Section 11.4

Figure 2. Individual, Mean, and Geometric Mean $AUC_{(0\text{-}inf)}$ versus ETI-204 Dose

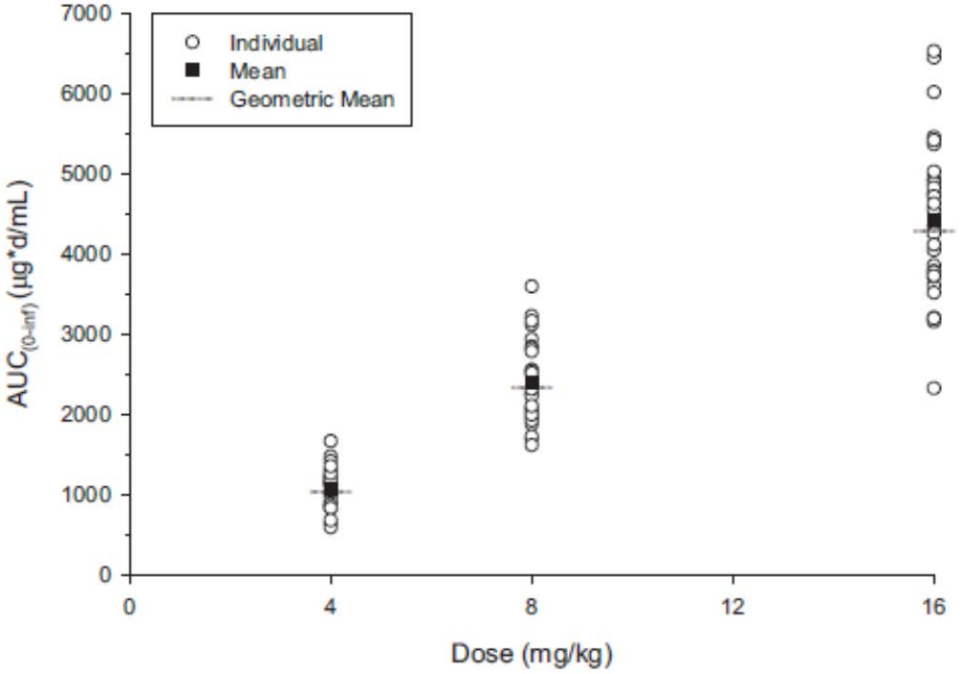
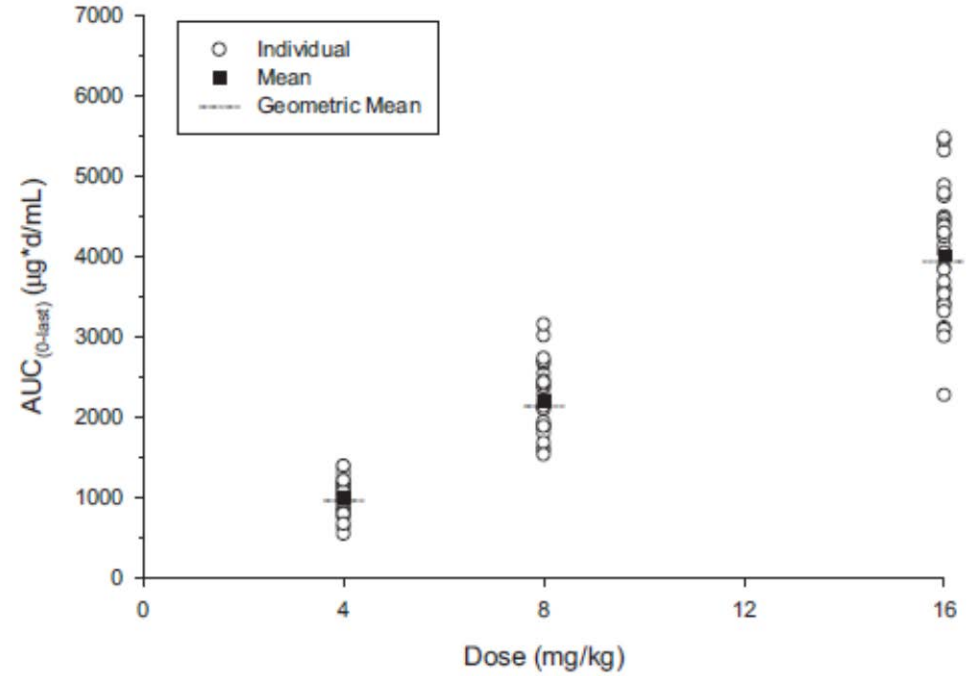


Figure 3. Individual, Mean, and Geometric Mean $AUC_{(0\text{-}last)}$ versus ETI-204 Dose



Source: AH105 Pharmacokinetic Report, Section 11.4

Figure 4. Individual, Mean, and Geometric Mean C_{max} versus ETI-204 Dose

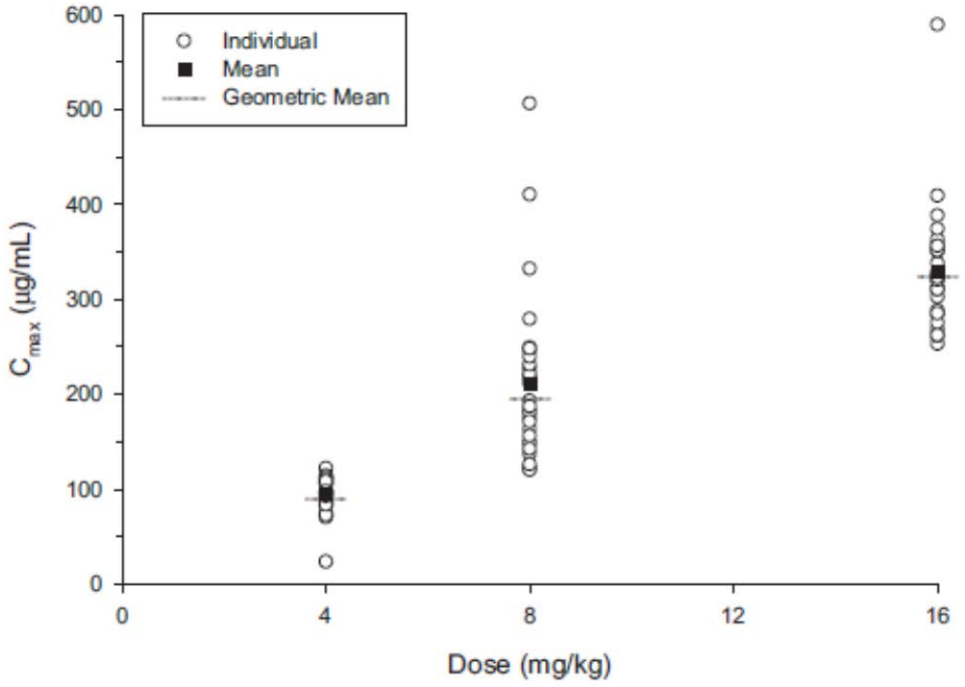
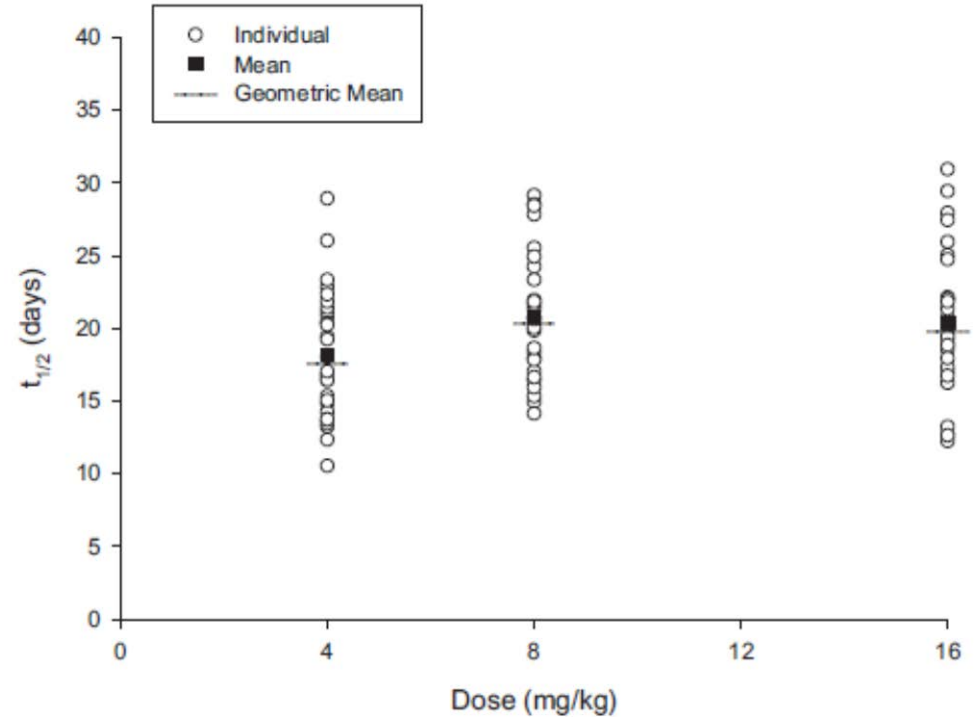


Figure 5. Individual, Mean, and Geometric Mean Half-life versus ETI-204 Dose



Source: AH105 Pharmacokinetic Report, Section 11.4

Figure 6. Individual, Mean, and Geometric Mean CL versus ETI-204 Dose

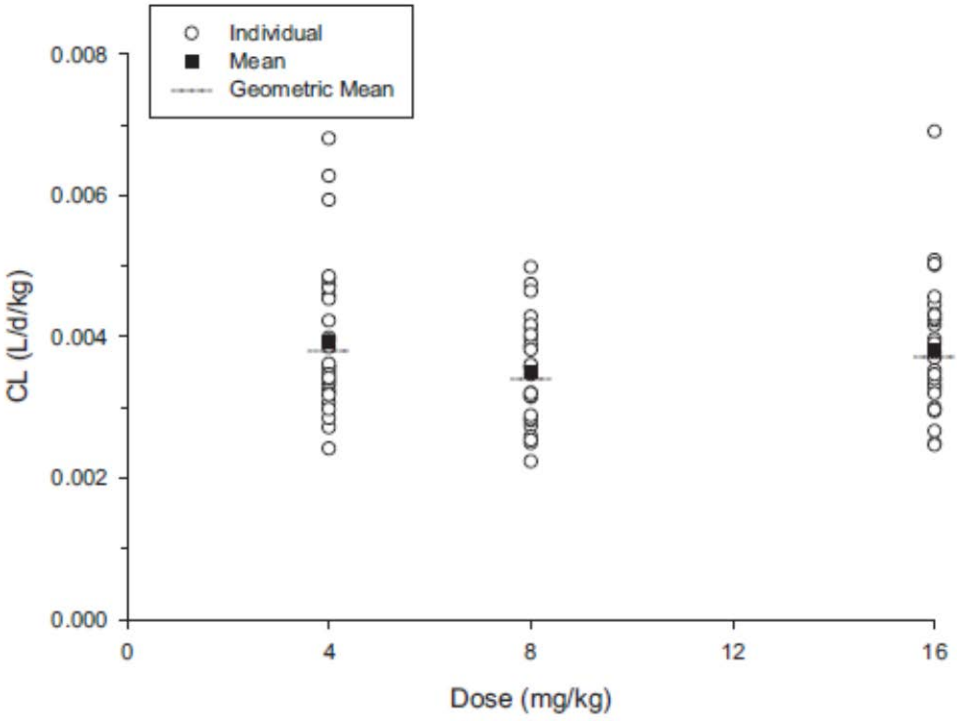


Table 5. Effect of Sex on Pharmacokinetics of ETI-204

Parameter (unit)	Sex	n	Geometric LS Means	Comparison Pair	Comparison Ratio (%)	Comparison 90% CI
$AUC_{(0\text{-}inf)}$/DN (µg·d/mL/mg)	Female	27	3.955	Female/Male	110.34	(100.86, 120.72)
	Male	59	3.585			
C_{max}/DN (µg/mL/mg)	Female	28	0.3066	Female/Male	102.59	(92.76, 113.45)
	Male	61	0.2989			
V_d (L)	Female	27	6.810	Female/Male	86.82	(80.91, 93.17)
	Male	59	7.844			

Note(s): CI = confidence interval; LS = least squares.

Table 6. Effect of BMI on Pharmacokinetics of ETI-204

Parameter (unit)	BMI Category[1]	n	Geometric LS Means	Comparison Pair	Ratio (%)	90% CI
$AUC_{(0\text{-}inf)}$/DN (µg·d/mL/mg)	Low	35	3.828	High/Low BMI	96.74	(88.43, 105.84)
	High	51	3.704			
C_{max}/DN (µg/mL/mg)	Low	36	0.2945	High/Low BMI	105.71	(95.59, 116.91)
	High	53	0.3113			
V_d (L)	Low	35	7.184	High/Low BMI	103.50	(96.44, 111.07)
	High	51	7.436			

1) Low BMI = ≥18.5 to 24.25 kg/m^2; High BMI = >24.25 to <30.0 kg/m^2

Note(s): CI = confidence interval; LS = least squares; BMI = body mass index (kg/m^2).

Source: AH105 Pharmacokinetic Report, Section 11.4

Immunogenicity

Six subjects randomized to receive ETI-204 tested positive for anti-treatment antibodies prior to receiving study medication. Of these 6 subjects, only 1 subject tested positive for anti-treatment antibodies after receiving ETI-204. Six of the 87 subjects (6.9%) who were tested following exposure to ETI-204 developed anti-treatment antibodies following dosing. One of these 6 subjects tested positive for anti-treatment antibodies prior to dosing and on Day 71 but tested negative for anti-treatment antibodies on Day 43. This compares to 1 of 18 subjects (5.6%) who tested positive for anti-treatment antibodies in the placebo group. The development of anti-treatment antibodies did not appear to be dose related as the number of subjects testing positive for anti-treatment antibodies following exposure to ETI-204 did not increase with increasing dose. The development of anti-treatment antibodies did not alter the pharmacokinetics of ETI-204. Individual $AUC_{(0\text{-}inf)}$ values for the subjects who developed anti-treatment antibodies following exposure to ETI-204 either exceeded the population mean of their dose group or if lower were within 1 standard deviation of the mean.

Reviewer Comment: Please refer to the OBP review for the assessment of ETI-204 immunogenicity following a single IV dose of 4, 8, and 16 mg/kg.

SAFETY RESULTS

No deaths occurred during the study. Treatment-emergent adverse events were reported in 58 of 90 (64.4%) subjects who received ETI-204 and 14 of 18 (77.8%) subjects who received placebo. The numbers of subjects who reported at least 1 treatment-emergent adverse event when administered the various treatments are as follows: placebo (14/18, 77.8%), 4 mg/kg ETI-204 (22/30, 73.3%), 8 mg/kg ETI-204 (17/30, 56.7%), and 16 mg/kg ETI-204 (19/30, 63.3%).

The most frequently occurring treatment-emergent adverse events (ie, a treatment-emergent adverse event that was reported in 3 or more subjects who received ETI-204) were headache (11/90, 12.2%), upper respiratory tract infection (10/90, 11.1%), nausea (9/90, 10.0%), erythema (7/90, 7.8%), nasal congestion (6/90, 6.7%), oropharyngeal pain (5/90, 5.6%), decreased appetite (4/90, 4.4%), pruritus (4/90, 4.4%), infusion site erythema (3/90, 3.3%), peripheral edema (3/90, 3.3%), increased blood creatine kinase (3/90, 3.3%), cough (3/90, 3.3%), rhinorrhea (3/90, 3.3%), and ecchymosis (3/90, 3.3%). Of these most frequently occurring treatment-emergent adverse events, decreased appetite, nasal congestion, oropharyngeal pain, localized pruritus, infusion site erythema, and increased creatine kinase were only reported for ETI-204 treated subjects and not for placebo-treated subjects.

Reviewer Comment: Please refer to the Clinical Review by Dr. Gopinath, Ramya for safety assessment of ETI-204 following a single IV dose of 4, 8, and 16 mg/kg.

APPLICANT'S DISCUSSION

ETI-204 exposure (AUC) increased in a dose-proportional manner. A 4-fold increase in dose from 4 mg/kg to 16 mg/kg resulted in an approximate 4-fold increase 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. The 90% CI for the slope of the test for dose proportionality for Cmax (0.83, 1.01) fell just below the predefined cutoff for the lower limit of this interval (0.84) showing this parameter increased in an approximately dose-proportional manner as well. Half-life ranged from approximately 18 to 21 days across the 3 treatment groups and was independent of dose. Mean Vd ranged from approximately 7 to 8 L across the 3 treatments suggesting ETI-204 distributes primarily in the vascular compartment in this population of healthy subjects.

Based on the results of this study, ETI-204 can be dosed based on body weight without regard to sex or BMI. The 90% CI for the ratios of the LS means comparing $AUC_{(0\text{-inf})}$/DN, C_{max}/DN, and Vd between females and males and the 2 BMI categories (≥18.5 to 24.25 kg/m^2 or >24.25 to <30.0 kg/m^2) were contained with the limits of 80% to 125% demonstrating there was no difference in the PK of ETI-204 based on sex or BMI category.

Anti-treatment antibodies developed in about 6.9% of the subjects after receiving ETI-204. The development of anti-treatment antibodies did not appear to be dose related as the number of subjects developing anti-treatment antibodies following exposure to ETI-204 did not increase with increasing dose. The development of anti-treatment antibodies did not alter the PK of ETI-204. Individual $AUC_{(0\ inf)}$ values for the subjects who developed anti-treatment antibodies following exposure to ETI-204 either exceeded the population mean of their dose group or if lower were within 1 standard deviation of the mean. This finding is important as it suggests the development of anti-treatment antibodies is not critical as it relates to individual ETI-204 exposure.

The incidence and pattern of AEs did not reveal any evidence of a dose-related effect of ETI-204 on the nature or incidence of AEs in this study. No trends or clinically relevant changes were noted in mean clinical laboratory, vital sign, or 12-lead ECG data, or physical examination findings following dosing.

Although numbers are limited, there was no evidence of clinically important differences in AE patterns between placebo and ETI-204 recipients. However 1 subject who received the 16 mg/kg dose did develop a widespread urticarial reaction during the infusion of ETI-204 which required discontinuation of the infusion. The subject had received a single dose of anthrax vaccine 20 months previously.

APPLICANT'S CONCLUSIONS:

• Doses of 4 mg/kg, 8 mg/kg, and 16 mg/kg of ETI-204 or placebo were generally well tolerated in this study when administered as a single IV infusion.
• Allowing for the disparity in numbers, there is no evidence for an increase in number or nature of AEs between placebo and ETI-204 recipients.
• There was no increase in the overall incidence or nature of AEs with increasing doses of ETI-204.
• No trends or clinically relevant changes were noted in mean clinical laboratory, vital sign, or 12-lead ECG data or physical examination findings following dosing.
• ETI-204 exposure increased in a dose-proportional manner across this range of doses.

• Half-life (18 to 21 days) did not change with dose. ETI-204 distributed primarily in the vascular compartment (7 to 8 L).
• There was no difference in the PK of ETI-204 based on sex or BMI category.
• The development of anti-treatment antibodies was not related to dose and did not appear to alter the PK of ETI-204.

REVIEWER ASSESSMENT:
Results from Study AH105 adequately determined the pharmacokinetics of ETI-204 after a single IV dose of 4, 8, 16 mg/kg. The applicant's pharmacokinetic conclusions based on these findings are valid. The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH105 was estimated to be 5.6% (5 out of 89 subjects), which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, in the placebo group, the positive predose concentrations were equal to or below 0.164 μg/mL for 4 of these subjects which were near the limits of the assay (0.100 μg/mL). For subject 2012, the predose value was 0.664 μg/mL which was equivalent to less than 0.2% of this subject's C_{max}. From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204. In addition, the development of anti-treatment antibodies did not alter the pharmacokinetics of ETI-204.

AH109:

A Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Repeat Administration of Intravenous ETI-204 in Adult Volunteers

Date(s): July 23, 2013– April 19, 2014
Sponsor: Elusys Therapeutics, Inc.
Clinical Site: Quintiles - Overland Park, 6700 W. 115th St., Overland Park, KS 66211
DaVita Clinical Research 825 S. 8th St. Suite 300, Minneapolis, MN 5540
Analytical Site: (b) (4)

OBJECTIVES:

Primary:

• To evaluate the safety and tolerability of repeat administration (two doses) of intravenous (IV) ETI-204 16 mg/kg in adult volunteers

Secondary:

• To evaluate the pharmacokinetics (PK) of ETI-204 after repeat IV administration
• To evaluate the immunogenicity of ETI-204 after repeat IV administration

STUDY DESIGN:

This was a double-blind, randomized, placebo-controlled, multicenter study. The total duration of the
study for each subject was approximately 220 days divided as follows:

• Screening: Days -28 to -2
• Three In-Unit Stays: Days -1 to 2; Days 13 to 15; and Days 119 to 121
• Out-of-Unit Visit Days: Day 8 (±2 days); Day 28 (±3 days); Day 43 (±3 days); Day 71 (±3 days); Day 85 (±3 days); Day 128 (±3 days); Day 134 (±3 days); Day 149 (±3 days); and Day 163 (±3 days)
• Final Visit: Day 191 (±3 days)

Subjects were randomized in a 1:1 ratio to one of the following two treatment sequences:
• Sequence A: ETI-204 on Days 1 and 14 and placebo on Day 120
• Sequence B: ETI-204 on Days 1 and 120 and placebo on Day 14

Subjects who qualified for entry into the study following completion of the Screening visit (Day -28 to
Day -2) arrived at the clinical research unit (CRU) on Day -1 following at least a 10-hour fast. On Day 1, qualified subjects were randomized and received a single IV dose of ETI-204. All subjects were pretreated with 50 mg oral diphenhydramine prior to the start of the study drug administration except 8 subjects who were randomized before the implementation of Amendment 1. Subjects were discharged from the CRU on Day 2 following completion of study assessments and returned to the CRU for an additional visit on Day 8 (±2 days).

For the second in-unit stay, subjects returned to the CRU on Day 13. The next day, Day 14, subjects were pretreated with 50 mg oral diphenhydramine and received study drug (either ETI-204 or placebo) according to their randomized sequence assignment. Subjects were discharged on Day 15 and returned
to the CRU for four additional visits on Days 28 (±3 days), 43 (±3days), 71 (±3 days), and 85 (±3 days).

For their third in-unit stay, subjects returned to the CRU on Day 119. On Day 120, subjects were pretreated with 50 mg oral diphenhydramine and received study drug (either ETI-204 or placebo) according to their randomized sequence assignment. Subjects were discharged on Day 121 and returned to the CRU for five additional visits on Days128 (±3days), 134 (±3days), 149 (±3days), 163(±3days), and 191 (±3days).

FORMULATIONS:
ETI-204 was supplied in sterile, (b) (4)-mL, clear, (b) (4) glass vials with gray stoppers that contained (b) (4) mL of clear, colorless to pale yellow solution consisting of 100 mg/mL ETI-204, 40 mM histidine, 200 mM sorbitol, and 0.01% polysorbate 80 with a pH of 5.5. Translucent particles may have been present. Matching placebo contained the same inactive components as ETI-204 and was provided in the same type vials as ETI-204.

ETI-204 bulk drug substance was manufactured, packaged, and labeled in accordance with current Good Manufacturing Practices at Lonza Biologics, Portsmouth, NH. Final drug product and placebo were manufactured, packaged, and labeled in accordance with current Good Manufacturing Practices at (b) (4). The ETI-204 and placebo lots used for this study were 3-FIN-1513 and 3-FIN-1491, respectively.

INCLUSION/EXCLUSION CRITERIA:
Healthy males and females of non-childbearing potential of ≥18 years of age without restrictions for body weight, body mass index, and smoking were enrolled.

DOSE AND ADMINISTRATION
Single doses of 16 mg/kg ETI-204 were administered via IV infusion (total volume of 250 mL) over 90 minutes (± 5 minutes) at a rate of approximately 3 mL/min using a Primary PlumSet™ infusion set with a 0.2 micron in-line filter and an appropriate infusion pump. 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 Day 1, 14, and 120.

PHARMACOKINETIC ASSESSMENTS:
Blood samples (3.5 mL) for analysis of ETI-204 serum concentrations (PK) were obtained on Day 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.

IMMUNOGENICITY ASSESSMENTS:
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.

BIOANALYTICAL ANALYSIS:
Serum samples were analyzed for ETI-204 at (b) (4), using a validated enzyme-linked immunosorbent assay method with an assay range of 100 ng/mL to 5000 ng/mL (Table 1). Recombinant anthrax protective antigen (rPA83) was used as the capture reagent; sheep anti-human IgG(Fc) HRP (monkey adsorbed) peroxidase conjugate was used as the detection reagent.

Table 1. Bioanalytical results of ETI-204 in serum (Bioanalytical study report 13-182)

Criterion	ETI-204	Comments
Calibration Range	100-5000 ng/mL	Satisfactory
LLOQ	100 ng/mL	Satisfactory
ULOQ	5000 ng/mL	Satisfactory
Linearity, mean R^2	Not reported	N/A
Accuracy	Within ±6.6%	Satisfactory
Precision, CV	≤8.9%	Satisfactory
Quality Control	300, 1500, 4000 ng/mL	Satisfactory
Accuracy (%RE)	Within ±6.4%	Satisfactory
Precision, CV	≤13.3 %	Satisfactory
Stability	• Samples were analyzed within 410 days of collection • Stability: 24 month at -70 ºC	Satisfactory

PHARMACOKINETIC/PHARMACODYNAMIC/STATISTICAL ANALYSIS:
PK parameters included maximum concentration (C_{max}); time to reach C_{max} (T_{max}); area under the concentration-time curve (AUC) from time 0 to 10 days ($AUC_{0\text{-}10\ days}$); AUC from time 0 to the time of last measurable concentration ($AUC_{0\text{-}last}$); AUC from time 0 extrapolated to infinite time ($AUC_{0\text{-}inf}$); mean residence time from time 0 extrapolated to infinite time ($MRT_{0\text{-}inf}$); terminal half-life ($t_{½}$); systemic clearance (CL); CL divided by weight (CL/kg); volume of distribution (Vd); Vd divided by weight (Vd/kg), volume of distribution at steady state (Vss), and Vss divided by weight (Vss/kg).

PD parameter was anti-therapeutic antibodies (ATA); exploratory PD parameters included IgE and plasma histamine levels.

PK parameters were summarized descriptively (mean, arithmetic standard deviation, arithmetic coefficient of variation, median, minimum, maximum, geometric mean, and number). PD and safety data were also summarized descriptively using the summary statistics noted above for PK parameters (except for geometric mean) or frequency counts and percentages.

RESULTS:
Study Population
A total of 70 subjects were randomized to receive study drug, 35 to Sequence A (16 mg/kg ETI-204 on Day 1 / 16 mg/kg ETI-204 on Day 14 / Placebo on Day 120) and 35 to Sequence B (16 mg/kg ETI-204 on Day 1 / Placebo on Day 14 / 16 mg/kg ETI-204 on Day 120). All 70 subjects received at least 1 completed dose of the study drug. Sixty (60) of the 70 subjects completed the study: 30 each from Sequence A and Sequence B. Two subjects were prematurely discontinued from the study by the investigator after the Day 85 visit, per protocol, after experiencing AEs (002-205 in Sequence A and 002-204 in Sequence B) following the first infusion of ETI-204. Two subjects withdrew consent (002-216 in
Sequence A due to relocation and 002-214 in Sequence B due to conflict with work schedule) and 4 subjects were lost to follow up (001-108 and 001-121 in Sequence A; 001-120 and 001-131 in Sequence B) after missing several scheduled visits and not responding to a certified letter from the site. Two subjects withdrew from the study due to protocol violation

Demographics

A summary of demographic and baseline characteristics for the study population is presented in Table 2. There were no substantial differences in demographic characteristics between Sequence A and Sequence B. All subjects in this study received 50 mg oral diphenhydramine approximately 30 minutes before each of the 3 scheduled study drug administration, with the exception of 8 subjects (001-102, 001-103, 002-202, and 002-203 in Sequence A; 001-101, 001-104, 002-201, and 002-204 in Sequence B) who did not receive diphenhydramine pre-treatment on Day 1.

Table 2. Demographics and Baseline Characteristics – Study AH109

Demographic		Statistic	Sequence A N=35	Sequence B N=35	Overall N=70
Age (years)		n	35	35	70
		Mean	43.0	43.3	43.1
		SD	14.71	16.76	15.65
		Median	43.0	46.0	43.5
		Min	23	19	19
		Max	71	78	78
Gender	Male	n (%)	22 (62.9%)	22 (62.9%)	44 (62.9%)
	Female	n (%)	13 (37.1%)	13 (37.1%)	26 (37.1%)
Race	American Indian or Alaska Native	n (%)	0 (0%)	2 (5.7%)	2 (2.9%)
	White	n (%)	25 (71.4%)	20 (57.1%)	45 (64.3%)
	Black or African American	n (%)	10 (28.6%)	12 (34.3%)	22 (31.4%)
	Other	n (%)	0 (0%)	1 (2.9%)	1 (1.4%)
Ethnicity	Hispanic or Latino	n (%)	2 (5.7%)	2 (5.7%)	4 (5.7%)
	Not Hispanic or Latino	n (%)	33 (94.3%)	33 (94.3%)	66 (94.3%)

Sequence A: 16 mg/kg ETI-204 on Day 1 / 16 mg/kg ETI-204 on Day 14 / Placebo on Day 120
Sequence B: 16 mg/kg ETI-204 on Day 1 / Placebo on Day 14 / 16 mg/kg ETI-204 on Day 120

Source: AH109 Pharmacokinetic Report, Section 10.3

ETI-204 Serum Pharmacokinetics

Data Excluded From Analysis

All 70 subjects who received ETI-204 were included in the PK population: 35 in Sequence A and 35 in Sequence B. The full complement of PK parameters could not be determined in all subjects. Individual concentration values for 4 subjects in Sequence A and 6 subjects in Sequence B were excluded from descriptive statistics and from the mean concentration vs time plots because the samples were collected outside the protocol-specified time window. In Sequence A, the Day 14, 8 hours sample from Subject 002-203 was collected 21 minutes late, the Day 28 sample from Subject 002-218 was collected 4 days late, the Day 15 sample from Subject 002-219 was collected 51 minutes late, and the Day 149 sample from Subject 002-235 was collected 4 days late. In Sequence B, the Day 121 sample from Subject 001-104 was collected 1.5 hours early, the Day 120, predose sample from Subject 001-118 was collected 4 days late, the Day 163 sample from Subject 001-129 was collected 4 days late, the Day 120, end-of-infusion sample from Subject 002-208 was collected 17 minutes late, the Day 120, predose sample from Subject 002-220 was collected 10 days late, and the Day 85 sample from Subject 002-230 was collected 19 days late. Concentration values from these samples were employed in PK parameter calculation using actual collection times.

Samples from the final 3 or more scheduled collection time points were not obtained from Subjects 001-108, 001-119, 001-121, and 002-216 in Sequence A. In Sequence B, the final 3 or more scheduled sample collections after the Day 1 dose were not obtained from Subject 001-120;

the final 3 or more scheduled sample collections after the Day 120 dose were not obtained from Subject 001-131. Available data through the final sample collection in these individuals were included in descriptive concentration statistics.

Subject 002-205 (Sequence A) did not receive the scheduled Day 14 dose; the Day 14 samples and all samples from Day 120 onward were not collected. As Subject 002-205 was not dosed in the same fashion as the others in Sequence A, concentration values from this individual were reported, but were excluded from mean concentration-time plots and from descriptive concentration statistics.

Samples were collected from Subject 002-214 (Sequence B) through Day 8 only, with one additional sample collected on Day 79 as the subject withdrew from the study. There were 3 additional subjects with missing, non-terminal phase serum samples: 2 subjects were missing one sample and one subject was missing 4 samples. A single sample was not collected from Subject 001-102 (Sequence A; Day 128) and Subject 001-107 (Sequence B; Day 1, 3 hours after the start of infusion). The Day 14 samples (predose, end-of-infusion, and 3 and 8 hours after the start of infusion) were not collected from Subject 002-204 (Sequence B). The missing samples were considered to have had no significant impact on the determination of PK parameters in these individuals.

The Day 120, end-of-infusion sample was collected from Subject 002-236 (Sequence A), but no concentration was reported because the sample was of insufficient volume to allow ETI-204 quantitation. The absence of an end-of-infusion sample in this subject on Day 120 was considered to have had no significant impact on the determination of PK parameters as the subject received a placebo dose on this day. No data were available for the Day 120 dose (Sequence B) for Subjects 001-120, 001-127,
002-204, and 002-214 as these individuals did not receive this dose.

ETI-204 Serum Concentrations and PK Parameters
Measurable ETI-204 concentrations were observed in the Day 1 predose serum sample in 5 subjects from the PK population (Subjects 001-117, 001-120, and 002-226 from Sequence A, and Subjects 001-126 and 002-220 from Sequence B). In these subjects, predose ETI-204 concentrations ranged from 0.131 to 0.260 µg/mL. The Sponsor stated that the measurable predose concentrations were considered to have had a negligible effect on calculated PK parameter values as the reported concentrations were only 0.034% to 0.14% of the concentration at the subsequent time point (end of infusion).

The sponsor stated that measurable levels in the predose samples likely represent non-specific cross-reactions to endogenous molecules and could not be attributed to an issue with the bioanalytical method. The five ETI-204-positive predose samples represent 7.1% of all predose serum samples collected, which is within the acceptable range that was established during assay validation and is consistent with industry standards. The industry standard for method validation of a ligand-binding assay such as enzyme linked immunosorbent assay requires selectivity to pass in 8 out of 10 blank matrix samples (up to 20% non-selectivity). During the ETI-204 assay validation, selectivity was observed in 9 out of 10 samples (10% non-selectivity). Therefore, the 7.1% positive predose incidence is lower than the 10% non-selectivity rate observed during ETI-204 method validation and is within the acceptable industry standard non-selectivity rate.

Reviewer Comment: There is no information regarding the specific selectivity criteria of a ligand-binding assay provided in the FDA draft Guidance for Industry-Bioanalytical Method Validation. Per the European Medicines Agency (EMA) Guideline on bioanalytical method

validation, Selectivity is tested by spiking at least 10 sources of sample matrix at or near the LLOQ. Selectivity should be evaluated at the low end of an assay where problems occur in most cases. It may be prudent also to evaluate selectivity at higher analyte concentrations. The accuracy should be within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated.

In the Sponsor's bioanalytical assay validation report (09-004), the potential for variable matrix-related interferences was evaluated in eight independent sources of Normal Human Serum at the targeted LQC (300 ng/mL) and HQC (3,000 ng/mL) concentrations. For all eight lots of Normal Human Serum tested, lot precision for each concentration, LQC (300 ng/mL) and HQC (3,000 ng/mL), was within the acceptance criteria of ≤ 20%, and ranged from 1.5% to 14.6%. The accuracy for all eight lots for each concentration was within the acceptance criteria of ± 20% of the nominal, ranging from -12.1% to 6.4%. In the Sponsor's bioanalytical assay validation report (11-069), the validation acceptance criteria for selectivity were set by the Sponsor as follows: ± 20% relative error (RE) of Nominal Value for at least 80% of samples; unspiked sample < LLOQ. The potential for variable matrix-related interferences was evaluated in 10 lots of Normal Human Serum at 0 ng/mL (unspiked) and low QC (300 ng/mL) concentrations. Results showed that 8 out of 10 (80%) of the matrix lots initially evaluated were within the acceptance criteria for %RE<20%; 9 of 10 (90%) of the unspiked samples were < LLOQ.

The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH109 was 7.1%, which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, the positive predose concentrations ranged from 0.131 to 0.260 µg/mL, representing 0.034% to 0.14% of the concentration at the subsequent time point (end of infusion). From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204. The adequacy of the ELISA assay of ETI-204 will be further assessed pending results of inspection of the corresponding bioanalytical site (b) (4)

Mean (± SD) ETI-204 concentration versus time profiles for Sequence A (16 mg/kg ETI-204 on Day 1 / 16 mg/kg ETI-204 on Day 14 / Placebo on Day 120) and Sequence B (16 mg/kg ETI-204 on Day 1 / Placebo on Day 14 / 16 mg/kg ETI-204 on Day 120) are presented in Figures 1 and 2. Pharmacokinetic parameters for ETI-for sequence A and Sequence B, Day 1 and Day 120, in healthy subjects are summarized in Table 3, Table 4, and Table 5.

Sequence A

ETI-204 attained maximum serum concentrations on Day 14, at or within 1 day after the end of the 1.5-hour infusion, in 33 out of the 34 subjects included in descriptive statistics for Sequence A. In the remaining individual (Subject 001-121), the time of maximum concentration occurred on Day 1, with Tmax at the first sampling time after the end of infusion (0.125 days). Overall, T_{max} ranged from 0.125 to 14.0 days relative to the commencement of infusion on Day 1. Median T_{max} was 13.1 days, which was approximately 1 hour after the end of infusion on Day 14. Mean $_{Cmax}$ was 506 µg/mL (Table 3).

Serum concentrations declined after the peak in a generally biexponential fashion, with the terminal phase (starting point for t½ determination) commencing at Day 27 or later across subjects in Sequence A. Mean t½ was 22.8 days and individual values ranged from 12.0 to 34.1 days across individuals (Table 3). The extrapolated portion (AUCextrap) of the total AUC(0-inf) value was less than 5% in all subjects.

CL in Sequence A ranged from 0.134 to 0.499 L/day, with a mean of 0.274 L/day (Table 3). This is less than 0.02% of hepatic or renal blood flow (2100 and 1800 L/day, respectively) and less than 0.2% of the glomerular filtration rate (180 L/day) in a 70 kg human, which suggests that the fraction of administered ETI-204 eliminated by the liver or unchanged via the kidney is negligible. Mean Vd was 8.69 L, ranging from 4.62 to 16.6 L (Table 3). This is greater than human plasma volume (3 L), but lower than extracellular fluid volume (18 L), suggesting that ETI-204 may distribute out of the vascular compartment, but not extensively.

Sequence B

The PK in Sequence B was treated as 2 separate 16 mg/kg doses (Day 1 and Day 120); Day 120 data were to be treated as if from a separate, independent dose only if the predose concentrations were all BLQ. If there was any ETI-204 carryover from the Day 1 dose (ie, measurable concentrations predose on Day 120), then the Day 120 dose was to be treated as a sequential dose to that on Day 1. PK parameters were calculated for the Day 120 dose, despite the fact that each subject had a measurable ETI-204 concentration in the Day 120 predose sample. The calculations were performed because the predose concentrations were 0.474 to 16.4 µg//mL, representing 0.09 to 5.5% of the subsequent end-of-infusion concentration), the impact on PK parameters determined for the Day 120 dose was considered to be negligible.

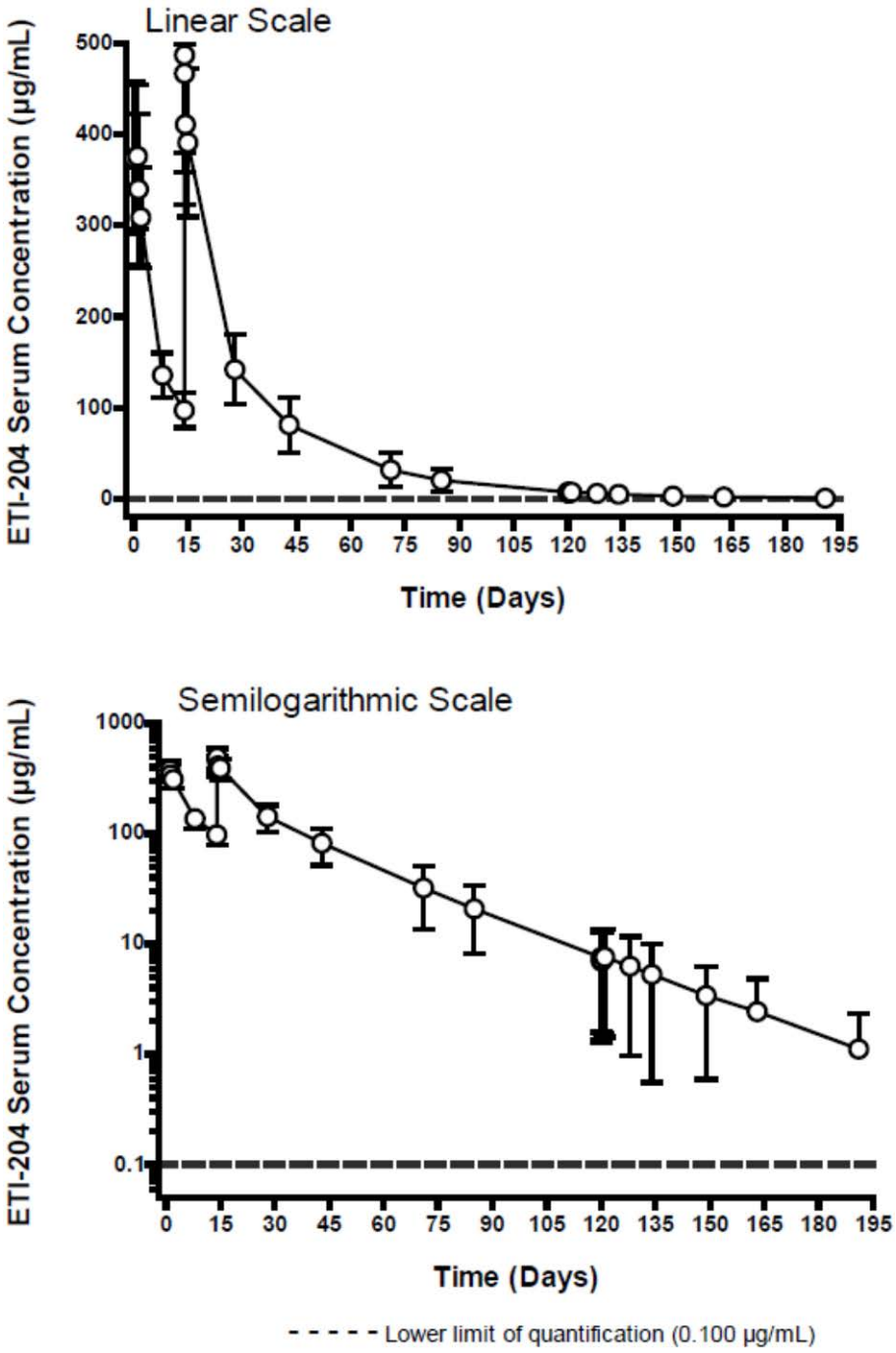
The disposition of ETI-204 after the Day 1 dose was virtually indistinguishable from that after the Day 120 dose. ETI-204 attained maximum serum concentrations at or within 24 hours after the end of the 1.5-hour infusion on each dosing day. Overall, T_{max} ranged from 0.0625 to 1.00 day (1.50 to 24 hours) and 0.0618 to 1.00 day (1.48 to 24 hours) after the beginning of ETI-204 infusion on Days 1 and 120, respectively (Tables 4 and 5). Respective median T_{max} was 0.125 days (3 hours) and 0.0743 days (1.78 hours). Mean C_{max} was 384 and 402 µg/mL after the Day 1 and Day 120 doses, respectively (Tables 4 and 5).

Serum concentrations declined after the peak in a generally biexponential fashion, with the terminal phase (starting point for t½ determination) commencing by Day 1 to Day 71 after the Day 1 dose and by Day 1 to Day 29 after the Day 120 dose. Mean t½ was 21.5 and 18.6 days after the Day 1 and Day 120 doses, respectively, with individual values ranging from 14.4 to 49.4 days for the Day 1 dose and from 13.1 to 25.0 days for the Day 120 dose (Tables 4 and 5). The average AUCextrap was 2% and 6% after the Days 1 and 120 doses, respectively. The total exposure after the combined Day 1 and Day 14 doses (Sequence A), as indicated by $AUC_{0\text{-}inf}$, was approximately twice that after a single 16 mg/kg dose, suggesting that PK was linear following the administration of a second dose 13 days after the first.

ETI-204 CL and Vd values for the Day 1 and Day 120 doses were similar to those observed in Sequence A. This indicates that the disposition of ETI-204 after two 16 mg/kg doses 14 days apart does not differ from that after a single 16 mg/kg dose.

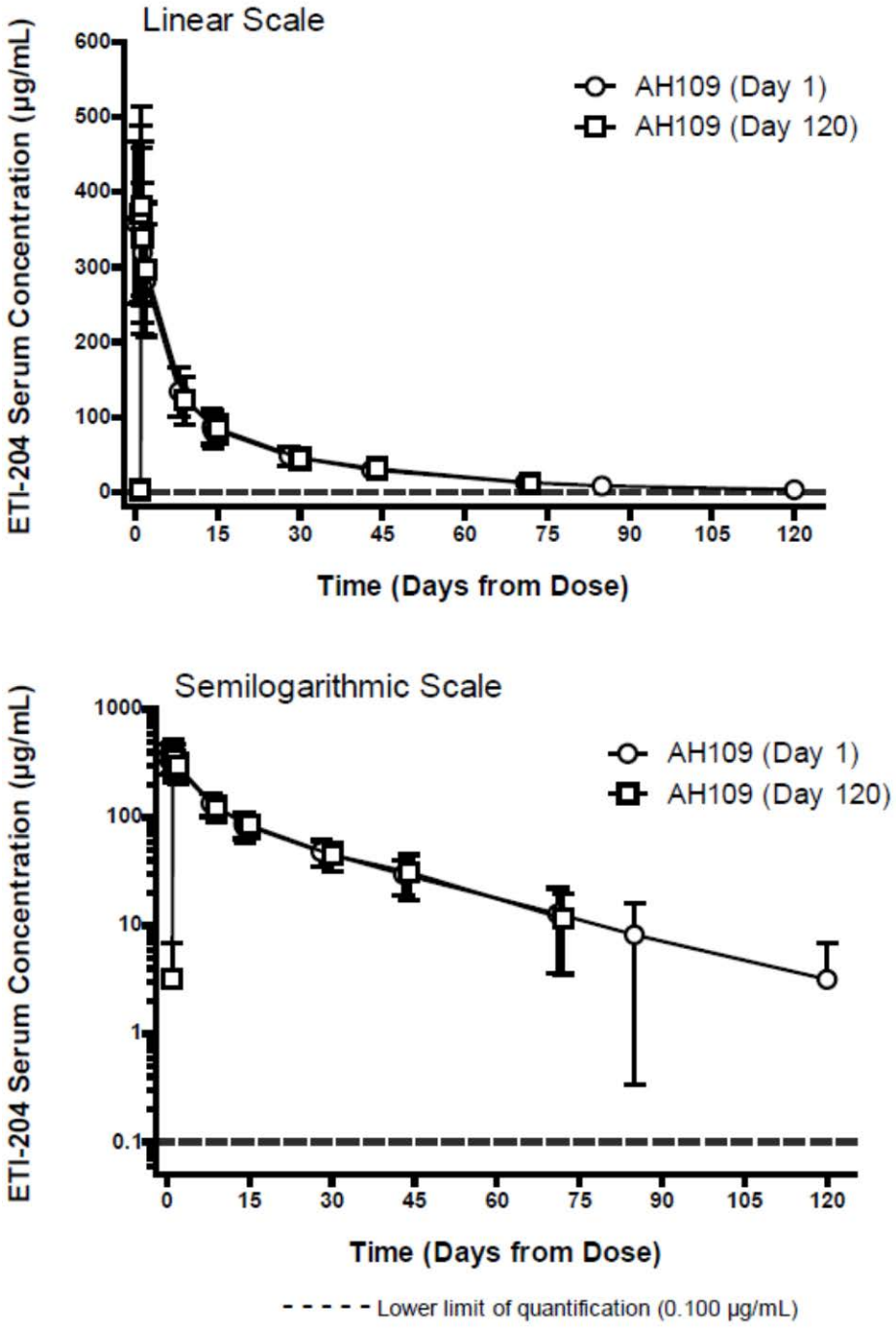
Inter-subject variability in PK was moderate, with CV values across parameters ranging from approximately 20% to 31% in Sequence A, and approximately 18% to 35% in Sequence B (not including T_{max}).

Figure 1. Mean (± SD) Serum Concentration-Time Profiles for ETI-204 for Sequence A (16 mg/kg ETI-204 on Day 1 / 16 mg/kg ETI-204 on Day 14 / Placebo on Day 120) in Healthy Subjects (Linear and Log Scale)



Source: AH109 Pharmacokinetic Report, Section 11.2

Figure 2. Mean (± SD) Serum Concentration-Time Profiles for ETI-204 for Sequence B (16 mg/kg ETI-204 on Day 1 / Placebo on Day 14 / 16 mg/kg ETI-204 on Day 120) in Healthy Subjects (Linear and Log Scale)



Source: AH109 Pharmacokinetic Report, Section 11.2

Table 3. Summary of ETI-204 Pharmacokinetic Parameters for Sequence A (16 mg/kg ETI-204 on Day 1 / 16 mg/kg ETI-204 on Day 14 / Placebo on Day 120) in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$AUC_{(0\text{-191 days})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)
N	34	34	32	32	32	32	32	32
Mean	506	12.8	10,200	10,300	10,300	22.8	0.274	8.69
SD	102	2.27	2500	2530	2480	5.82	0.0862	2.65
CV%	20.2	17.6	24.4	24.5	24.2	25.6	31.4	30.5
Min	315	0.125	6290	6300	6300	12.0	0.134	4.62
Median	520	13.1	10,200	10,200	10,200	22.8	0.260	8.52
Max	739	14.0	17,200	17,400	17,200	34.1	0.499	16.6
Geometric mean	496	NC	9970	10,000	9990	22.0	0.262	8.32

NC: not calculated
Source: AH109 Pharmacokinetic Report, Section 11.3

Table 4. Summary of ETI-204 Pharmacokinetic Parameters for Sequence B, Day 1 (16 mg/kg ETI-204 on Day 1 / Placebo on Day 14 / 16 mg/kg ETI-204 on Day 120) in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$AUC_{(0\text{-120 days})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)	Vss (L)
N	35	35	34	34	34	34	34	34	34
Mean	384	0.134	4550	4690	4560	21.5	0.300	8.75	7.20
SD	103	0.164	1220	1370	1220	6.73	0.104	2.09	1.49
CV%	26.7	122.4	26.7	29.3	26.7	31.2	34.7	24.0	20.8
Min	200	0.0625	1950	1980	1970	14.4	0.106	4.39	3.73
Median	360	0.125	4320	4440	4300	20.1	0.302	8.56	7.17
Max	577	1.00	8890	9580	8890	49.4	0.699	15.6	10.0
Geometric mean	371	NC	4410	4520	4420	20.8	0.284	8.51	7.04

NC: not calculated
Source: AH109 Pharmacokinetic Report, Section 11.3

Table 5. Summary of ETI-204 Pharmacokinetic Parameters for Sequence B, Day 120 (16 mg/kg ETI-204 on Day 1 / Placebo on Day 14 / 16 mg/kg ETI-204 on Day 120) in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)	Vss (L)
N	31	31	30	27	27	27	27	27
Mean	402	0.122	4300	4400	18.6	0.313	8.33	7.01
SD	134	0.166	1010	796	3.43	0.0760	2.39	2.32
CV%	33.4	136.4	23.6	18.1	18.5	24.3	28.6	33.1
Min	160	0.0618	3210	3290	13.1	0.202	4.41	3.27
Median	342	0.0743	4070	4200	18.4	0.301	7.99	7.07
Max	702	1.00	7660	6080	25.0	0.481	15.1	14.3
Geometric mean	381	NC	4190	4330	18.3	0.304	8.02	6.66

* The data reported for Day 120 cannot be considered definitive because residual ETI-204 concentrations from the Day 1 dose were present in all subjects prior to the Day 120 dose. The data are reported for illustrative purposes only.

NC: not calculated

Source: AH109 Pharmacokinetic Report, Section 11.3

Pharmacodynamics

Measurable (ie, titer ⩾1:10) postdose ATA values were observed in 2 subjects. Subject 001-114 (Sequence A) had a 1:40 titer on Days 120 and 191, and Subject 002-231 (Sequence B) had titers of 1:40 and 1:80 on Days 163 and 191, respectively. The presence of ATA did not appear to have an impact on ETI-204 disposition in these individuals. The shapes of the ETI-204 concentration-time profiles in these subjects were not noticeably different from the rest of the subject population and did not display evidence of nonlinearity. In addition, PK parameters for both subjects were consistent with those of the other subjects in the study, falling within the range of values observed in their respective groups.

Reviewer Comment: Please refer to the OBP review for the assessment of ETI-204 immunogenicity following 2 repeat doses of IV ETI-204 at 16 mg/kg.

SAFETY RESULTS

No deaths were reported during the study. One non-drug related SAE (ankle fracture) was reported during the study. Study drug was permanently discontinued in 2 subjects due to a hypersensitivity reaction on Day 1. Both subjects completed the infusion on Day 1, but did not receive any subsequent doses. Overall 61 (87.1%) subjects reported at least one AE during the study. The observed frequencies of AEs ranged from 37.1% to 62.9% for ETI-240 compared to 45.7% to 65.7% for placebo. The number of subjects who experienced AEs were similar between Sequence A and Sequence B on Day 1 (ETI-204 versus ETI-204), on Day 14 (ETI-204 versus placebo), and on Day 120 (placebo vs. ETI-204). The majority of the AEs were of mild intensity (87.1%). The most commonly reported AE was somnolence attributable to the administration of predose diphenhydramine for the prevention of hypersensitivity reactions. No clinically significant changes or adverse trends were identified for vital signs, safety laboratory parameters, or ECGs following the administration of ETI-204 compared to placebo.

Reviewer Comment: Please refer to the Clinical Review by Dr. Gopinath, Ramya for safety assessment of ETI-204 following 2 repeated IV doses of 16 mg/kg given 14 days and 120 days apart.

APPLICANT'S DISCUSSION AND CONCLUSION

The primary dispositional PK parameters, CL and Vd, were similar when ETI-204 was administered as a single 16 mg/kg dose and as two 16 mg/kg doses given sequentially on Days 1 and 14. The total exposure after the combined Day 1 and Day 14 doses, as indicated by AUC0-inf, was approximately twice that after a single 16 mg/kg dose, suggesting that PK was linear following the administration of a second dose 13 days after the first.

The disposition of ETI-204 when a second dose was administered on Day 120 was virtually identical to that after the first dose on Day 1. PK parameters after the second dose could not be considered definitive because residual ETI-204 concentrations from the first dose were present in serum at the time the Day 120 dose was administered. However, as the predose concentrations were considered to have no noticeable impact on the Day 120 PK, the parameters could be used for comparative purposes.

ETI-204 CL was a negligible fraction of hepatic and renal blood flow, as well as glomerular filtration rate, which suggests that the fraction of administered ETI-204 eliminated by the liver or unchanged via the kidney is negligible. Vd was greater than blood volume, but lower than extracellular fluid volume, which suggests that ETI-204 may distribute out of the vascular compartment, but not extensively.

The administration of ETI-204 at 16 mg/kg up to twp doses given 14 days or 4 months apart was generally well tolerated in adult volunteers. The sequence of study drug administration did not appear to affect the safety profile of ETI-204. There were no drug-related SAEs reported. Overall, the number of subjects who experienced AEs was similar between ETI-204 and placebo on Day 14 and Day 120. The majority of the AEs were of mild intensity and the overall incidence of severe AEs was low (5.7%). The most frequent study drug-related AEs were local infusion site reactions, common among IV administered drugs.

REVIEWER ASSESSMENT:

Results from Study AH109 adequately determined the pharmacokinetics of ETI-204 after repeated dosing, separated by 14 and 120 days. The applicant's pharmacokinetic conclusions based on these findings are valid. The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH109 was 7.1%, which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, the positive predose concentrations ranged from 0.131 to 0.260 µg/mL, representing 0.034% to 0.14% of the concentration at the subsequent time point (end of infusion). From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204.

AH110:
An Open-Label, Randomized, Parallel Group Study to Assess the Safety, Tolerability, and Pharmacokinetics of ETI-204 Alone and in the Presence of Ciprofloxacin in Adult Volunteers

Date(s): October 29, 2013– April 9, 2014
Sponsor: Elusys Therapeutics, Inc.
Clinical Site: Quintiles - Phase I Services, 6700 W. 115th Street, Overland Park, KS 66211
Analytical Site: (b) (4)

OBJECTIVES:
Primary:

The primary objective of the study was to evaluate the safety and tolerability of intravenous (IV) ETI-204 alone and in the presence of IV and oral ciprofloxacin.

Secondary:

- To evaluate the pharmacokinetics (PK) of IV ETI-204 alone and in the presence of IV and oral ciprofloxacin
- To evaluate the immunogenicity of IV ETI-204

Exploratory:

- To evaluate the effect of ETI-204 on the PK of IV and oral ciprofloxacin by comparing the ciprofloxacin PK data from this study with published, historical ciprofloxacin PK data

STUDY DESIGN:
This was an open-label, randomized, parallel group study of IV ETI-204 administered alone and in the presence of IV and oral ciprofloxacin in 40 adult volunteers randomized in a 1:1 ratio to either:

- Group 1: IV ETI-204 16 mg/kg infused over 90 minutes on Day 1 followed by 400 mg IV dose of ciprofloxacin on Day 1, then 750 mg BID oral ciprofloxacin from Day 2 through the morning of Day 9
- Group 2: IV ETI-204, 16 mg/kg infused over 90 minutes on Day 1

The total duration of the study for each subject was approximately 100 days divided as follows:

- Screening: Days -28 to -2
- In-Unit Phases: Days -1, 1 and 2 [all subjects]; Days 8, 9 and 10 [Group 1 only]
- Out-of-unit Visits: Day 9 [Group 2 only]; Day 16 (+/- 3 days); Day 29 (+/- 3 days); Day 43 (+/-
3 days)
- Final Visit: Day 71 (+/- 3 days)

All subjects were pretreated with 50 mg oral diphenhydramine approximately 30 minutes prior to the start of the ETI-204 infusion. The end of the study (ie, study completion date) was defined as the date of the last visit of the last subject undergoing the study.

FORMULATIONS:
ETI-204
ETI-204 was supplied in sterile, (b) (4) mL, clear, (b) (4) glass vials with gray stoppers that contained (b) (4) mL of clear, colorless to pale yellow solution consisting of 100 mg/mL ETI-204, 40

mM histidine, 200 mM sorbitol, and 0.01% polysorbate 80 with a pH of 5.5. Translucent particles may have been present. ETI-204 bulk drug substance was manufactured, packaged, and labeled in accordance with
current Good Manufacturing Practices (GMP) at Lonza Biologics, Portsmouth, NH. Final drug product was manufactured, packaged, and labeled in accordance with current GMP standards at (b) (4). ETI-204 drug supplies were shipped to clinical sites by (b) (4). The ETI-204 lot for the study was 3-FIN-1513.

Ciprofloxacin
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).

INCLUSION/EXCLUSION CRITERIA:
Healthy males and females of non-childbearing potential of ≥18 years of age without restrictions for body weight, body mass index, and smoking were enrolled.

DOSE AND ADMINISTRATION
ETI-204
Using each subject's weight (kg), the pharmacist calculated the correct concentration of ETI-204 in the dosing solution (0.9% sterile sodium chloride) to deliver a dose of 16 mg/kg in a total volume of 250 mL. Single doses of 16 mg/kg ETI-204 were IV infused over 90 minutes (± 5 minutes) at a rate of approximately 3 mL/min using a Primary PlumSet™ infusion set with a 0.2 micron in-line filter and an appropriate infusion pump. When the infusion was complete (ie, when the IV bag was empty and before the drip chamber of the IV tubing was empty), the infusion bag and line were flushed with an additional 40 mL of sterile 0.9% saline to ensure that the entire contents of the infusion bag and line were administered. The total dose volume of 250 mL plus the saline flush (minus the priming volume) were infused. Study drug was administered to the subject within 24 hours of initial dilution. All subjects were premedicated with 50 mg oral diphenhydramine approximately 30 minutes prior to the start of the ETI-204 infusion on Day 1.

Ciprofloxacin
Subjects randomized to Group 1 received single IV doses of ciprofloxacin 400 mg infused over 60 minutes on Day 1, immediately following the ETI-204 administration. Subjects also received ciprofloxacin 750 mg orally every 12 hours on Days 2 through 8 and a single 750 mg dose of oral ciprofloxacin on the morning of Day 9. The dose of oral ciprofloxacin (750 mg every 12 hours) evaluated in this study is the highest recommended oral dose, which has been shown to result in C_{max} and AUC_{0-24} that approximate those seen with the highest recommended IV dose of ciprofloxacin (400 mg every 8 hours).

Reviewer Comment: Per CIPRO (ciprofloxacin hydrochloride) labels, the recommended dose for inhalational anthrax (post-exposure) is 400 mg (IV) or 500 mg (oral) BID for 60 days. This dose regimen of ciprofloxacin was used in the DDI study of raxibacumab and ciprofloxacin (BLA 125349), i.e., a single IV ciprofloxacin (400 mg) dose on Day 0 immediately followed by a single IV raxibacumab (40 mg/kg) dose, a second IV ciprofloxacin (400 mg) dose 12 hours later, and then PO ciprofloxacin (500 mg Q12h, Days 1 to 7) for a total of 13 doses. In the current DDI study of ETI-204 and ciprofloxacin, only one 400 mg IV dose of ciprofloxacin was used on Day 1 immediately following the ETI-204 administration. In addition, a higher dose of oral ciprofloxacin (750 mg BID, the highest recommended oral dose for ciprofloxacin) was administered on Day 2 to Day 9 morning. Given the long half-life of ETI-204 (~20 days), the dose

regimen of ciprofloxacin used in this DDI study appear appropriate to evaluate the DDI potential of ciprofloxacin on ETI-204.

PHARMACOKINETIC ASSESSMENTS:
Blood samples (3.5 mL) for analysis of ETI-204 serum concentrations (PK) were obtained on Day 1 at predose, at the end of ETI-204 infusion, and 2.5, 4.5 and 7.5 hours after the start of the ETI-204 infusion; blood samples for PK assessments were collected after ECGs and vital signs were recorded and deviations of up to +/15 minutes from specified post-dose timepoints were allowed. On the remaining PK sampling days, [Day 2 (24 hours), Days 9, 16, 29, 43, and 71], blood samples were obtained within ± 2 hours of the original infusion time, whenever possible. The actual time of sample collection was recorded.

Blood samples (3 mL) for analysis of IV ciprofloxacin PK were obtained predose (prior to IV infusion of ETI-204) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours following the start of the ciprofloxacin infusion. Blood samples (3 mL) for analysis of oral ciprofloxacin PK were obtained at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours after the last dose.

IMMUNOGENICITY ASSESSMENTS:
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 9, 29, 43, and 71.

BIOANALYTICAL ANALYSIS:
ETI-204 concentrations in human serum were measured using a validated ELISA method. Ciprofloxacin concentrations in human plasma were measured by a validated LC-MS/MS method (Table 1).

Table 1. Bioanalytical results of ETI-204 in human serum by ELISA (Study report 13-084) and ciprofloxacin in human plasma by LC-MS/MS

Criterion	ETI-204	Ciprofloxacin	Comments
Calibration Range	100-5000 ng/mL	10-2000 ng/mL	Satisfactory
LLOQ	100 ng/mL	10 ng/mL	Satisfactory
ULOQ	5000 ng/mL	2000 ng/mL	Satisfactory
Linearity, mean R^2	Not reported	Not reported	N/A
Accuracy	Within ±9.7%	Within ±1.2%	Satisfactory
Precision, CV	≤7.2%	≤4.1%	Satisfactory
Quality Control	300, 1500, 4000 ng/mL	30, 750, 1500 ng/mL	Satisfactory
Accuracy (%RE)	Within ±6.5%	Within ±8.9%	Satisfactory
Precision, CV	20.7%, 8.5%, and 8.1% for the QCL, QCM, and QCH samples, respectively	≤6.1%	Satisfactory
Stability	• Samples were analyzed within 192 days of collection • Stability: 24 month at -70 ºC	• Samples were analyzed within 192 days of collection Stability: 215 days in human plasma and K_2EDTA at -70 ºC	Satisfactory

PHARMACOKINETIC/PHARMACODYNAMIC/STATISTICAL ANALYSIS:

ETI-204

PK parameters included maximum concentration (C_{max}); time to reach C_{max} (T_{max}); area under the concentration-time curve (AUC) from time 0 to 10 days ($AUC_{0\text{-}10\ days}$); AUC from time 0 to the time of last measurable concentration ($AUC_{0\text{-}last}$); AUC from time 0 extrapolated to infinite time ($AUC_{0\text{-}inf}$); mean residence time from time 0 extrapolated to infinite time ($MRT_{0\text{-}inf}$); terminal half-life ($t_{½}$); systemic clearance (CL); CL divided by weight (CL/kg); volume of distribution (Vd); Vd divided by weight (Vd/kg), volume of distribution at steady state (Vss), and Vss divided by weight (Vss/kg).

Ciprofloxacin

PK parameters of oral ciprofloxacin at steady state included maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), minimum observed serum concentration (C_{min}), time of C_{min} (T_{min}), area under the curve of the plasma concentration during the dosing interval ($AUC_{0\text{-}tau}$), terminal phase rate constant (λ_z), terminal half-life ($t_{½}$), apparent oral clearance (CL/F), and apparent volume of distribution (Vd/F).

Anti-ETI204 antibodies: The PD parameter was anti-therapeutic antibodies (ATA).

Statistical Assessment

ETI-204 and ciprofloxacin concentrations and PK parameters were summarized with descriptive statistics by treatment group. The effect of ciprofloxacin on the PK of ETI-204 was based on a between-group comparison of the PK parameters for ETI-204 with and without ciprofloxacin. To this end, a one-way analysis of variance (ANOVA) was estimated for the log-transformed parameters with a fixed effect for treatment group (ETI-204 plus ciprofloxacin and ETI-204 alone). Geometric least-squares means (LSMs) per treatment, corresponding 95% confidence intervals (CI), ratios of geometric LSMs for ETI-204 plus ciprofloxacin over ETI-204 alone, and corresponding 90% CIs were estimated. Lack of a PK interaction due to ciprofloxacin was concluded if the 90% CI for these ratios falls within the 80% to 125% interval. The effect of ETI-204 on the PK of ciprofloxacin was evaluated through a comparison of the ciprofloxacin PK data from this study with published, historical ciprofloxacin PK data.

RESULTS:

Study Population

A total of 40 subjects (20 in ETI-204 alone group and 18 in ETI-204+ciprofloxacin group) were enrolled and all subjects were included in the Safety Population. One male subject in the ETI-204 + ciprofloxacin group withdrew prematurely on Day 1 for personal reasons, after having received the ETI-204 IV and ciprofloxacin IV doses, and did not complete all the study assessments.

Demographics

A summary of demographic and baseline characteristics for the study population is presented in Table 2. There were no substantial differences in demographic characteristics between the study groups.

Table 2. Demographics and Baseline Characteristics – Study AH110

Demographic	ETI-204 + Ciprofloxacin N=20	ETI-204 Alone N=20	Overall N=40
Age (years)			
N	20	20	40
Mean	33	33	33
SD	14.0	11.8	12.8
Median	27	30	29
Min	18	18	18
Max	60	59	60
Sex			
Male	12 (60.0%)	12 (60.0%)	24 (60.0%)
Female	8 (40.0%)	8 (40.0%)	16 (40.0%)
Race			
White	14 (70.0%)	14 (70.0%)	28 (70.0%)
Black or African American	3 (15.0%)	5 (25.0%)	8 (20.0%)
American Indian/Alaska Native	3 (15.0%)	1 (5.0%)	4 (10.0%)
Ethnicity			
Hispanic or Latino	6 (30.0%)	1 (5.0%)	7 (17.5%)
Not Hispanic or Latino	14 (70.0%)	19 (95.0%)	33 (82.5%)
Body Weight (kg)			
N	20	20	40
Mean	75.8	78.4	77.1
SD	18.26	16.63	17.29
Median	73.4	78.0	76.1
Min	51.6	49.8	49.8
Max	123.9	111.9	123.9
Height (cm)			
N	20	20	40
Mean	169.4	169.5	169.4
SD	9.11	7.29	8.15
Median	168.8	169.8	169.0
Min	154.2	156.4	154.2
Max	188.1	182.5	188.1
BMI (kg/m2)			
N	20	20	40
Mean	26.2	27.1	26.7
SD	4.75	4.80	4.74
Median	25.2	26.7	26.0
Min	19.2	18.9	18.9
Max	39.5	36.9	39.5

Screening values are used except for Weight, which is Day -1.
N = number of subjects randomized

Source: AH110 Pharmacokinetic Report, Section 10.3

ETI-204 Serum Pharmacokinetics

Data Excluded From Analysis

Of the 40 subjects who received ETI-204, 38 were included in the PK population. The PK population comprised all 20 subjects who received ETI-204 alone and 18 subjects who received ETI-204 + ciprofloxacin. Two subjects in the ETI-204 + ciprofloxacin group received partial

doses of ETI-204 (Subjects 001-103 and 001-133 discontinued study drug due to AEs) and were excluded from the PK population (Appendix 16.2.1 Listing 16.2.3-1). Concentration data and PK parameters for subjects who received a partial dose of ETI-204 were reported, but were excluded from summary statistics and additional analysis.

ETI-204 Serum Concentrations and PK Parameters

Measurable ETI-204 concentrations were observed in the predose serum sample in four subjects from the PK population (Subjects 001-101, 001-114, and 001-120 in the ETI-204 alone group; Subject 001-112 in the ETI-204 + ciprofloxacin group). In these subjects, predose ETI-204 concentrations ranged from 0.159 to 1.83 μg/mL. The Sponsor stated that the measurable predose concentrations were considered to have had a negligible effect on calculated PK parameter values as the reported concentrations were only 0.029% to 0.47% of the concentration at the subsequent time point (end of infusion). The Sponsor also stated that the four ETI-204-positive predose samples represent 10% of all predose serum samples collected, which is within the acceptable range (10% nonselectivity) that was established during assay validation and is consistent with industry standards (20% nonselectivity).

Reviewer Comment: There is no information regarding the specific selectivity criteria of a ligand-binding assay provided in the FDA draft Guidance for Industry-Bioanalytical Method Validation. Per the European Medicines Agency (EMA) Guideline on bioanalytical method validation, Selectivity is tested by spiking at least 10 sources of sample matrix at or near the LLOQ. Selectivity should be evaluated at the low end of an assay where problems occur in most cases. It may be prudent also to evaluate selectivity at higher analyte concentrations. The accuracy should be within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated.

In the Sponsor's bioanalytical assay validation report (09-004), the potential for variable matrix-related interferences was evaluated in eight independent sources of Normal Human Serum at the targeted LQC (300 ng/mL) and HQC (3,000 ng/mL) concentrations. For all eight lots of Normal Human Serum tested, lot precision for each concentration, LQC (300 ng/mL) and HQC (3,000 ng/mL), was within the acceptance criteria of ≤ 20%, and ranged from 1.5% to 14.6%. The accuracy for all eight lots for each concentration was within the acceptance criteria of ± 20% of the nominal, ranging from -12.1% to 6.4%. In the Sponsor's bioanalytical assay validation report (11-069), the validation acceptance criteria for selectivity were set by the Sponsor as follows: ± 20% relative error (RE) of Nominal Value for at least 80% of samples; unspiked sample < LLOQ. The potential for variable matrix-related interferences was evaluated in 10 lots of Normal Human Serum at 0 ng/mL (unspiked) and low QC (300 ng/mL) concentrations. Results showed that 8 out of 10 (80%) of the matrix lots initially evaluated were within the acceptance criteria for %RE<20%; 9 of 10 (90%) of the unspiked samples were < LLOQ.

The observed positive predose samples (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH110 was 10%, which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, the positive predose concentrations ranged from 0.159 to 1.83 μg/mL, representing 0.029% to 0.47% of the concentration at the subsequent time point (end of infusion). From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204. The adequacy of the ELISA assay of ETI-204 will be further assessed pending results of inspection of the corresponding bioanalytical site (b) (4)

Mean (± SD) ETI-204 concentration versus time data are presented for the PK population across the sampling time course in Figure 1. Pharmacokinetic parameters for ETI-204 following single intravenous administration of 16 mg/kg alone and with ciprofloxacin in healthy subjects are summarized in Table 3 and Table 4, respectively.

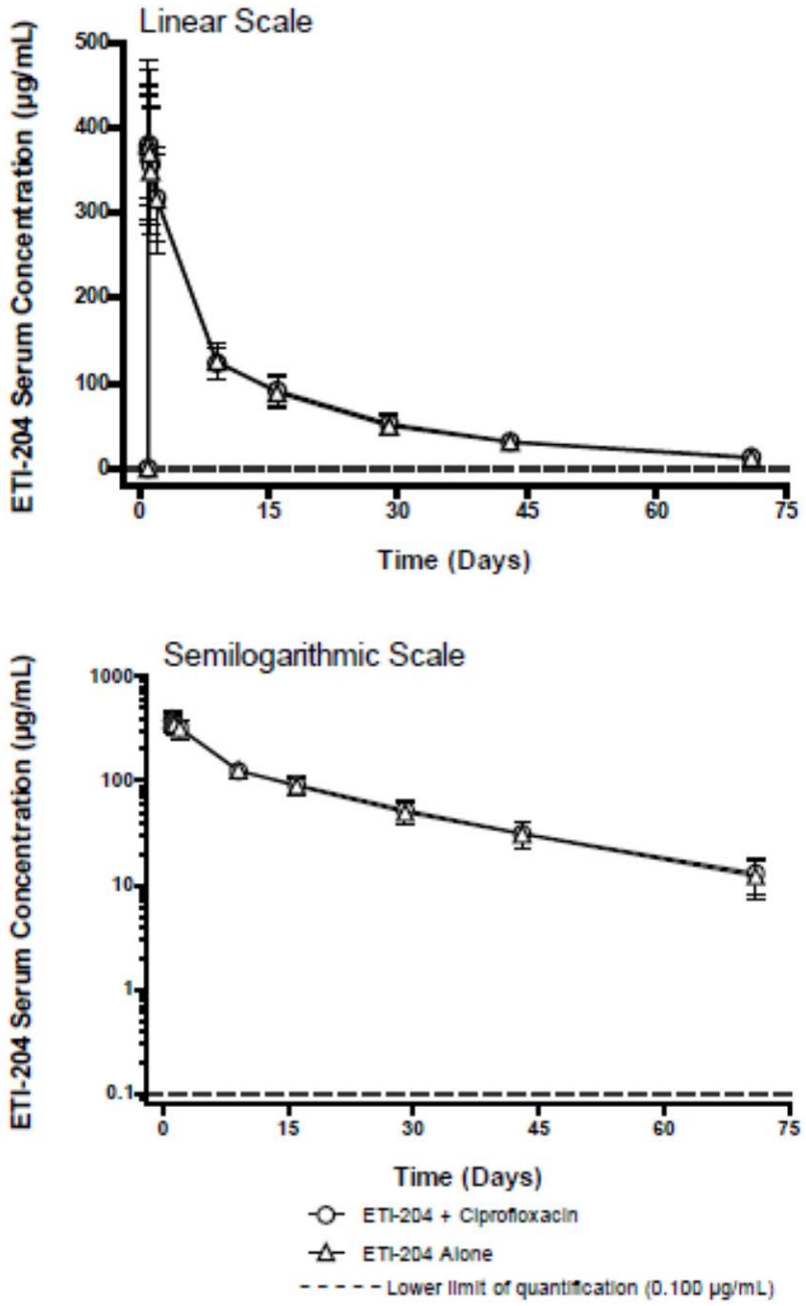
Overall, ETI-204 Tmax ranged from 0.0625 to 1.0 day (1.5 to 24 hours) after the beginning of ETI-204 infusion. Median Tmax in both the ETI-204 alone and ETI-204 + ciprofloxacin groups was 0.104 days (2.5 hours). Mean Cmax in the ETI-204 alone and ETI-204 + ciprofloxacin groups was 402 and 397 μg/mL, respectively.

Serum concentrations declined after the peak in a generally biexponential fashion, with the terminal phase (starting point for $t_{1/2}$ determination) commencing by Day 9 or later in all subjects. Individual $t_{1/2}$ values ranged from 11.3 to 27.8 days across all subjects; mean $t_{1/2}$ was 19.5 days and 19.0 days in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively.

All collected Day 71 samples had quantifiable ETI-204 concentrations. Of the 37 subjects for whom an $AUC_{(0\text{-inf})}$ value could be determined, only 2 (5%) had an extrapolated AUC portion (AUCextrap) greater than 20% of the total AUC(0-inf) value. In the remaining 35 subjects, the average AUCextrap was approximately 7%. Therefore, ETI-204 PK was considered to have been adequately characterized with the sampling schedule used in this study. Mean (range) CL values were 0.268 L/day (0.160 to 0.370 L/day) and 0.247 L/day (0.171 to 0.466 L/day) in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively. These mean values are less than 0.02% of hepatic or renal blood flow (2100 and 1800 L/day, respectively) and less than 0.2% of the glomerular filtration rate (180 L/day) in a 70 kg human, which suggests that the fraction of administered ETI-204 eliminated by the liver or unchanged via the kidney is negligible. Mean (range) Vss was 6.28 L (3.93 to 10.7 L) and 5.68 L (4.38 to 7.13 L) in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively. These are greater than estimated human plasma volume (3 L), but lower than estimated extracellular fluid volume (18 L), suggesting that ETI-204 may distribute out of the vascular compartment, but not extensively. Intersubject variability in PK was moderate, with CV values across parameters ranging from approximately 16% to 34% (excluding T_{max}).

In general, ETI-204 PK parameters (C_{max} and AUC) were similar after administration of ETI-204 alone to those after co-administration with ciprofloxacin (Table 5).

Figure 1. Mean (± SD) Serum Concentration-Time Profiles for ETI-204 Following Single Intravenous Administration of 16 mg/kg with and without Ciprofloxacin in Healthy Subjects (Linear and Log Scale)



Source: AH110 Pharmacokinetic Report, Section 11.2

Table 3. Summary of ETI-204 Pharmacokinetic Parameters Following Single Intravenous Administration of 16 mg/kg IV Alone in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)	Vss (L)
N	20	20	20	19	19	19	19	19
Mean	402	0.206	4514	4891	19.5	0.268	7.57	6.28
SD	91.0	0.276	792	897	4.14	0.0583	2.58	1.68
CV%	22.6	134	17.5	18.3	21.2	21.8	34.1	26.7
Min	256	0.0625	3124	3293	11.3	0.160	4.27	3.93
Median	381	0.104	4606	5015	19.8	0.254	7.19	6.35
Max	598	1.00	5800	6265	27.8	0.370	13.9	10.7
Geometric mean	393	NC	4446	4809	19.1	0.261	7.19	6.08

NC: not calculated

Table 4. Summary of ETI-204 Pharmacokinetic Parameters Following Single Intravenous Administration of 16 mg/kg IV with Ciprofloxacin in Healthy Subjects

Statistic	C_{max} (µg/mL)	T_{max} (day)	$AUC_{(0\text{-last})}$ (µg·day/mL)	$AUC_{(0\text{-inf})}$ (µg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	Vd (L)	Vss (L)
N	18	18	17	16	16	16	16	16
Mean	397	0.161	4603	4990	19.0	0.247	6.59	5.68
SD	63.7	0.214	791	942	3.00	0.0732	1.34	0.986
CV%	16.1	133	17.2	18.9	15.8	29.7	20.3	17.4
Min	305	0.0625	3285	3472	14.3	0.171	4.70	4.38
Median	383	0.104	4570	4984	18.7	0.224	6.56	5.57
Max	529	1.00	6236	6796	25.5	0.466	9.64	7.13
Geometric mean	392	NC	4541	4908	18.8	0.239	6.47	5.60

NC: not calculated

Source: AH110 Pharmacokinetic Report, Section 11.3

Table 5. Summary Statistical Assessment of ETI-204 Pharmacokinetic Parameters after Administration with and without Ciprofloxacin

Parameter (Units)	Ratio of Geometric LS Means (Test/ Reference)[a] (%)	90% Confidence Interval of the Ratio[b]
C_{max} (µg/mL)	99.9	89.9, 111
$AUC_{0\text{-}last}$ (µg·day/mL)	102	92.6, 113
$AUC_{0\text{-}inf}$ (µg·day/mL)	102	91.5, 114

[a] Difference of least-squares (LS) means of natural log transformed data between test (ETI-204 + ciprofloxacin) and reference (ETI-204 alone) was obtained from ANOVA and then transformed back to the original scale to obtain ratio of Geometric LS mean (expressed as percent).
[b] 90% confidence interval of difference of LS means was obtained from ANOVA and then transformed back to the original scale to obtain 90% confidence interval for the ratio (expressed as a percent).

Source: AH110 Pharmacokinetic Report, Section 11.3

Ciprofloxacin Plasma Pharmacokinetics

Plasma concentration-time profiles of ciprofloxacin following a single 400 mg IV dose on Day 1 and after oral dosing of 750 mg ciprofloxacin twice-daily on Day 9 on Day 1 and Day 9 were presented in Figure 2. PK parameters of ciprofloxacin on Day 1 and Day 9 were summarized in Table 6 and Table 7, respectively. The PK parameters of ciprofloxacin in this study were also compared with literature values shown in Table 8.

Ciprofloxacin concentrations in the predose plasma samples for all subjects on Day 1 were BLQ. Predose ciprofloxacin concentrations ranged from 0.267 to 0.906 µg/mL on Day 9, which reflected the systemic accumulation of ciprofloxacin after twice-daily multiple oral doses. The mean ciprofloxacin plasma concentration vs. time profile was multiexponential in appearance, with the terminal phase beginning as early as 1.5 hours after the beginning of the IV infusion and 4 hours after the oral dose.

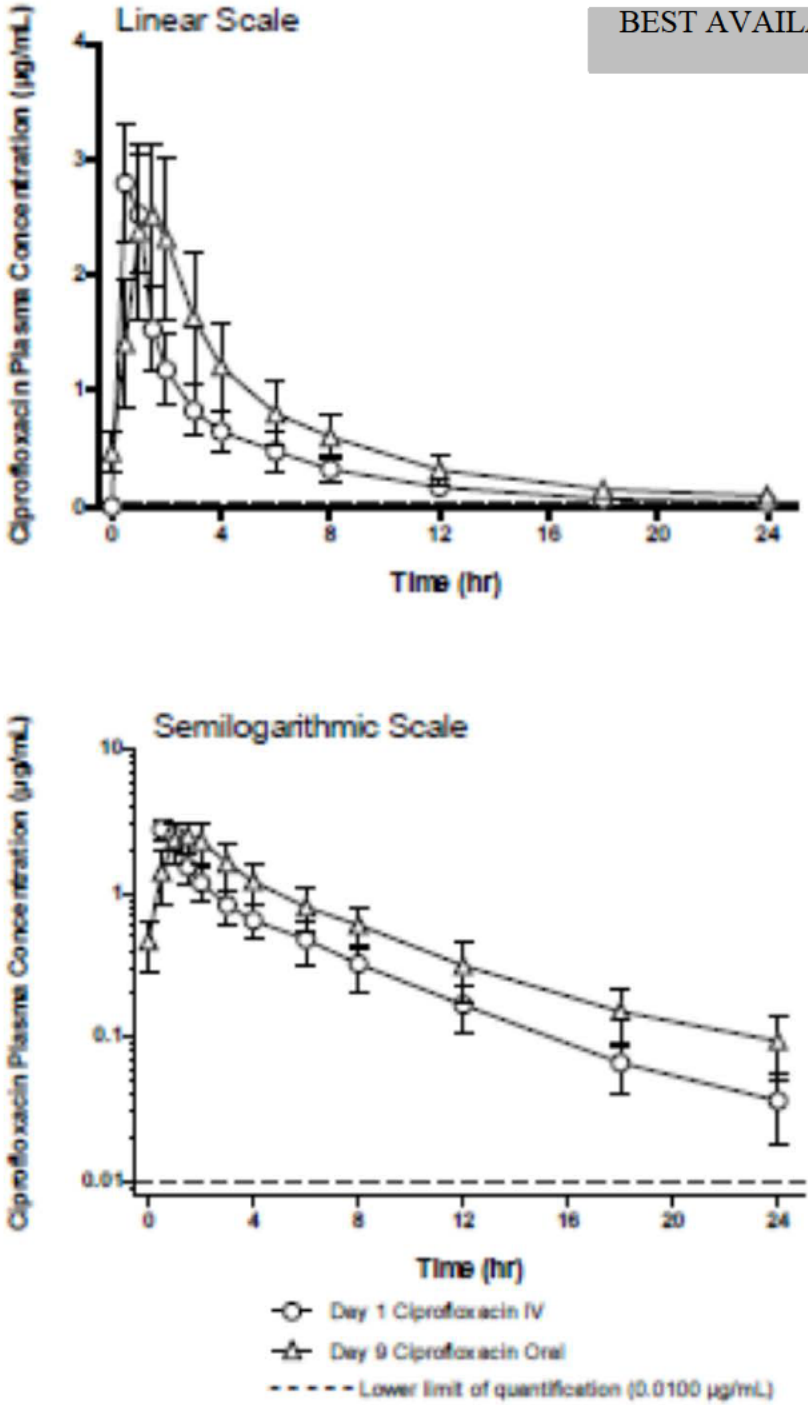
Following an IV dose, maximum plasma ciprofloxacin concentrations were attained at the end of the 1.0-hour infusion or at the sampling time point just prior to it (0.5 hr). The Cmax after the IV dose was 2.86 µg/mL. Plasma ciprofloxacin concentrations declined after the peak in a generally multiexponential fashion, with the terminal phase (starting point for $t_{1/2}$ determination) generally commencing as early as 1.5 hours after the start of infusion. Individual $t_{1/2}$ values ranged from 3.80 to 6.09 hours across all subjects; mean $t_{1/2}$ was 4.92 hours. Mean (range) CL and Vss values were 44.2 L/hr (29.5 to 64.7 L/hr) and 218 L (139 to 308 L), respectively. The disposition of ciprofloxacin after a single 400 mg IV dose in this study was generally similar to that described in the literature (Table 8). In one study, mean $t_{1/2}$ values of 4.3 and 4.4 hours were reported following a single 300 mg or 400 mg IV ciprofloxacin dose, respectively [Lettieri, et al, 1992]. The reported mean $AUC_{(0\text{-}inf)}$ after a 400 mg IV dose (11.4 µg· hr/mL), CL (600 mL/min, or 36 L/hr, averaged over both doses) and Vss (178 L after both doses) are within the range of values observed in the present study (Table 5).

Following multiple oral dosing, maximum plasma ciprofloxacin concentrations were attained by 0.5 to 2 hours postdose across subjects. Mean and median Tmax values were 1.30 hr and 1.50 hr,

respectively. Mean C_{max} was 2.78 µg/mL. Plasma ciprofloxacin concentrations declined after the peak in a generally biexponential fashion, with the terminal phase (starting point for $t_{1/2}$ determination) commencing between 4 and 12 hours postdose. Individual $t_{1/2}$ values ranged from 5.11 to 9.19 hours across all subjects; mean $t_{1/2}$ was 6.55 hours. Mean C_{min} was 0.342 µg/mL, and mean and median Tmin values were 8.47 and 12 hours, respectively. Tmin was either 0 or 12 hours in individual subjects, and mean ±SD ciprofloxacin concentrations at predose (0.466 ±0.178 µg/mL) and at 12 hours postdose (0.314 ±0.137 µg/mL) on Day 9 were similar, suggesting that trough concentrations were likely at steady-state by Day 9. This is consistent with expectations for a drug with a mean $t_{1/2}$ of 6.55 hours, which would be predicted to reach steady-state in approximately 2 days. Ciprofloxacin PK after multiple, twice-daily 750 mg oral doses in this study was generally comparable to literature values (Table 7). In one study, it was asserted that ciprofloxacin was at steady state after 4 days of 750 mg twice daily oral dosing [Shah et al, 1994], and the reported mean Day 4 ciprofloxacin C_{max}, $AUC_{(0\text{-}12),}$ and oral clearance values of 3.59 µg/mL, 15.8 µg hr/mL, and 896 mL/min (53.8 L/hr), respectively, are within the range of values observed in this study (Table 7). Half-life was not provided in this paper, but other investigators reported a mean ciprofloxacin $t_{1/2}$ of 6.4 hours after a single 750 mg oral dose [Lettieri, et al, 1992], which is comparable to that observed in the current study.

Reviewer Comment: This study was not designed to evaluate the effect of ETI-204 on ciprofloxacin PK; however, ciprofloxacin disposition following a single 400 mg IV dose (co-administration with ETI-204) and multiple 750 mg twice daily oral doses, was similar to that reported in the literature, which indicates that ciprofloxacin PK may not be altered when co-administered with ETI-204.

Figure 2. Mean (±SD) Plasma Concentration Profiles for Ciprofloxacin (Day 1 vs Day 9)



Source: AH110 Pharmacokinetic Report, Section 11.2

Table 6. Summary Pharmacokinetic Parameters for Ciprofloxacin after a Single 400 mg Intravenous Dose

Statistic	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{(0\text{-last})}$ (µg·hr/mL)	$AUC_{(0\text{-inf})}$ (µg·hr/mL)	$t_{1/2}$ (hr)	CL (L/hr)	Vd (L)	Vss (L)
N	18	18	17	17	17	17	17	17
Mean	2.86	0.626	9.28	9.55	4.92	44.2	317	218
SD	0.474	0.210	2.14	2.22	0.640	10.8	102	56.8
CV%	16.6	33.5	23.1	23.2	13.0	24.4	32.2	26.1
Min	2.01	0.500	5.99	6.18	3.80	29.5	189	139
Median	2.82	0.500	9.41	9.74	5.04	41.1	299	204
Max	3.93	1.00	13.1	13.5	6.09	64.7	518	308
Geometric mean	2.82	NC	9.04	9.30	4.88	43.0	303	211

NC: not calculated

Table 7. Summary Pharmacokinetic Parameters for Ciprofloxacin after Multiple 750 mg Twice-Daily Oral Doses

Statistic	C_{max} (µg/mL)	T_{max} (hr)	C_{min} (µg/mL)	T_{min} (hr)	$AUC_{(0\text{-tau})}$ (µg·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	Vd/F (L)
N	17	17	17	17	17	17	17	17
Mean	2.78	1.30	0.342	8.47	12.4	6.55	66.2	627
SD	0.624	0.402	0.118	5.64	3.23	1.09	24.2	243
CV%	22.4	31.0	34.4	66.5	26.2	16.6	36.6	38.8
Min	1.59	0.500	0.117	0	5.18	5.11	43.0	345
Median	2.82	1.50	0.320	12.0	12.3	6.43	61.0	579
Max	4.35	2.03	0.567	12.0	17.4	9.19	145	1289
Geometric mean	2.71	NC	0.321	NC	11.9	6.47	63.1	589

NC: not calculated

Source: AH110 Pharmacokinetic Report, Section 11.3

Table 8. Comparison of Mean Ciprofloxacin PK Parameters in AH110 to Literature Values

Route	Study	Dose (mg)	C_{max} (µg/mL)	$t_{1/2}$ (hr)	$AUC_{(0-12)}$ (µg·hr/mL)	$AUC_{(0-inf)}$ (µg·hr/mL)	CL (L/hr)	Vss (L)
IV[a]	AH110	400	2.86 (0.474)	4.92 (0.640)	NA	9.55 (2.22)	44.2 (10.8)	218 (56.8)
	Lettieri	300	3.2 (0.7)	4.0 (0.6)	NA	8.6 (1.5)	36.2 (7.6)	178 (42)
	Lettieri	400	4.0 (0.6)	4.4 (6.8)	NA	11.4 (1.6)	35.8 (4.9)	178 (37)
PO[b]	AH110	750	2.78 (0.624)	6.55 (1.09)	12.4 (3.23)	NA	66.2 (24.2)[c]	NA
	Shah	750	3.59 (1.34)	NR	15.8 (6.15)	NA	53.8 (18.4)[c]	NA
	Lettieri	750[a]	NA	6.4 (1.6)	NA	NA	NA	NA

Values are mean (SD)
NA – not applicable; NR – not reported
[a] Single dose
[b] After multiple, twice-daily doses
[c] Oral clearance (CL/F)

Source: AH110 Pharmacokinetic Report, Section 11.3

Pharmacodynamics

One subject (5.0%) in the ETI-204 alone group and no subjects in the ETI-204 + ciprofloxacin group had treatment-emergent ATA. Subject 001-135 was negative for ATA at Screening, Day 9, Day 29 and Day 43, and positive for ATA on Day 71 with titers of 1:80. The presence of ATA did not appear to have an impact on ETI-204 disposition on this individual and no AEs were associated with the development of ATA.

Reviewer Comment: Please refer to the OBP review for assessment of ETI-204 immunogenicity following a single IV administration of ETI-204.

SAFETY RESULTS

Overall, the percentage of subjects with AEs was similar in the ETI-204 + ciprofloxacin (70.0%) and ETI-204 alone groups (65.0%), and there were no SAEs or deaths during the study. The most frequently reported AEs were somnolence (ETI-204 + ciprofloxacin, 25.0%; ETI-204 alone, 30.0%) and upper respiratory tract infection (ETI-204 + ciprofloxacin, 10.0%; ETI-204 alone, 25.0%). Only subjects in the ETI-204 + ciprofloxacin group experienced urticaria (3 [15.0%), diarrhea (2 [10.0%]) and nausea (2 [10.0%]) compared to the ETI-204 alone group.

Reviewer Comment: Please refer to the Clinical Review by Dr. Gopinath, Ramya for safety assessment of ETI-204 following a single IV dose of 16 mg/kg with and without ciprofloxacin.

APPLICANT'S CONCLUSIONS:

- All samples collected from subjects in the PK population (n=38) from the end of infusion through Day 71 had quantifiable ETI-204 concentrations. ETI-204 PK was considered to have been adequately characterized with the sampling scheme employed, as only 5% of subjects had an extrapolated AUC portion > 20% of the total $AUC_{(0-inf)}$.
- Mean ETI-204 C_{max} was 402 and 397 µg/mL in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively, and median T_{max} was 0.104 days (2.5 hours) in both groups.

- Median $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ were similar in both the ETI-204 alone and ETI-204 + ciprofloxacin groups (4606 and 4570 µg·day/mL, respectively) (5015 and 4984 µg·day/mL, respectively).
- ETI-204 concentrations declined in a biexponential fashion with a mean terminal $t_{1/2}$ of 19.5 and 19.0 days in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively.
- Mean CL of ETI-204 was 0.268 and 0.247 L/day in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively, which represents a negligible fraction of estimated hepatic and renal blood flow, as well as glomerular filtration rate.
- Mean Vss of ETI-204 was 6.28 and 5.68 L in the ETI-204 alone and ETI-204 + ciprofloxacin groups, respectively, which suggests that ETI-204 may distribute out of the vascular compartment, but not extensively.
- ETI-204 disposition was not altered by co-administered ciprofloxacin.
- Ciprofloxacin disposition following a single 400 mg IV dose and after multiple, 750 mg twice daily oral doses was similar to that reported in the literature; steady state concentrations appeared to have been reached following twice-daily oral administration by Day 9.
- The percentage of subjects with AEs was similar in the ETI-204 + ciprofloxacin and ETI-204 alone groups. Somnolence (ETI-204 + ciprofloxacin, 25.0%; ETI-204 alone, 30.0%) and upper respiratory infection (ETI-204, 10.0%; ETI-204 alone, 25.0%) were the most frequently reported AEs.
- There were no deaths or SAEs were reported. Two subjects in the ETI-204 + ciprofloxacin group permanently discontinued study drug before completion of the ETI-204 infusion due to AEs but completed all the study procedures.
- Four subjects reported hypersensitivity infusion-related AEs but none were serious, three were moderate and four were mild.
- One subject in the ETI-204 alone group developed treatment-emergent ATA on Day 71, which did not appear to alter ETI-204 disposition and were not associated with AEs.
- Changes in laboratory parameters, vital signs, and ECGs were isolated and not clinically significant.
- The results of this study indicate that ETI-204 can be safely administered in combination with ciprofloxacin and without impact to the PK of either product.

REVIEWER ASSESSMENT:
Results from Study AH110 adequately determined the pharmacokinetics of ETI-204 after a single IV dose of 16 mg/kg with and without coadministration of ciprofloxacin. The applicant's pharmacokinetic conclusions based on these findings are valid. The observed positive predose samples for ETI-204 (>BLQ of 100 ng/mL) indicates the presence of low affinity cross-reactive antibodies in the human serum that interfere with the ELISA assay of ETI-204. The incidence of positive predose samples in Study AH110 was 10%, which was within the 10% non-selectivity rate observed during ETI- 204 method validation. In addition, the positive predose concentrations ranged from 0.159 to 1.83 µg/mL, representing 0.029% to 0.47% of the concentration at the subsequent time point (end of infusion). From a clinical pharmacology perspective, the positive predose concentrations appear to have a negligible effect on calculated PK parameters of ETI-204.

4.2. Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

BLA Number	125509 (SDN 1)
Submission Dates:	March 20, 2015
Submission Type:	Original Biologics License Application
Brand Name:	Anthim®
Generic Name:	Obiltoxaximab
Drug Class:	IgG1 monoclonal antibody
Dosage Form/Route:	IV Infusion Solution
Dosage Strengths:	600 mg/6mL solution in a single-use vial (100 mg/mL)
Proposed Indication:	Treatment of 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.
Proposed Dose:	Adults: a single intravenous (IV) 16 mg/kg infusion over 90 minutes Pediatric dosing: 16 mg/kg for weight > (b) (4) kg; 24 mg/kg for weight between 15 to (b) (4) kg; 32 mg/kg for weight less than 15 kg
Applicant:	Elusys Therapeutics, Inc. (Elusys), Pine Brook, New Jersey
OCP Division:	Division of Clinical Pharmacology 4; Division of Pharmacometrics
OND Division:	Division of Anti-Infective Products (DAIP)
Clinical Pharmacology Reviewer	Zhixia (Grace) Yan, Ph.D.
Pharmacometrics Reviewer:	Fang Li, Ph.D.
Team Leader:	Kimberly Bergman, Pharm.D. Jeffry Florian, Ph.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

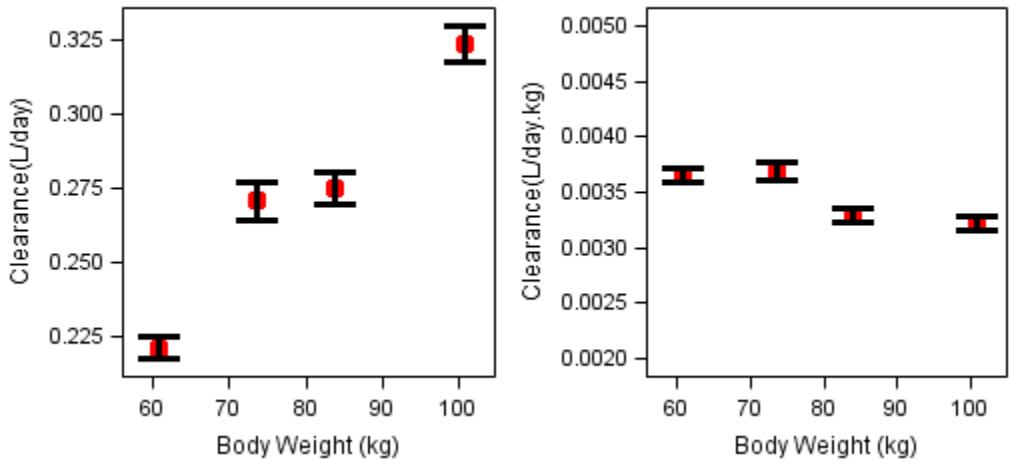
The purpose of this review is to address the following key questions.

1.1.1 Are there any covariates that significantly influence ETI-204 (obiltoxaximab) pharmacokinetics (PK) in humans based on population PK analysis?

Based on population PK analysis with data from three healthy human studies (AH102, AH104, and AH105), it was identified that ETI-204 clearance in adults was significantly influenced by body weight. As shown in Figure 1, clearance increased with increasing body weight such that the clearance for humans with mean body weight of 60 kg (first quartile) was 32% lower than humans with mean body weight of 100 kg (fourth quartile). However, body weight-adjusted clearance (clearance per kg) was not much different among body weight quartiles, with the fourth quartile being 12% lower than the first quartile. Therefore, the weight-based dosing as proposed by the applicant is reasonable. It should be noted that weight-based dosing slightly overcorrects for the body weight/clearance relationship, which is why body weight normalized clearance is slightly higher in the first body weight quartile compared to the fourth body weight quartile. This is not unexpected as the allometric scaling coefficient for clearance identified from the population PK analysis (0.68 [95% CI: 0.53, 0.82]) was less than 1 (i.e., a scaling coefficient of 1 would imply that clearance changes linearly with body weight and mg/kg dosing would result in similar exposures across all body weights). This overcorrection in dosing necessitates alterations to the 16 mg/kg dosing regimen in subjects with lower body weights, which is discussed in more detail in Question 1.1.3 regarding pediatric dosing.

Besides body weight, Caucasian race was associated with an 18% lower clearance compared to non-Caucasians, female subjects had a 14% lower clearance than males, and subjects of age 65 years and older had an 11% lower clearance than subject less than 65 years of age. However, these differences in clearance were not considered to necessitate any dosing adjustments. Due to the molecular weight of ETI-204 (~148 kDa) and as ETI-204 disposition is not mediated by hepatic or renal elimination processes, the effects of renal or hepatic insufficiency were not evaluated during population PK analysis.

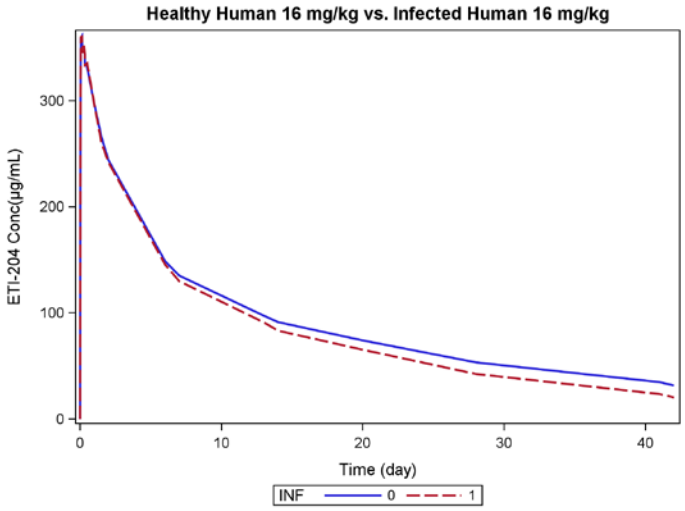
Figure 1: Effect of Body Weight on ETI-204 Clearance in Healthy Adult Human



Source: Figure generated by the reviewer using the output from the applicant's final population PK model in healthy humans

In the animal models, anthrax infection was associated with increased clearance, ~20% lower AUC_{inf} relative to uninfected animals, and comparable C_{max} values. This difference was characterized in the cynomolgus monkey population PK analysis by including a parallel nonlinear elimination term to describe target-mediated drug disposition (TMDD) for ETI-204 during an ongoing infection. The analogous parameter for infected humans cannot be estimated; instead, the parameterization identified from cynomolgus monkey was scaled and included in the human population PK model to obtain ETI-204 AUC_{inf} and C_{max} predictions for infected humans. The simulated PK profiles and calculated PK parameters for ETI-204 in healthy and infected humans are shown in Figure 2 and Table 1. ETI-204 concentrations are predicted to be almost identical over the first 7 days with no difference in C_{max}. AUC_{inf} is predicted to be 17% lower in infected humans compared to healthy humans for a dose of 16 mg/kg. This difference in exposure is not expected to require any dose adjustments, but it is relevant for the purposes of comparing human exposures to exposures from the fully effective dose in animals.

Figure 2: Simulated ETI-204 PK profile in Healthy and Infected Humans Administered a 16 mg/kg IV dose



Source: Figure generated by the reviewer using simulated data from the sponsor's final model

Note: Healthy human (INF=0); Infected human (INF=1), the lines are median concentrations

Table 1: Estimated ETI-204 Exposure in Healthy and Infected Humans Based on Simulation Results with the Population PK Modeling in Humans

	AUC_{inf} (µg•day/mL)			C_{max} (µg/mL)		
	Median	5th Perc.	95th Perc.	Median	5th Perc.	95th Perc.
Healthy Humans 16 mg/kg	4893	3119	7528	359	240	536
Infected Humans 16 mg/kg	4068	2393	6507	360	239	535

1.1.2 Is the proposed dosing regimen of 16 mg/kg for human adults in the treatment of inhalational anthrax acceptable?

Yes, the proposed dosing regimen of 16 mg/kg administered intravenously over 90 minutes for adults is acceptable. As there is no identified biomarker or relevant link between the animal exposure-response relationship and the exposure-response relationship in humans, the clinical pharmacology review team focused on a comparison of exposures (AUC_{inf} and C_{max}) in humans administered 16 mg/kg to that of either 16 mg/kg (applicant's fully effective dose) or 14.5 mg/kg (clinically pharmacology review team's fully effective dose) in infected animals (Guidance for Industry: Product Development Under the Animal Rule, 2015). The 16 mg/kg ETI-204 dosing regimen produces a mean AUC in humans that is 2.6-fold higher than the AUC observed in infected cynomolgus monkeys administered 16 mg/kg and 2.9-fold higher than the clinically pharmacology review team's fully effective dose of 14.5 mg/kg. This dosing regimen also results

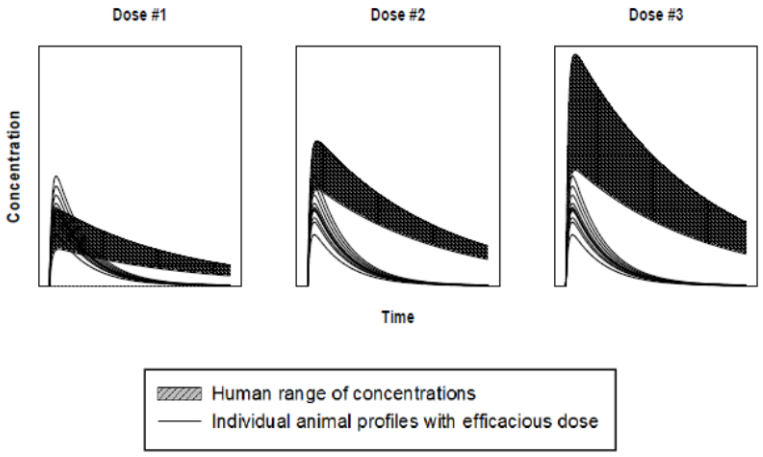
in a mean human C_{max} that is comparable to that in rabbits and cynomolgus monkeys that survived when administered the fully effective dose. The clinical pharmacology review team considers this overlapping C_{max} acceptable as ETI-204 concentrations are anticipated to exceed the maximum protective antigen (PA) concentrations for >7 days and by several orders of magnitude at C_{max}. As there is partial overlap of AUC_{inf} and C_{max} with 16 mg/kg in humans to that of 16 mg/kg in animals, further evaluation of a 24 mg/kg dose can also be considered. The 24 mg/kg ETI-204 dose is predicted to achieve AUC_{inf} exposures completely exceeding those in animals at the fully effective dose, though evaluation of this higher dose may be hindered by concerns of increased hypersensitivity reactions.

The proposed dose regimen in humans was identified based on comparing ETI-204 exposure data in humans administered 16 mg/kg with predicted exposure in monkeys administered a fully effective dose of 14.5 mg/kg. According to the Agency's 'Product Development Under the Animal Rule' Guidance:'

> "when the E/R relationship is established in animals, but there is no evidence of a relevant link (e.g., biomarker, AUC/MIC) that can predict an effetive drug exposure in humans, it may be reasonable to assume that the E/R relationship in humans will be similar to the E/R relationship in animals and use a conservative approach to human dose selection. Dose selected for human should provide exposures that exceed those associated with the fully effective dose in animals, ideally by several-fold, if the drug's safety profile allows such dosing."

The treatment of inhalation anthrax is one such example where this approach is applicable. The Guidance includes a set of three PK comparisons between humans and animals to assist in the interpretation of the appropriateness of human dosing when using PK criteria (Figure 3). An ideal dose situation is when the full range of human exposure (both C_{max} and overall exposure) exceeds the exposures of each animal administered the fully effective dose (Dose #3, right). In contrast, if neither C_{max} or AUC in humans exceeds that observed in animals (Dose #1, left), then the proposed human dosing would be considered unacceptable (in the absence of scientific justification). The scenario encountered for ETI-204, however, best mirrors the middle results where the exposure of human exceeds that in animals while a portion of human data C_{max} overlaps with that of the C_{max} from animals (Dose #2, middle). This scenario may be considered acceptable based on the degree of overlap in AUC between humans and animals, and data to support that C_{max} is not primarily responsible for efficacy or is of sufficient magnitude to maintain efficacy despite not exceeding exposures in animals.

Figure 3: Comparisons of Animal and Human PK Data to Support the Selection of an Effective Dose in Humans.

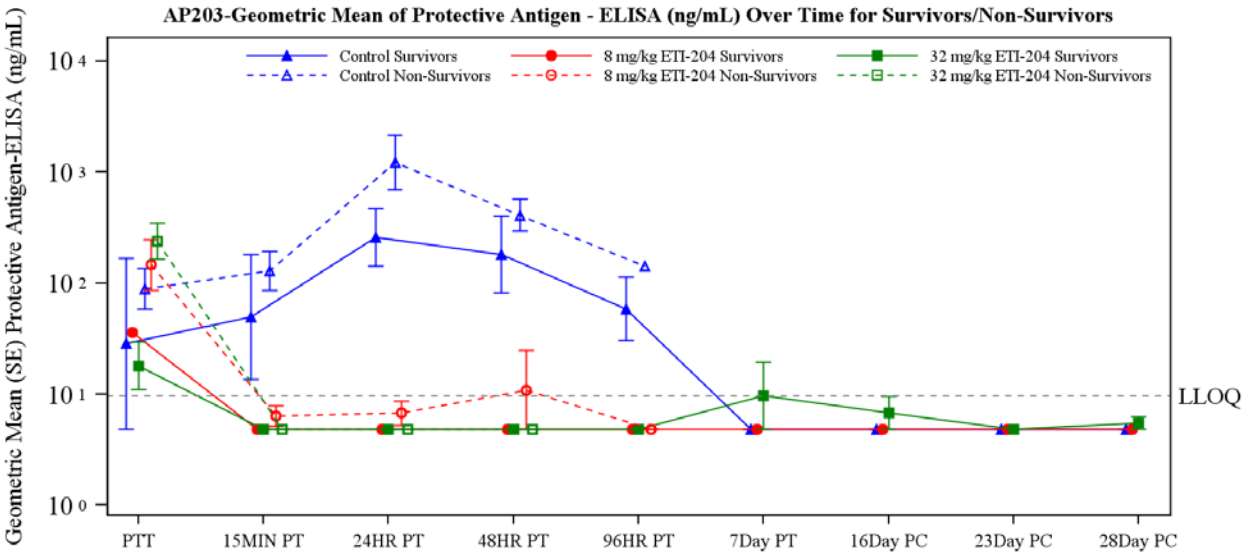


Sources: Figure 2 on page 28 of FDA Guidance for Industry: Product Development Under the Animal Rule

The fully effective dose of ETI-204 in infected animals was identified as 14.5 mg/kg dose based on an independent assessment by the clinical pharmacology review team (see analyses by Dr. Grace Yan). Briefly, monotherapy studies with ETI-204 doses ranging between 1 to 32 mg/kg (and including placebo) were tested in multiple studies with infected rabbits (AR021, AR033) and cynomolgus monkeys (AP201, AP204, AP203, and AP202). ETI-204 dose and bacteremia load prior to initiation of treatment were identified as significant factors influencing survival in both rabbits and monkeys (i.e., survival increased with higher doses and decrease with higher pre-treatment bacteremia loads). Based on the modeling analysis conducted by the applicant and the clinical pharmacology reviewer, 16 mg/kg is predicted to be on the plateau of the dose-survival curve in animals. The clinical pharmacology review team identified the fully effective dose as 14.5 mg/kg based on these analyses (equivalent to the ED_{90} from the dose-response relationship) and subsequent analyses will focus on comparisons of 16 mg/kg in humans to both 16 mg/kg and 14.5 mg/kg in animals. (Note: The Applicant's proposed fully effective dose is 16 mg/kg, which is 10% higher than that identified by the clinical pharmacology review team, but corresponds to a dose explicitly studied in animals.)

Assessment from animal studies also leads the clinical pharmacology review team to conclude that C_{max} is not the primary PK parameter associated with survival benefits for the current dosing route and infusion duration (see analyses by Dr. Grace Yan). While there was a significant dose-dependent survival relationship following ETI-204 treatment, which could imply a C_{max} effect on efficacy (linear PK so C_{max} increases proportionally with higher dosing), a comparison with protective antigen (PA) time course post-administration suggests the ETI-204 dosing is sufficient to suppress circulating levels after 15-minutes post-administration (Figure 4). The highest individual PA concentration at the time of treatment in infected rabbits and monkeys treated with 16 mg/kg (studies AR033 and AP202) was 0.068 µg/mL (1.07 nM) and 9.67 µg/mL (153 nM), respectively.

Figure 4: Geometric Means of Protective Antigen Over Time for Survivors/Non-Survivors in Cynomolgus Monkeys (AP203)



Source: Summary of Clinical Pharmacology Page 340

Observed PK parameters after 16 mg/kg in healthy human are summarized in Table 2. The mean C_{max} following a single 16 mg/kg dose of ETI-204 in healthy human was 376 µg/mL, which is comparable to the C_{max} observed in rabbits and cynomolgus monkeys administered 16 mg/kg that were infected with inhalational anthrax; The mean $AUC_{(0\text{-}inf)}$ from studies AH104, AH105, and AH110 was about 4843 µg•d/mL, which was 5.3-fold of the exposure in rabbits and 2.6-fold of the exposure in cynomolgus monkeys. This increase in exposure is consistent with the longer $t_{1/2}$ in humans (~ 20 days) compared to rabbits (~ 2 days) and cynomolgus monkeys (~ 6 days).

Table 2: ETI-204 Pharmacokinetic Parameters (Mean and SD) after a Single 16 mg/kg IV dose in Healthy Human Subjects from Studies AH105, AH104, and AH110

Study	**N**	**C_{max} (µg/mL)**	**$AUC_{(0\text{-}last)}$ (µg•d/mL)**	**$AUC_{(0\text{-}inf)}$ (µg•d/mL)**
AH105	29	330 (63.5)	4012 (774)	4410(1002)
AH104	202	400 (91.2)	4770 (1160)	5170 (1369)
AH110	38	399 (78.3)	4560 (783)	4950 (884)

Values are Mean (SD); N is the number of subject in the PK population (AUC could not be determined in all subjects in the PK population in Studies AH104 and AH110)

Source: Adapted from Table 55 on page 199 of applicant's Summary of Clinical Pharmacology Studies.

As described in Question 1.1.1, PK data from 'infected' (referred to moving forward as infected) humans are not available but were instead simulated using a nonlinear clearance term identified

from cynomolgus monkeys describing differences in clearance between infected and healthy cynomolgus monkeys. Simulations were conducted to compare the ETI-204 concentration-time profile (Figure 5) and calculate AUC_{inf} and C_{max} (Table 3) in infected humans administered IV 16 mg/kg and infected cynomolgus monkeys administered IV 16 mg/kg and 14.5 mg/kg, respectively. The C_{max} of humans and cynomolgus monkeys administered 16 mg/kg are comparable. However, the AUC_{inf} in humans administered 16 mg/kg is predicted to exceed that in cynomolgus monkeys administered 14.5 mg/kg or 16 mg/kg, though a percentage of humans will have AUC_{inf} overlapping the 95th percentile in cynomolgus monkeys. This situation with the proposed ETI-204 dose is similar to 'Dose #2' as described in the Guidance (Figure 3).

Figure 5: **Simulated ETI-204 Concentration-Time Profile in Infected Humans Administered IV 16 mg/kg and Infected Cynomolgus Monkeys Administered IV 16 mg/kg (left) and 14.5 mg/kg (right)**

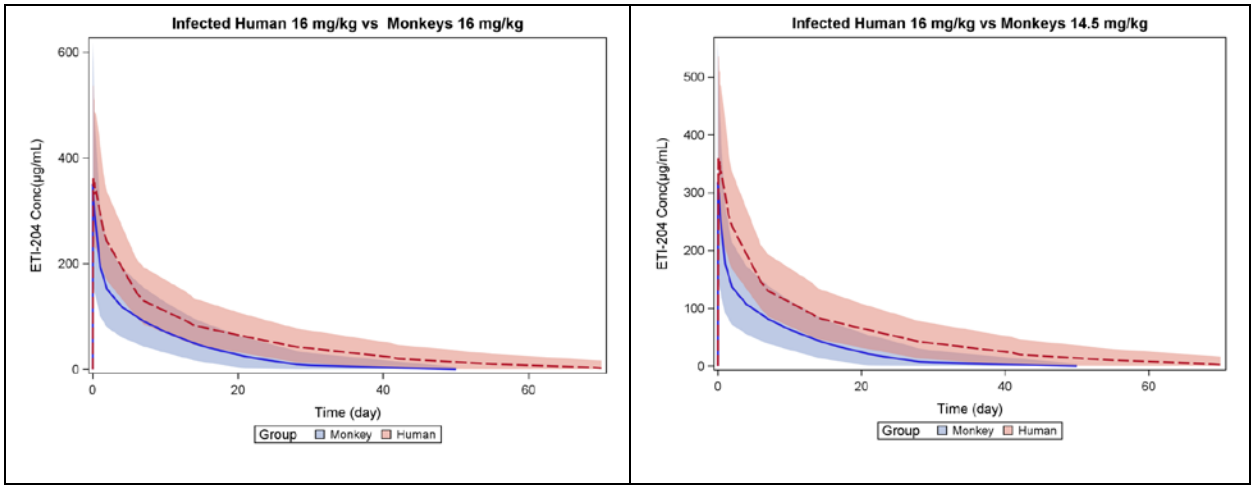


Table 3: Simulated ETI-204 Exposure in Humans Administered 16 mg/kg and Infected Monkeys Administered 16 mg/kg and 14.5 mg/kg

Population Human Dataset	AUC_{inf} (µg•day/mL)			C_{max} (µg/mL)		
	Median	5th Perc.	95th Perc.	Median	5th Perc.	95th Perc.
Infected Humans 16 mg/kg	4068	2393	6507	360	239	535
Infected Monkeys 16 mg/kg	2490	1363	4148	351	173	610
Infected Monkeys 14.5 mg/kg	2228	1214	3721	318	157	553

As there is partial overlap of AUC_{inf} and C_{max} with 16 mg/kg in humans with the exposures for 16 mg/kg in cynomolgus monkeys, further simulations were conducted to compare human exposures for a theoretical dose of 24 mg/kg to infected monkey exposures after 16 mg/kg or 14.5 mg/kg, respectively. As shown in Figure 6 and Table 4, the full-range of human exposure (AUC_{inf}) is predicted to exceed the exposure from animals. For such human dosing, the C_{max} would also exceed exposures from the fully effective dose in animals by ~50%. Therefore, a dose of 24

mg/kg could also be considered as acceptable, though additional studies in human volunteers would be necessary to establish safety with this dosing as it exceeds the highest exposures evaluated in humans. Given the identified hypersensitivity adverse events with ETI-204, however, the reviewer considers the sponsor can explore a higher dose in future studies if it is feasible.

Figure 6: Simulated ETI-204 Concentration-Time Profile in Infected Human after IV 24 mg/kg and Infected Monkeys after IV 16 mg/kg (left) and 14.5 mg/kg (right)

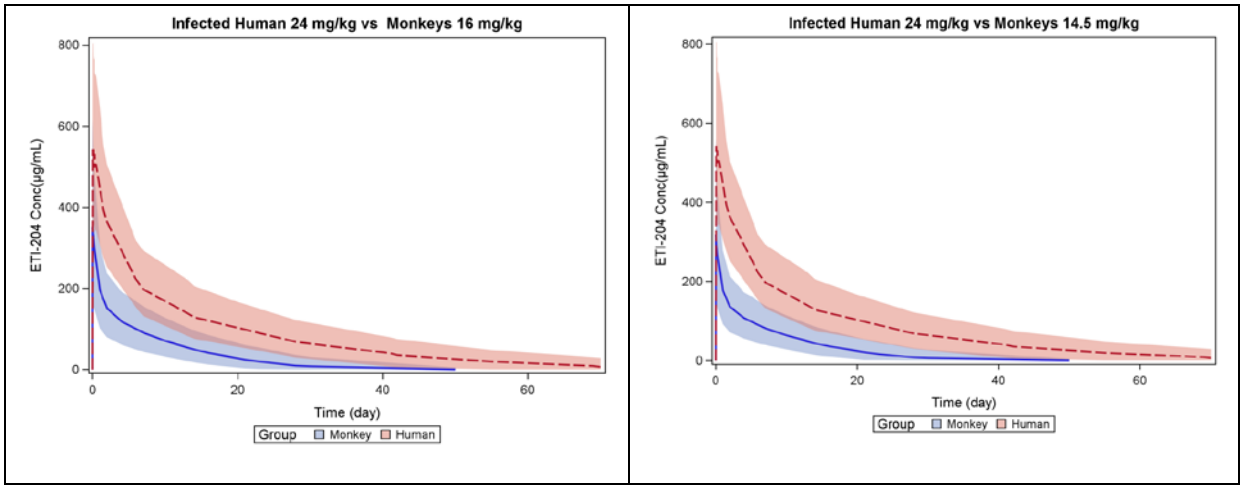


Table 4: Simulated ETI-204 Exposure in Infected Humans Administered 24 mg/kg and Infected Monkeys Administered 16 mg/kg and 14.5 mg/kg

Population Human Dataset	AUC_{inf} (µg•day/mL)			C_{max} (µg/mL)		
	Median	5^{th} Perc.	95^{th} Perc.	Median	5^{th} Perc.	95^{th} Perc.
Infected Humans 24 mg/kg	6393	3878	10142	540	358	803
Infected Monkeys 16 mg/kg	2490	1363	4148	351	173	610
Infected Monkeys 14.5 mg/kg	2228	1214	3721	318	157	553

1.1.3 Is the proposed ETI-204 dosing regimen for pediatric subjects for the treatment inhalational anthrax acceptable?

In general, the applicant's proposed pediatric dosing regimen is acceptable (Table 5); however the reviewer recommends that pediatric subjects (and adults) with body weight between (b) (4) kg be administered 16 mg/kg rather than the applicant's proposed dosing of (b) (4) mg/kg. With the applicant's proposed dosing of (b) (4) mg/kg, AUC_{inf} in pediatric subjects with body weights (b) (4) kg would be 29% greater than the median AUC_{inf} in adults (Figure 8). Alternatively, if these pediatric subjects were administered 16 mg/kg, then the median AUC_{inf} would be 15% lower than the median exposure in adults. Given concerns regarding hypersensitivity with ETI-204 and that the animal data showed meaningful survival at ETI-204 doses as low as 8 mg/kg, the reviewer

considers exposures slightly lower than the adult median to be preferable to exposures exceeding the adult median (equivalent to 20 mg/kg in adults) until additional safety data would be available.

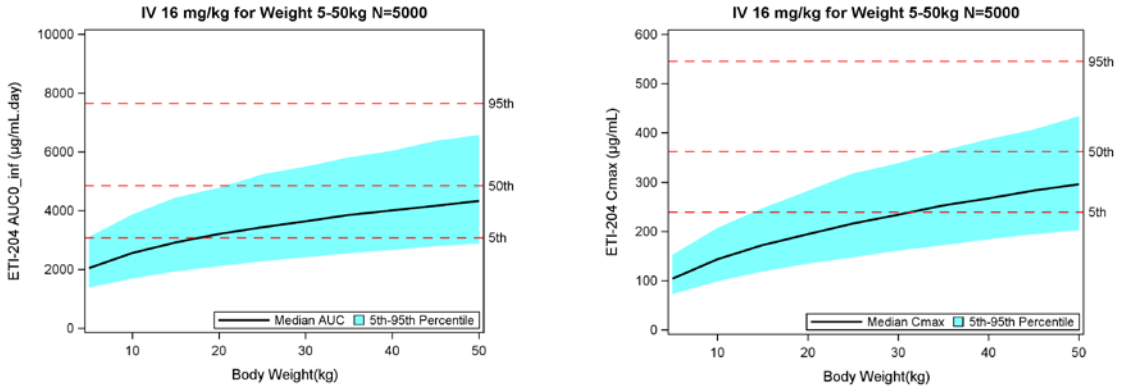
Table 5: Applicant's and Reviewer's Proposed ETI-204 Dosing Based on Body Weight Cutoffs

Body Weight Range	Applicant's Dosing	Reviewer's Dosing
<15 kg	32 mg/kg	32 mg/kg
15 to <40 kg	24 mg/kg	24 mg/kg
40 to (b) (4)	(b) (4) mg/kg	16 mg/kg
(b) (4)		

This application did not contain any clinical data in pediatric subjects as it is considered unethical to conduct ETI-204 pharmacokinetic studies in healthy pediatric subjects as the studies 'do not provide a direct clinical benefit' and may 'present more than a minor increase over minimal risk' (i.e., hypersensitivity) (see General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, Guide for Industry). However, given the proposed indication for ETI-204, it is considered important to have pediatric dosing recommendations in the label should the need arise to administer this therapeutic. To obtain dosing recommendations for pediatric subjects, the final ETI-204 population PK model for adults was extrapolated to body weights between 1 to 50 kg. As discussed in Question 1.1.1, the mg/kg dosing is an overcorrection of the effect of body weight on clearance, which would lead to underdosing at lower body weights with ETI-204 16 mg/kg. This is illustrated below in Figure 7.

According to simulations with the final population PK model for humans, ETI-204 AUC_{inf} in pediatric subjects would be lower than the median in adults (4893 µg/mL/d) over the entire range of 5 to 50 kg (60% and 5% lower than the adult median for these two body weights) if administered 16 mg/kg. The C_{max} values in children were also predicted to be lower compared to those in adults (73% to 20% lower over a body weight range of 5 to 50 kg).

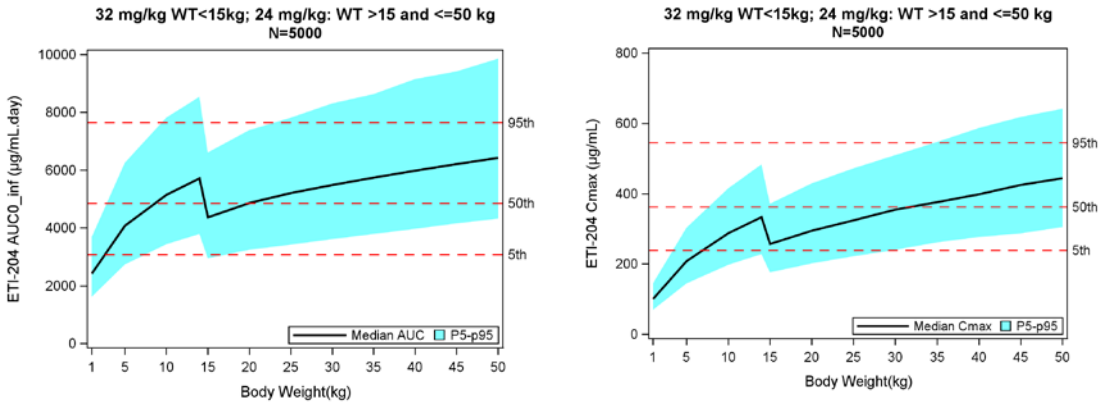
Figure 7: Simulated ETI-204 AUC_{inf} vs. Body Weight in Healthy Pediatric Subjects Administered 16 mg/kg IV ETI-204 with Comparisons to Healthy Adult Exposures from 16 mg/kg



Note: Reference lines of 5th, 50th, and 95th are estimated ETI-204 exposure in Healthy adults at 5th, 50th, and 95th percentile, respectively; Figures were generated by the reviewer with simulations using the applicant's final population PK model for humans.

Based on the relationship between body weight and ETI-204 clearance, the applicant proposed ETI-204 dosing of 24 mg/kg for pediatrics 15 to (b) (4) kg and 32 mg/kg for pediatrics less than 15 kg. Simulated ETI-204 exposures (AUC_{inf} and C_{max}) in pediatrics versus body weight based on the applicant's proposed dosing are shown below in Figure 8. These simulations were conducted by the reviewer to verify the applicant's predicted pediatric exposures and are in reasonable agreement with results provided by the applicant in their modeling and simulation report (see Section 3).

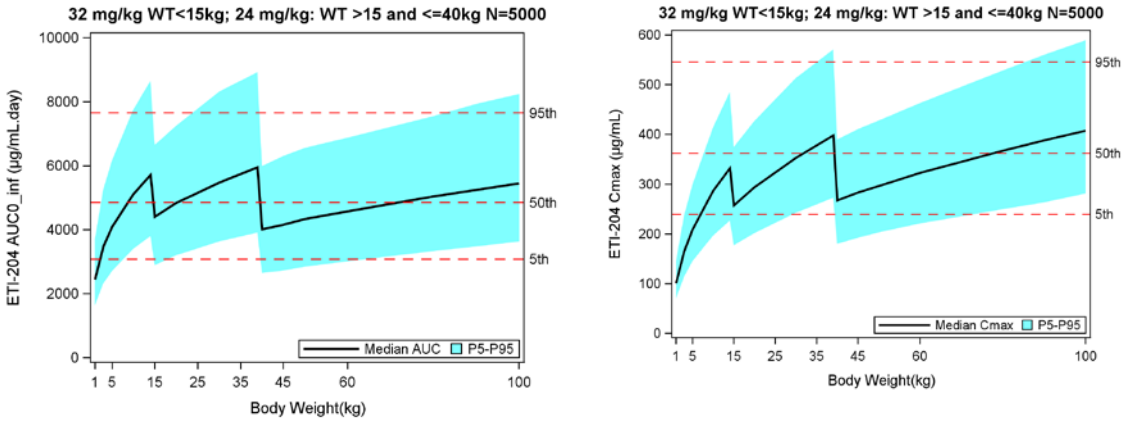
Figure 8: Simulated ETI-204 $AUC_{0\text{-}inf}$ vs. Body Weight in Healthy Pediatric Subjects Administered the Proposed Dose by the Applicant with Comparisons to Healthy Adult Exposures from 16 mg/kg.



The applicant considers the predicted pediatric exposure by the proposed dose to be comparable to that of adults across body weights of 1 to 50 kg. However, the reviewer considers the predicted exposures in pediatrics [redacted] kg to exceed adult exposures by an excessive amount that warrants alternative dosing. As shown in the Figure 8 (left), the exposure in pediatric subjects greater than 40 kg is 29% higher than the median AUC_{inf} in healthy adults.

To address this body weight range, the reviewer conducted simulations in pediatrics with body weight 40 to 50 kg assuming administration of 16 mg/kg. Dosing used by the reviewer was otherwise unchanged from the dosing proposed by the applicant. The simulated exposure for the reviewer's proposed dosing regimen versus body weight is shown in Figure 9 and is predicted to result in AUC_{inf} exposures that are 15% less than the adult median for pediatric subjects with body weight 40 to 50 kg. Based on the simulations, both AUC_{inf} and C_{max} of ETI-204 in pediatrics will fall within the range of exposures observed and predicted in healthy adults. The reviewer considers the slight under-exposure in this pediatric body weight range relative to adults to be preferable to over-exposure due to hypersensitivity concerns with ETI-204, which may be dose-related.

Figure 9: Simulated ETI-204 $AUC_{0\text{-}inf}$ vs. Body Weight in Healthy Pediatric Subjects (N=5000) Administered Adjusted Dosing Regimen with Comparisons to Healthy Adult Exposures from 16 mg/kg



ETI-204 dosing for pediatric subjects weighing between 1 kg and 5 kg was given specific considerations as predicting ETI-204 exposure in these young ages (predominantly neonates) is even more challenging than those weighing 5 kg and above. The allometric coefficient estimated from adult data may not be appropriate for this young population. A commonly used allometric coefficient for clearance is 0.75 while for some monoclonal antibody a body weight/clearance scaling coefficient of 0.5 has been identified. Sensitivity analyses were conducted by the reviewer comparing ETI-204 PK parameters in neonates and those in healthy adults using allometric scaling values between 0.5 and 0.75. As indicated in **Figure 29**, ETI-204 exposure will be lower than the exposure in healthy adults if the allometric coefficient was 0.5, 0.68, and 0.75, respectively.

While the reviewer recognizes uncertainty in the estimated ETI-204 exposure for neonates and that underexposure is possible with 32 mg/kg, this dosing recommendation represents our best projection for appropriate dosing in this population. Even with the possibility of underexposure with 32 mg/kg, the resulting exposure would still be similar to exposures in monkeys administered the fully effective dose. Therefore, the reviewer considers 32 mg/kg as an appropriate dose for pediatrics between 1 to 5 kg.

1.2 Recommendations

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed this application from a clinical pharmacology perspective. The reviewer agrees with the applicant's conclusions and proposed labeling language from the population PK analysis. In addition, the reviewer recommends approval of 16 mg/kg IV for the treatment and for prophylaxis of inhalational anthrax in adults. For adults and pediatrics weighing 40 kg and above, the reviewer recommends a dose of 16 mg/kg; for pediatrics weighing 15 mg to 40 kg, the recommended dose is 24 mg/kg; for pediatrics weight 1 to 15 kg, the recommended dose is 32 mg/kg.

2 PERTINENT REGULATORY BACKGROUND

Elusys therapeutics, Inc. (Elusys) submitted this original biological license agreement (BLA) to seek marketing approval for Anthim ® (ETI-204, obiltoxaximab), a monoclonal antibody (mAb) for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs. Anthim also has the proposed indication for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Anthim was developed under FDA's Animal Rule regulation (601.90) in accordance with 21 CFR Part 601, subpart H (approval of biologic product when human efficacy studies are not ethical or feasible). Anthim received orphan drug designation on June 9, 2006 and was granted FDA Fast Track Status on May 6, 2005.

Anthim is a liquid solution and is proposed to be administered as a single intravenous (IV) 16 mg/kg infusion over 90 minutes. Pediatric dosing recommendation based on modeling was also provided in the BLA.

3 RESULTS OF APPLICANT'S ANALYSIS

The applicant submitted a population PK and dose-response survival analysis report titled "Population Pharmacokinetic and Survival Analysis Modeling of ETI-204 in Healthy and Anthrax-Infected Subjects". This report included population PK analyses for healthy and infected rabbits, healthy and infected monkeys, and healthy humans with simulations for infected humans and pediatrics. A survival analysis based on combined animal data to inform the fully effect dose was also included in the report. The results of applicant's analysis are summarized in this section as follows.

3.1 Population PK analysis

Objectives: the objectives of the analysis were the following:

- Characterize ETI-204 population pharmacokinetics (PKs) in healthy and infected New Zealand White (NZW) rabbits, in healthy and infected cynomolgus monkeys, and in healthy humans.
- Develop survival models to describe ETI-204 dose-response in rabbits and cynomolgus monkeys.
- Identify an ETI-204 dose, via modeling, that is likely to be maximally efficacious for preclinical efficacy trials for treatment of inhalational anthrax.
- Extend the human PK model to include a term for the effect of inhalation anthrax infection on exposure based on information from infected cynomolgus monkey PK model.
- Perform population PK simulations using the 'infected' human model to derive ETI-204 human exposures for the proposed dose.

Data: Ten studies were included in the population PK modeling and survival analysis, with one in healthy rabbits (AR010), one in anthrax infected rabbits (AR033), one in healthy cynomolgus monkeys (AP116), four in infected cynomolgus monkeys (AP201, AP202, AP203, and AP204), and three in healthy humans (AH102, AH104, AH105). In the combined healthy and infected rabbit data set, there were 96 NZW rabbits with 791 PK samples. For the cynomolgus monkey PK data set, there were 150 monkeys with 929 observations included. For the human population PK dataset, there were 303 subjects with 2830 observations from three studies in healthy humans (AH102, AH104, and AH105).

PK Modeling: The applicant developed three population PK models with NONMEM software version 7, Level 2.0 (ICON Development Solutions, Hanover, MD), one for New Zealand (NZW) rabbits, one for cynomolgus monkeys, and one for healthy human volunteers, respectively.

The ETI-204 PK in rabbits was described by a two-compartment model. Absorption kinetics following intramuscular (IM) administration were described by first-order absorption (k_a) and adjustment for bioavailability of IM administration compared to IV (F1). Target mediated drug disposition (TMDD) in infected NZW was approximated via parallel nonlinear elimination for infected animal only, parameterized in terms of V_{max} and K_m Volume and clearance terms were fixed to typical allometric coefficients of 1 and 0.75, respectively. The population PK model to describe ETI-204 PK in healthy and infected NZW rabbits is shown in Equation 1:

$$CL = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{3.165(\text{kg})}\right)^{0.75} \cdot \exp^{\eta_{CL}} \quad healthy$$

$$CL = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{3.165(\text{kg})}\right)^{0.75} \cdot \exp^{\eta_{CL}} + \left(\frac{V_{max} \cdot \exp^{\eta_{Vmax}} \cdot C_p}{K_m + C_p}\right) \quad infected$$

$$V_c = \theta_{Vc} \cdot \left(\frac{WT_i(\text{kg})}{3.165(\text{kg})}\right)^{1.0} \cdot \exp^{\eta_{Vc}}$$

$$V_p = \theta_{Vp} \cdot \left(\frac{WT_i(\text{kg})}{3.165(\text{kg})}\right)^{1.0} \cdot \exp^{\eta_{Vp}}$$

$$Q = \theta_Q \cdot \left(\frac{WT_i(\text{kg})}{3.165(\text{kg})}\right)^{0.75} \cdot \exp^{\eta_Q}$$

$$k_a = \theta_{ka}$$

$$F1 = \theta_{F1}$$

Source: Applicant's population PK modeling report page 23

The ETI-204 PK in cynomolgus monkeys was described by a two-compartment model. Absorption kinetics following IM administration were described by first-order absorption k_a and an adjustment for bioavailability of IM administration compared to IV (F1). TMDD in infected cynomolgus monkeys was approximated via parallel nonlinear elimination for infected animals only, parameterized in terms of V_{max} and K_m Volume and clearance terms were fixed to typical allometric coefficients of 1 and 0.75, respectively. The population PK model to describe ETI-204 PK in healthy and infected cynomolgus monkeys is shown in Equation 2:

$$CL = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{2.88(\text{kg})}\right)^{0.75} \cdot \exp^{\eta_{CL}} \quad healthy$$

$$CL = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{2.88(\text{kg})}\right)^{0.75} \cdot \exp^{\eta_{CL}} + \left(\frac{V_{max} \cdot \exp^{\eta_{Vmax}} \cdot C_p}{K_m + C_p}\right) \quad infected$$

$$V_c = \theta_{Vc} \cdot \left(\frac{WT_i(\text{kg})}{2.88(\text{kg})}\right)^{1.0} \cdot \exp^{\eta_{Vc}}$$

$$V_p = \theta_{Vp} \cdot \left(\frac{WT_i(\text{kg})}{2.88(\text{kg})}\right)^{1.0}$$

$$Q = \theta_Q \cdot \left(\frac{WT_i(\text{kg})}{2.88(\text{kg})}\right)^{0.75}$$

$$k_a = \theta_{ka}$$

$$F1 = \theta_{F1}$$

Source: Applicant's population PK modeling report page 24

The PK of ETI-204 in healthy human was described by a two-compartment model with first-order elimination and no absorption model, since all subjects were administered only IV ETI-204. Allometric exponents for volume and clearance terms were estimated instead of fixing to typical values. The final model to describe ETI-204 PK in humans is shown in Equation 3:

$$CL = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta_{CL,WT}} \cdot \theta_{RACE}^{NON-WHITE} \cdot (AGE/51)^{\theta_{AGE}} \cdot \exp^{\eta_{CL}}$$

$$V_c = \theta_{Vc} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta_{Vc,WT}} \cdot \exp^{\eta_{Vc}}$$

$$V_p = \theta_{Vp} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta_{Vp,WT}} \cdot \exp^{\eta_{Vp}}$$

$$Q = \theta_Q \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta_{Q,WT}}$$

Source: Applicant's population PK modeling report page 26

Results: Population PK Modeling

Population PK Modeling for New Zealand White Rabbits

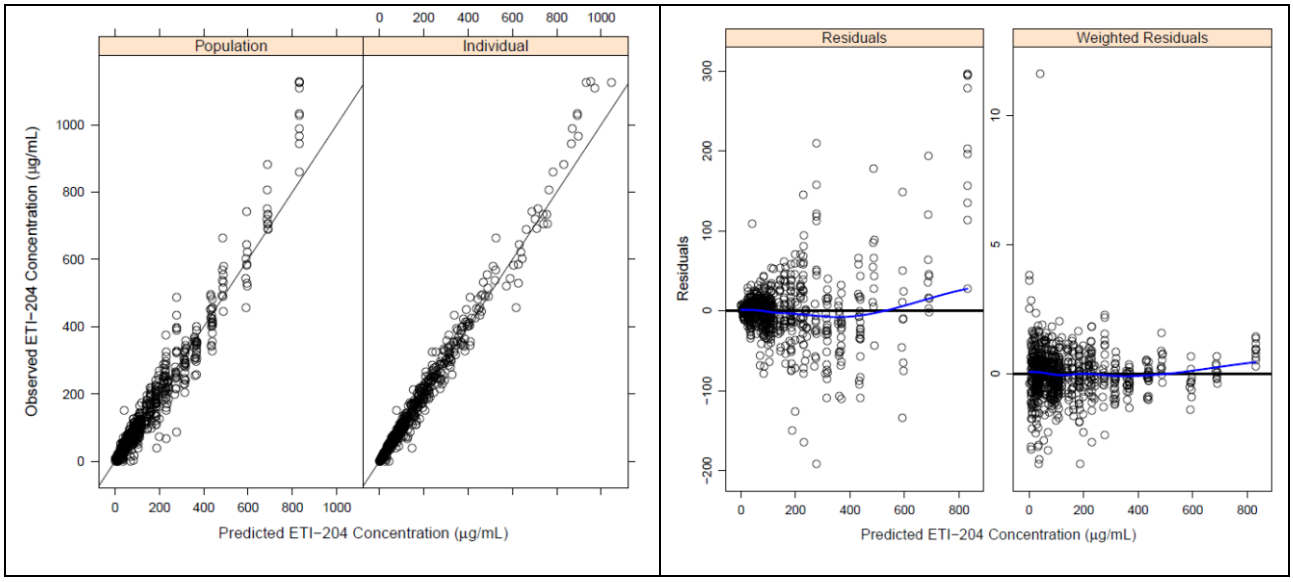
The applicant's PK modeling parameter estimates and goodness-of-fit plots for NZW rabbits are shown in Table 6 and Figure 10, respectively.

Table 6: New Zealand White Rabbit Population PK Modeling Parameter Estimates and %RSE from Population PK Model, 95% CI from Bootstrap

Description	Model	Estimate	%RSE	95% CI	Variability
clearance	$CL \sim \theta_1 \cdot (WT/3.165)^{0.75} \cdot e^{\eta_1}$	0.0263 L/d	6.18	(0.0239,0.0375)	
central volume of distribution	$V_c \sim \theta_2 \cdot (WT/3.165)^{1.0} \cdot e^{\eta_2}$	0.114 L	4	(0.104,0.12)	
peripheral volume of distribution	$V_p \sim \theta_3 \cdot (WT/3.165)^{1.0} \cdot e^{\eta_3}$	0.0744 L	9.32	(0.0598,0.097)	
intercompartmental clearance	$Q \sim \theta_4 \cdot (WT/3.165)^{0.75}$	0.119 L/d	14.9	(0.083,0.154)	
first-order absorption rate	$k_a \sim \theta_5$	0.961 d^{-1}	13.9	(0.27,1.43)	
bioavailability	$F \sim \theta_6$	0.899	9.94	(0.788,1.43)	
maximum velocity for nonlinear clearance	$V_{max} \sim \theta_7 \cdot e^{\eta_4}$	0.912 $ug/mL/d$	29.9	(0.000506,1.68)	
ETI-204 concentration to reach half Vmax	$K_m \sim \theta_8$	10.4 ug/mL	53.6	(-0.266,39.5)	
interindividual variability of CL	$IIV_{CL} \sim \Omega_{1.1}$	0.0461	47.3	(0.0214,0.221)	%CV = 21.7
interindividual CL-Vc covariance	$cov_{CL,Vc} \sim \Omega_{2.1}$	0.00395	209	(-0.0181,0.0447)	CORR = 0.0942
interindividual variability of Vc	$IIV_{Vc} \sim \Omega_{2.2}$	0.0382	26.8	(0.0142,0.0983)	%CV = 19.7
interindividual CL-Vp covariance	$cov_{CL,Vp} \sim \Omega_{3.1}$	-0.00686	296	(-0.252,0.0679)	CORR = -0.0842
interindividual Vc-Vp covariance	$cov_{Vc,Vp} \sim \Omega_{3.2}$	-0.0198	107	(-0.0859,0.0211)	CORR = -0.267
interindividual variability of Vp	$IIV_{Vp} \sim \Omega_{3.3}$	0.144	61.6	(0.0684,0.549)	%CV = 39.4
interindividual CL-Q covariance	$cov_{CL,Q} \sim \Omega_{4.1}$	0.0109	378	(-0.188,0.108)	CORR = 0.399
interindividual Vc-Q covariance	$cov_{Vc,Q} \sim \Omega_{4.2}$	0.00409	1060	(-0.109,0.095)	CORR = 0.164
interindividual Vp-Q covariance	$cov_{Vp,Q} \sim \Omega_{4.3}$	-0.0453	174	(-0.206,0.124)	CORR = -0.938
interindividual variability of Q	$IIV_Q \sim \Omega_{4.4}$	0.0162	841	(0.00859,1.07)	%CV = 12.8
interindividual variability of Vmax	$IIV_{Vmax} \sim \Omega_{5.5}$	1.19	42.2	(0.118,5.53)	%CV = 151
proportional error	$err_{prop} \sim \Sigma_{1.1}$	0.0317	3.38	(0.021,0.0412)	%CV = 17.8

Source: Table 2 on page 38 of applicant's Pop PKPD report

Figure 10: **Goodness-of-fit plots for Final Model for New Zealand White Rabbits**



Source: Adapted from Figure 3 and Figure 4 on page 55 and 66 of applicant's population PKPD report

Reviewer's comments: The population PK analysis of ETI-204 in NZW rabbits is acceptable. The goodness-of-fit plots indicate that the observed ETI-204 concentration data in NZW Rabbit were well captured by the final model.

Population PK Modeling for Cynomolgus Monkeys

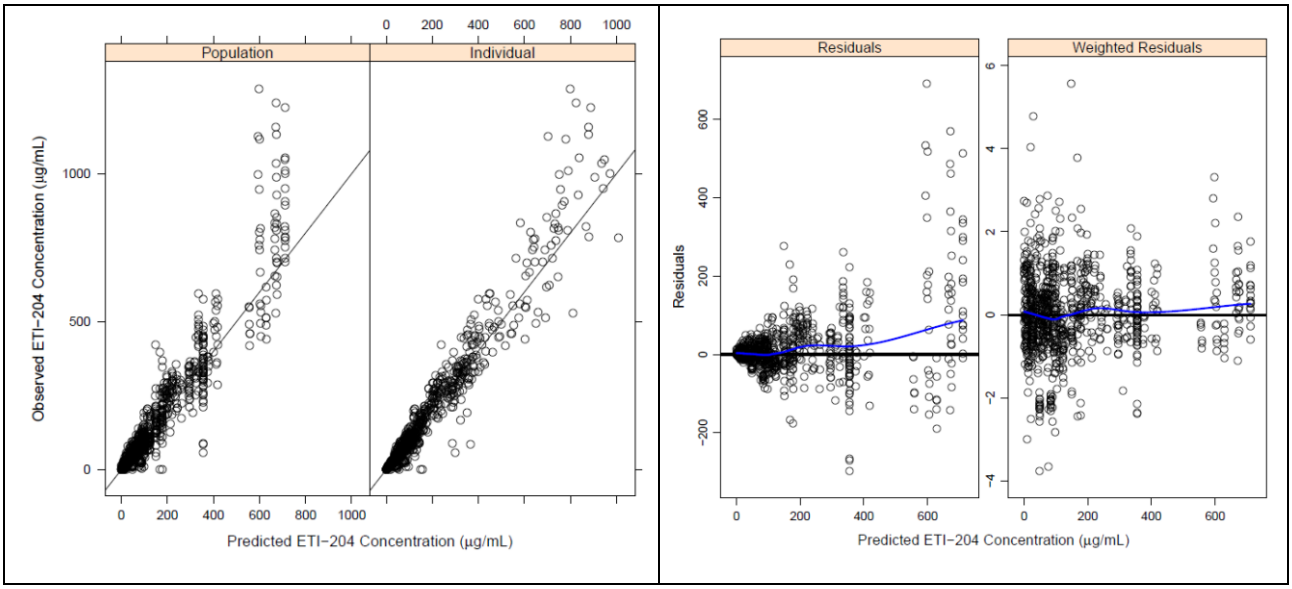
The PK modeling parameter estimates and goodness-of-fit plots for cynomolgus monkeys are shown in Table 7 and Figure 11, respectively. The visual predictive check (VPC) for infected monkeys is shown in Figure 12.

Table 7: Cynomolgus Monkey Population PK Modeling Parameter Estimates and %RSE from Population PK Model, 95% CI from Bootstrap

Description	Model	Estimate	%RSE	95% CI	Variability
clearance	$CL \sim \theta_1 \cdot (WT/2.88)^{0.75} \cdot e^{\eta_1}$	0.0191 L/d	5.1	(0.0162, 0.0223)	
central volume of distribution	$V_c \sim \theta_2 \cdot (WT/2.88)^{1.0} \cdot e^{\eta_2}$	0.134 L	3.39	(0.127, 0.141)	
peripheral volume of distribution	$V_p \sim \theta_3 \cdot (WT/2.88)^{1.0} \cdot e^{\eta_3}$	0.123 L	3.89	(0.109, 0.138)	
intercompartmental clearance	$Q \sim \theta_4 \cdot (WT/2.88)^{0.75}$	0.089 L/d	11.2	(0.0785, 0.103)	
maximum velocity for nonlinear clearance	$V_{max} \sim \theta_5 \cdot e^{\eta_4}$	0.275 $ug/mL/d$	17.6	(0.0671, 0.903)	
ETI-204 concentration to reach half Vmax	$K_m \sim \theta_6$	3.21 ug/mL	20.5	(1.12, 35.6)	
first-order absorption rate	$k_a \sim \theta_7$	3.89 d^{-1}	12.8	(2.96, 5.08)	
bioavailability	$F \sim \theta_8$	0.895	18.6	(0.777, 1.02)	
interindividual variability of CL	$IIV_{CL} \sim \Omega_{1,1}$	0.111	30.1	(0.0323, 0.198)	%CV = 34.3
interindividual CL-Vc covariance	$cov_{CL,Vc} \sim \Omega_{2,1}$	0.0497	35.7	(0.0121, 0.085)	CORR = 0.626
interindividual variability of Vc	$IIV_{Vc} \sim \Omega_{2,2}$	0.0569	20.5	(0.0311, 0.0885)	%CV = 24.2
interindividual CL-Vp covariance	$cov_{CL,Vp} \sim \Omega_{3,1}$	-0.147	72.4	(-0.326, 0.00372)	CORR = -0.471
interindividual Vc-Vp covariance	$cov_{Vc,Vp} \sim \Omega_{3,2}$	-0.0436	125	(-0.163, 0.0666)	CORR = -0.195
interindividual variability of Vmax	$IIV_{Vmax} \sim \Omega_{3,3}$	0.883	55.9	(0.227, 2.16)	%CV = 119
proportional error	$err_{prop} \sim \Sigma_{1,1}$	0.0779	3.44	(0.0635, 0.0963)	%CV = 27.9

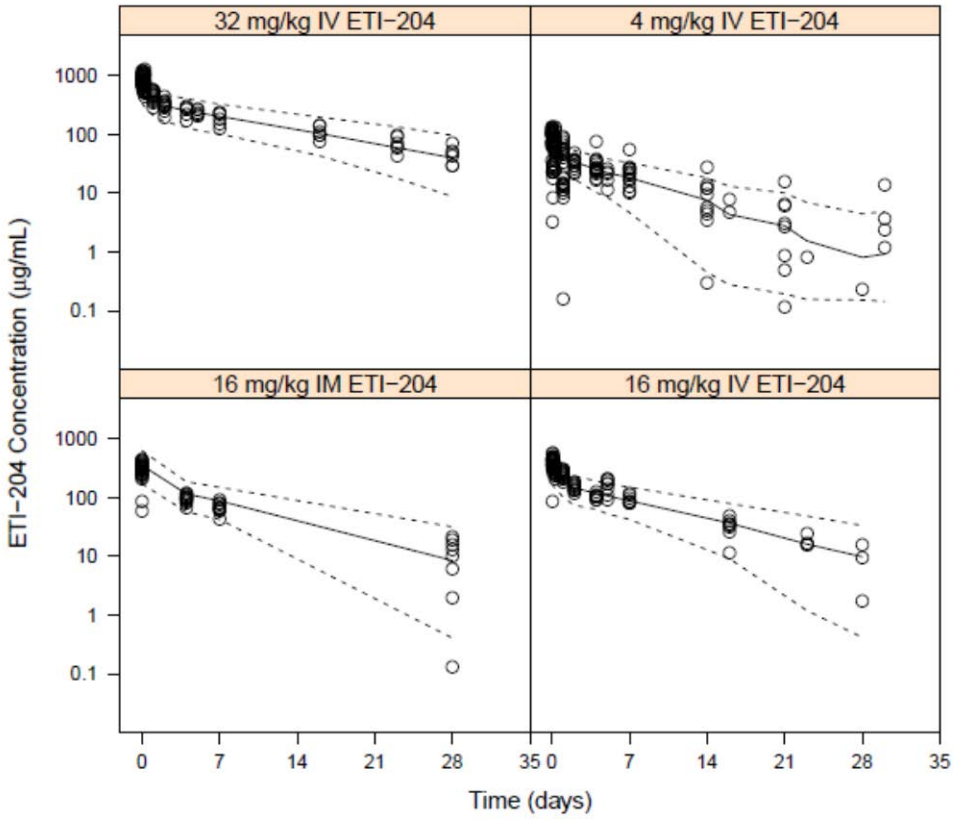
Source: Table 3 on page 38 of applicant's Pop PKPD report

Figure 11: **Goodness-of-fit plots for Final Model for Cynomolgus Monkeys**



Source: Adapted from Figure12 and Figure 13 on page 65 and 66 of applicant's population PKPD report

Figure 12: **Population PK Model Visual Predictive Check for Infected Cynomolgus Monkeys**



Note: Solid line is the median ETI-204 concentration from 200 simulated trials, dashed lines are the simulated 90% prediction interval, and open circles are observed values

Source: Adapted from Figure 18 on page 71 of applicant's population PKPD report

Reviewer's comments: The final population PK model of ETI-204 for cynomolgus monkey is acceptable. The model parameter estimates as shown in Table 7 are reasonable as assessed by %RSE and 95% confidence intervals. Except for a few high concentrations, the individual prediction of ETI-204 concentrations versus observed ETI-204 concentration as shown in the goodness-of-fit plots (Figure 11) suggests that most of the observed ETI-204 concentration data in cynomolgus monkey were well captured.. The VPC plot (Figure 12) indicates that the model was able to predict ETI-204 concentrations in infected cynomolgus monkeys. Independent analysis by the reviewer verified the sponsor's analysis. However, as the applicant did not provide goodness-of-fit plots stratified by infection, the reviewer generated those plots as shown in Section 4.

Population PK Modeling for Healthy Human Adults

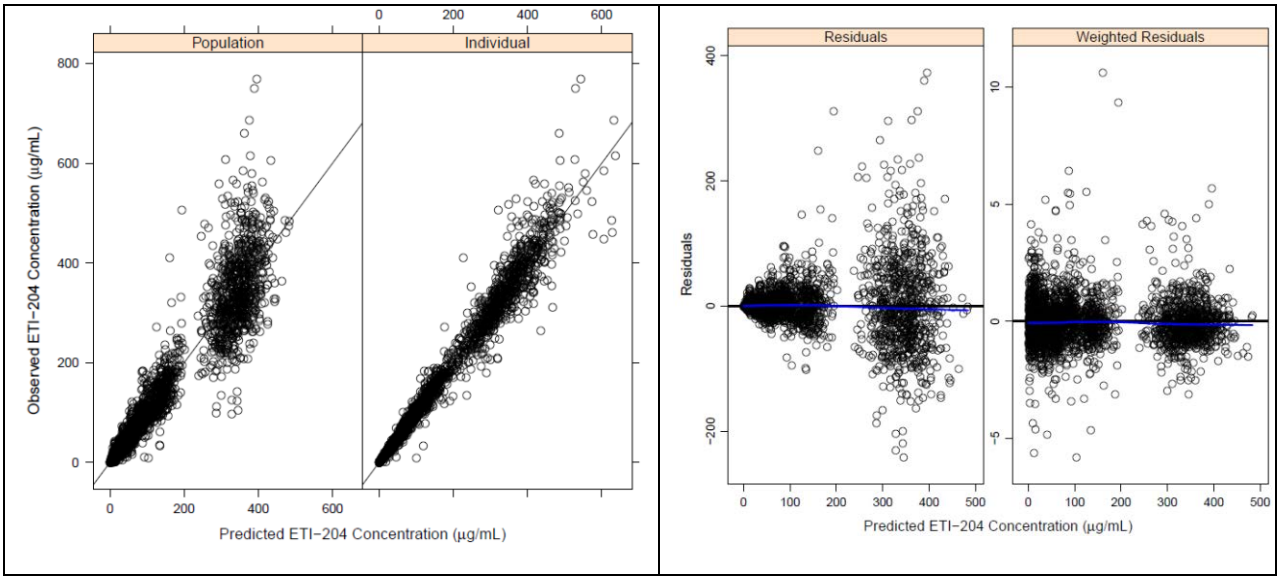
The PK modeling parameter estimates and goodness-of-fit plots for healthy human adults are shown in Table 8 and Figure 13, respectively. The VPC plot is shown in Figure 14.

Table 8: Human Population PK Modeling Parameter Estimates and %RSE from Final Population PK Model (95% CI from Bootstrap)

Description	Model	Estimate	%RSE	95% CI	Variability
clearance	$CL \sim \theta_1 \cdot \theta_{10}^{RACE} \cdot (WT/51)^{\theta_{11}} \cdot (WT/70)^{\theta_6} \cdot e^{\eta_1}$	0.233 L/d	2.02	(0.224, 0.242)	
central volume of distribution	$V_c \sim \theta_2 \cdot (WT/70)^{\theta_7} \cdot e^{\eta_2}$	3.21 L	1.44	(3.12, 3.29)	
peripheral volume of distribution	$V_p \sim \theta_3 \cdot (WT/70)^{\theta_8} \cdot e^{\eta_3}$	2.73 L	2.33	(2.62, 2.84)	
intercompartmental clearance	$Q \sim \theta_4 \cdot (WT/70)^{\theta_9} \cdot e^{\eta_4}$	0.473 L/d	5.67	(0.427, 0.516)	
body weight effect on on CL	θ_6	0.677	10.3	(0.531, 0.815)	
body weight effect on on Vc	θ_7	0.55	11.1	(0.426, 0.67)	
body weight effect on on Vp	θ_8	0.486	23	(0.33, 0.703)	
body weight effect on on Q	θ_9	0.174	167	(0.01, 0.666)	
non-white race effect on CL	θ_{10}	1.21	2.95	(1.15, 1.29)	
age effect (greater than 50 years) on CL	θ_{11}	-0.298	44.8	(-0.58, -0.041)	
interindividual variability of CL	$IIV_{CL} \sim \Omega_{1.1}$	0.0623	12.5	(0.049, 0.0777)	%CV = 25.4
interindividual CL-Vc covariance	$cov_{CL,Vc} \sim \Omega_{2.1}$	0.0277	21.2	(0.0183, 0.0408)	CORR = 0.568
interindividual variability of Vc	$IIV_{Vc} \sim \Omega_{2.2}$	0.0384	13.6	(0.0288, 0.0491)	%CV = 19.8
interindividual CL-Vp covariance	$cov_{CL,Vp} \sim \Omega_{3.1}$	0.0243	29.9	(0.0109, 0.0387)	CORR = 0.358
interindividual Vc-Vp covariance	$cov_{Vc,Vp} \sim \Omega_{3.2}$	0.0316	19.9	(0.0204, 0.0432)	CORR = 0.592
interindividual variability of Vp	$IIV_{Vp} \sim \Omega_{3.3}$	0.0743	17.6	(0.0499, 0.102)	%CV = 27.8
proportional error	$err_{prop} \sim \Sigma_{1.1}$	0.0172	7.88	(0.0146, 0.0199)	%CV = 13.1

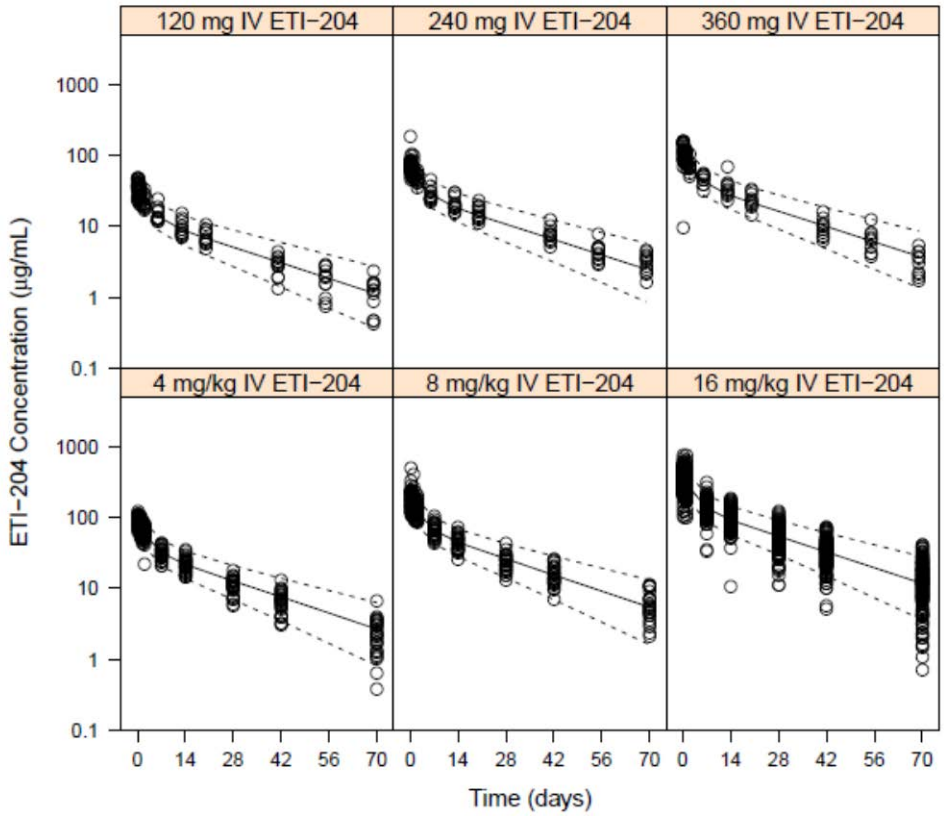
Source: Table 5 on page 40 of applicant's Pop PKPD report

Figure 13: Goodness-of-fit plots for Final Model for Humans



Source: Adapted from Figure 28 and Figure 29 on page 81 and 82, respectively, of applicant's Pop PKPD report.

Figure 14: **Population PK Model Visual Predictive Check for Humans**



Note: Solid line is the median ETI-204 concentration from 200 simulated trials, dashed lines are the simulated 90% prediction interval, and open circles are observed values.

Source: Figure 36 on page 89 of applicant's Pop PKPD report

Reviewer's comments: The applicant's population PK analyses are acceptable. The final model for humans was assessed by the modeling parameter estimates(Table 8), the goodness-of-fit plots (Figure 13), and the visual predictive check (Figure 14).The parameter estimates are reasonable as indicated by the small %RSE for critical PK parameters. The goodness-of-fit plots indicate that the observed ETI-204 concentration data in healthy humans were well captured by the final model, and the visual predictive check of the final model suggests that the model was able to predict ETI-204 concentrations in healthy humans. Independent analysis was conducted by the reviewer which verified the applicant's analyses. The final model for humans was used by the reviewer for simulations in order to support dosing recommendations in human adults and children.

While the sponsor conducted population PK modeling and simulations in monkeys and healthy humans, and the fittings were found acceptable, no direct comparison between PK profiles in humans and cynomolgus monkeys. As such, independent analysis was conducted to compare PK profiles of cynomolgus monkeys and humans. With the applicant's final population PK models, additional simulations were performed by the reviewer to estimate ETI-204 exposure in human adults and monkeys assuming varying dosing regimens. The results are summarized in Section 4 below.

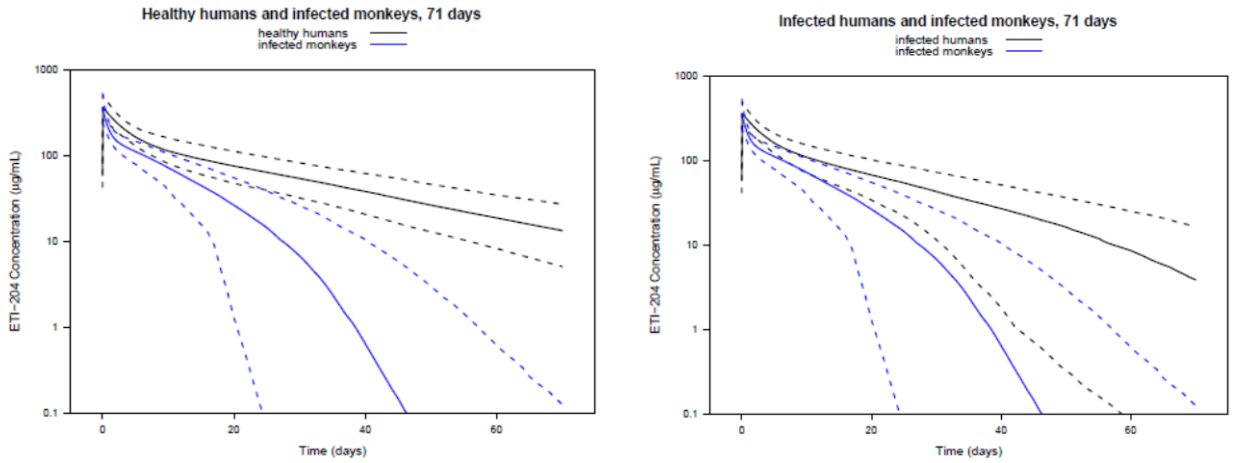
3.2 Simulations in Human Adults

Simulations were performed for 500 typical human subjects (weight=75 kg) administered 16 mg/kg ETI-204 for both healthy and infected populations. These simulation results were compared to those performed for infected monkeys (3 kg) administered 16 mg/kg.

ETI-204 exposures in infected humans were simulated. The nonlinear clearance model term from the cynomolgus monkey model was added to the human population PK model and allometrically scaled to human body size where all parameters were defined as the estimates from the uninfected human model except for V_{max}, K_m, and $\eta_{Vmax,}$ which were obtained from the cynomolgus monkey population PK model.

Simulation results comparing a 16 mg/kg IV dose in infected monkeys and humans are shown in Figure 15, Table 9, and Table 10. Median maximum concentration (C_{max}) for healthy and projected infected humans was slightly higher than those for monkeys, although the overall distributions were generally comparable. Area under the concentration time curve from time zero to infinity (AUC_{inf}) was predicted to be almost 2-fold higher in infected humans compared to infected monkeys, while AUC_{inf} for healthy humans was more than 2-fold higher.

Figure 15: **Population PK Simulation Results: Comparison of ETI-204 Concentrations Following a 16 mg/kg Dose in Infected Cynomolgus Monkeys and Healthy Humans**



Note: Results are shown as the median concentration (solid lines) and 90% prediction interval (dashed lines) from 1000 simulated typical humans (weigh=75 kg) or monkeys (3 kg).

Source: Adapted from Figure 48 on page 101 of sponsor's Population PK report

Table 9: Summary of Simulated $AUC_{0\text{-}inf}$ (µg/mL•day) for Humans (75 kg, Infected and Healthy) and Monkeys (3 kg, Infected) Administered 16 mg/kg ETI-204

Population	N	Q5	Q25	median	mean	Q75	Q95
Healthy Humans	500	3240	4210	4910	4980	5630	6960
Infected Humans	500	2370	3270	4010	4070	4740	6040
Infected Monkeys	500	1160	1600	1920	1970	2270	3010

Source: Table 9 on page 44 of sponsor's population PKPD report

Table 10: Summary of Simulated C_{max} (µg/mL) for Humans (75 kg, Infected and Healthy) and Monkeys (3 kg, Infected) Administered 16 mg/kg ETI-204

Population	N	Q5	Q25	median	mean	Q75	Q95
Healthy Humans	500	297	348	386	388	423	490
Infected Humans	500	298	342	377	382	419	481
Infected Monkeys	500	262	310	366	371	420	512

Source: Table 8 on page 43 of sponsor's population PKPD report

Simulations were also performed to examine the effects of covariates on ETI-204 human exposures. C_{max} was unaffected by age and race. For the typical 50 kg subject, a 22% and 23% decrease in C_{max} is observed for healthy and infected humans, respectively, relative to a typical human of 75 kg. For the typical 125 kg subject, C_{max} increased by 24% in both healthy and infected humans, compared to a typical 75 kg subject.

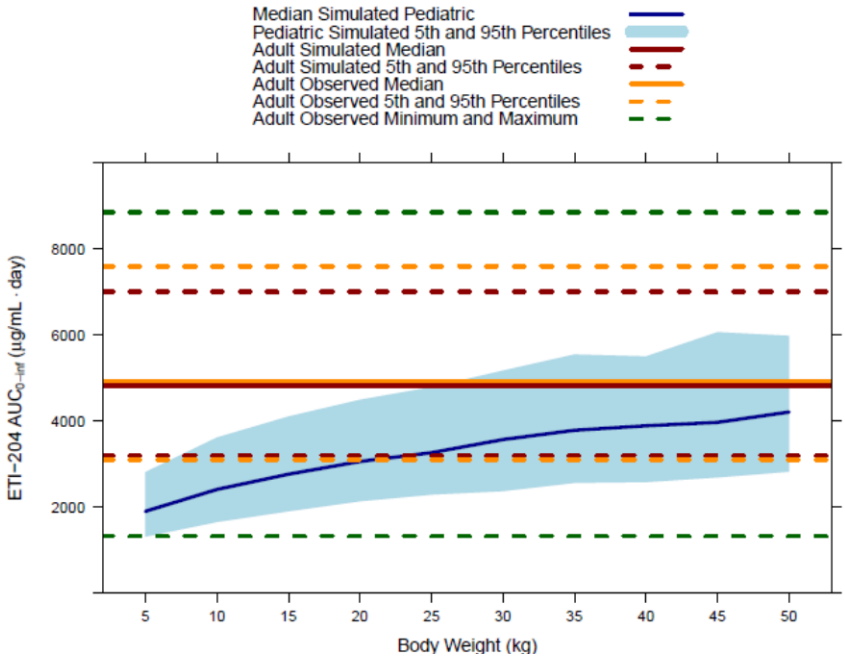
All median human AUC_{inf} values were greater than double the median monkey value, with the exception of infected non-white race humans (179% of monkeys), healthy 125 kg humans (197% of monkeys) and infected 50 kg humans (171% of monkeys).

3.3 Simulations of ETI-204 Exposure in Children

Population PK simulations for healthy pediatric subjects administered 16 mg/kg IV ETI-204 were also conducted to determine pediatric dosing that would achieve comparable exposures to healthy adults administered 16 mg/kg dose. The simulation results for healthy pediatric subjects are shown in Figure 16-Figure 19. Results for infected pediatric were similar therefore are now shown here. The model used to simulate pediatric exposure is the same as shown above for adults. Because ETI-204 is eliminated by non-specific proteolysis, a minimal effect of enzyme or renal maturation on ETI-204 clearance (CL) is expected. Therefore, no maturation effect was included in the simulation model.

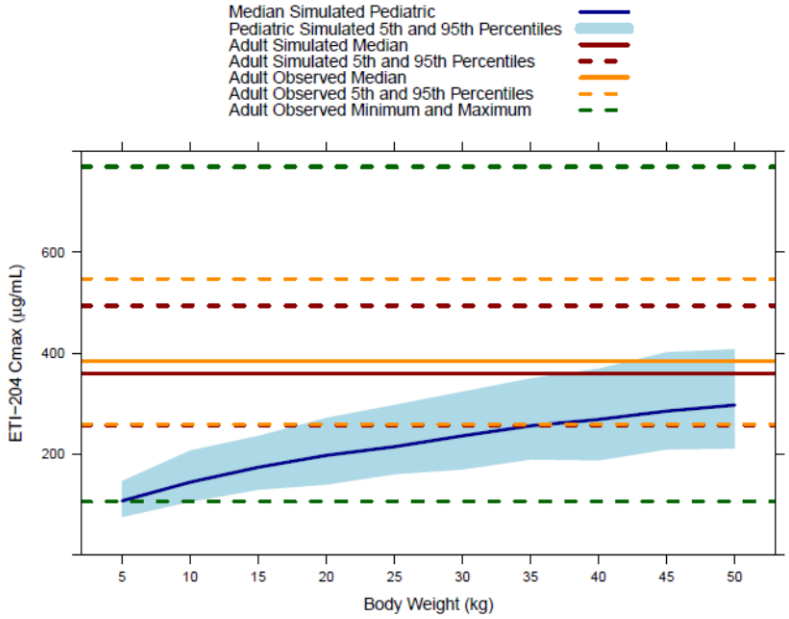
Five hundred pediatric subjects were simulated for each weight bin from 5 to 50 kg, in 5 kg increments. AUC_{inf} and C_{max} were derived from each simulated subject, and plots were constructed to compare exposure distributions across pediatric weight range to that of an adult weighing 75 kg. Based on this analysis the applicant proposed that: i) pediatric subjects weighing less 15 kg be administered 32 mg/kg; ii) pediatric subjects weighing 15 to (b) (4) kg be administered 24 mg/kg; and iii) pediatric subjects weighing > (b) (4) kg be administered 16 mg/kg.

Figure 16: Simulated ETI-204 $AUC_{0\text{-}inf}$ vs. Body Weight in Healthy Pediatric Subjects Administered 16 mg/kg IV ETI-204: Results are compared to Simulated and Observed Exposure for Healthy Adults



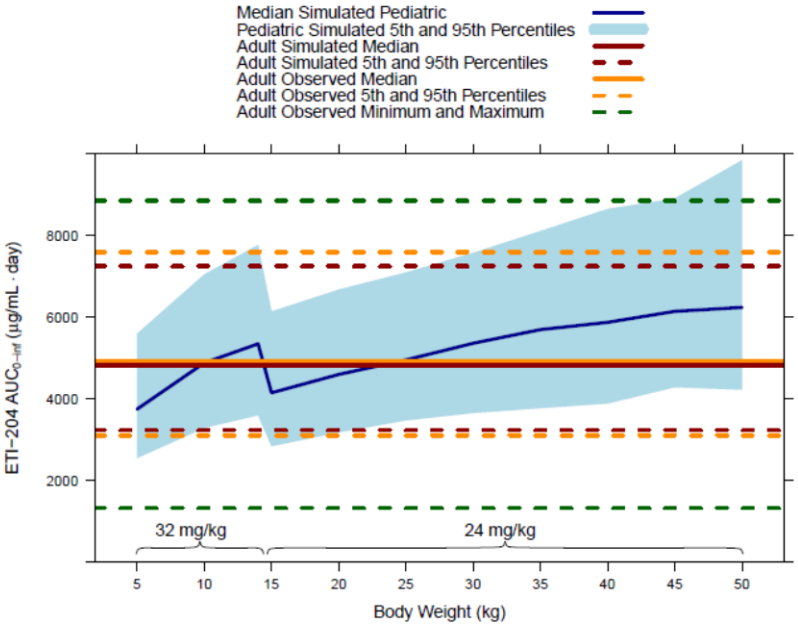
Source: Figure 1 on page 11 of sponsor's population PK report Amend1

Figure 17: Simulated ETI-204 C_{max} vs. Body Weight in Healthy Pediatric Subjects Administered 16 mg/kg IV ETI-204: Results are Compared to Simulated and Observed Exposures for Healthy Adults.



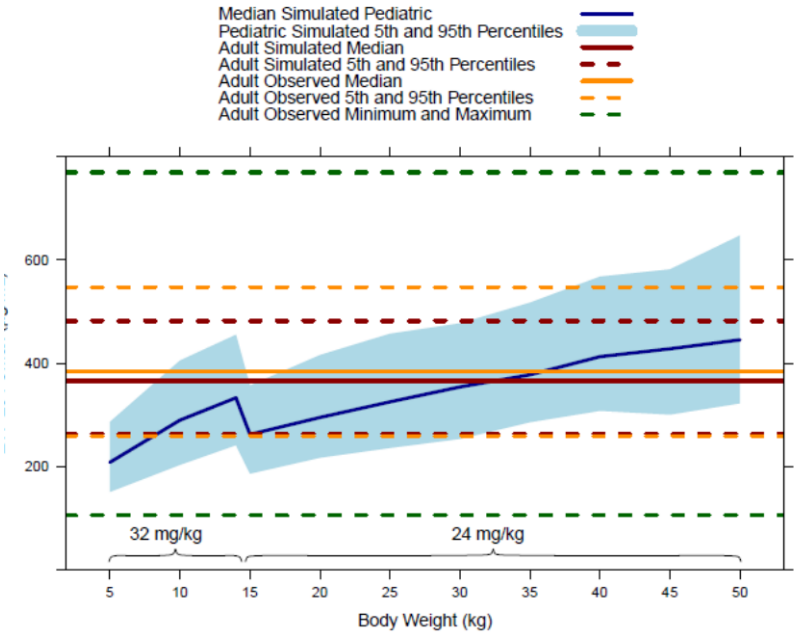
Source: Figure 2 on page 12 of sponsor's population PK report Amend1

Figure 18: Simulated ETI-204 AUC_{inf} vs. Body Weight in Healthy Pediatric Subjects Following Dose Adjustment: Results Are Compared to Simulated and Observed Exposure for Healthy Adults.



Source: Figure 5 on page 15 of sponsor's population PK report Amend1

Figure 19 Simulated ETI-204 vs. Body Weight in Healthy Pediatric Subjects Following Dose Adjustment-Results Are Compared to Simulated and Observed Observation Exposure for Healthy Adults



Source: Figure 6 on page 15 of sponsor's population PK report Amend1

Reviewer's Comments: There were no PK studies in pediatric subjects, and the pediatric PK profile was extrapolated from population PK models for humans. The applicant simulated ETI-204 PK profile at body weights between 5-50 kg with 500 subjects and compared these exposures with the exposure from healthy adult subjects with body weight of 75 kg administered 16 mg/kg. To obtain more stable 5th and 95th percentile predictions, it would be more appropriate to simulate using more subjects (N=5000 or more). The reviewer conducted such simulations with more subjects (N=5000) at 1 kg increments. The results were similar with those shown in the applicant's analysis; however, the reviewer considers the pediatric exposures in the body weight range of (b) (4) *kg when administered* (b) (4) *mg/kg to be excessive. The median AUC_{inf} in this range of body weight was about 29% higher than the median AUC_{inf} in healthy humans, with lots of subjects reaching 200% relative to human median $AUC_{inf..}$ Safety events such as hypersensitivity for this level of exposure in this group of pediatric subjects are a concern. Therefore, the reviewer proposes ETI-204 dosing of 16 mg/kg for pediatric subjects weighing between* (b) (4) *kg. More detailed discussions about this recommendation are in Question 1.1.3.*

4 REVIEWER'S ANALYSIS

4.1 Introduction

The efficacy of ETI-204 was evaluated in two well-characterized animal models of inhalational anthrax, New Zealand White rabbits, and cynomolgus monkeys. The pharmacokinetics and safety of ETI-204 were assessed in healthy volunteers. PK properties in infected human were derived with population PK model with model parameters from healthy humans and infected monkeys.

No clinical studies were conducted in children, and the PK of ETI-204 in children was extrapolated from PK model for healthy adults. Therefore, it is important to assess the validity of the final population PK model for monkeys and human.

In this review, the pharmacometrics reviewer performed an independent analysis to evaluate the PK of the proposed dose in healthy and infected adults and pediatric subjects. The overall objective was to determine whether the proposed dosing for adults and pediatric subjects are adequate.

4.2 Objectives

1. evaluate the adequacy of sponsor's population PK model for monkeys and healthy human
2. conduct simulations comparing ETI-204 exposure parameters in healthy and infected humans to that of healthy and infected monkeys at various doses
3. determine whether the proposed dose for pediatric subjects is acceptable, and if not, determine alternative dosing recommendations

4.3 Methods

4.3.1 Data Sets

The applicant's datasets for population PK were used for independent analysis. Data sets used are summarized in Table 11.

Table 11: Analysis Data Sets

Study Number	**Name**	**Link to EDR**
Tranpk2.csv.txt 20.ctl.txt	PK dataset from studies in healthy human Final model code for human	\\Cdsesub4\nonectd\BLA125509\5811361\Metrum Download 16_Dec_2014\data\derived
Trannhp.csv.txt 501.ctl.txt	PK dataset from studies in monkeys Final model code for monkeys	\\Cdsesub4\nonectd\BLA125509\5811361\Metrum Download 16_Dec_2014\data\derived

4.3.2 Software

NONMEM (Version 7.2) installed on a 48-core Linux cluster was used for all population PK analyses. An R package "popPK" developed by FDA was used for post-NONMEM graphing and reporting; SAS for windows 9.3 was used for all other graphing and statistical analyses.

4.3.3 Models

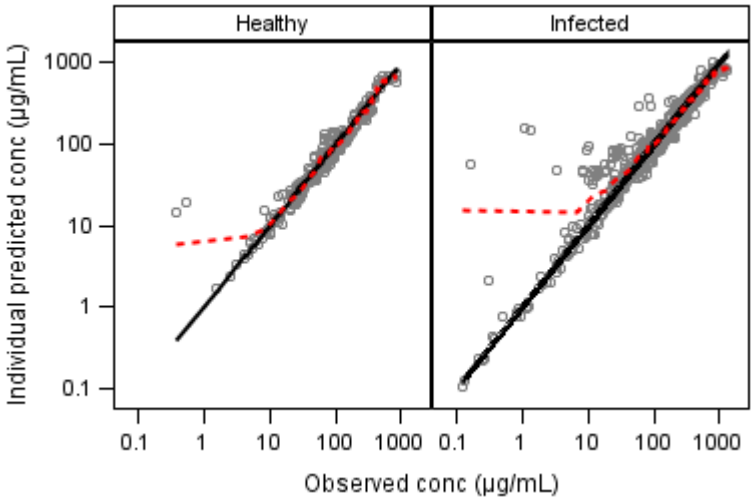
The sponsor's population PK datasets and final models were used for testing the fitting adequacy and evaluating the parameter estimates.

4.4 Results

4.4.1 Population PK Analysis

The reviewer conducted independent diagnostics to evaluate the fitting of the final models in cynomolgus monkeys and healthy humans. The goodness-of-fit plots for healthy and infected monkeys using the final population PK model are shown in Figure 20. Except for a few low concentrations, the model was able to describe the observed concentrations in both healthy and infected monkeys. Based on these diagnostic plots, the reviewer considers the effect of infection on PK to be well-identified in the cynomolgus monkey model and considers it reasonable to include the infection factor in the human population PK model to predict the impact of anthrax infection on ETI-204 exposure in this population.

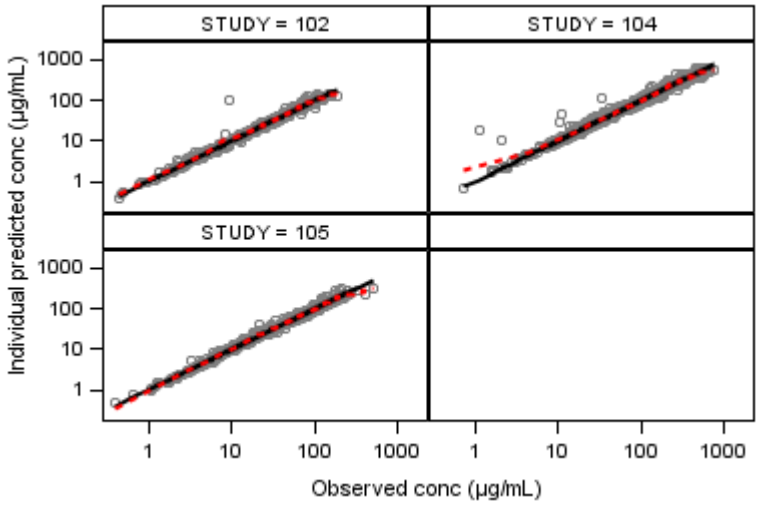
Figure 20: Predicted versus Observed Plasma ETI-204 Concentrations in Healthy and Infected Monkeys



Note: the red lines are lowess smooth lines showing the trend

The goodness-of-fit plots for healthy humans stratified by study are shown in Figure 21. There was a good agreement between observed ETI-204 concentrations and model-predicted concentrations. The model was adequate in describing the observed values.

Figure 21: Predicted versus Observed Plasma ETI-204 Concentrations in Healthy Humans by Study



Note: the red lines are lowess smooth lines showing the trend

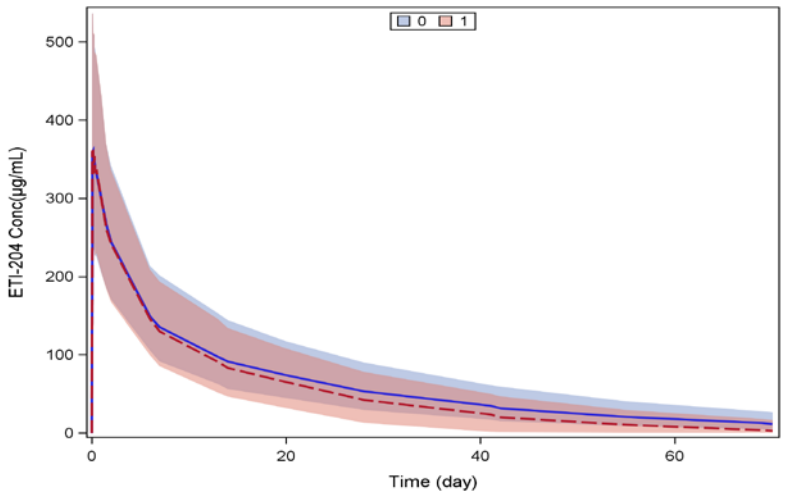
4.4.2 ETI-204 Exposure in Healthy and Infected Humans

A difference in ETI-204 clearance was observed in infected animals compared to healthy animals. Infected monkeys had about 25% higher clearance relative to healthy monkeys. A similar trend was observed in rabbits. This phenomenon was explained by TMDD, in which binding of the antibody to its therapeutic target (protective antigen, PA) leads to a more rapid removal of the biologic agent from the circulation. This was addressed in population PK analysis via parallel, non-linear elimination for infected animals. For the same reason, infected humans are expected to have a higher clearance than those observed in healthy humans.

Exposure in healthy and infected humans following a 16 mg/kg dose is presented in Figure 2 (see page 4). The presence of infection is associated with a minimal effect on C_{max}, while mean $AUC_{(0-inf)}$ is decreased by approximately 20%. This magnitude of reduction in unlikely to be clinically significant because ETI-204 concentrations between infected and healthy human were almost identical until after 7 days. The neutralization of PA occurred in a very short time (Figure 4, page 7), and the AUC in infected human remains 5.3- and 2.6-fold higher than those in infected rabbits and monkeys, respectively.

Additional simulations were conducted by the reviewer to generate exposures for the range of body weights included in the population PK analysis. This is different from the applicant's analysis, where only exposures for a body weight of 75 kg was evaluated. The ETI-204 concentration-time profiles are shown in Figure 22 and the PK parameters are summarized in Table 12. Infected healthy AUC_{inf} is about 17% lower relative to healthy subjects, while C_{max} values were similar.

Figure 22: Simulated ETI-204 Concentration-time Profile in Healthy and Infected Humans Adults of All Weights after a Single IV Dose of 16 mg/kg



Note: Healthy humans: infection=0; Infected Humans: infection=1

Table 12: ETI-204 Concentration-time Profile in Humans Included in the Population PK Analysis Administered a Single IV Dose of 16 mg/kg

Humans (All Weights)	AUC_{inf} (µg•day/mL)			C_{max} (µg/mL)		
	Median	5^{th} percent	95^{th} percent	Median	5^{th} percent	95^{th} percent
Healthy Humans 16 mg/kg	4893	3119	7528	359	240	536
Infected Humans 16 mg/kg	4068	2393	6507	360	239	535

4.4.3 Comparison of ETI-204 Exposure in Human and Infected Monkeys

Simulated ETI-204 exposures (AUC_{inf}, and C_{max}) in human adults after administration of 16 mg/kg, 24 mg/kg, and 32 mg/kg were compared with those in monkeys after administration of 16 mg/kg, and 14.5 mg/kg. The 16 mg/kg in humans is the proposed labeling dose while the 16 mg/kg in monkeys was the applicant's fully effective dose. The 14.5 mg/kg dose was identified by the clinical pharmacology review team as the fully effective dose. The results are summarized in Table 13, and illustrated in Figure 23-Figure 28.

Table 13: Simulated ETI-204 Exposure in Healthy and Infected Humans and in Infected Monkeys Administered the Listed Doses

Population and Dose	AUCinf (µg•day/mL)			Cmax (µg/mL)		
	Median	5th perc.	95th perc.	Median	5th perc.	95th perc.
Healthy Humans 16 mg/kg	4893	3119	7528	359	240	536
Infected Humans 16 mg/kg	4068	2393	6507	360	239	535
Healthy Humans 24 mg/kg	7339	4679	11292	538	359	804
Infected Humans 24 mg/kg	6393	3878	10142	540	358	803
Healthy Humans 32 mg/kg	9785	6239	15056	717	479	1072
Infected Humans 32 mg/kg	8770	5395	13782	721	478	1071
Infected Monkeys 14.5 mg/kg	2228	1214	3721	318	157	553
Infected Monkeys 16 mg/kg	2490	1363	4148	351	173	610

Figure 23: Simulated ETI-204 Concentration-time Profile in Infected (left) and Healthy (right) Human Adults Administered 16 mg/kg and Infected Monkeys Administered 16 mg/kg

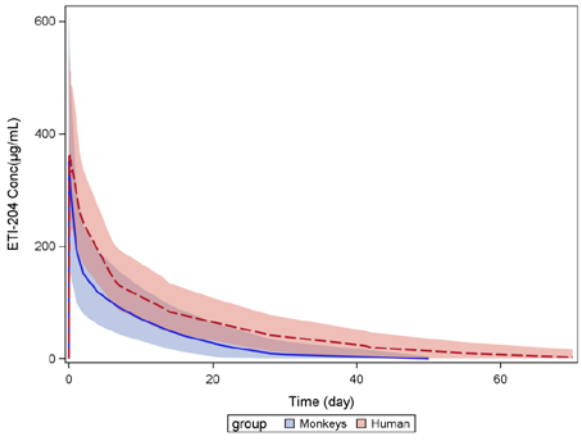
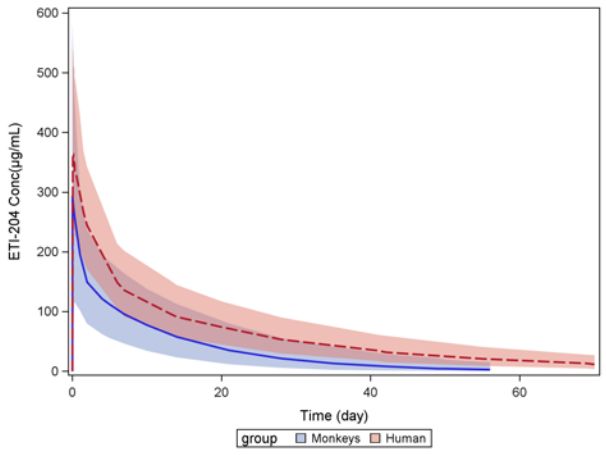
Infected human vs. Infected Monkeys	Healthy human vs. Infected Monkeys
	

Figure 24: Simulated ETI-204 Concentration-time Profiles in Infected (left) and Healthy (right) Human Adults Administered 24 mg/kg and Infected Monkeys Administered 16 mg/kg

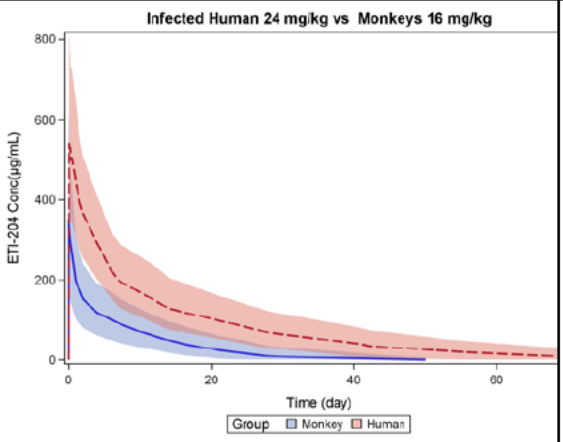
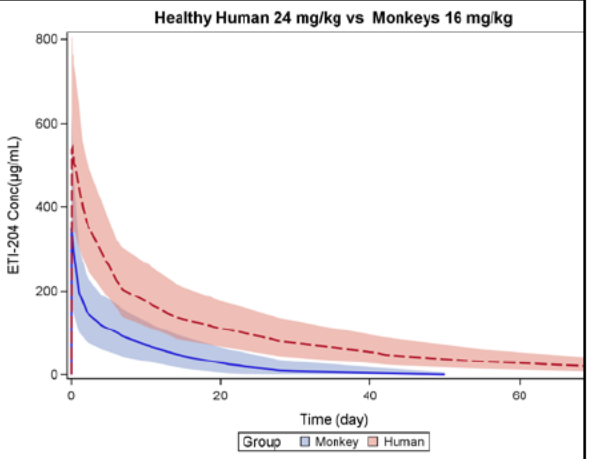
Infected humans vs. Infected Monkeys	Healthy Humans vs. Infected Monkeys
	

Figure 25: Simulated ETI-204 Concentration-time Profiles in Infected (left) and Healthy (right) Human Adults Administered 32 mg/kg and Infected Monkeys Administered 16 mg/kg

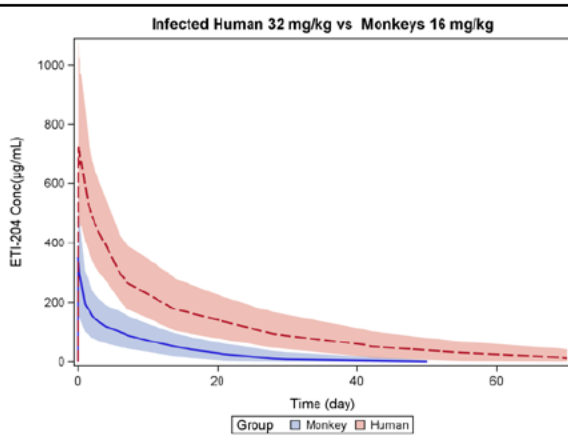
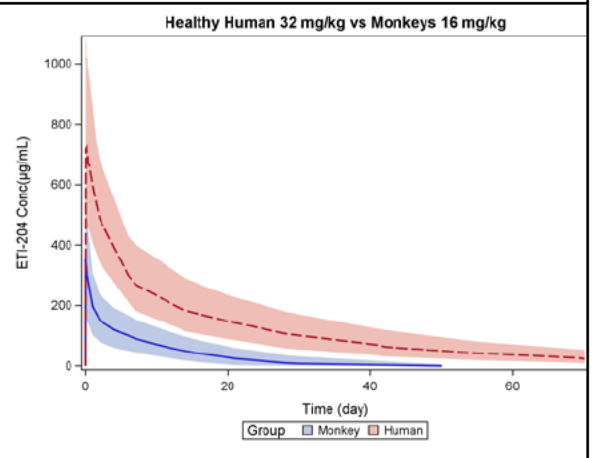
Infected humans vs. Infected Monkeys	Healthy humans vs. Infected Monkeys
	

Figure 26: Simulated ETI-204 Concentration-time Profiles in Infected (left) and Healthy (right) Human Adults Administered 16 mg/kg and Monkeys Administered 14.5 mg/kg

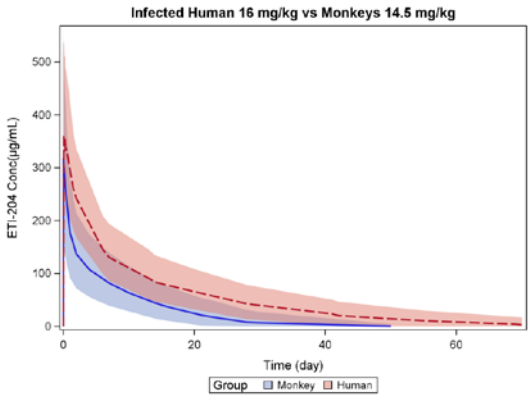
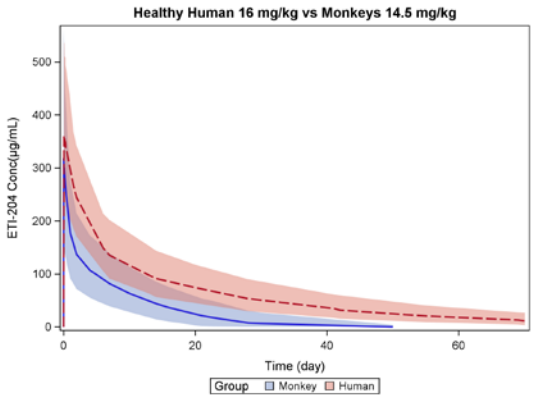
Infected humans vs. Infected Monkeys	Healthy humans vs. Infected Monkeys
	

Figure 27: Simulated ETI-204 Concentration-time Profiles in Infected (left) and Healthy (right) Human Adults Administered 24 mg/kg and Infected Monkeys Administered 14.5 mg/kg

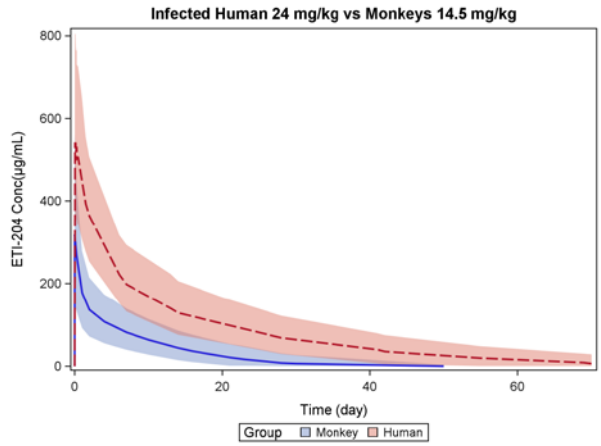
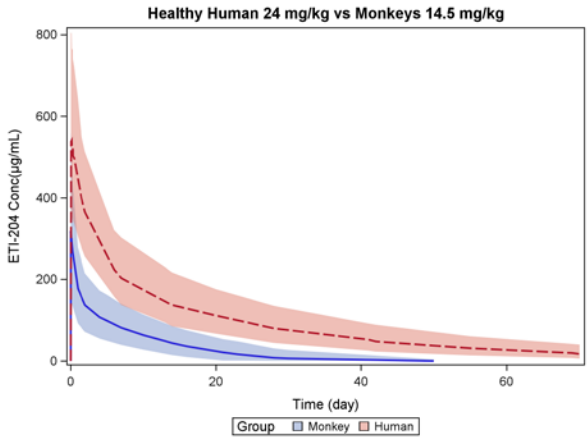
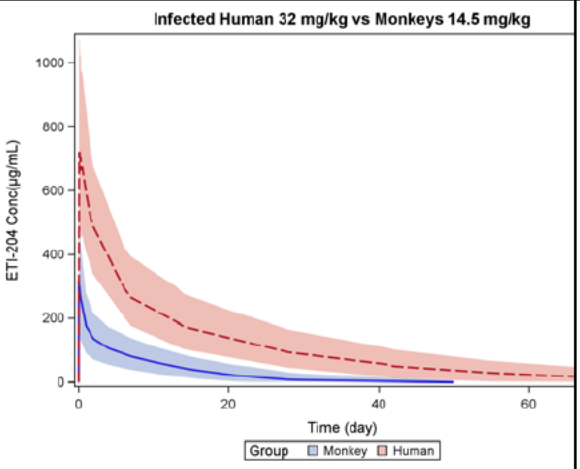
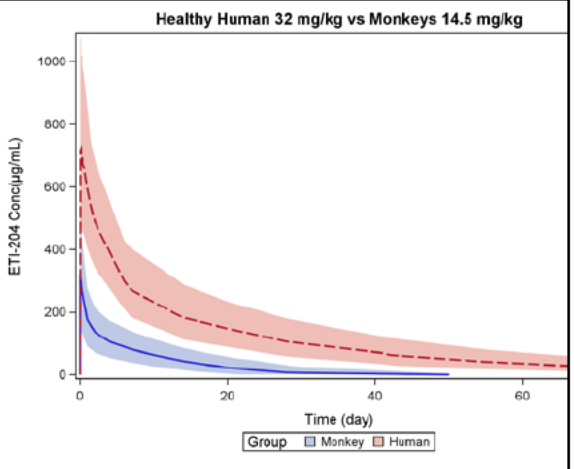
Infected Humans vs. Infected Monkeys	Healthy Humans vs. Infected Monkeys
	

Figure 28: Simulated ETI-204 Concentration-time Profiles in Infected (left) and Healthy (right) Human Adults Administered 32 mg/kg and Infected Monkeys Administered 14.5 mg/kg

Infected Humans vs. Infected Monkeys	Healthy Humans vs. Infected Monkeys





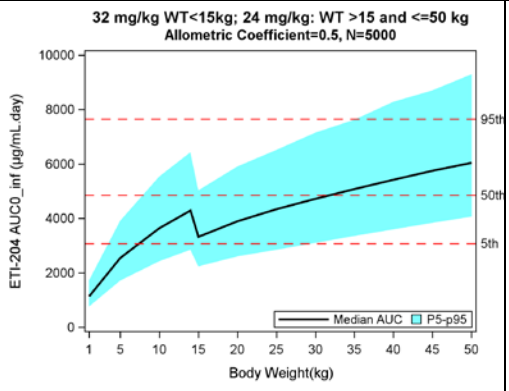
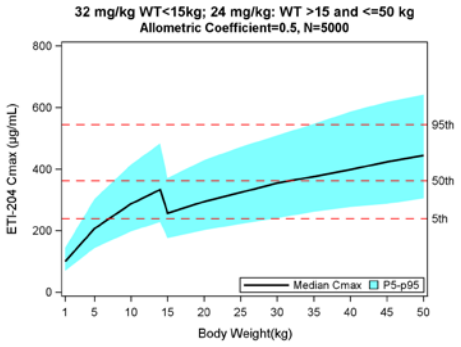
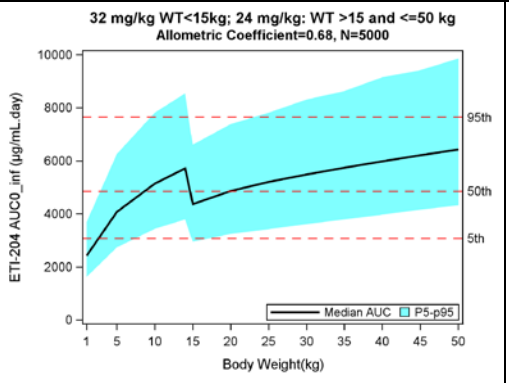
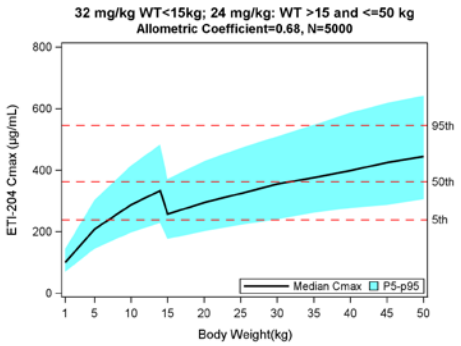
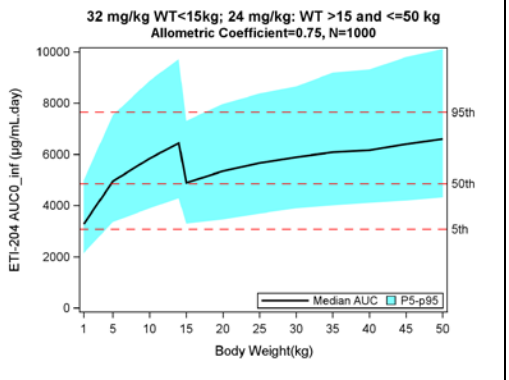
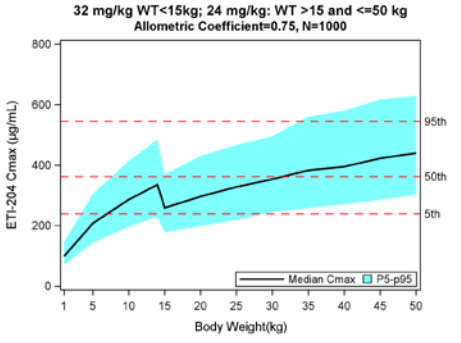
4.4.4 Simulations of ETI-204 Exposure in Children

Additional simulations for ETI-204 exposure in pediatric subjects were conducted by the reviewer to verify the sponsor's analysis as shown in section 3.3. The reviewer's analysis identified a subset of pediatric patients where ETI-204 exposure may be unacceptably high and recommended an alternative dosing regimen for this population. For pediatrics (and adults) weighing between 40 to 50 kg, a dose 16 mg/kg is recommended. More detailed explanation and analyses for the recommendation are described above in Question 1.1.3.

The greatest uncertainty in the estimated ETI-204 exposure lies in neonates or premature infants with body weights between 1 to 5 kg. The sponsor did not simulate ETI-204 concentrations in subjects less than 5 kg, but proposed a dose of 32 mg/kg for pediatric subjects less than 15 kg. Predicting ETI-204 concentrations in neonates or premature infants is very challenging. The allometric coefficient for ETI-204 clearance used for estimating pediatric exposure was 0.68 (identified from the adult population PK model), which is different from the commonly used scaling factor of 0.75. In addition, some monoclonal antibodies have shown a body weight/clearance relationship with an allometric coefficient value as low as 0.5. As we have no pediatric data with ETI-204 to refine the estimated allometric coefficient for this submission, a sensitivity analysis was conducted by the reviewer to evaluate the impact of varying allometric coefficient values on simulated ETI-204 exposures in pediatric subjects. The PK profiles in pediatric subjects weighing between 1 to 50 kg were simulated with allometric coefficient values on clearance of 0.5, 0.68, and 0.75. The AUC_{inf} and C_{max} values were calculated, plotted against body weight, and the results are shown in Figure 29. No matter what allometric coefficient is used, subjects weighing (b) (4) kg are expected to have exposure exceeding those in healthy adults when administered (b) (4) mg/kg, and the results support the reviewer's recommendation to dose adjust to 16 mg/kg in this body weight range. For subjects weighing <5 kg, ETI-204 AUC_{inf} and C_{max} would be lower than those in adults.

While the reviewer recognizes uncertainty in the estimated ETI-204 exposure for neonates and that underexposure is possible with 32 mg/kg, this dosing recommendation represents our best projection for appropriate dosing in this population. Even with the possibility of underexposure with 32 mg/kg, the resulting exposure would still be similar to exposures in monkeys administered the fully effective dose. Therefore, the reviewer considers 32 mg/kg as an appropriate dose for pediatrics between 1 to 5 kg.

Figure 29: Simulated ETI-204 Exposure in Healthy Humans with Body Weights between 1 kg to 50 kg Stratified by Allometric Coefficient Value

Allometric Coefficient Value	AUC_{inf}	C_{max}
0.5		
0.68		
0.75		

Listing of Analyses Codes and Output Files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Pk_human.sas	Post NONMEM analysis for PK in humans	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\obiltoxaximab_BLA125509_FL\PPK Data\Reviewer\Ex18_anthim\human\sas
Pk_nhp.sas	Post NONMEM analysis for PK in monkeys	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \obiltoxaximab_BLA125509_FL\PPK Data\Reviewer
Simulation2.sas	Simulations of ETI-204 expoure in human adults and monkeys.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\obiltoxaximab_BLA125509_FL\PPK Data\Reviewer\simulations\human
Peds_sim16.sas	Simulations of ETI-204 PK profile for pediatric dosing	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\obiltoxaximab_BLA125509_FL\PPK Data\Reviewer\simulations\human

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/s/

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