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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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Indication: Intravenous treatment of Inhalation Anthrax
Applicant: Human Genome Sciences, Inc. (HGS)
Review Division: Division of Anti-Infective Products (DAIP)
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1 Executive Summary

1.1 Introduction

BLA #125349 was originally submitted by Human Genome Science (HGS) on May 14, 2009 for FDA approval of the first in class, NME, raxibacumab, a recombinant, fully humanized, IgG1 λ monoclonal antibody directed against protective antigen (PA), as an adjunctive treatment to the available antibiotic therapy for patients diagnosed with inhalation anthrax. Antibacterial treatment is directed toward *Bacillus anthracis* (anthrax) eradication and has no activity against any of the toxins produced by the bacterium, including lethal toxin (LT) and edema toxin (ET). Protective antigen (PA) is the central component secreted by *B. anthracis* responsible for translocation of toxic enzymes, edema factor (EF) and lethal factor (LF), that when combined with PA becomes ET and LT, respectively. Proof-of concept studies in the initial application showed high affinity binding of raxibacumab to PA resulted in a survival advantage in a rat lethal toxin infusion model, pre-exposure and post-exposure prophylaxis animal model studies, and several drug efficacy studies of raxibacumab with and without antibiotic in inhalation anthrax animal models (NZW rabbit and cynomolgus macaque). Drug safety assessed in human volunteers and in a battery of nonclinical studies in healthy rabbits and non-human primates showed no evidence of toxicity at the maximum proposed, single therapeutic dose of intravenous raxibacumab to be administered to human adults of 40 mg/kg.

However, in pivotal raxibacumab monotherapy studies submitted to the original BLA submission in 2009, an exaggerated inflammatory response in the CNS was noted in the raxibacumab treated non-surviving animals compared to placebo non-survivors in inhalation anthrax infection models (rabbits and monkeys); histopathology in survivors was not assessed. Although survivors were euthanized in the combination levofloxacin /raxibacumab rabbit efficacy studies, the high efficacy of the fluoroquinolone limited the number of animals that died from anthrax in the active treatment arm (1 lethality to anthrax in the active treatment arm). Similarly, only 1 animal died after anthrax exposure in the combination ciprofloxacin/raxibacumab study conducted in non-human primates and no surviving monkeys were euthanized. In both combination animal efficacy studies submitted to the original BLA, the added benefit of raxibacumab treatment to antibiotic therapy could not be determined with the high survival outcome observed in both species challenged with inhalational anthrax. To address these deficiencies identified during review and in the AIDAC (anti-infective drugs advisory committee) discussion of the original submission, the sponsor conducted two additional nonclinical studies that are the subject of the current BLA resubmission dated June 15, 2012. The two new studies submitted in the BLA resubmission include the following: 1) the CNS toxicity study with raxibacumab conducted in NZW rabbits challenged with inhalation anthrax; 2) the added benefit combination efficacy study of raxibacumab and levofloxacin administered to NZW rabbits challenged with inhalational anthrax. Please note that the original pharm/tox review of the nonclinical studies submitted in the initial BLA application can be found in the action package dated 11/13/2009; the content of this review will not be summarized in the current BLA resubmission review.

1.2 Recommendations

1.2.1 Approvability

From a pharmacology/toxicology perspective, this application is approvable. There are no significant adverse nonclinical findings related to the drug product in the submitted nonclinical CNS toxicity study or added benefit study in rabbits that should adversely impact its approvability for the intended indication.

1.2.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.2.3 Labeling

8.1 Pregnancy

Pregnancy Category B.

A single embryonic-fetal development study was conducted in pregnant, healthy New Zealand White rabbits administered two intravenous doses of raxibacumab up to 120 mg/kg (three times the human dose on a mg/kg basis) on gestation days 7 and 14. No evidence of harm to the pregnant dam or the fetuses due to raxibacumab was observed. C_{max} values in rabbits after dosing with 120 mg/kg were 3629 mcg/mL and 4337 mcg/mL after the first and second dose of raxibacumab respectively; these are more than 3 and 4 times the mean C_{max} values in humans. Estimates of exposure (AUC) were not generated in the embryo-fetal rabbit study. No adequate and well-controlled studies in pregnant women were conducted. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk.

13.2 Animal Toxicology

Anthrax infected rabbits and monkeys administered an intravenous injection of raxibacumab (40 mg/kg) at time of PA toxemia reproducibly showed greater severity of CNS lesions (bacteria, inflammation, hemorrhage, and necrosis) in non-surviving animals compared to dead placebo control animals, with no difference in mean time to death from spore challenge. The raxibacumab monoclonal antibody appears unable to penetrate the CNS until compromise of the blood brain barrier (BBB) during the later stages of anthrax infection. The most severe brain lesions in rabbits were associated with bacteria and raxibacumab tissue binding in a similar pattern as endogenous IgG antibody that (b) (4) leaked across the compromised BBB. Surviving rabbits and monkeys at the end of the 28 day studies showed no microscopic evidence of CNS lesions. CNS toxicity was not observed in healthy monkeys administered raxibacumab (40 mg/kg) or in GLP combination treatment studies with antibiotics in rabbits (levofloxacin) or in monkeys (ciprofloxacin) at any time.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

565451-13-0

Generic Name

raxibacumab; Human IgG1 λ monoclonal antibody (mAb) against the protective antigen (PA) of *Bacillus anthracis* for treatment of inhalation anthrax

Code Name

HGS1021

Chemical Name

PA mAb

Molecular Formula/Molecular Weight

(b) (4) / 145.9 kDa as measured by ESI-MS

Structure or Biochemical Description

Raxibacumab is a fully human IgG1 antibody comprised of 2 identical light chains and 2 identical heavy chains. (b) (4)

Pharmacologic Class

Anti-protective antigen monoclonal antibody (Anti-PA mAb)

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 11,069: Raxibacumab

IND 102,964: Raxibacumab

BLA125349: Raxibacumab

2.3 Drug Formulation

Raxibacumab is a sterile, liquid formulation in single-dose vials intended for intravenous injection. Each vial contains 50 mg/mL raxibacumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 18 mg/mL glycine, 10 mg/mL sucrose, and 0.2 mg/mL (w/v) polysorbate 80 pH 6.5.

2.4 Comments on Novel Excipients

See original review.

2.5 Comments on Impurities/Degradants of Concern

See original review.

2.6 Proposed Clinical Population and Dosing Regimen

None.

2.7 Regulatory Background

- IND 11069 submitted May 22, 2003 to the Center for Biologics Evaluation and Research (CBER).
- Fast track designation was granted August 15, 2003.
- Orphan Product Development granted on November 12, 2003.
- Additional characterization studies submitted to demonstrate comparability between investigative M10 product (Phase 1 trial, PAM-NH-01, and proof of concept animal studies) and final M11 formulated product for licensure (animal efficacy studies, rabbit Segment II study, human raxibacumab /ciprofloxacin trial, large safety and repeat dose trials).
- Orphan Drug designation granted on February 20, 2008.
- Pre-BLA Meeting on October 21, 2008. HGS submitted all outstanding animal and clinical study reports to support delivery of raxibacumab to the SNS, the assay qualification reports of the nonclinical and clinical assays, and the updated drug stability and lot release data.
- Agreement reached on January 23, 2009 between HGS and FDA to allow the manufacture, purchase, and stock pile of raxibacumab in the U.S. Strategic National Stockpile (SNS) for use as treatment of inhalation anthrax.
- BLA 125349 submitted to FDA electronically on May 14, 2009.
- A Division of Special Investigations (DSI) audit of the clinical and analytical findings of the clinical pharmacokinetic studies (HGS1021-C1063; HGS1021-C1064; HGS1021-C1069) for the quantitation of raxibacumab and ciprofloxacin cited multiple analytical deficiencies that diminished accuracy and reliability of PK findings (report submitted to DSPTP October 7, 2009).
- Complete Response Letter sent to HGS on November 14, 2009 requiring the following: 1) rabbit added benefit (ciprofloxacin:raxibacumab) anthrax inhalation study; 2) rabbit anthrax inhalation study with raxibacumab to examine CNS

toxicity in non-surviving animals; 3) revision of analytic procedures and re-analysis of PK samples obtained from human studies HGS1021-C1063, HGS1021-C1064, and HGS1021-C1069; 4) re-assay of PK samples from animal studies 682-G005758, 724-G005829, and G923702)

Resubmission of BLA:

- Type A meeting held on January 29, 2010 between HGS and Agency to discuss pathway to address deficiencies listed in CR letter. Agreed with HGS that re-assay of nonclinical toxicokinetic samples from raxibacumab study 6962-140 and 6962-173 would not to be completed because of the age of the samples and minimal impact of revision of the ECL assay and reanalysis on study outcome.
- Nonclinical protocol to examine CNS toxicity in raxibacumab treated NZW rabbits exposed to inhalation anthrax submitted for assessment on May 4, 2010.
- Special Protocol Assessment requested for added benefit study with raxibacumab and levofloxacin as post-exposure inhalation anthrax treatment in NZW rabbits on July 1, 2010.
- Pre-BLA Resubmission Meeting held on March 19, 2012.
- BLA 125349 re-submitted to FDA electronically on June 15, 2012.
- PDUFA goal date is December 15, 2012.

3 Studies Submitted

3.1 Studies Reviewed

Study No. 1141-CG920871: "Added Benefit of Raxibacumab with Levofloxacin vs. Levofloxacin as Post-exposure Treatment in the New Zealand White Rabbit Inhalation Anthrax Model"

Study No. 1103-G923704: "Evaluation of Raxibacumab as a Therapeutic Treatment Against Inhalation Anthrax in the New Zealand White Rabbit Model" (CNS study)

Note: Figures/Tables used in this review were copied from the Applicant's Study Reports.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

BLA 125349 Pharmacology/Toxicology Review – Miller, T.J. (2009)

4 Special Toxicology Studies

Study title: Evaluation of Raxibacumab as a Therapeutic Treatment Against Inhalation Anthrax in the New Zealand White Rabbit Model (CNS Toxicity Study)

Study no.:	1103-G923704
Study report location:	CBER EDR
Conducting laboratory and location:	Battelle Biomedical Research Center St. Route 142 Jefferson, OH 43162
Date of study initiation:	June 7, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Raxibacumab, (Lot #71128), purity: 100%

Key Study Findings

- Mortality was 54% in raxibacumab versus 100% in placebo in anthrax treated rabbits.
- 95% of animals dosed with anthrax were bacteremic prior to treatment; non-surviving animals in both groups showed bacteria in the CNS and in terminal brain tissue.
- Plasma PA levels were similar in non-surviving animals in both groups; absent in surviving animals treated with raxibacumab at Day 28 post challenge
- Plasma raxibacumab levels were similar in surviving and non-surviving animals; low levels of raxibacumab detected in CSF of both non-surviving and surviving animals
- Anti-drug antibodies were detected in a majority of surviving animals and negative in non-surviving animals; raxibacumab did not impact TNA titers.
- Gross and histopathologic lesions in non-survivors primarily due to anthrax infection; greater CNS lesions in raxibacumab animals compared to placebo due to compromised BBB.
- On Day 28 post-challenge, all surviving rabbits treated with raxibacumab were negative for bacteremia and bacteria in CSF and brain, and had no CNS lesions.

Methods

Doses: 40 mg/kg
Frequency of dosing: Single Dose
Route of administration: Intravenous (vascular access port [VAP])
Dose volume: 0.8 mL/kg
Formulation/Vehicle: Raxibacumab: Liquid formulation (50 mg/mL) in formulation buffer containing 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, 0.2 mg/mL polysorbate 80, pH 6.5.
Vehicle: Formulation buffer
Species/Strain: Rabbit / New Zealand White (NZW)
Number/Sex/Group: 24/treatment group (\approx 50:50 male/female)
Age: Mean 7.7 months
Weight: Mean: 2.7 kg (female) and 4.3 kg (male)
Satellite groups: None
Deviation from study protocol: Minor protocol deviations during the in-life phase are not considered to have an impact on study results,

Objectives:

- To assess terminal pathology in select organs, particularly in the CNS, in both surviving and non-surviving rabbits
- To evaluate the efficacy of raxibacumab as a monotherapy against lethality in rabbits with inhalation anthrax

Study Design:

This was a parallel-group, blinded, randomized, placebo-controlled GLP monotherapy study to evaluate drug-induced pathology in the brain and other select organ systems after raxibacumab treatment in the rabbit inhalation anthrax model. Survival, bacteremia, raxibacumab and protective antigen (PA), kinetics, and raxibacumab immunohistochemistry were also examined.

Methods:

The study was conducted at Battelle Biomedical Research Center, West Jefferson, OH. Forty-eight (50% male, 50% female), 7 months old New Zealand White rabbits (*Oryctolagus cuniculus*) with surgically implanted VAPs (vascular access ports), weighing between 2-5 kg at randomization were randomized into two treatment groups (placebo control and 40 mg/kg raxibacumab) and then further randomized into 1 of 2 aerosol challenge days and challenge order (See Table 1 below).

Table 1. Treatment Groups

Groups	N	Dose	Route/Frequency	Treatment Point
Group 1 (Placebo)	24	Placebo ¹	IV / single dose	Individual treatment times based on serum PA levels ²
Group 2	24	40 mg/kg	IV / single dose	

¹ Raxibacumab buffer, administered at an equivalent dose in mL/kg to Group 2

² Each rabbit received raxibacumab or placebo immediately upon its 1st positive PA result in the qualitative ECL assay.

(Adapted from HGS' Study Report, p. 14)

On their designated challenge day, each animal was placed into a plethysmography chamber and aerosol challenged with a targeted 200 LD₅₀ [2.1×10^7 spores] inhaled dose of *B.anthraxis* (Ames strain) spores. Aerosol concentrations of *B.anthraxis* were quantified by determination of colony forming units (cfu) in effluent streams. Test article or control buffer was administered in a single intravenous bolus of 40 mg/kg raxibacumab or buffer (placebo) upon detection of a positive qualitative PA results (\approx 16-48 hr post-challenge) using a chemiluminescence (ECL) assay. Surviving animals were euthanized on Day 28 post challenge. The study director, technical staff and study pathologists were blinded to treatment.

The dose of raxibacumab selected is the proposed dose for licensure (40 mg/kg) and is based on pivotal rabbit and monkey therapeutic efficacy studies, and safety profile in human clinical trials

Animal observations and temperature monitoring occurred every 6 hours between 18 and 168 hours post-challenge, and twice daily on all other study days (beginning 3 days prior to challenge). Body weights were collected during quarantine and on study day 0 for calculating dose volumes of test article and control buffer. Death or euthanasia was recorded at the time observed and a complete necropsy was performed. Blood samples were collected for several time points and assayed to assess bacteremia, plasma PA, plasma raxibacumab concentrations, immunogenicity (anti-raxibacumab antibodies), and toxin neutralizing antibodies (TNA) (See Table 2 below). No raxibacumab PK or PA kinetic modeling was performed. Cerebrospinal fluid was collected at necropsy and assessed for *B.anthraxis*, quantitative PA and raxibacumab concentrations. Complete gross necropsies were conducted on all rabbits. Brain, lungs, spleen, liver, kidney, and mediastinal/bronchial lymph nodes were collected and evaluated in all animals for gross and microscopic findings. A brain sample was collected for bacterial assessment at necropsy. All tissues were then fixed by immersion into formalin; brain and spleens were post-fixed in 70% ethanol and dissected into the following 4 sections:

- (A) cerebral cortex (frontal parietal), corpus collosum, and basal ganglia;
- (B) hippocampus, cerebral cortex (temporal-parietal), thalamus/hypothalamus;
- (C) cerebellum including vermis and hemispheres, and medulla;
- (D) Midbrain (colliculi).

Prepared slides from the 4 brain sections were processed with the following stains and by immunohistochemistry (IHC):

- (A) Bielschowsky stain for neurodegeneration and neurofibrillary plaques;
- (B) Fluoro-Jade C stain for acute neuronal degeneration;
- (C) IHC for Glial Fibrillary Acid Protein (GFAP) to detect chronic or healed damage;
- (D) IHC for Raxibacumab;
- (E) IHC for Rabbit IgG.

The study pathologist was blinded to the treatment until after the slides were read.

Table 2. Blood Collection and Assay Schedule

Time Point	Allowed Variance	Blood Tube type/ Approximate Blood Volume	Bacteremia (Culture)	Plasma PA Level (via ECL assay) Performed Onsite	PA Levels via ECL (plasma shipped to HGS)	Raxibacumab Assay (PK) (plasma shipped to HGS)	Immunogenicity and TNA Analysis (plasma shipped to HGS)
Day -6	-	EDTA ~2.0 ml EDTA ~2.0 ml	X	X	X	X	X
16hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
20hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
24hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
28hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
32hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
36hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
40hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
44hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
48hr PC [^]	± 30 min	EDTA ~2.0 ml	X	X	X		
PTT	-	EDTA ~2.0 ml	X	X	X	X	
5min PTx	+ 5 min	EDTA ~1.5 ml			X	X	
4hr PTx	± 15 min	EDTA ~1.5ml			X	X	
10hr PTx	± 30 min	EDTA ~1.5 ml			X	X	
24hr PTx	± 60 min	EDTA ~1.5 ml	X		X	X	
48hr PTx	± 60 min	EDTA ~1.5 ml	X		X	X	
72hr PTx	± 60 min	EDTA ~1.5 ml	X		X	X	
7 days PC ^b	-	EDTA ~2.0 ml	X		X	X	
14 days PC ^b	-	EDTA ~2.0 ml	X		X	X	
21 days PC ^b	-	EDTA ~2.0 ml	X		X	X	
28 days PC ^b	-	EDTA ~2.0 ml EDTA ~ 2.0 ml	X		X	X	X
Terminal ^{c, d}	-	EDTA ~2.0 ml	X		X	X	

PC Post-Challenge

PTx Post-Treatment

PTT Prior to Treatment

X Indicates sample collection scheduled

[^] Post-challenge, pre-treatment blood draws stopped once decision to treat had been made.

^a Post-challenge pre-treatment bleed time points were calculated based on one median challenge time per challenge day.

^b Blood samples 7, 14, 21 and 28 days post-challenge were not collected from the VAP.

^c If collection was possible.

^d Animals which survived to the end of study (day 28) did not have a terminal sample collected.

(Table 2 on page 16 in the Battelle Study Report)

Results

Anthrax Exposure

The two treatment groups were comparable with respect to sex, weight, and age at randomization. Anthrax spore challenge was slightly greater in the raxibacumab treatment group however the average dose in the placebo group was confirmed to be lethal as all placebo treatment animals succumbed to disease following challenge. The anthrax spore challenge by treatment group is shown in Table 3 below.

Table 3. Average Challenge Doses (LD₅₀ equivalent)

Challenge Day	Average Challenge Dose (SD)
A	142 (± 45)
B	149 (± 36)
Group	Average Challenge Dose (SD)
1 (40 mg/kg Raxibacumab)	154 (± 41)
2 (Buffer - placebo)	138 (± 39)

(Table 3 on page 21 in the Battelle Study Report)

Timing of Treatment

Treatment with raxibacumab was triggered in each animal individually by the first qualitative positive plasma PA result (ECL). Animals in the placebo and raxibacumab treatment groups were treated at a mean time of 32.3 and 28.6 hours after challenge, respectively. There were no significant differences in toxemia or bacteremia between treatment groups at time of intervention.

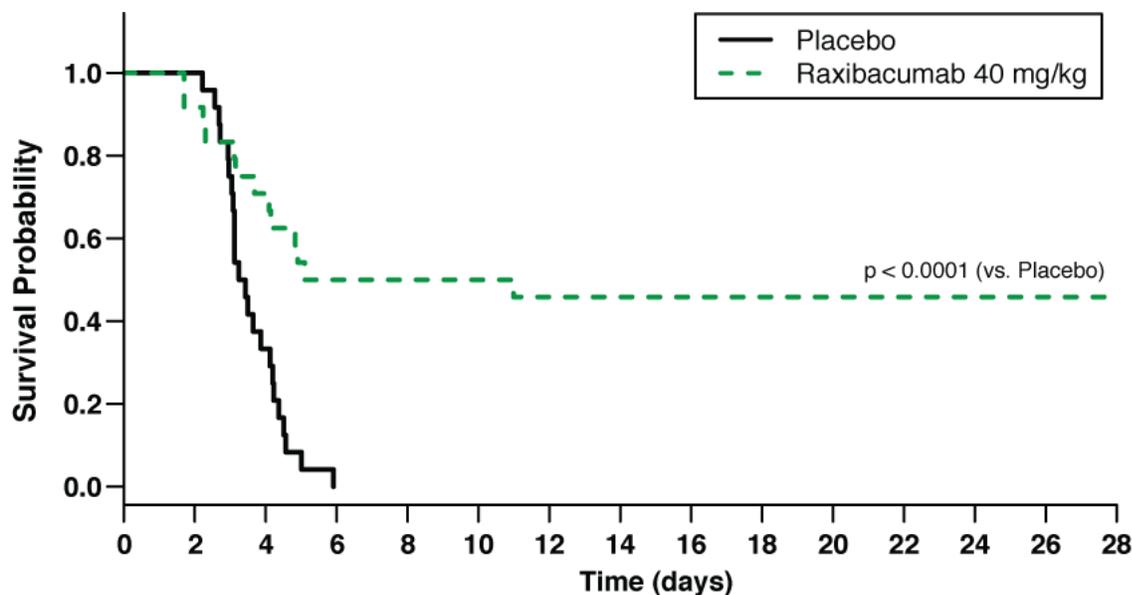
Mortality and Survival

The mortality for both study groups of rabbits challenged with inhalation *B.anthraxis* is shown in Table 4 below. None of the placebo animals survived, whereas 46% (11/24) of the raxibacumab treated animals survived to Day 28. Most of the survivors (11/13) in the raxibacumab-treated group were female in this study.

Table 4. Primary Efficacy Analysis, Survival at Day 28 Post-Challenge

	<i>Placebo</i>	<i>Raxibacumab</i>	<i>Difference (Raxi – Placebo) (95% CI)(%)</i>	<i>P-value</i>
ITT animals	0/24 (0.0%)	11/24 (45.8%)	45.83 (25.27, 67.18)	0.0002
Toxemic animals at or before treatment	0/24 (0.0%)	10/23 (43.48%)	43.48 (22.86, 65.51)	0.0002
Bacteremic animals at or before treatment	0/22 (0.0%)	9/22 (40.91%)	40.91 (19.93, 63.65)	0.0014
Animals excluding non- anthrax death	0/24 (0.0%)	11/23 (47.8%)	47.8 (26.6, 69.4)	<0.0001

The sponsor reported a greater time of survival in animals both toxemic/bacteremic at treatment initiation with a median time to death (TTD) of 3.3 days for placebo versus 8.0 days (p-values ranging from 0.0002 to 0.0007) for the raxibacumab group (see Figure 5.1-1 below).



(Figure 7-3 on page 35 of HGS study report).

Figure 1. Survival Time During 28-day Study Period in Rabbits Toxemic and/or Bacteremic at Treatment Initiation

Additional analysis on survival time observed in non-surviving rabbits that died prior to Day 28 showed no significant difference in mean TTD post-challenge in raxibacumab and placebo treated animals (mean 3.99 versus 3.59 days, respectively), with an approximate difference of only 9.7 hours (Note: The TTD listed is an estimate of the time to death post-challenge since a majority of dead animals in both groups were found dead in their cages). Figure 2 shows the distribution of time to death post-challenge for animals that died in the placebo and raxibacumab groups. The raxibacumab animal (#L35568) that died at 263.7 hours after anthrax challenge did not have extravascular bacteria and the cause of death is not likely anthrax related (note: the study pathologist indicated possible renal infection of a parasitic fungi (*Encephalitozoon cuniculi*)).

Figure 2 below shows the distribution of time to death post-challenge for animals that died in the placebo and raxibacumab groups. The raxibacumab animal (#L35568) that died at 263.7 hours after anthrax challenge did not have extravascular bacteria and the cause of death is not likely anthrax related (note: the study pathologist indicated possible renal infection of a parasitic fungi (*Encephalitozoon cuniculi*)).

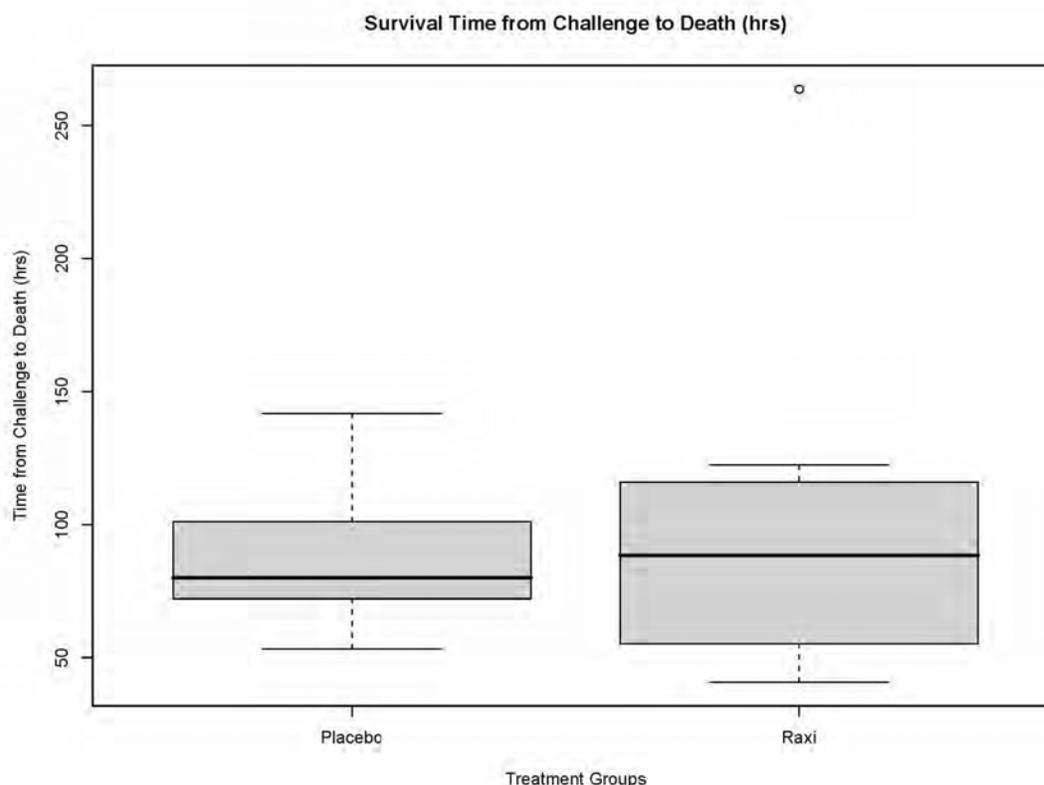


Figure 2. Survival Time from Challenge to Death in Non-Surviving Raxibacumab and Placebo Treated Animals

Clinical Observations

Ninety-six percent (23/24) of the placebo treated animals were found dead on study, whereas 62% (8/13) of the raxibacumab treated animals that died on study were found dead in their cages. The remainder of the non-surviving raxibacumab treated animals (5/13) was euthanized moribund prior to scheduled termination. Commonly observed clinical signs first noted on study day 2 (48 hours) post-challenge included lethargy, inappetence, stool abnormalities, and respiratory abnormalities. Severe facial and neck edema were observed in 3 rabbits (1 placebo [L35556] and 2 raxibacumab animals [L35581 and L35566]); the placebo treated animal was euthanized and the 2 raxibacumab treated animals recovered spontaneously.

Three raxibacumab treated animals (L35554, L35548, L35561) showed ataxia, impaired respiration, no front or hind limb use, and/or seizures, requiring euthanization on Days 3-5. In raxibacumab treated animals that survived to 28 days post challenge, most animals appeared normal by day 7 post-challenge. However, 3 raxibacumab treated animals (L35530, L35531, L35550) showed delayed, impairment of front or hind limb use on study days 11, 12, and 17, respectively, which were generally resolved within a few days of initial observation. The sponsor claimed these hind limb effects to be

unrelated to challenge and treatment based on the delay of onset relative to other abnormal clinical observations in animals exposed to anthrax.

Body Temperature Results

The majority of animals challenged with anthrax had expected elevated temperatures on Study Days 2-6, with increased temperatures lagging behind appearance of PA or bacteremia, consistent with findings in previous rabbit inhalation anthrax studies.

(Reviewer's comment: Although pyrexia developed in nearly all infected rabbits, pyrexia is not considered a suitable trigger for treatment initiation because both antigenemia (Increase in plasma PA levels) and bacteremia precede development of pyrexia¹).

Blood, CSF, and Brain Tissue Culture Levels of *B.anthraxis*

Ninety-four percent (45/48) of rabbits dosed with anthrax were bacteremic prior to treatment. Nearly all (34/37) placebo and raxibacumab treated animals that died prior to the 7 day post-challenge time point showed positive bacteremia results.

CSF was successfully collected from 65% (24/37) of the rabbits that died on study and all (11/11) rabbits that survived to 28 days post-challenge. All (19/19) of the placebo-treated animals from which a CSF sample could be collected had a positive bacteria culture; eighty percent (4/5) of the non-surviving raxibacumab treated animals from which a CSF sample could be collected was positive for bacteria. Similarly, 100% (24/24) of the rabbits in the placebo group and 92% (12/13) of the non-surviving raxibacumab treated animals showed positive bacteria levels in their terminal brain tissue. Bacterial infiltration into the CNS (both in the CSF and nervous tissue) was confirmed in nearly all non-surviving animals in the placebo and raxibacumab groups.

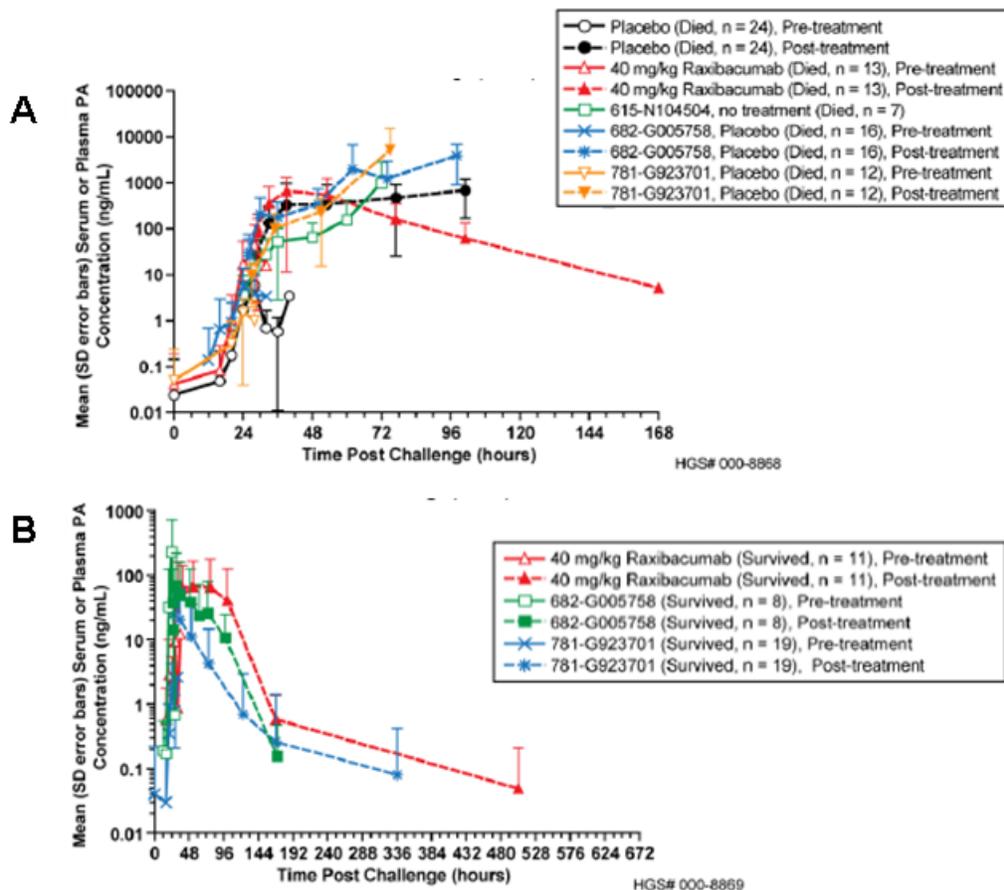
All (11/11) surviving rabbits were negative for bacteremia 7 days post-challenge and showed no bacteria in the CSF or brain tissue cultures by day 28.

Quantitative Plasma and Cerebrospinal Fluid (CSF) PA Levels

The sponsor's mean plasma PA concentration-time profiles for the dead and surviving animals treated with placebo or 40 mg/kg raxibacumab are shown below in Figure 2 (data from other studies included in graph). Non-surviving animals in both groups showed a similar PA profile that appeared different from surviving animals. Up to the time of treatment, mean plasma PA concentrations were similar to the placebo group. After treatment, the few non-surviving raxibacumab treated rabbits that survived beyond the mean TTD (2.89 days post-treatment) showed a relative decrease in plasma PA concentrations (Figure 2A). However, in surviving animals in the raxibacumab group, mean plasma PA concentration-time profiles showed an approximate 10-fold lower magnitude of the mean peak plasma PA concentration compared to placebo. The decrease in plasma PA concentrations could be the result of raxibacumab-PA complex

¹ Yee, S.B., Hatkin, J.M., Dyer, D.N., Orr, S.A., Pitt M.L.M. (2010). Aerosolized *Bacillus anthracis* Infection in New Zealand White Rabbits: Natural History of Intravenous Levofloxacin Treatment. *Comparative Medicine*. **60**(6); 461-468.

formation and decreased detection in the assay, or from decreased bacteremia via increased bacterial clearance or inhibition of spore germination².



(Figures 6-4 and 6-5 on page N-24 of the Battelle study report)

Figure 3. Plasma PA Concentration-Time Profiles in non-surviving (A) and surviving (B) rabbits administered a single IV bolus dose placebo or 40 mg/kg raxibacumab after detection of PA toxemia

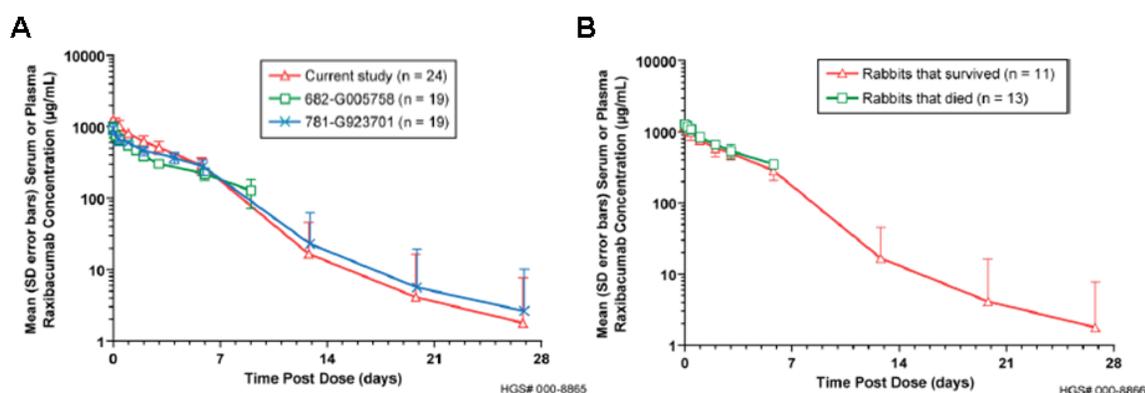
None (0/11) of the surviving raxibacumab animals showed measurable PA levels in the CSF. In animals that died, CSF PA levels were highly variable in both treatment groups, ranging from not detectable to > 966 ng/mL (0% to 37% of concurrent plasma PA concentrations in the placebo group). The high variability of PA levels in the subset of animals from which CSF could actually be collected made comparisons of mean PA levels difficult to interpret.

² Welkos, S., Little, S., Friedlander, A., Fritz, D., and Fellows, P. (2001). The role of antibodies to *Bacillus anthracis* and anthrax toxin components in inhibiting the early stages of infection by anthrax spores. *Microbiology*. **147**, 1677-1685.

(Reviewer's Comment: It's not clear from the assay descriptions if the raxibacumab and PA assays can accurately measure the amount of raxibacumab-PA or PA-TNA complexes. The assay results therefore may be difficult to interpret when trying to determine the amount of total raxibacumab and PA levels in the plasma and CSF. In addition, the difficulty encountered during CSF collection from study animals may also help explain the highly variable data for CSF PA obtained in this study).

Raxibacumab Concentrations in Plasma and the CSF

The mean observed plasma raxibacumab concentration-time profile for the 40 mg/kg raxibacumab dose group is similar to the drug profile obtained in other studies, included in Figure 3A for comparison below. Also, plasma raxibacumab concentrations in dead and surviving raxibacumab treated rabbits were similar indicating survival was not attributed to differences in raxibacumab exposure (Figure 3B).



(Figures 6.1 and 6-2on pages N-18 and N-19 of the Battelle study report)

Figure 4. Mean plasma raxibacumab concentration-time profiles in rabbits administered a single IV bolus 40 mg/kg raxibacumab after PA detection compared with results from other studies (A); mean raxibacumab plasma levels in dead and surviving rabbits administered 40 mg/kg raxibacumab after detection of PA (B).

Overall, raxibacumab appears to minimally distribute into the CSF of treated animals. Similar to the CSF PA results, raxibacumab concentrations in the CSF measured in (4/13) treated rabbits that died (limited by an inability to collect sufficient CSF) showed variable results ranging from < 1 µg/mL to 545 µg/mL (0.2-88% of the concurrent plasma raxibacumab concentration). Raxibacumab was detected in the CSF of a few surviving animals at very low concentrations (range: 0 to 0.331 µg/mL). However, highly variable raxibacumab CSF data in the subset of animals from which CSF could actually be collected made comparisons of mean raxibacumab levels difficult to interpret.

Immunogenicity (Anti-Raxibacumab Antibodies) and TNA Titer Results

Immunogenicity and TNA titer results were available at pre-dose for all animals and for Day 28 in survivors only; no post-dose titer data is available for animals that died before Day 28 due to assay interference of plasma raxibacumab.

At pre-dose, (3/24) rabbits in the placebo group were positive for anti-raxibacumab antibodies with post-dose outcome unknown for all animals in this group (all animals died). Of the surviving animals in the raxibacumab treatment group, (3/11) were negative for anti-raxibacumab Ab at baseline and post-dose; (7/11) rabbits were negative at baseline and positive for anti-raxibacumab Ab post-dose; and (1/11) rabbits was positive for anti-raxibacumab AB at baseline and post-dose. All (13/13) non-survivors in the raxibacumab group were negative for anti-raxibacumab antibodies at pre-dose with the post-dose outcome unknown. Although 8/11 surviving rabbits were anti-raxibacumab antibody positive, the diminished raxibacumab exposure generally observed after Days 6-7 post-treatment did not appear to affect survival suggesting one or more of the following: 1) the anti-raxibacumab antibodies were not neutralizing; 2) raxibacumab was present but the assay was unable to measure the complexes; 3) adequate immunologic response to bacteria and toxins after 6-7 days post-challenge can prevent further death in this group.

Raxibacumab did not interfere with development of endogenous toxin neutralizing antibodies (TNA); high TNA titers ($\mu \approx 2175$) detected only in surviving rabbits 28-days post-treatment were generated in the presence of high plasma raxibacumab levels after treatment.

(Reviewer's comment: Immunogenicity and TNA titer was determined at pre-dose for all animals and on Day 28 only in survivors due to assay interference of high raxibacumab levels observed in prior studies. No post-dose immunogenicity or TNA titer data is available for animals that died during the study prior to Day 28).

Necropsy and Histopathology

Adequate Battery

Yes; Protocol specified tissues only – brain, kidneys, liver, lungs, spleen, gross lesions, mediastinal/bronchial lymph nodes)

Peer Review

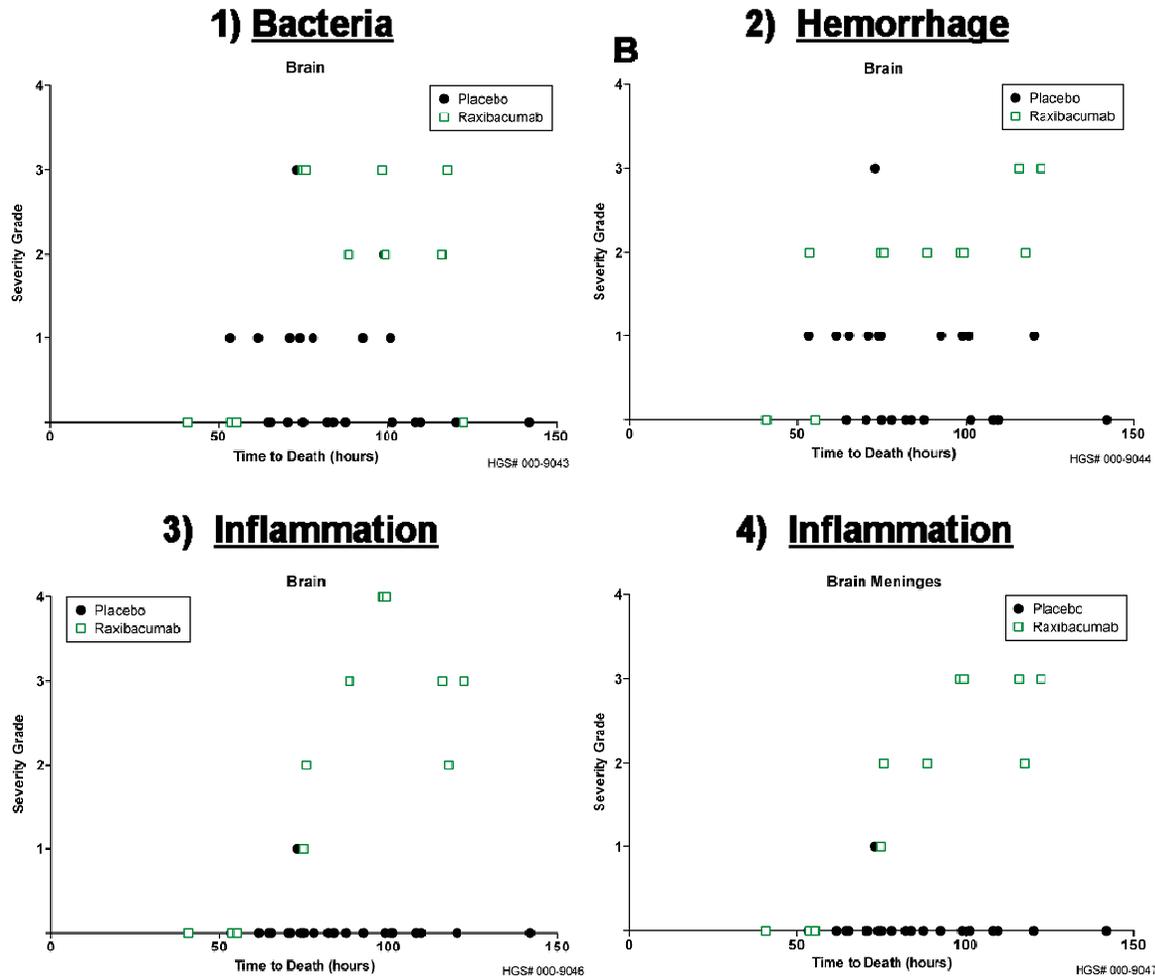
Yes.

Gross lesions in rabbits found dead or euthanized moribund include discoloration or foci of the appendix and brain (hemorrhage and inflammation), enlargement of bronchial and mediastinal lymph nodes (edema, fibrin exudation, hemorrhage), and fluid (effusion) in the body cavities and thymus. These lesions consistent with anthrax infection³ were found primarily in rabbits that died or became moribund during the study, correlated histologically with acute suppurative inflammation, necrosis, hemorrhage,

³ Zaucha, G.M., Pitt, L.M, Estep, J., Ivins, B.E., and Friedlander, A.M. (1998). The pathology of experimental anthrax in rabbits exposed by inhalation and subcutaneous inoculation. *Arch Pathol Lab Med.* 122(11): 982-992

edema, vasculitis, and the presence of large-rod shaped bacteria in the appendix, brain, kidney, liver, lung, bronchial and mediastinal lymph nodes, spleen, and thymus. In surviving animals in the raxibacumab group euthanized on Day 28, no gross lesions attributed to infection or treatment were detected, however, several minor lesions including continued inflammation, increased macrophage counts, lymph node and splenic hyperplasia, and chronic inflammation in the lungs suggests recovery of a septicemic event.

Non-surviving animals in the raxibacumab treatment group more commonly showed brain lesions (bacteremia, inflammation, hemorrhage, and/or necrosis) of greater incidence and severity when compared to non-surviving animals in the placebo group (See Figure 4, Table 5 below). Also, non-surviving animals within the raxibacumab treatment group that lived the longest appeared to show the greatest lesions. The lesions appeared widespread throughout the brain; no specific brain region appeared preferentially affected. Bacterial colonization of the brain was far more severe in the raxibacumab group compared to control. General inflammation commonly found throughout the brain, especially in the cerebral cortex, hippocampus, ventricular system, cerebellum, and meninges of raxibacumab treated animals was nearly non-existent in placebo group animals. Similarly, necrosis was more common in the non-surviving raxibacumab treated animals, specifically in the cerebellum, cerebral cortex, and parenchymal tissue, and was absent in the placebo group. Fluoro-Jade C staining for necrosis/neurodegeneration was only present in the raxibacumab treated rabbits; no significant GFAP positive staining of neural tissue was detected. Like in raxibacumab treated animals, brain hemorrhage was detected in placebo animals at many sites but with mostly diminished incidence and severity compared to the treated group; however, hemorrhage in brain meninges was similar in incidence and severity in both groups. Cerebrovascular necrosis/vasculitis observed in raxibacumab treated brains was generally absent in placebo. No brain lesions were observed in surviving animals.



Adapted from HGS study report Figures 13-1, 13-6, 13-11, and 13-12 (pp 133-144)

Figure 5. Severity of Brain 1) Bacteria, 2) Hemorrhage, 3) Inflammation, and 4) Inflammation (Meninges) by Time of Death in Non-Survivors

Table 5. CNS Histopathology Findings in Non-Survivors

Group	Raxibacumab Incidence (Mean Severity)	Placebo Incidence (Mean Severity)
Number In Group	24	24
Mortality	54%	100%
# dead	13	24
Bacteria, Extravascular	7 (1.4)	8 (0.5)
Hemorrhage(s)		
Hemorrhage(s), Cerebellum	8 (1.1)	2 (0.1)
Hemorrhage(s), Cerebral Cortex, Fronto-Parietal	6 (0.5)	3 (0.2)
Hemorrhage(s), Cerebral Cortex, Temporo-Parietal	5 (0.5)	3 (0.1)
Hemorrhage(s), Hippocampus	4 (0.5)	0 (0)
Hemorrhage(s), Meninges	9 (1.0)	9 (0.5)
Hemorrhage(s), Midbrain	4 (0.5)	4 (0.2)
Hemorrhage(s), Thalamus	6 (0.5)	3 (0.1)
Inflammation		
Inflammation, Cerebellum	3 (0.4)	0 (0)
Inflammation, Cerebral Cortex, Fronto-Parietal	6 (0.7)	0 (0)
Inflammation, Cerebral Cortex, Temporo-Parietal	6 (0.8)	0 (0)
Inflammation, Heterophils	8 (1.7)	1 (0)
Inflammation, Hippocampus	4 (0.4)	0 (0)
Inflammation, Meninges	8 (1.5)	1 (0)
Inflammation, Ventricular System	4 (0.5)	0 (0)
Necrosis		0 (0)
Necrosis, Cerebellum	3 (0.3)	0 (0)
Necrosis, Cerebral Cortex, Fronto-Parietal	4 (0.4)	0 (0)
Necrosis, Cerebral Cortex, Temporo-Parietal	5 (0.5)	0 (0)
Necrosis, Parenchyma	6 (0.8)	0 (0)
Vasculitis/Cerebrovascular Necrosis	6 (0.7)	1 (0)
Acute Neurodegeneration, FluoroJade-C	5 (na)	0 (na)
Raxibacumab (=) staining, CNS tissue	12 (na)	0 (na)

Severity is defined as 1=minimal, 2=mild, 3=moderate, 4=severe

na: Severity not applicable, severity grade not provided.

(Ada

pted from Table 8-6 on page 44-45 of the HGS study report)

A strong immunopositive correlation of brain lesions with frequency, location, and intensity of raxibacumab and IgG staining of the brain was observed in non-surviving raxibacumab treated animals. An overlapping pattern of IgG and raxibacumab staining of neurons and neuropil was often observed in regions rich with bacteria, inflammation, and/or necrosis. Infection, circulating bacterial toxins, and/or inflammation (including sepsis) has been shown to enhance blood brain barrier (BBB) permeability⁴. Based on these results, it appears that raxibacumab and endogenous IgG, both with a limited capacity to cross an intact BBB, may have leaked non-specifically across the damaged blood brain barrier during bacterial meningitis in the raxibacumab group. Only one placebo animal (#L35576) that showed a severe score for meningitis also stained positive for IgG in the brain suggesting compromise of the blood brain barrier sufficient for IgG and raxibacumab leakage did not generally occur in the placebo group. Surviving animals also may have experienced an altered BBB early in the progression of the disease, as greater IgG positive staining of vascular endothelium, meninges, and neuropil was observed in raxibacumab treated survivors compared to unchallenged

⁴ De Vries, H.E., Kuiper, J., De Boer, A.G., Van Berkel, T.J.C., Breimer, D.D. (1997). The blood brain barrier in neuroinflammatory diseases. *Pharm. Rev.* **49**(2); 143-155.

controls. However, no raxibacumab staining of brain tissue was observed in the surviving animals at Day 28.

Despite the greater adverse changes in the brain, raxibacumab was effective in reducing histopathology in all other organs examined outside of the CNS, including the appendix, liver, lung, lymph nodes, kidney and spleen in both non-surviving and surviving animals (see Table 6 and 7 below). Bacteremia, inflammation, hemorrhage and necrosis all appeared significantly diminished in incidence and severity (>> 50%) in non-surviving raxibacumab treated animals compared to placebo. The large reduction of extravascular bacteria in organs in the raxibacumab animals was most striking, with generally a small number of non-surviving animals with low residual levels of bacteria (severity score: 0-0.7), primarily in the draining bronchial and mediastinal lymph nodes. Hepatocellular necrosis of similar incidence but slightly greater severity was observed in raxibacumab treated animals compared to placebo. Despite the inhalation route of delivery of the spores, the lungs did not appear to be the target organ for anthrax toxicity, with only minor inflammation, no hemorrhage or necrosis, and little fibrin accumulation detected in both placebo and raxibacumab treated animals. Although important to the initial pathogenesis establishing systemic infection, inhalation anthrax is not considered a primary pulmonary disease⁵.

⁵ Barnes, J.M. (1947). The development of anthrax following the administration of spores by inhalation. *Br. J. Exp. Pathol.* **28(6)**: 385-394.

Table 6. Histopathology Findings of Selected Non-CNS Organs in Non-Surviving Rabbits

Group	Raxibacumab Incidence (Mean Severity)	Placebo Incidence (Mean Severity)
Number In Group	24	24
Mortality	54%	100%
# dead	13	24
Appendix		
Bacteria, Extravascular	0 (0)	6 (1.4)
Hemorrhage	1 (1.0)	6 (1.4)
Necrosis, Lymphoid	1 (3.0)	7 (1.9)
Blood Vessels		
Bacteria, Intravascular	2 (0.3)	20 (2.4)
Raxibacumab (+) Staining, Plasma	13 (3.8)	0 (0)
Kidney		
Bacteria, Extravascular or Glomerular	2 (0.4)	20 (1.8)
Liver		
Bacteria	0 (0)	13 (1.3)
Necrosis, Hepatocellular	8 (1.2)	8 (0.6)
Sinusoidal Leukocytosis	4 (0.4)	13 (1.0)
Lung		
Bacteria, Extravascular or Septal	2 (0.4)	21 (2.3)
Fibrin Accumulation	1 (0.1)	6 (0.5)
Inflammation, Heterophils Predominating	5 (0.7)	14 (0.9)
Lymph Node, Bronchial		
Bacteria, Extravascular or Septal	3 (0.7)	22 (3.0)
Fibrin Accumulation	7 (1.4)	22 (2.3)
Hemorrhage(s)	8 (1.3)	21 (2.3)
Inflammation, Heterophils Predominating	6 (0.8)	21 (2.6)
Necrosis, Lymphoid	8 (1.9)	20 (3.1)
Lymph Node, Mediastinal		
Bacteria, Extravascular or Septal	4 (0.8)	24 (3.6)
Fibrin Accumulation	10 (1.7)	20 (1.9)
Hemorrhage(s)	8 (1.6)	22 (2.1)
Inflammation, Heterophils Predominating	11 (1.5)	22 (2.5)
Necrosis, Lymphoid	10 (2.0)	22 (3.2)
Spleen		
Bacteria	1 (0.3)	22 (3.3)
Fibrin Accumulation	10 (2.0)	11 (1.0)
Inflammation, Heterophils Predomination	6 (0.9)	10 (0.8)

Severity is defined as 1=minimal, 2=mild, 3=moderate, 4=severe

(Table

8-6 on page 44-45 of the HGS study report)

Table 7. Histopathology Findings of Selected Organs in Surviving Rabbits

Group	Raxibacumab Incidence (Mean Severity)
Number In Group	24
Mortality	54%
# survivors	11
Appendix	
Blood Vessels	
Raxibacumab Positive Staining, Plasma	3 (0.4)
Brain	
Acute neurodegeneration, Fluorojade-C	1 (na)
Hemorrhage(s)	1 (0.2)
Hemorrhage(s), meninges	1 (0.2)
Hemorrhage(s), ventricular system	1 (0.1)
Kidney	
Inflammation, heterophils predominating	1 (0.1)
Tubule-interstitial nephritis	1 (0.1)
Liver	
Lung	
Inflammation, chronic/acute chronic	3 (0.4)
Lymph Node, Bronchial	
Hemorrhage(s)	1 (0.1)
Increased macrophage numbers	1 (0.2)
Inflammation, heterophils predominating	5 (0.6)
Hyperplasia, lymphoid tissue	3 (0.4)
Lymph Node, Mediastinal	
Edema	1 (0.1)
Hemorrhage(s)	1 (0.1)
Inflammation, heterophils predominating	5 (0.6)
Spleen	
Hemosiderosis	8 (1.3)
Hyperplasia, lymphoid tissue	6 (0.9)
Increased macrophage numbers	1 (0.1)
Inflammation, Heterophils predominating	8 (1.1)

Severity is defined as 1=minimal, 2=mild, 3=moderate, 4=severe
na: Severity not applicable, severity grade not provided

(Reviewer's Comments: In the initial monotherapy efficacy studies submitted to the original NDA submission in monkeys (Study #: 724-G005829) and rabbits (Study #:682-G005758, 1103-C923704), anthrax challenged animals treated with levofloxacin and raxibacumab that died during the study showed greater severity of bacteria, inflammation, hemorrhage, and necrosis in the brain than animals that died in the placebo group. The sponsor originally claimed that the extended time to death in the raxibacumab treated animals compared to placebo allowed more time for the disease to progress in the brain. This was supported by a lower incidence of adverse microscopic findings in the CNS of placebo animals that died within 48 hours of challenge, and low incidence of meningitis in inhalational anthrax exposed rabbits described in the natural

history studies in the published literature. In (Zaucha et al., 1998)⁶ low incidence of hemorrhage reported in the presence of bacilli is typically observed in the brain and meninges of aerosol-exposed rabbits, most likely due to the absence of leukocyte infiltration into the brain, different from what is observed in humans and non-human primates. For both the previous and current studies conducted by HGS however, statisticians in DAIP argued that there is no statistical difference in mean time to death between the animals that died

Dosing Solution Analysis

The concentration of test article and control material was confirmed using a volumetric method described in SOP QCC-2852 Rev. 4.0. The measured sample concentration for raxibacumab samples (triplicate) showed %RSD concentrations 0.9-1.2% of the expected concentration (50 mg/mL). No protein was detected in the placebo buffer.

Summary and Conclusion

The current study examined histopathology in raxibacumab and placebo treated NZW rabbits that either survived or succumbed to a lethal inhalation challenge with *B.anthraxis*. Both the estimated survival benefit of raxibacumab monotherapy (54% vs 100% in the placebo group) and the development of CNS lesions with raxibacumab treatment mirrors previous findings in earlier efficacy studies with raxibacumab versus placebo in spore challenged rabbits and non-human primates. A more detailed evaluation of the gross and microscopic evaluation of several different regions of the brain (i.e. cerebellum, cerebral cortex, hippocampus, meninges, midbrain, and thalamus) in surviving and non-surviving rabbits showed that brain lesions (bacteremia, inflammation, hemorrhage, and/or necrosis) occurred predominantly in non-surviving rabbits in the raxibacumab and placebo treatment groups; surviving animals showed no brain lesions or raxibacumab staining of neural tissue and no clinical signs of CNS toxicity. Non-surviving animals, particularly in the raxibacumab treatment group, showed widespread lesions throughout several different regions of the brain with no specific region any more susceptible than another. Both raxibacumab and IgG stained neuropil, neurons, and glial cell types in the brains of non-surviving animals; the similarity of staining patterns suggests non-specific leakage of plasma containing antibodies across a damaged blood brain barrier. The study pathologist noted that parabrachial neurons that stained intensely with both raxibacumab and IgG can be exposed to greater concentrations of circulating immunoglobulins due to their proximity to the ependyma where the BBB is less well-developed. The CNS findings in non-surviving raxibacumab treated rabbits in this study mirrored results obtained from previous raxibacumab placebo trials in the original BLA submission. The clinical relevance of these findings remains unknown due to the absence of lesions in surviving animals in the raxibacumab treatment group.

⁶ Zaucha, G.M., Pitt, L.M, Estep, J., Ivins, B.E., and Friedlander, A.M. (1998). The pathology of experimental anthrax in rabbits exposed by inhalation and subcutaneous inoculation. *Arch Pathol Lab Med.* 122(11): 982-992

Study title: Added Benefit of Raxibacumab with Levofloxacin vs. Levofloxacin as Post-Exposure Treatment in the New White Rabbit Inhalation Anthrax Model

Study no.: 1141-CG920871
Study report location: CBER EDR
Conducting laboratory and location: Battelle Biomedical Research Center
St. Route 142
Jefferson, OH 43162
Date of study initiation: January 24, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Raxibacumab, (Lot #71128), purity: 100%
Levofloxacin, (Lot #AEB2V00), purity:

Key Study Findings

- (76/180) anthrax treated rabbits survived to 84 hours post-challenge and were randomized for delayed treatment with raxi/levo or levo alone
- Nearly all animals were bacteremic and toxemic at treatment initiation
- 82% of raxi/levo and 65% of rabbits treated with levo alone survived to Study Day 35.
- A 17.2% trend toward greater survival with raxibacumab treatment was detected.
- All raxibacumab treated animals showed raxibacumab in plasma; plasma raxibacumab levels were less in animals that died compared to survivors.
- Levofloxacin exposure in rabbits was comparable to intermediate clinical exposure.
- Surviving rabbits on Study Day 35 showed anti-drug antibodies and no raxibacumab effect on TNA titers.
- Gross and histopathologic lesions in non-survivors primarily due to anthrax infection; no brain histopathology was noted in any raxibacumab treated animals.
- On Study Day 35, all surviving rabbits treated with raxibacumab were negative for bacteremia and toxemia, and had no gross or microscopic findings.

Methods

Doses: Raxibacumab: 40 mg/kg; Levofloxacin (50 mg/kg/day)
 Frequency of dosing: Raxibacumab: Single Dose; Levofloxacin: SID for three days
 Route of administration: Levofloxacin – gastric intubation; raxibacumab - Intravenous (vascular access port [VAP]) or marginal ear vein
 Dose volume: 0.8 mL/kg
 Formulation/Vehicle: **Raxibacumab:** Liquid formulation (50 mg/mL) in formulation buffer containing 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, 0.2 mg/mL polysorbate 80, pH 6.5.
Levofloxacin: Levofloxacin® Oral solution (25 mg/mL) as supplied – without dilution.
 Species/Strain: Rabbit / New Zealand White (NZW)
 Number/Sex/Group: 90/treatment group (≈ 50:50 male/female)
 Age: Mean 7 months
 Weight: Mean: 2.75 kg (female) and 4.5 kg (male)
 Satellite groups: None
 Deviation from study protocol: Minor protocol deviations during the in-life phase are not considered to have an impact on study results,

Objective: To evaluate the added benefit of raxibacumab when administered as a therapeutic agent in combination with levofloxacin at a pre-determined timepoint against lethality due to inhalation exposure of *B. anthracis* in New Zealand White (NZW) rabbits.

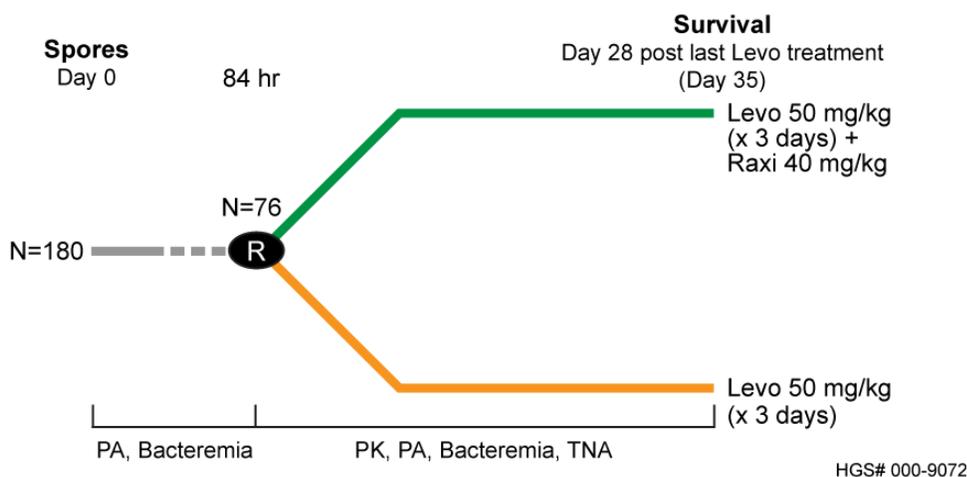
Study Design:

This was a parallel-group, randomized, blinded, GLP efficacy study to evaluate the added benefit of raxibacumab to levofloxacin as therapeutic treatment when administered at 84 hours post challenge in the NZW rabbit inhalation anthrax model. PA kinetics, raxibacumab and levofloxacin PK, and anti-raxibacumab and toxin neutralizing antibodies (TNA) were also examined.

Methods:

The study was conducted at Battelle Biomedical Research Center, West Jefferson, OH. One hundred and eighty (50% male, 50% female), 7 month old New Zealand White rabbits (*Oryctolagus cuniculus*) with surgically implanted VAPs (vascular access ports), weighing between 2-5 kg at randomization were first randomized into 1 of 6 aerosol challenge days (30 animals/challenge day). On their designated challenge day, each animal was placed into a plethysmography chamber day and aerosol challenged with a targeted 200 LD₅₀ [2.1×10^7 spores] inhaled dose of *B. anthracis* (Ames strain) spores. Aerosol concentrations of *B. anthracis* were quantified by determination of colony

forming units (cfu) in effluent streams. At 84 ± 4 hours post-challenge exposure time⁷, surviving animals (N = 76) were further randomized into two groups; levofloxacin + buffer (active control) or levofloxacin + 40 mg/kg raxibacumab (See figure 5 below). Levofloxacin (50 mg/kg) was administered by gastric intubation and raxibacumab and buffer were injected intravenously into the VAP. Animals were dosed with 3 doses of levofloxacin, initially at 84 hours, and then at 24 ± 1 hour thereafter for another 2 days. The primary endpoint is survival 28 days after the last dose of levofloxacin. Surviving animals were euthanized on Day 35 post challenge. The study director, technical staff and study pathologists were blinded to treatment until completion of the in-life phase of the study.



(Figure 5-1 on page 13 of the HGS study report)

Figure 6. Study Design (Study #: 1141-CG920871)

The dose of raxibacumab selected is the proposed dose for licensure (40 mg/kg) and is based on pivotal rabbit and monkey therapeutic efficacy studies, and safety profile in human clinical trials. The dose of levofloxacin in this study (50 mg/kg) was chosen to mimic intermediate human exposures of levofloxacin observed in the clinic when administered at approved doses (500 and 750 mg).

Animals were observed every 6 hours from challenge time up to 10 days post-challenge, and then twice daily. Body temperature was monitored twice daily and body weights were collected during quarantine and on study day 0 for calculating dose volumes of test article and control material. Death or euthanasia was recorded at the time observed and a complete necropsy was performed. Blood samples were collected for several time points and assayed to assess bacteremia, plasma PA, plasma raxibacumab and IG levels, immunogenicity (anti-raxibacumab antibodies), and toxin neutralizing antibodies (TNA) (See Table 8 below). Complete gross necropsies were

⁷ The fixed post median challenge time of 84 ± 4 hrs was chosen to approximate a $\approx 55\%$ survival rate observed during human anthrax attacks in 2001. Since treatment with a full humanized dose of levofloxacin administered to rabbits after detection of systemic anthrax disease resulted in a high survival rate of 85-100%, any added benefit of raxibacumab to the antibiotic treatment would be difficult to show with treatment at initial detection.

conducted on all rabbits. Brain, lungs, spleen, liver, kidney, and mediastinal/bronchial lymph nodes were collected and evaluated in all animals for gross and microscopic findings. The study pathologist was blinded to the treatment administered to each rabbit until after the slides were read. The histologic assessment conducted by the study pathologist was subject to peer-review.

Table 8. Blood Collection and Assay Schedule

Timepoint	Sample ID	Volume						
			Bacteremia By Culture	PA	Raxibacumab	Levofloxacin ^f	TNA	IG
Study Day 0 (Pre-Challenge)	Day 0	~3mL	X	X	X	X	X	X
12 h post-challenge & every 12 hours until treatment ^a	12hPC	~1mL	X	X				
	24hPC	~1.5mL	X ^c	X				
	36hPC	~1mL	X	X				
	48hPC	~1mL	X	X				
	60hPC	~1mL	X	X				
	72hPC	~1mL	X	X				
Immediate prior-to-1st-treatment blood sample ^b	PTT	~3mL	X ^c	X	X	X		
5 min post raxibacumab dose	5mPTR	~1mL		X	X			
2 h post 1st levofloxacin dose	2hPTL1	~2mL	X	X		X		
8 h post raxibacumab dose	8hPTR	~1mL		X	X			
24 h post 1 st levofloxacin dose prior to 2 nd levofloxacin dose ^b	24hPTL1	~2.5mL	X ^c	X	X	X		
2 h post 2 nd levofloxacin dose	2hPTL2	~2mL	X	X		X		
24 h post 2 nd levofloxacin dose prior to 3 rd levofloxacin dose ^b	24hPTL2	~2mL	X	X	X	X		
2 h post 3 rd levofloxacin dose	2hPTL3	~2mL	X	X		X		
24 h post 3 rd levofloxacin dose	24hPTL3	~2mL	X			X		
2 days post 3 rd levofloxacin dose / 96 h post raxibacumab dose	2dPTL3	~3mL	X ^c	X	X	X		
3 days post 3 rd levofloxacin dose	3dPTL3	~1mL	X	X				
7 days post raxibacumab dose ^d	7dPTR	~2mL	X	X	X			
14 days post raxibacumab dose ^d	14dPTR	~2mL	X	X	X			
21 days post raxibacumab dose ^d	21dPTR	~2mL	X	X	X			
28 days post raxibacumab dose ^d	28dPTR	~4mL	X	X	X		X	X
Terminal ^d		~4mL	X ^e	X	X	X		X

^a = Post-challenge pre-treatment bleed time point were calculated based on one median challenge times per challenge day.

^b = Specimen was collected 30 min (\pm 10 min) prior to the scheduled dose.; ^c = Quantitative culture was performed.

^d = Blood samples were not collected from the VAP.

^e = Levofloxacin MIC was performed on positive terminal blood cultures collected from animals that received at least one treatment and succumbed to disease prior to 35 days post-challenge.

^f = 1mL of whole blood was collected into a chilled EDTA tube, additional whole blood required for other assays was collected in an EDTA tube at room temperature. Only animals that received at least one dose of levofloxacin had samples subjected to levofloxacin analysis.

(Table 4 on page 15 in the Battelle Study Report)

Results

Seventy-six animals survived to 84 hours and were randomized to the two treatment arms: 37 to the levofloxacin arm and 39 to the levofloxacin + raxibacumab arm. The two treatment groups were comparable with respect to sex, weight, age at randomization.

Anthrax Exposure

The mean challenge dose of all 6 challenge days of $\approx 188 \times LD_{50}$ exceeded the LD_{50} dose killing approximately 58% of the animals by the predetermined treatment time (84 hours). Anthrax spore challenge was greater in the levofloxacin + raxibacumab treatment group than the levofloxacin + buffer group (active control). The minimum exposure in the levofloxacin + buffer group was 83 LD_{50} and it is likely at this dose no animals would survive without treatment. Additional analyses were conducted to see if there was any effect of the LD_{50} doses on either survival to day 84, survival rate post treatment, and time to death post treatment and no associations were found.

Table 9. Average Challenge Doses (LD_{50} equivalent)

Challenge Day	Average Challenge Dose (SD)
A	176 (± 35)
B	179 (± 45)
C	209 (± 38)
D	184 (± 38)
E	194 (± 48)
F	182 (± 58)
Treatment Group	Average Challenge Dose (SD)
Raxibacumab	197 (± 49)
Raxibacumab Buffer	174 (± 43)
Non-Treated	189 (± 43)

(Adapted from Table 5 on page 22 of the Battelle Study Report)

Mortality/Survival

Of 180 study animals originally challenged with anthrax, 104 animals succumbed to disease prior to the protocol directed treatment time (84 ± 4 hrs) and were excluded from the study. Thirty seven (37) animals were treated with at least one dose of levofloxacin (50 mg/kg) and a single dose of buffer (0.8 mL/kg); thirty nine (39) animals were treated with at least one dose of levofloxacin (50 mg/kg) and a single dose of raxibacumab (40 mg/kg) (See table 3 below).

Table 10. Animal Disposition

	Levo	Levo/Raxi	Total
Animals challenged			180
Animals Randomized (survived to 84 hours)	37	39	76
Animals Treated	37	39	76
Survived to 28 days after last levofloxacin dose			
Survived	24	32	56
Died	13	7	20

Analysis Population				
	Intent-to-Treat (ITT)	37	39	76
	Toxicemic at or before treatment initiation	37	39	76
	Bacteremic at or before treatment initiation	37	38*	75

*L34828 not bacteremic during the entire study, survived.

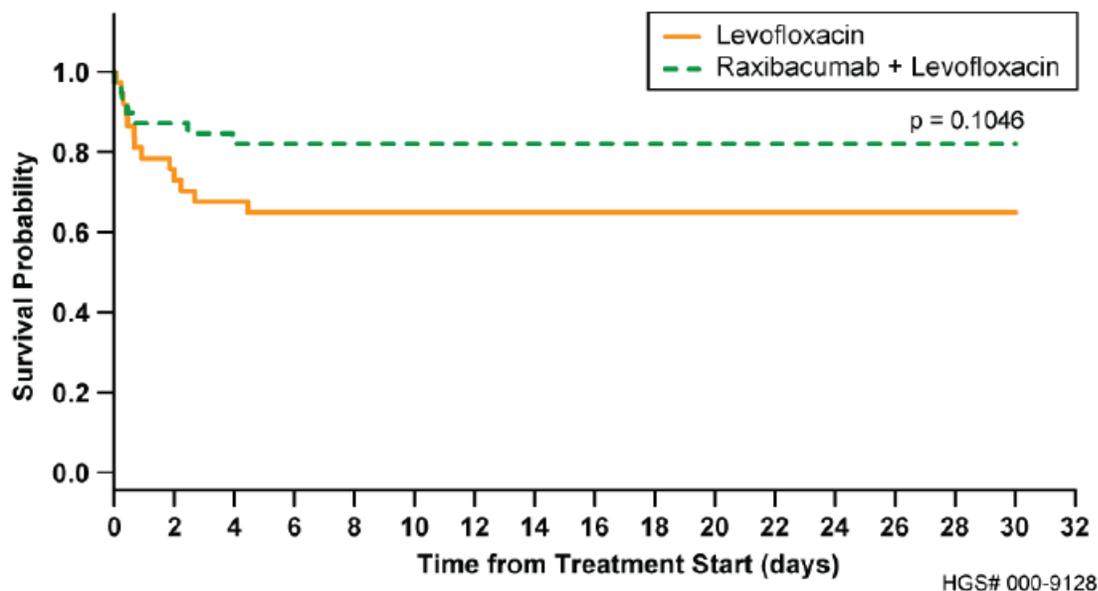
Of the 37 animals treated with levofloxacin and buffer, 24 animals (64.86%) survived to Study Day 35 after the last dose of levofloxacin. Of the 39 animals treated with levofloxacin and raxibacumab, 32 animals (82.05%) survived through Study Day 28. Although not statistically significant ($p=0.0874$), a trend towards greater survival of 17.19% ($p = 0.0874$) was observed when both levofloxacin and raxibacumab were administered (See table 4 below).

Table 11. Day 28 Survival Rate

Study	Levo	Levo/Raxi	Difference (Levo/Raxi – Levo) (95% CI)	P-value ¹
ITT animals	24/37 (64.9%)	32/39 (82.1%)	17.2 (-2.4, 36.7)	0.0874
Bacteremic at or before treatment initiation	24/37 (64.9%)	31/38 (81.6%)	16.7 (-3.0, 36.4)	0.0998

¹ 2-sided likelihood ratio chi-square test

The following figures shows the survival curves for randomized animals (see figure 2 below).



(Figure 1 from Battelle Study Report, pg 23).

Figure 7. Survival Time from Treatment Initiation

In examining the subpopulation of non-surviving animals that died prior to Day 28 post-treatment, the mean time from spore challenge to death was found to be similar, 4.9 days in the levofloxacin alone compared to 4.7 days in the levofloxacin+raxibacumab treatment group. Animals that survived until Day 9 post-challenge in either treatment group remained alive until the scheduled terminal euthanization on Day 35. (Note: The TTD listed is an estimate of the time to death post-challenge since a majority of dead animals in both groups were found dead in their cages). The treatment effect of raxibacumab over levofloxacin was similar in males and female animals. For males, levofloxacin survival was 11/18 (61.1%) compared to raxibacumab+levofloxacin survival of 15/18 (83.3%). Similarly, for females, levofloxacin survival was 13/19 (68.4%) compared to raxibacumab+levofloxacin survival of 17/21 (81.0%).

Clinical Observations (Post-Treatment)

Sixty-two percent (8/13) of the non-surviving levofloxacin/buffer treated animals were found dead on study, whereas 71% (5/7) of the levofloxacin/raxibacumab treated animals that died on study were found dead in their cages. The remainder of the non-surviving raxibacumab (5/13) and buffer treated animals (2/7) were euthanized moribund prior to scheduled termination. Commonly observed clinical signs first noted on Study Days 2-3 (48-72 hours) post treatment included lethargy, inappetance, stool abnormalities, and respiratory abnormalities. Raxibacumab treated and buffer treated animals that survived to Day 35 post-challenge mostly appeared normal by Day 10-11 post-challenge with exception of a few animals that demonstrated inappetance and/or minor stool abnormalities. Facial swelling was observed in a single animal (L33741) from Days 4-12, coinciding with appearance of respiratory abnormalities (Day 4-10), that survived through Day 35 post-challenge. All abnormal clinical observations were considered typical in animals exposed to anthrax.

Body Temperature Results

The majority of animals challenged with anthrax had expected elevated temperatures on Days 2-6 following exposure to *B.anthraxis*, with increased temperatures lagging behind appearance of PA or bacteremia, consistent with findings in previous rabbit inhalation anthrax studies.

(Reviewer's comment: Although pyrexia developed in nearly all infected rabbits, pyrexia is not considered a suitable trigger for treatment initiation because both antigenemia (Increase in plasma PA levels) and bacteremia precede development of pyrexia⁸).

Blood Culture Levels of *B.anthraxis*

Qualitative blood cultures showed positive bacteremia results in 179/180 animals challenged with *B.anthraxis*; 75/76 (98%) of animals that were treated at 84 ± 4 hrs were positive for bacteremia prior to treatment (37 randomized to levofloxacin and 38 randomized to levofloxacin+raxibacumab. For the levofloxacin+raxibacumab treatment

⁸ Yee, S.B., Hatkin, J.M., Dyer, D.N., Orr, S.A., Pitt M.L.M. (2010). Aerosolized *Bacillus anthracis* Infection in New Zealand White Rabbits: Natural History of Intravenous Levofloxacin Treatment. *Comparative Medicine*. **60**(6); 461-468.

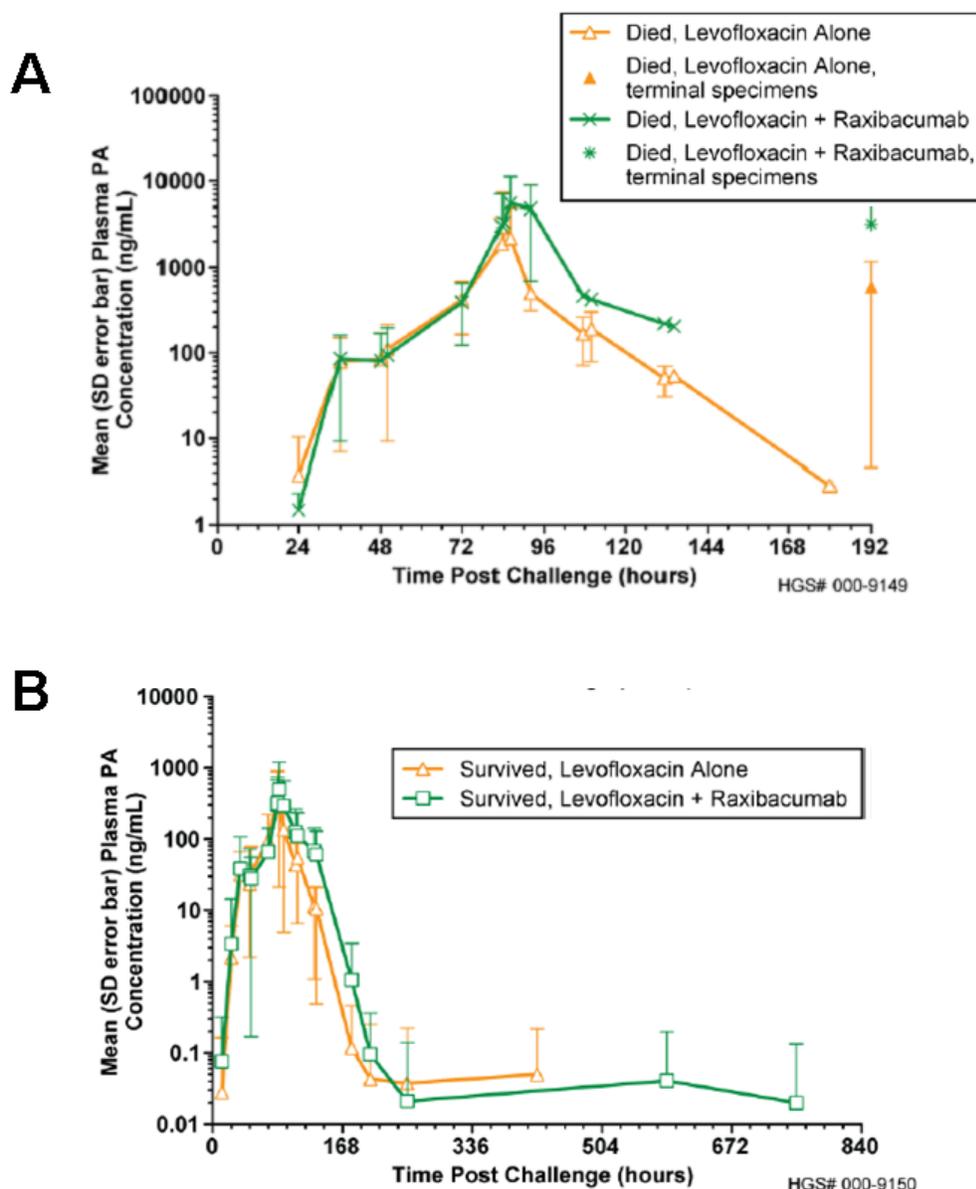
group, within 2 hours after the first dose of levofloxacin, 38/39 animals treated with raxibacumab were alive and 16/39 animals (41%) were already negative for bacteremia. For the levofloxacin alone group, within 2 hours after the first dose of levofloxacin, 36/37 animals treated with buffer were alive and 10/37 (27%) were negative for bacteria. At 24 hours after treatment, 32 animals (82%) treated with levofloxacin+raxibacumab and 29 animals (78%) treated with levofloxacin+buffer were negative for bacteria in blood cultures. Two animals positive for blood cultures 24 hours after the first dose of levofloxacin+raxibacumab (L35259 and L35261) were negative for blood cultures 2 hours after receiving the second dose of levofloxacin).

Of the 13 animals treated with raxibacumab buffer that died, 11 animals were not bacteremic at death. Of the 7 animals treated with raxibacumab that died, 4 animals were not bacteremic at death.

Quantitative Plasma PA Results

No animals demonstrated pre-spore challenge levels of PA. The sponsor's mean plasma PA concentration-time profiles for the dead (Figure 3A) and surviving (Figure 3B) animals treated with levofloxacin vs. levofloxacin+40 mg/kg raxibacumab are shown below. Comparison of the PA kinetics for treated rabbits that died and survived showed a general overlap in PA kinetic estimates, with the exception of both the height and duration of the first and second plateau in PA levels; plateau height and duration appeared approximately 10-fold greater in rabbits that died compared to rabbits that survived. This 10-fold difference in PA was particularly noticeable at the time of treatment (84 hrs post-challenge); animals that survived to 84 hours post-challenge had significantly less plasma PA than non-surviving animals at this time point. Declining plasma PA levels after the timing of the second plateau were mostly associated with negative bacteremia results. For all surviving animals in the treatment groups, plasma PA concentrations declined below the LLOQ by the end of the study. The decrease in plasma PA concentrations may be the result of raxibacumab-PA complex formation and decreased detection in the assay, or from decreased bacteremia via increased bacterial clearance or inhibition of spore germination⁹.

⁹ Welkos, S., Little, S., Friedlander, A., Fritz, D., and Fellows, P. (2001). The role of antibodies to *Bacillus anthracis* and anthrax toxin components in inhibiting the early stages of infection by anthrax spores. *Microbiology*. **147**, 1677-1685.



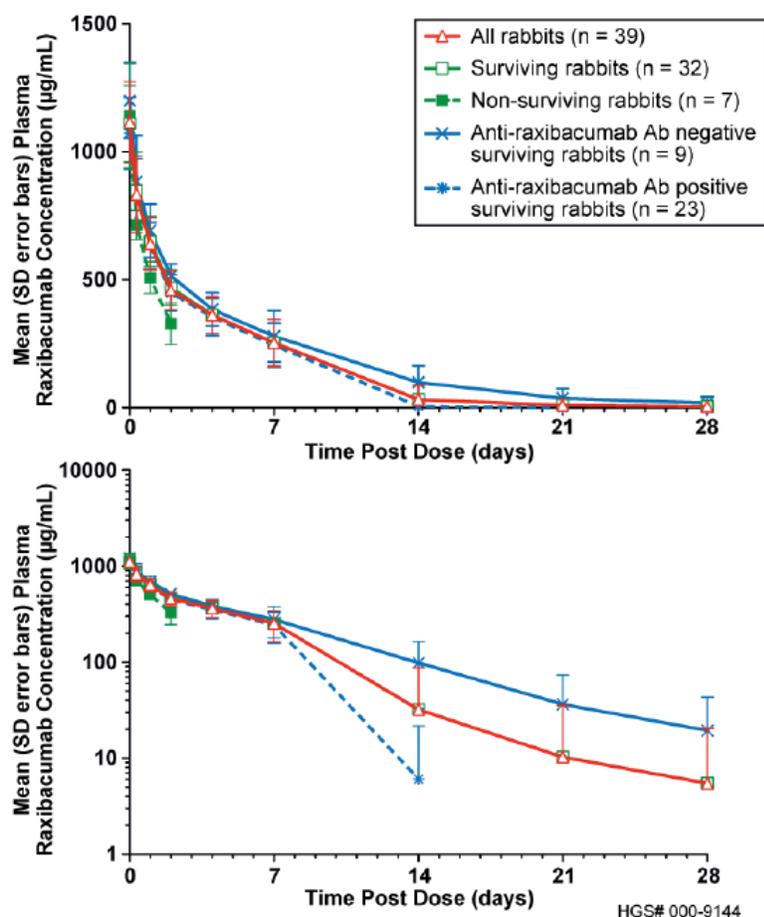
(Adapted from figures 5-7 and 5-8 on page 402-403 of the Battelle study report)

Figure 8. Plasma PA Concentration-Time Profile in Treated Rabbits that Died (A) and Survived (B)

Raxibacumab Pharmacokinetics

Raxibacumab was not detected in the pre-dose specimens for any animal or in levofloxacin only treated animals. Following treatment with raxibacumab, all animals in the levofloxacin+raxibacumab treatment group showed raxibacumab in specimens collected post-dosing. The mean observed raxibacumab concentration-time profile for animals treated with at least one dose of levofloxacin and a single dose of raxibacumab is provided in Figure 6. The apparent increase in raxibacumab clearance in surviving animals > 7 days post-treatment is associated with presence of plasma anti-raxibacumab antibody levels in several rabbits at each time point (Anti-drug antibodies present in the serum of raxibacumab treated animals are known to interfere with the

raxibacumab PK assay). From the graph, mean plasma raxibacumab concentrations for rabbits that died were lower than those for surviving rabbits. Delayed delivery of raxibacumab (≈ 84 h post challenge) to animals in the current study appear to have minimal affect on PK when compared with results obtained in prior studies in which raxibacumab (40 mg/kg) was administered IV at time of PA toxemia (≈ 26 hours) in inhalational anthrax infected rabbits.



(Figure 5-2 on page 390 of the Battelle study report)

Figure 9. Plasma Raxibacumab Concentration-Time Profiles in Rabbits Administered qdx3 IG 50 mg/kg Levofloxacin Doses in Combination with a Single IV 40 mg/kg Raxibacumab Dose

Following IV raxibacumab administration, distribution of raxibacumab appears to be initially restricted to plasma volume, but then subsequently distributes to tissues. Clearance of raxibacumab from plasma appears multi-phasic with a mean initial elimination half-life ($t_{1/2\alpha}$) of 0.4 days and second terminal elimination half-life ($t_{1/2\beta}$) of 4.7 days. Raxibacumab clearance appears to increase with weight. The raxibacumab PK parameters in rabbits administered raxibacumab and levofloxacin are shown in Table 5 below.

Table 12. Raxibacumab PK Parameters in Rabbits Administered Raxibacumab and Levofloxacin

Primary Parameters	Mean ¹	CV% ¹
V ₁ (mL)	112.17 (1.9%)	10.8 (26.6%)
CL (mL/day)	28.12 (5.5%)	27.5 (31.0%)
Effect of weight (WT) on CL (mL/day) ²	CL x (WT/3.12) ^{1./43} (42.1%)	
At 2.75 kg	22.56	
At 3.00 kg	26.26	
At 3.12 kg	28.12	
At 3.25 kg	30.19	
At 3.50 kg	34.35	
At 3.55 kg	35.21	
V ₂ (mL)	60.22 (7.5%)	20.6 (87.8%)
CLD ₂ (mL/day)	73.62 (10.6%)	27.6 (61.9%)
Residual Variability, CV(%)	6.2% (51.7%) CV% for proportional error component 45.5 µg/mL (41.2%) SD for additive error component	
Secondary Parameters	Mean ± SD ³	
C _{max} (µg/mL)	1114 ± 138	
AUC _{0-∞} (µg·day/mL)	4590 ± 1106	
t _{1/2,α} (days)	0.36 ± 0.05	
t _{1/2,β} (days)	4.67 ± 1.10	
MRT (days)	6.40 ± 1.63	
V _{ss} (mL/kg)	56.00 ± 5.74	

Abbreviations: CV%, coefficient of variation; V₁, volume of distribution for the central compartment; CL, clearance; V₂, volume of distribution for the peripheral compartment; CLD₂, intercompartmental clearance; SD, standard deviation; C_{max}, maximum plasma drug concentration; AUC_{0-∞}, area under the plasma drug concentration-time curve from time 0 to infinite time; t_{1/2,α}, elimination half-life for the 1st phase; t_{1/2,β}, elimination half-life for the 2nd (terminal) phase; MRT, mean residence time; V_{ss}, volume of distribution at steady-state.

¹ Values in parentheses represent the relative standard error (SE) of the estimate.

² WT was normalized to the median body weight for the raxibacumab/levofloxacin group (3.12 kg).

³ Based on the post hoc estimates for the individual rabbits.

Source: [Appendix 17](#) and [Appendix 20](#) of HGS AB50409.INF.0.046 ([Appendix K](#) of the Battelle study report) (Table 09-3 on Page 58 of the HGS Study Report)

Levofloxacin Pharmacokinetics

No measurable plasma levofloxacin concentrations were detected in any pre-dose specimens. Co-administration of raxibacumab had no effect on plasma concentrations of levofloxacin at any timepoint. PK analysis of levofloxacin in animals dosed with Levofloxacin® oral solution IG qd x 3 in the presence or absence of a single IV dose of raxibacumab (40 mg/kg) showed comparable levofloxacin exposure observed in humans administered the approved 500 or 750 mg levofloxacin dose as described in the Levaquin® package insert (Table 6).

Table 13. Levofloxacin Exposures for Rabbits in the Current Study Compared with Human Exposures Administered 500 or 750 mg Levofloxacin Doses (in the Labeling)

Levofloxacin Dosing	C _{max,n} (µg/mL)	C _{min,n} (µg/mL)
Rabbit, based on PK results from current study ¹		
1 st Dose	6.2	0.4
2 nd Dose	7.5	0.5
3 rd Dose	7.0	0.8
Human, based on information provided in Levaquin [®] product labeling		
500 mg	5.7	0.5
750 mg	8.6	1.1

Abbreviations: C_{max,n}, maximum plasma levofloxacin concentration after the nth dose, defined as the concentration measured 2 hours after the dose; C_{min,n}, minimum plasma levofloxacin concentration after the nth dose, defined as the concentration measured just prior to the subsequent dose, or at 24 hours after the 3rd dose.

¹ Mean values for Group 2 (levofloxacin alone).

Sources: Appendix 10 and Levaquin[®] package insert, 2011.

(Table 5-2 on page 388 of the Battelle study report)

(Reviewer's comment: The sponsor reported that several individual samples at different time points (2 and 23.5 hrs) were switched prior to analysis (peak and trough values appeared to be reversed). Exclusion of these samples had minimal impact on the overall PK analysis).

Immunogenicity (Anti-Raxibacumab Antibodies) and TNA Titer Results

(Reviewer's comment: Immunogenicity and TNA titer was determined at pre-dose for all animals and on Day 28 (post-treatment) only in survivors due to assay interference of high raxibacumab levels observed in prior studies. No post-dose immunogenicity or TNA titer data is available for animals that died during the study prior to Day 28 post-treatment).

Plasma samples were assessed for anti-raxibacumab antibodies using a 2-part ECL-based assay including a preliminary screening assay and an inhibition of binding assay to confirm antibody positivity. The overall incidence of anti-raxibacumab antibody in the raxibacumab-treated group at Day 28 post-treatment was 23/32 (72%), excluding the 7 non-survivors for whom immunogenicity outcome is unknown. Three (8%) of the raxibacumab treated animals were positive for anti-raxibacumab antibody prior to spore challenge and on Day 28 post-treatment. The remaining 20 surviving animals positive for raxibacumab antibody in the raxibacumab group on Day 28 were negative prior to spore challenge.

At pre-dose, (3/37) rabbits in the levofloxacin control group were positive for anti-raxibacumab antibody prior to spore challenge again and 28 days post-treatment; a 4th

rabbit (in the same group) was negative for anti-drug antibody on Study Day 0 and was positive at day 28 post-treatment.

TNA (toxin neutralizing antibody) titers were similar at 28 days post treatment in levofloxacin alone and levofloxacin + raxibacumab treated animals. TNA was not detected prior to spore challenge. Raxibacumab did not interfere with development of endogenous toxin neutralizing antibodies (TNA); high TNA titers ($\mu \approx 5000$) detected only in surviving rabbits 28-days post-treatment were generated in the presence of high plasma raxibacumab levels after treatment.

Necropsy and Histopathology

Adequate Battery

Yes; Protocol specified tissues only – brain, kidneys, liver, lungs, spleen, gross lesions, mediastinal/bronchial lymph nodes)

Peer Review

Yes.

Complete necropsies were performed on animals found dead or euthanized, including animals surviving to terminal euthanization on Day 28 post-treatment. Gross lesions in rabbits found dead or euthanized moribund include discoloration or foci of the appendix and brain (hemorrhage and inflammation), enlargement of bronchial and mediastinal lymph nodes (edema, fibrin exudation, hemorrhage), and fluid (effusion) in the body cavities and thymus. These findings were considered by the reviewing pathologist to be typical of anthrax infection in rabbits¹⁰. Microscopic findings consistent with anthrax¹⁰ were present in all rabbits that died or became moribund during the study including acute suppurative inflammation, necrosis, hemorrhage, edema, and vasculitis in the appendix, brain, kidney, liver, lung, bronchial and mediastinal lymph nodes, spleen, and thymus (Table 9). Anthrax related findings in the brain (meningeal and parenchymal hemorrhage and meningeal vascular necrosis) were present in only two non-surviving animals in the levofloxacin only treated animals. No brain histopathology was noted in any raxibacumab treated animals. Large-rod shaped bacteria characteristic of *B.anthraxis* was present in the brain, lung, lymph nodes, and spleen of a three levofloxacin and one levofloxacin + raxibacumab animals that died during the study; the remaining treated animals that died before Day 35 in both groups lacked visible bacteria in any organs examined. All dead animals however were bacteremic at the time of death with associated inflammation and/or hemorrhage typical of anthrax infection in one or more of the organs examined. In contrast, there were no anthrax-related microscopic findings in any animals that survived until Day 35.

Table 14. Incidence and mean severity of selected microscopic observations in non-surviving animals

Tissue/Observation		Levofloxacin (50 mg/kg x 3) + Placebo Incidence (mean severity) N = 13	Levofloxacin (50 mg/kg x 3) + Raxibacumab (40 mg/kg) Incidence (mean severity) N = 7
Brain	Number Examined	13	6
Bacteria, meninges		1 (0.2)	0 (0)
Hemorrhage(s)		2 (0.3)	0 (0)
Hemorrhage(s), Cerebellum		1 (0.1)	0 (0)
Hemorrhage(s), Cerebral Cortex, Fronto-Parietal		2 (0.2)	0 (0)
Hemorrhage(s), Cerebral Cortex, Temporo-Parietal		1 (0.1)	0 (0)
Hemorrhage(s), Meninges		1 (0.2)	0 (0)
Hemorrhage(s), Thalamus		1 (0.1)	0 (0)
Necrosis, Meningeal vascular		1 (0.2)	0 (0)
Necrosis, Parenchyma		1 (0.1)	0 (0)
Kidney	Number Examined	13	7
Tubular Atrophy		1 (0.2)	0 (0)
Liver	Number Examined	13	7
Necrosis, Hepatocellular		6 (0.7)	2 (0.6)
Sinusoidal Leukocytosis		2 (0.2)	1 (0.1)
Lung	Number Examined	13	7
Bacteria		2 (0.4)	-
Hemorrhage		5 (0.7)	2 (0.3)
Necrosis, BALT		4 (0.9)	1 (0.6)
Fibrin exudation, alveolar		4 (0.7)	2 (0.3)
Heterophilic inflammation		4 (0.7)	1 (0.3)
Lymph Node, Bronchial	Number Examined	13	7
Bacteria		2 (0.3)	0 (0)
Fibrin exudation		9 (1.6)	5 (2.3)
Hemorrhage(s)		8 (0.9)	5 (0.9)
Heterophilic inflammation		2 (0.3)	4 (0.9)
Necrosis, lymphoid		11 (2.6)	6 (2.6)
Lymph Node, Mediastinal	Number Examined	13	7
Bacteria		2 (0.5)	1 (0.3)
Fibrin exudation		8 (1.6)	5 (1.6)
Hemorrhage(s)		8 (1.2)	5 (1.1)
Heterophilic inflammation		1 (0.2)	3 (0.6)
Necrosis, lymphoid		11 (2.3)	5 (2.1)
Spleen	Number Examined	13	6
Bacteria		0 (0.0)	1 (0.2)
Fibrin exudation		4 (0.5)	3 (0.8)
Heterophilic inflammation		2 (0.2)	1 (0.3)
Necrosis, lymphoid		3 (0.6)	1 (0.3)

- no value given

Source: [Table 7](#) and [Table 8, Appendix Q](#) of the Battelle study report

(Reviewer's comment: Unlike in the monotherapy studies with raxibacumab in rabbits and monkeys challenged with inhalational anthrax, no incidence of brain lesions (hemorrhage, inflammation, bacteria, necrosis) was detected in non-surviving rabbits in the current study treated with either levofloxacin alone or levofloxacin + raxibacumab. The rapid eradication of bacteria in the brain and most other organs as a result of antibiotic treatment appeared to have diminished the severity of lesion throughout the body, including the adverse, additive or synergistic effects of raxibacumab on the brains of animals observed in other studies with detectable meningitis. After all, development

of anthrax meningitis has been shown to require expression of both anthrax toxins, edema factor and lethal factor (van Sorge et al., 2008).

Dosing Solution Analysis

The concentration of test article and control material was confirmed using the ECL raxibacumab detection assay described in SOP CLI-3212, ver. 3.0. The measured sample concentration for raxibacumab samples (triplicate) showed raxibacumab concentrations > 50 mg/mL, within 20% of the expected concentration (50 mg/mL). No raxibacumab was detected in the placebo buffer. Since the Levaquin® Oral Solution was administered as provided from the manufacturer no dose confirmation was performed for levofloxacin.

Summary and Conclusion

The primary objective of this study was to assess the added benefit of raxibacumab to levofloxacin treatment of inhalation *B.anthraxis* exposure to prevent lethality in rabbits when administered in combination at 84 hours post-spore challenge (The fixed post median challenge time of 84 ± 4 hrs was chosen to approximate a $\approx 55\%$ survival rate observed during human anthrax attacks in 2001). Delay of treatment to 84 hours post challenge to 180 rabbits spore-challenged with a target dose of $200 \times LD_{50}$ of inhalation anthrax resulted in a survival rate of $\approx 42\%$. Nearly all animals that survived to 84 hours post-challenge were bacteremic prior to treatment. At 84 hours post-challenge, co-treatment of randomized survivors ($n=76$) with levofloxacin+raxibacumab showed a positive trend toward greater survival of $\approx 17\%$ ($p=0.0874$) compared to levofloxacin alone. Delay of treatment to 84 hours with raxibacumab and levofloxacin had no effect on bacterial elimination with levofloxacin or on plasma concentrations and PK profiles of either drug at any timepoint. Raxibacumab treatment generated significant anti-drug antibodies in a majority (23/24) levofloxacin treated surviving animals and had no significant impact on development of toxin neutralizing antibodies. Despite increased clearance of raxibacumab detected in survivors > 7 days post challenge (likely resulting from binding to anti-drug antibodies); the greater survival rate in the raxibacumab treatment group indicates no significant impact of drug-antibody binding on efficacy of raxibacumab in the treated survivors. Although a positive, statistically relevant added benefit result was not achieved with this under-powered study design, there appears to be a trend towards greater survival in rabbits when raxibacumab is co-administered with levofloxacin 84 hours post-challenge to inhalational anthrax exposure. When combined with safety data in healthy animals and human volunteers, as well as with positive results from previously conducted placebo trials with raxibacumab in rabbits and non-human primates, the complementary mechanism of action to the antibiotic appears to justify its use in patients diagnosed with inhalation anthrax disease.

5 Integrated Summary and Safety Evaluation

Raxibacumab is a fully human, IgG1 monoclonal antibody antitoxin raised against the protective antigen (PA) of *Bacillus anthracis* for intravenous treatment of inhalational anthrax. Raxibacumab works by delivery of the human recombinant antitoxin antibody directly to the anthrax infected subject to immediately quench circulating PA levels, persisting until immunity to the bacterium and associated toxins can develop. Its efficacy has been demonstrated in multiple animal trials, both as a monotherapy and in combination with antibiotics. Its safety has been demonstrated in healthy adults.

Raxibacumab is the first monoclonal antibody antitoxin against anthrax to seek licensure under Animal Rule (21 CFR 601, Subpart H, 2002). HGS submitted the BLA for Raxibacumab to the FDA on May 14, 2009, containing efficacy studies of raxibacumab alone and in combination with antibiotic treatment against inhalational anthrax in both rabbits and non-human primates. Severe CNS findings in non-surviving, anthrax challenged animals treated with raxibacumab, the inability to determine added benefit of raxibacumab to antibiotic treatment, and failure to pass inspection of data quality in PK measurements of antibiotics and raxibacumab caused to the Division to issue a CR letter November 14, 2009. Since that time, the applicant completed and submitted two additional GLP, nonclinical studies with raxibacumab to anthrax spore challenged (200 x LD₅₀), New Zealand White rabbits to further understand both the CNS toxicity with raxibacumab monotherapy and the potential for added benefit of raxibacumab to levofloxacin combination treatment.

Raxibacumab treatment in both nonclinical studies improved survival benefit for rabbits challenged with inhalational anthrax when compared to placebo (mortality index of 54% vs 100% in placebo) and when combined with levofloxacin (survival trend $\approx 17\%$ ($p=0.0874$) greater than with levofloxacin alone). The estimated survival benefit of raxibacumab monotherapy mirrors findings in earlier efficacy studies with raxibacumab placebo trials in spore challenged rabbits and non-human primates. Prior combination efficacy studies in rabbits challenged with inhalational anthrax upon toxemia failed to show a difference in survival rates ($\approx 95\%$) between levofloxacin and levofloxacin/raxibacumab combination groups. The current added benefit study with delayed treatment to 84 hours shows a trend towards greater survival in anthrax challenged rabbits when raxibacumab is combined with levofloxacin therapy, but is limited by prospectively acknowledged lack of statistical significance due to inadequately powered study design. Non-surviving animals in both studies showed no difference in mean time to death from initiation of spore challenge with raxibacumab treatment, with and without levofloxacin co-administration.

Surviving animals in both studies showed no significant gross or microscopic findings attributable to spore-challenge or treatment in any tissue, including brain; raxibacumab staining of neural tissue (CNS study); or any significant clinical signs of CNS toxicity at any time during the course of the study (both studies). Non-surviving animals primarily died of lesions characteristic of inhalation anthrax exposure, including hemorrhage, inflammation, necrosis, edema, and effusion of critical organs. Despite the extensive systemic effects observed in placebo animals in the monotherapy trial, no notable CNS

histopathology was observed. Likewise, animals co-administered raxibacumab and levofloxacin were devoid of any microscopic CNS changes. Only non-surviving, spore-challenged animals treated with raxibacumab in the monotherapy trials showed CNS lesions (inflammation, hemorrhage, bacteria, and necrosis) of high incidence and severity (Grade 1-4), throughout different regions of the brain. In the added benefit study, *B.anthraxis* was observed in the brain, lung, lymph nodes, and spleen of a few animals in both groups; a majority of animals showed no visible bacteria in any organs examined. Levofloxacin mediated elimination of visceral bacteria appears to reduce the severity of anthrax related effects, particularly increased CNS lesions (hemorrhage, inflammation, bacteria, and necrosis) observed in the brains of raxibacumab treated animals in the monotherapy trials. One question remaining is why non-surviving raxibacumab animals in the placebo trial showed greater bacteria levels, inflammation, hemorrhage, and necrosis in the brain compared to placebo animals when non-surviving animals from both groups died at a similar time post-challenge. Simply, severe inflammation and hemorrhage in the non-surviving raxibacumab animals that lived longest did not necessarily correlate with highest bacteria levels.

High levels of bacteria detected in the brains of non-surviving raxibacumab treated animals in the CNS study suggest a greater opportunistic proliferation of *B.anthraxis* within the brain compared to other organs. It's suspected that raxibacumab is mostly excluded from the CNS in the early stages of the infection until the circulating toxins and bacterial meningitis disrupt endothelial cell tight junctions and compromise the integrity of the BBB. Several mechanisms believed to contribute to blood brain permeability in anthrax include the host acute-phase response induced by bacterial proteases, effects of LT on endothelial cells, perturbation of cell-cell signaling in adherence junctions, and oxidative cell damage by bacterial products¹⁰. In contrast, high plasma concentrations of raxibacumab immediately after treatment significantly diminished all other organ bacteria levels (except brain), with marked reduction in incidence and severity of pathologic findings compared to placebo. The mechanism by which raxibacumab reduces the bacterial load in well-vascularized organs (except brain) is unknown. A separate in vitro study described in the literature showed that purified anti-PA antibodies can stimulate phagocytic uptake of spores by macrophages; and inhibit spore germination¹¹. This might explain how raxibacumab could reduce the bacterial load in well-vascularized organs outside of the BBB, and also why bacterial loads remained high in the brain of treated animals. Also, lethal toxin (LT)-induced immunosuppression may contribute to bacterial invasion and dissemination in all tissues including the brain¹². Reversal of LT immunosuppression with raxibacumab treatment might occur in

¹⁰ Mukherjee, D.V., Tonry, J.H., Kim, K.S., Ramarao, N., Popova, T.G., Bailey, C., Popov, S., and Chung, M-C. (2011). *Bacillus anthracis* protease InhA increases blood brain barrier permeability and contributes to cerebral hemorrhages. *PLOS one*. **6**(3); e17921.

¹¹ Welkos, S., Little, S., Friedlander, A., Fritz, D., and Fellows, P. (2001). The role of antibodies to *Bacillus anthracis* and anthrax toxin components in inhibiting the early stages of infection by anthrax spores. *Microbiology*. **147**, 1677-1685.

¹² Sun, C., Fang, H., Xie, T., Auth, R.D., Patel, N., Murray, P.R., Snoy, P.J., Frucht, D.M. (2012). Anthrax lethal toxin disrupts intestinal barrier function and causes systemic infections with enteric bacteria. *Plos One*. **7**(3); e33583-e33583.

tissues to which raxibacumab readily distributes; raxibacumab is generally excluded from brain until the BBB is compromised. However, upon compromise of BBB integrity, raxibacumab distribution to the brain and subsequent response of “re-activated” immune cells to proliferating bacteria and perhaps raxibacumab bound to nervous tissue may help explain the greater CNS lesions in the non-surviving raxibacumab treated animals compared to placebo.

Immunopositive staining for raxibacumab (and IgG) in the CNS study is greatest in frequency and intensity in the brain regions with the most severe lesions, particularly areas of significant inflammation and infection. Although the exact mechanism(s) by which raxibacumab might enhance anthrax related lesions in the brain is unknown, it's clear that in the absence of antibiotic therapy, raxibacumab treated rabbits develop greater CNS pathology than in spore challenged placebo treated animals. Raxibacumab staining was not measured in the added benefit study, but based on the general absence of brain histopathology with delayed levofloxacin treatment, it's likely the blood brain barrier remained intact and raxibacumab remained excluded from the brain. Natural history studies of inhalation anthrax in rabbits published in the scientific literature state the following “A low incidence of hemorrhage with bacilli occurred in the brain and meninges of aerosol exposed rabbits. The lesion in rabbits differed from that seen most often in human or in nonhuman primates in that it was devoid of any accompanying leukocyte infiltrate.”¹³

Neither the delay of treatment to 84 hours or co-administration of raxibacumab and levofloxacin in the added benefit study had any significant effect on antimicrobial activity of levofloxacin or PK profiles of either drug. Levofloxacin rapidly eliminated bacteremia; by 24 hours post-treatment > 75% of animals in both the combination and levofloxacin alone groups were negative for bacteria in blood. The addition of raxibacumab to levofloxacin appeared to enhance bacterial clearance with a slightly greater number of surviving animals negative for bacteria within 2 hours after the first treatment. Also, raxibacumab and levofloxacin PK profiles for each drug when administered in combination appeared similar to previous studies in which each drug was administered individually to inhalational anthrax animals, despite the 84 hour delay in treatment. Levofloxacin administered to rabbits at a dose normalized to the highest recommended human dose actually resulted in plasma levels similar to an intermediate clinical exposure.

Anti-drug antibodies to raxibacumab were detected in a majority of animals after raxibacumab treatment in both studies; pre-existing antibodies to raxibacumab were detected in only a few animals. Increased clearance of raxibacumab detected in survivors > 7 days post challenge likely resulted from binding to anti-drug antibodies. However, the greater survival rate in the raxibacumab treatment group indicates no significant impact of drug-antibody binding on efficacy of raxibacumab in the treated survivors. Similarly, development of high plasma titers of toxin neutralizing antibodies (TNA) occurred with both raxibacumab and levofloxacin treatment. The innate and/or

¹³ Zaucha, G.M., Pitt, M.L.M., Estep, J., Ivins, B.E., Friedlander, A.M. (1998). The pathology of experimental anthrax in rabbits exposed by inhalation and subcutaneous anthrax. *Arch.Pathol. Lab. Med.* **122** (11); pg. 982-992.

acquired immune response in rabbits to PA and other anthrax toxins appear unaffected by either treatment despite rapid clearance of bacteremia.

In the absence of any significant CNS pathology or clinical symptoms in survivors, no positive staining of raxibacumab with neural tissues in survivors, and in consideration of both the seriousness of the indication and the recommendation that this drug be co-administered with CNS penetrating antibiotics (ie. doxycycline, levofloxacin, ciprofloxacin, etc) to patients diagnosed with inhalation anthrax infection, it's likely these findings will pose minimal risk to patients in the clinic. Similarly, although a positive, statistically relevant added benefit result was not achieved with this under-powered study design, there appears to be a trend towards greater survival in rabbits when raxibacumab is co-administered with levofloxacin 84 hours post-challenge to inhalational anthrax exposure. Also, raxibacumab has been shown not to interfere with levofloxacin efficacy or with the innate or acquired immunity response to bacteria and/or bacterial toxins. When combined with safety data in healthy animals and human volunteers, as well as with positive results from previously conducted placebo trials with raxibacumab in rabbits and non-human primates, the complementary mechanism of action to the antibiotic appears to justify its use in patients diagnosed with inhalation anthrax disease.

6 Appendix/Attachments

None.

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

/s/

TERRY J MILLER
11/20/2012

WENDELYN J SCHMIDT
11/20/2012

I concur with Dr. Miller's assessment on the adequacy and interpretation of the data submitted for this NDA and agree that raxibacumab can be approved from the pharmacology/toxicology perspective.

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: Battelle Memorial Institute (BMI)
City, State: Columbus, OH
EI Dates: 10/09-12/2012 and 10/15-17/2012
FDA Participants: Andria L. Kuhlman, ORA Investigator, CIN-DO
Hugh M. McClure III, ORA Investigator, National Expert in Bioresearch
Monitoring, CIN-DO
LuAnn McKinney, D.V.M., CDER Veterinary Pathologist
Zhou Chen, M.D., Ph.D., OSI Pharmacologist
Abhijit Raha, Ph.D., OSI Pharmacologist

Inspectional Highlights:

- The Quality Assurance Unit (QAU) failed to document deviations in accordance with three Battelle Standard Operating Procedures (SOPs) when the study directors of studies 1103-G923704 and 1141-CG920871 failed to respond to QAU audit reports within 14 calendar days from the date of issue.
- Staff failed to check air flow/room pressure and diffusion of light conditions every six months in rooms JM8-36 and JM8-42 where the rabbits for study 1103-G923704 were housed.
- The QAU failed to note that although the pathology narrative of the final report for study 1141-CG920871 stated that gross observations for the appendix and sacculus rotundus of rabbit L33742 were not correlated with microscopic observations, the histology processing record indicated that sections of these tissues were not trimmed-in or embedded into blocks and slides were not cut and stained for microscopic evaluation.
- The study director failed to note that the Individual Animal Pathology Record (IAPR) incorrectly listed animals L35536, L35557, and L35559 on Study 1103-G923704 as "Moribund Euthanasia", although the Anesthesia and Euthanasia records stated that the animals died prior to scheduled euthanization.
- The pathology narrative stated that the thymus of rabbit L35576 underwent histopathological evaluation although the histology processing record did not include the thymus and no histology slides were generated or examined.

Studies Audited During This Inspection

BLA: 125,349
Review Div.: Division of Anti-Infective Products (DAIP)
Sponsor: Human Genome Sciences, Inc. (Rockville, MD)
Test Article: Raxibacumab
Study No: 1103-G923704
Study Title: "Evaluation of Raxibacumab as a Therapeutic Treatment against Inhalation Anthrax in the New Zealand White Rabbit Model"
Study Initiation Date: June 7, 2010

Final Report Date: February 21, 2012

Study No: 1141-CG920871

Study Title: “Added Benefit of Raxibacumab with Levofloxacin vs. Levofloxacin as Post-Exposure Treatment in the New Zealand White Rabbit Inhalational Anthrax Model”

Study Initiation Date: January 10, 2011

Final Report Date: May 21, 2012

Background: The Battelle Memorial Institute (BMI) is located in Columbus, OH. This facility performs a wide variety of toxicology safety evaluation studies for the pharmaceutical and biotechnology industries, and specializes in cardiovascular (using telemetry), neurobehavioral and pulmonary primary test systems. Battelle conducts nonclinical toxicology studies for the NIH, NCI, and DOD and is a primary laboratory for the National Toxicology Program (NTP). Examination of the Battelle West Jefferson and King Facilities’ Master Schedules of nonclinical studies conducted after the previous inspection in December 2011 showed that 45% and 84% of all studies were GLP, respectively. Virtually all the GLP studies are relevant to CDER.

Current Inspection: This was a FY 2013, CDER PDUFA GLP directed inspection. The primary objective of the inspection was to audit all study records concerning studies 1103-G923704 and 1141-CG920871 (cited above) to confirm the data integrity and verify that the studies were conducted in compliance with 21 CFR Part 58 -- Good Laboratory Practice (GLP). Histologic slides, in particular, under both routine and special stains, were examined for concurrence with listed tissues examined and histologic diagnoses. In addition, this inspection also covered the following areas: evaluations of the records of the study director and Quality Assurance Unit (QAU); facility operations; equipment; adequacy of training of personnel involved in the studies; archiving practices; test and control articles; animal care; and environmental conditions.

At the conclusion of the inspection, Form FDA 483 was issued to management on October 17, 2012 citing four violations of 21 CFR Part 58. Our evaluation of the Form FDA 483 observations (**in bold type below**) (**Attachment 1**) and the firm’s two respective written responses to the FDA 483 observations dated October 24, 2012 (**Attachment 2**) and October 30, 2012 (**Attachment 3**) follow.

OBSERVATION 1: The quality assurance unit failed to determine whether any deviations from approved protocols or standard operating procedures had been made with proper authorization and documentation. [21 CFR 58.35(b)(5)]

(Note: The regulation pertaining to Observation 1, listed in 21 CFR 58.35(b)(5), is the following: “The quality assurance unit shall determine that no deviations from approved

protocols or standard operating procedures were made without proper authorization and documentation.”)

A. The QAU failed to document SOP deviations (see table below) in source records in accordance with SOP MREF.XII-001-2, BBRC.XII-001-03, or COR2-005-00 when the study directors in Battelle studies 1103-G923704 and 1141-CG920871 failed to provide their responses to the QAU within 14 calendar days from dates of audit report issuance.

Battelle Study No.	Audit No., Description of Study Document Audited	Date Reported to Study Director	Date Response Received from Study Director (Days from Issuance of Audit Report)
1103-G923704	CAQ-9123, Aerosol Binder	Aug 24, 2010	Oct 6, 2010 (43 days)
1103-G923704	CAQ-9382, Vivo Binder	Nov 2, 2010	Apr 26, 2011 (175 days)
1103-G923704	CAQ-9479, Microbiology Equipment Binder	Nov 30, 2010	Apr 1, 2011 (122 days)
1103-G923704	CAQ-9488, Microbiology Binder	Dec 2, 2010	Apr 1, 2011 (120 days)
1103-G923704	CAQ-10141, Raxibacumab Immunochem. Binder	June 16, 2011	July 12, 2011 (26 days)
1141-CG920871	CAQ-9851, Treatment/Control Prep., Aerosol Challenge, Enumerations, Weighings, Clinical Observations, Body Temperatures, Blood Draws, Treatment Administration	Mar 30, 2011	May 11, 2012 (408 days)
1141-CG920871	CAQ-9928, Aerosol Binder and Summary Tables, Phase II	Apr 20, 2011	Dec 15, 2011 (239 days)
1141-CG920871	CAQ-9960, Aerosol Binder and Summary Tables, Phase I	May 3, 2011	Dec 16, 2011 (227 days)
1141-CG920871	CAQ-9995, Phase I Microbiology Binder and GAP Audit with Vivo Records	May 17, 2011	Mar 21, 2012 (309 days)
1141-CG920871	CAQ-10024, Phase I	May 20, 2011	Mar 21, 2012 (306 days)

	Microbiology Equipment Binder		
1141-CG920871	CAQ-10307, Vivo Binder and Vivo General Records Binder	Aug 10, 2011	Jan 17, 2012 (160 days)
1141-CG920871	AUD-545, Phase III Aerosol Binder and Summary Tables	Nov 10, 2011	Dec 27, 2011 (47 days)
1141-CG920871	AUD-664, Phase II Vivo Binder	Nov 29, 2011	Jan 17, 2012 (49 days)
1141-CG920871	AUD-677, Phase II Microbiology Binder	Nov 30, 2011	Jan 17, 2012 (48 days)
1141-CG920871	AUD-764, Phase III Vivo Binder	Dec 8, 2011	Jan 17, 2012 (40 days)
1141-CG920871	AUD-768, Phase III Microbiology Binder	Dec 8, 2011	Jan 30, 2012 (53 days)
1141-CG920871	AUD-1316, Clinical Observations Table	Feb 1, 2012	Mar 5, 2012 (33 days)
1141-CG920871	AUD-1547, Pathology Data, Draft Pathology Narrative	Feb 28, 2012	Mar 29, 2012 (30 days)
1141-CG920871	AUD-1580, Phase II Microbiology Equipment Binder	Mar 1, 2012	Mar 22, 2012 (21 days)
1141-CG920871	AUD-1584, Phase III Microbiology Equipment Binder	Mar 2, 2012	Mar 22, 2012 (20 days)
1141-CG920871	AUD-1835, Inhalation Exposure Report	Mar 26, 2012	Apr 10, 2012 (15 days)

Firm's Response: In their October 24, 2012 response, the firm stated that when requested response dates were exceeded in the past, the QAU did not identify these incidents as SOP deviations because the three SOPs (cited above) stated that a response will be "requested" within 14 days of issuance of an audit report, but there was no requirement for a response. However, the firm acknowledged the need to more actively monitor audit reports, which remain open for an extended period of time.

The firm promised to perform the following corrective actions: 1) the over-arching Corporate SOP, SOP COR.II-005, will be revised to indicate that audit reports, which are not completed within a defined timeframe from the date of issue, will be reported to management on a quarterly basis, and 2) a deviation report will be prepared for each of the study files for the cited SOP items noted in the table above.

In their October 30, 2012 response, the firm furnished a deviation report for the study audits (see table above) in which the QAU audit findings were not responded to in 14 days or less from their dates of issuance by the study directors of studies 1103-G923704 and 1141-CG920871. Their response letter states that “SOP COR.II-005 is being reviewed and will be revised to provide additional clarification regarding audit report response timeliness.”

Although we are in agreement with the firm’s response, the revised version of SOP COR.II-005 specifying the timeframe that audit reports need to be completed from the date of issue should be submitted to the Agency when available. This observation does not impact the quality or integrity of the data for studies 1103-G923704 and 1141-CG920871.

B. Battelle SOP Number BBRC.IV-003-07, Standard Operating Procedure (SOP) for Monitoring Air Changes and Air Pressure in the Animal Rooms and Laboratories requires that HVAC staff check air flow and room pressure in all animal rooms approximately every six months to verify that each animal holding room receives a minimum of ten air changes per hour. In the case of animal rooms JM8-36 and JM8-42, the required air flow and room pressure checks were only performed once in 2010 on January 28, 2010. These animal rooms housed New Zealand White rabbits for Study Number 1103-G923704.

C. Battelle SOP Number BBRC.IV-002-09, Standard Operating Procedure (SOP) for Monitoring Room Lighting in Animal Rooms requires that diffusion of light throughout the animal housing area be monitored approximately every six months. In the case of animal rooms JM8-36 and JM8-42, light diffusion monitoring was only performed once in 2010 on January 28, 2010. These animal rooms housed New Zealand White rabbits for BBRC Study Number 1103-G923704.

Firm’s Response: In their October 24, 2012 response, the firm acknowledged their inability to produce the records requested at the inspection to address the observations cited in Observations 1b and 1c. The firm further stated that a deviation was not issued immediately because of the possibility of locating the air and light monitoring records for the time period. Deviation reports related to the missing records were prepared as corrective measures. However, in their October 30, 2012 response, the firm did not furnish the deviation reports related to the missing records as proof of its corrective measures in response to Observations 1b and 1c.

The firm’s response to these observations is inadequate. An SOP deviation should have been issued when the air and light monitoring reports were first identified as missing. However, these observations are not likely to impact the quality or integrity of the data for study 1103-G923704.

OBSERVATION 2: The quality assurance unit failed to review the final study report to assure that such report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study.[21 CFR 58.35(b)(6)]

Specifically, the pathology narrative section of the final study report for Study 1141-CG920871 stated that the gross observations for the appendix and sacculus rotundus of New Zealand White Rabbit L33742 are not correlated with microscopic observations. However, the histology processing record for Animal L33742 indicated that sections of the appendix and sacculus rotundus were not trimmed-in or embedded into blocks and slides were not cut and stained for microscopic evaluation.

Firm's Response: In their October 24, 2012 response, the firm acknowledged this observation after the QAU re-reviewed the report for study 1141-CG920871 and its accompanying pathology narrative. As a result, the firm implemented the following corrective actions: 1) the anatomical pathology narrative was revised to clarify why the gross lesions found in rabbit L33742 could not be correlated to microscopic findings; 2) after gross necropsy and microscopic evaluation of other tissues collected in accordance with the protocol, the study pathologist confirmed that rabbit L33742 died from anthrax ; and 3) the study director concluded that there was no impact upon the study of not evaluating the two gross lesions for rabbit L33742. The firm will amend the final report for study 1141-CG920871 to incorporate the revised anatomical pathology narrative.

In their October 30, 2012 response, the firm submitted a copy of the amended pathology narrative as well as an amendment to the final report for study 1141-CG920871. The amended pathology narrative was clarified by stating that not all gross lesions exhibited by animal L33742 could be correlated to microscopic findings because the gross lesions were not processed to slides for microscopic evaluation.

The firm's response to this observation is adequate. Because the appendix and sacculus rotundus are not the primary target organs of *Bacillus anthracis* inhalational anthrax, this observation does not impact the quality or integrity of the data for study 1141-CG920871.

OBSERVATION 3: The study director failed to assure that all experimental data, including observations of unanticipated responses of the test system, were accurately recorded and verified. [21 CFR 58.33(b)]

Specifically, in Study 1103-G923704, Animals L35536, L35537, and L35559 were found dead during the study prior to administration of B-Euthanasia solution. However, in the "Individual Animal Pathology Record" and in the "Evaluation of Raxibacumab as a Therapeutic Treatment against Inhalation Anthrax in the New Zealand White Rabbit Model", these animals were incorrectly listed as "Moribund Euthanasia."

Firm's Response: In their October 24, 2012 response, the firm acknowledged that the three animals were all determined to be moribund and required euthanasia. The error occurred because the "Individual Animal Pathology Records" (IAPR) for these animals documented the type of death as "moribund euthanized." However, a QC review identified that all three animals were

anesthetized and had terminal blood samples collected, but all died prior to the administration of the euthanasia solution. The inaccurate IAPR was referenced during the preparation of the final pathology narrative. Thus, the type of death for these three animals was correctly reported in the final study report but the type of death for these animals was reported as moribund euthanized in the final pathology narrative.

As corrective measures, the firm corrected the type of death on the IAPRs of the three rabbits as “Found Dead” and the pathology narrative was amended to correctly report the type of death for the three rabbits as “Found Dead”. The final study report will be amended to incorporate the revised anatomical pathology narrative.

In their October 30, 2012 response, the firm provided a copy of the amended anatomic pathology narrative as well as an amendment to the final report for study 1103-G923704. The anatomic pathology narrative was revised to correctly report the type of death for animals L35536, L35557, and L35559 in study 1103-G923704.

The firm’s response to this observation is adequate. This observation does not impact quality or integrity of the data for study 1103-G923704.

OBSERVATION 4: Not all nonclinical laboratory studies were conducted in accordance with the protocol. [21 CFR 58.130(a)]

Specifically, the thymus for Animal L35576 was listed as examined in the histopathological evaluation for Study 1103-G923704. However, the examination of the thymus was not listed in the protocol and the Histology Processing Record for Animal L35576 does not include the thymus.

Firm’s Response: Battelle acknowledged the observation. In their October 24, 2012 response, the firm stated that the note made in the footer of the individual animal summary table for animal L35576 mentioned the thymus as a tissue examined microscopically and found unremarkable because the study pathologist made an entry error. Battelle stated that the final pathology narrative for study 1103-G923704 has been amended to correct this mistake. In the future, Battelle also plans to amend the final report for study 1103-G923704 in order to incorporate the revised anatomical pathology narrative.

In their October 30, 2012 response, the firm provided a copy of the amended anatomic pathology narrative as well as an amendment to the final report for study 1103-G923704. The firm revised the anatomic pathology narrative by deleting the text that the thymus for animal L35576 was examined microscopically and found unremarkable.

Although the firm’s response states that the observation was due to an error made by the study

pathologist, the finding illustrates a failure of the QAU to fulfill their responsibility of assuring the integrity of the data in the final study report because the error should have been identified during an audit. In addition, the observation also demonstrates a failure of the study director to verify and confirm the details in the final study report. Since the thymus is not a primary target organ of *Bacillus anthracis* inhalational anthrax, this observation does not impact the quality or integrity of the data for study 1103-G923704.

Recommendations:

- During this inspection, studies 1103-G923704 and 1141-CG920871 were both confirmed as conducted under 21 CFR Part 58-Good Laboratory Practice (GLP).
- None of the four observations (cited above) impact the integrity of the data generated for studies 1103-G923704 and 1141-CG920871. Therefore, the data generated for studies 1103-G923704 and 1141-CG923704 are suitable for Agency review.
- The next surveillance inspection should confirm that the firm has implemented corrective actions for the deficiencies noted above. Considering an 84% GLP workload at the King Avenue facility since December 2011, the next inspection should be conducted in two years.
- Recommended HQ classification: Voluntary Action Indicated (VAI)

Date Assigned: 7/27/2012
FACTS: 1427896
Inspection Type: ___ Routine Surveillance X Directed
FDA 483 Issued: ___ No X Yes
Letter Issued: ___ None (CDER) X Untitled Letter
 ___ Warning Letter ___ Rejection of Study

Date EIR Received by OSI: Not Available
Date EIR Received by Reviewer: Not Available
1st Draft Review Completed: 10/25/2012

Inspection Conclusion: VAI
District Decision: VAI
Final HQ Classification: VAI

cc: via DARRTS

CDER OSI PM TRACK

OSI/Moreno

OSI/DBEGLPC/Taylor/Bonapace/Chen/Matthews/Raha/CF

HFD-120/LuAnn McKinney (DNP)

HFD-520/Jane Dean (DAIP)

HFR-CE4525/Mishelle Harriger (BIMO)

HFR-CE450/Virginia Connelly (DIB)

HFD-CE4530/Andria L. Kuhlman, Hugh M. McClure III

Draft: AR 10/25/2012; ZC 10/25/2012, 11/2/2012; LM 10/26/2012; AR 10/31/2012, 11/1/2012, 11/2/2012

Edits: CRB 10/27/2012, 11/2/2012; WHT 11/2/2012

OSI File: GLP0825

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/s/

ABHIJIT RAHA
11/04/2012

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11/05/2012

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11/05/2012

CHARLES R BONAPACE
11/05/2012

WILLIAM H TAYLOR
11/07/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125349 Applicant: Human Genome Sciences, Inc. Stamp Date: June 15, 2012

**Drug Name: Raxibacumab NDA/BLA Type: Class 2
Submission to Complete Response Letter**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		The proposed drug has no specific abuse potential.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

TERRY J MILLER
07/11/2012

WENDELYN J SCHMIDT
07/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 125349
Sponsor's letter date 5/13/2009
CDER stamp date: 5/14/2009
Product: Raxibacumab
Indication: Intravenous treatment of Inhalation Anthrax
Sponsor: Human Genome Sciences, Inc. (HGS)
Review Division: Division of Special Pathogen and Transplant
Products
Reviewer: Terry J. Miller, Ph.D.
Supervisor/Team Leader: William H. Taylor, Ph.D.
Division Director: Renata Albrecht, M.D.
Project Manager: Rebecca McKinnon (Saville), Pharm.D.

Template Version: August 5, 2009

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a pharmacology/toxicology perspective, this application is approvable. There are no significant adverse nonclinical findings observed in healthy animals in the studies reviewed.

1.1.2 Additional Nonclinical Findings

An increase in incidence and/or severity of adverse CNS findings in raxibacumab-treated animals (compared with controls) were observed in pivotal animal efficacy studies in New Zealand White rabbits and cynomolgus monkeys with inhalational anthrax disease. *B. anthracis* is known to cause adverse CNS effects. However, the role of raxibacumab in potentiating these effects, if any, is unknown.

Additional nonclinical findings which have unknown significance include binding of raxibacumab to thyroid in human and non-human primate ex vivo tissues, and the questionable quality of immunogenicity data in animal studies.

1.1.3 Labeling



1.2 Brief Discussion of Nonclinical Findings

1.2.1 Basis of Recommendation/Clinical Implication

The decision to support approval of raxibacumab for the treatment of inhalational *Bacillus anthracis* disease is based on the absence of adverse findings in the nonclinical toxicity studies and the lack of a clear, plausible association between raxibacumab and adverse CNS effects seen in pivotal efficacy studies conducted in diseased animals.

Nonclinical Pharmacology/Toxicology Studies in healthy animals

Two ex vivo tissue cross-reactivity studies with raxibacumab (study nos. 1494-95 and 1M1634) showed strong, punctuate, intracellular staining of thyroid tissues from human and monkey donors in both studies, but not in thyroid tissues from rabbits. However, evaluation of the findings from the repeat dose 120-day toxicity study in healthy monkeys (study no: 6962-140) showed no thyroid histopathology or abnormal levels of circulating thyroid hormones. Therefore, the human implication of this finding remains unknown. Weak, inconsistent staining of several other tissues observed in the earlier ex vivo tissue cross-reactivity study using raxibacumab manufactured by a developmental process were not observed in any species in the later cross-reactivity study using raxibacumab manufactured by the current process, M11, for commercial use.

Raxibacumab administered to healthy cynomolgus monkeys by I.V. and S.C. injections at 40 mg/kg/day, once per day every 12 days for 3 doses , and followed 54 days later by a single I.M. 40 mg/kg dose (in the I.V.-dosed monkeys only), showed no test article related effects (Study no: 6962-140). All monkeys tolerated treatment with raxibacumab well by all three routes of administration and showed no test article effect on the clinical parameters tested. The data collected in this 120-day toxicity study

in healthy cynomolgus monkeys support a NOAEL of 40 mg/kg – identical to the proposed clinical dose for raxibacumab. Slow intravenous injection of raxibacumab in cynomolgus monkeys resulted in a 2.5 times greater C_{max} value (< 1000 µg/mL) but only slightly greater AUC_(0-∞) exposure (1.2 times) compared to an S.C. dose, with near equal t_{1/2} of 12-14 days. Despite the long half life, optimal for scavenging free PA in anthrax disease, raxibacumab induced no significant antibody neutralization with multiple dosing up to 12 days between doses. Dose-normalization of serum levels after repeat dosing showed nearly identical PK after a single dose indicating dose linearity of raxibacumab. Serum concentration profiles of raxibacumab were similar in both sexes.

Similarly, intravenous treatment with raxibacumab up to 120 mg/kg (3 times the clinical dose) on gestation days 7 and 14 was well tolerated by healthy pregnant rabbits and appears to pose no significant risk for maternal health, abnormal pregnancy or drug-related teratology while used for the prevention or treatment of infection by *Bacillus anthracis*. With respect to the teratology portion of the main study, there were no deaths or significant treatment-related adverse effects observed in the fetuses from raxibacumab-treated dams. The only potential treatment related effect in the teratology portion of the study was a slight increase in the skeletal variation findings (unossified 5th sternebra and presence of 13th rudimentary ribs) in the high dose group. However, these minor variations do not impact the conformity or well-being of the animal, and thus were not considered an adverse effect. Therefore, the data support the stated NOAEL of 120 mg/kg for both maternal and fetal effects. Toxicokinetic analysis showed proportionally higher serum concentrations for the 120 mg/kg relative to the 40 mg/kg group at all time points in both the main and TK studies. Additionally, dose normalized serum raxibacumab levels were the same across doses and groups, showing linearity in response similar to findings in cynomolgus monkeys.

In both healthy cynomolgus monkeys and pregnant healthy rabbits, raxibacumab does not appear to cause a significant immunogenic response above background levels. This evidence supports the PK findings of dose linearity in the absence of any significant dose neutralization in both animal models in the pharmacology/toxicology studies and in patients evaluated in the clinical trials (PAM-NH-01, HGS1021-C1064, HGS1021-C1069). However, in both animal studies, the assays used to determine immunogenicity appeared not to be reliable or sensitive in the presence of either high serum raxibacumab concentrations (> 150 µg/mL) or perhaps other interfering anti-PA-antibodies with high titer levels in normal, untreated animals. When combined with highly variable individual animal data, the impact of unreliable immunogenicity data for raxibacumab on studies in healthy and anthrax infected animals remains unclear.

Pivotal Efficacy Studies in Animal Models of Infection

Two pivotal efficacy studies 682-G005758 (NZW rabbits) and 724-G005829 (cynomolgus monkeys), were conducted in anthrax infected animals (by inhalation exposure to *Bacillus anthracis* spores at 200 x LD₅₀) under the “Animal Rule” (21 CFR 601.90 for biological products). Due to the nature of *B. anthracis* disease, human efficacy trials with raxibacumab cannot be conducted in a well-controlled clinical setting.

The results from these studies showed an unexpected increase in incidence and/or severity of central nervous system (CNS) lesions in raxibacumab treated animals (among non-surviving animals), compared to the placebo treatment groups (among non-survivors). CNS lesions included fibrinoneutrophilic inflammation, hemorrhage, fibrinoid or neuropil necrosis, and widespread bacterial infiltration (intra-, peri-vascular areas, subarachnoid space, choroid plexus. In both species, brain was the only organ with more severe pathologic findings in raxibacumab groups than in placebo animals. The etiology of these findings, including the specific role of raxibacumab, is presently unknown.

In toxicity studies in healthy animals, and in safety, tolerability, and pharmacokinetic trials in healthy volunteers, raxibacumab appeared to be reasonably safe and well-tolerated. In the absence of any clear, plausible association between raxibacumab and CNS pathology, the pharmacology/toxicology decision to support approval of raxibacumab remains unchanged.

(Pivotal efficacy studies in animals were reviewed by clinical reviewers, and those reviews may be found elsewhere.)

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number: CAS#: 565451-13-0

2.1.2 Product Names

Non-Proprietary Names: raxibacumab; Human IgG1 λ monoclonal antibody (mAb) against the protective antigen (PA) of *Bacillus anthracis* for treatment of inhalation anthrax

Proprietary Name: ABthrax™

2.1.3 Code Name: HGS1021

2.1.4 Chemical Name: PA mAb

2.1.5 Molecular Formula/Molecular Weight

(b) (4) / 145.9 kDa as measured by ESI-MS

2.1.6 Pharmacological Class

Anti-protective antigen monoclonal antibody (Anti-PA mAb)

2.1.7 Structure

Raxibacumab is a fully human IgG1 antibody comprised of 2 identical light chains and 2 identical heavy chains.

(b) (4)

(b) (4)

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 11,069: Evaluation in healthy volunteers for the eventual prophylactic and therapeutic treatment of anthrax infection (HGS)

IND 102,964: Intravenous Administration of Raxibacumab as a Therapeutic Agent for Treatment of Inhalation Anthrax (CDC)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Raxibacumab is a sterile, liquid formulation in single-dose vials intended for intravenous injection. Each vial contains 50 mg/mL raxibacumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 18 mg/mL glycine, 10 mg/mL sucrose, and 0.2 mg/mL (w/v) polysorbate 80 pH 6.5.

2.3.2 Comments on Novel Excipients

No novel excipients were used in the final formulation of this product. The concentration of each excipient and its function identified in this product can be found in Table 2.3.2.1, copied from BLA 125349. Based on the indication, proposed clinical dosing, and relatively low concentrations of excipients, there does not appear to be any indication that excipients used in this product will pose any significant toxicological risk to patients.

Table 2.3.2.1 Excipients for raxibacumab

Excipients	Concentration (mg/mL)	Function
Citric Acid (b) (4)	0.13	(b) (4)
Sodium Citrate (b) (4)	2.8	
Sucrose	10	
Glycine	18	
Polysorbate 80	0.2	

Table 3.2.P.2-1 from pg. 7 (3.2.P.2 Pharmaceutical Development)

2.3.3 Comments on Impurities/Degradants

The impurities identified in the final raxibacumab product were determined by the applicant to be primarily (b) (4) related impurities. Based on the indication, proposed clinical dosing, and relative low levels of (b) (4) (b) (4) impurities, there does not appear to be any indication that impurities detected in the product will pose any significant toxicological risk to patients.

Table 2.3.3.1 List of raxibacumab (b) (4) impurities

Impurity	Source	Mean levels
(b) (4)		

Table from pg 56, Table 2.3.S.3-4, Drug Substance

2.4 Proposed Clinical Population and Dosing

Raxibacumab is indicated for (b) (4) (b) (4)

(b) (4) The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. Raxibacumab can be administered alone or in combination with antibiotics. Raxibacumab should be administered immediately upon presumptive diagnosis of inhalation anthrax. Diphenhydramine administered within 1 hour prior to treatment with raxibacumab is recommended for the prevention of infusion and hypersensitivity reactions.

2.5 Regulatory Background

IND submission, Fast Track, and Orphan Designation

A pre-IND meeting request and briefing package was submitted to the FDA on August 28, 2002 and the pre-IND meeting between Human Genome Sciences (HGS) and the agency was held on October 10, 2002. The objective of this meeting was to discuss the proposed clinical development of raxibacumab, a fully human IgG₁ antibody against the protective antigen (PA) protein of *Bacillus anthracis*. The original IND application for raxibacumab was subsequently filed to the FDA on May 22, 2003 and included a Phase 1 protocol to evaluate the safety, tolerability, and pharmacokinetic profile of raxibacumab in healthy volunteers (Protocol PAM-NH-01).

On June 13, 2003, HGS requested Fast Track designation for submission of its BLA for raxibacumab as post-exposure prophylaxis and adjunctive therapy of inhalation anthrax disease, which was granted by the Agency on August 15, 2003. A request for Orphan Drug designation for raxibacumab for the treatment of subjects with inhalation anthrax was submitted to the Office of Orphan Product Development on July 29, 2003. The Office of Orphan Product Development granted this request on November 12, 2003 for the treatment of anthrax.

Meetings and Interactions

On October 11, 2005, an End of Phase 1 meeting was held between the Agency and HGS to address chemistry, manufacturing, and controls (CMC) issues and discuss additional nonclinical/clinical studies necessary to support licensure and use under Emergency Use Authorization (EUA) for the post-exposure treatment of anthrax.

In a series of follow-up meetings and written correspondences in 2006 between HGS and the Agency, the following topics were addressed: 1) the size of the human safety database, 2) the need for repeat dose exposure, 3) need for safety evaluation of raxibacumab in combination with antibiotics, 4) a requirement to demonstrate efficacy in 2 species (rabbits and monkeys), exposed to anthrax prior to raxibacumab administration, 5) acceptance of serum PA as a trigger for treatment, and 6) the need for clinically relevant antibiotic exposure in animals in the raxibacumab/antibiotic combination studies.

In 2006, the raxibacumab manufacturing process underwent significant changes including [REDACTED] ^{(b) (4)} HGS provided the data from the release and characterization studies to demonstrate comparability of the M10 (Phase 1 trial, PAM-NH-01, and proof of concept animal studies) and M11 manufacturing processes proposed for licensure (animal efficacy studies, rabbit reproduction study, human raxibacumab/ciprofloxacin trial, large safety trial, and repeat dose trial).

In 2007, HGS submitted the protocols for the pivotal animal efficacy studies and completed those studies that same year. In 2008, the protocols for raxibacumab antimicrobial combination studies in both rabbits and cynomolgus monkeys were reviewed by FDA and in-life portions of these studies were completed in the summer of 2008. Clinical protocols for evaluation of the raxibacumab single and double-dose pharmacokinetics and safety trials, alone and in combination with ciprofloxacin, in healthy human volunteers, were evaluated by the FDA and all clinical trials were completed in summer 2008.

In the spring of 2008, HGS submitted to FDA all outstanding animal and clinical study reports to support the delivery of raxibacumab to the Strategic National Stockpile (SNS), the assay qualification reports for the nonclinical and clinical assays, and the updated drug stability and lot release data. A pre-BLA meeting was held on October 21, 2008.

Recommendation for Stockpiling

In parallel with Agency discussions with HGS, agreement was reached in December 2007 on the studies needed from HGS to support an IND submission by the Centers for Disease Control and Prevention (CDC) for emergency clinical use of raxibacumab manufactured and purchased from HGS and stored in the U.S. Strategic National Stockpile (SNS).

On January 23, 2009, following review of data submitted under IND 11,069 and the clinical protocol submitted by the CDC under IND 102,964, the Division determined that raxibacumab (40 mg/kg, IV) is acceptable for emergency treatment of clinical inhalational anthrax disease. FDA acknowledged that HGS and CDC have in place the conditions requested by FDA to allow raxibacumab to be shipped to and stored in the SNS. HGS then requested a number of labeling exceptions under the interim final rule, "Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile" (72 FR 73589). The Review Division worked with HGS to update the Investigator's Brochure to include a balanced summary of the findings from the studies reviewed, including a discussion of the limitations of those studies, and granted HGS's requests for labeling exceptions on January 27, 2009.

3 Studies Submitted

3.1 Studies Reviewed

- Cross-reactivity study of HGS1021 – raxibacumab with normal human, cynomolgus monkey, and New Zealand white rabbit tissues (Study No. IM 1634).

3.2 Studies Not Reviewed

- Animal studies submitted to BLA 125349 in which animals were exposed to *B. anthracis* spores, including natural (disease) history studies, proof-of-concept and efficacy studies, were reviewed by clinical reviewers, including clinical pharmacologists, clinical (mathematical) statisticians, and clinical microbiologists. Pharmacology/toxicology reviewers participated in discussions of those study results at all review stages.
- Pharmacokinetics of the PAmAb587 in BALB/c mice (Study no. AB50409.INF.0.014).
- Pharmacokinetics of the PAmAb587 in Fisher 344 rats (Study no. AB50409.INF.0.015).
- Biodistribution of 111In-labeled raxibacumab in rodents following IV or SC injection.
- Collection of samples for determination of PK of PA mAb after a single IV, SC, or IM dose to rabbits (Study No. AB50409.INF.0.016) to accompany 6962-137 to accompany Study No. 6962-173).
- Collection of samples for determination of PK of PA mAb after a single IV, SC, or IM dose to cynomolgus monkeys (Study No. AB50409.INF.0.017) from studies 6962-137 and 6962-136.

3.3 Previous Reviews Referenced

- Cross reactivity of PA mAb with human and cynomolgus monkey tissues ex vivo (Study No. 1494-95)
- 120-day toxicity study with PA mAb in cynomolgus monkeys (b) (4) 6962-140).
- A toxicokinetic analysis of (b) (4) Study No. 6962-140, "120-day toxicity study with PA mAb in cynomolgus monkeys (Study No. AB50409.INF.034 to accompany Study No. 6962-140).
- Immunogenicity of PA mAb following repeated SC or IV administration in cynomolgus monkeys (Study No. AB50409.INF.037 to accompany Study No. 6962-140).
- Intravenous study for effects on embryo-lethal development and toxicokinetics with Raxibacumab in rabbits (Study No. 6962-173).
- Pharmacokinetics of raxibacumab in pregnant New Zealand white rabbits following two intravenous injections given 7 days apart (GLP embryo-fetal toxicology study; (Study No. AB50409.INF.038 to accompany Study No. 6962-173).
- Immunogenicity results for rabbit embryo-fetal raxibacumab toxicity study (AB50409.INF.037 to accompany Study No. 6962-173).

4 Pharmacology

4.1 Primary Pharmacology

Primary pharmacology experiments are reviewed by clinical microbiology reviewers.

4.2 Secondary Pharmacology

Two secondary pharmacologic ex vivo tissue cross-reactivity studies (Studies no. 1494-95 and 1M1634) for raxibacumab were conducted using human, cynomolgus monkey, and New Zealand White (NZW) rabbit (Study 1M1634 only) donor tissues.

Summary:

In both cross-reactivity studies with HGS1021 (raxibacumab, PA mAb), the thyroid was a target organ of cross-reactive binding with PA mAb, showing intense, punctuate, staining of cytoplasmic granules in follicular epithelium. In study 1494-95 (2003) the intensity of staining was noted to be greater in monkey than human, in contrast with study 1M1634 (2008), which showed equally intense binding in both human and monkey donor tissue, with no positive staining observed in the rabbit. (Rabbit tissues were not evaluated in the 2003 study.) The clinical significance of the specific binding of raxibacumab with ex vivo monkey and human thyroid tissue is presently unknown.

Weak, inconsistent staining of skeletal muscle and thyroid (both humans and monkeys), endometrium (humans only), and breast and prostate (monkeys only) tissues were also reported in the earlier study and were not observed in the latter. The difference in results between the two cross-reactivity studies may be attributed to product from different manufacturing processes used in each study having slightly dissimilar affinities for binding specific or non-specific binding sites. In summary, apart from the thyroid binding, no significant positive staining above background levels was detected in the majority of donor tissues from human, cynomolgus monkey, and New Zealand White rabbit at the antibody concentrations evaluated.

The absence of positive tissue cross-reactivity in rabbits as compared to humans and monkeys indicates the limited value of the rabbit as a toxicity animal model.

1. **Cross-reactivity of PA mAb with human and cynomolgus monkey (*Macaca fascicularis*) tissues ex vivo.** ^{(b) (4)} Study Number 1495-95; Final Cross-Reactivity Report: August 27, 2003. This study was originally reviewed in this division by Dr. William Taylor for IND submission 11,069 (Summary Review Only).

The primary objective of this GLP immunohistochemistry study was to identify and characterize target antigen-specific (cross-reactive) binding of raxibacumab with normal ex vivo tissues from human and cynomolgus monkeys. Tissue slides were rinsed and treated to preserve morphology, quench endogenous peroxide activity, and block non-specific IgG binding sites. Pre-complexed PA mAb (Lot #: 02A21109) or anti human IgG (negative control) antibody was incubated with tissues and control cells (*E.coli*) at 12.5 and 2.5 µg/mL followed by incubation with streptavidin horseradish-peroxidase (HRP) and diaminobenzidine (DAB) chromagen substrate for microscopic visualization. Two *Escherichia coli* (*E.coli*) strains that differentially express the protective antigen (PA) served as the positive and negative controls. All tissue sections were deemed adequate with positive staining with an anti-CD31 antibody. Slides were evaluated to identify tissue or cell type stained and scored for both staining intensity and staining frequency. The following mammalian tissues were evaluated for PA mAb cross-reactivity:

Adrenal	Eye	Ovary	Striated muscle
Bladder	Fallopian tube	Pancreas	Testes
Blood	Gastrointestinal tract	Parathyroid	Thymus
Bone marrow	Heart	Pituitary	Thyroid
Breast	Kidney glomerulus	Placenta	Tonsils
Cerebellum	Kidney tubule	Prostate	Ureter
Cerebral cortex	Liver	Skin	Uterus (cervix)
Colon	Lung	Spinal cord	Uterus (endometrium)
Endothelium	Lymph node	Spleen	

The majority of tissues from human and cynomolgus monkeys showed no positive staining when treated with PA mAb at either concentration. At the higher antibody concentration, positive staining was observed in tissues including skeletal muscle and thyroid (humans and monkeys), endometrium (humans only), and breast and prostate (monkeys only). At the lower concentration, only human skeletal muscle stained positive. Minimal non-specific background staining was observed with both PA mAb and the negative control IgG₁ antibody in macrophages, neutrophils, granulocytes, glandular secretion, cytoplasmic pigments, interstitium, adipose tissues, hepatocytes, and kidney tubular epithelium.

Positive staining in the human and monkey tissues with PA mAb was generally identified as weak, inconsistent, and difficult to identify. Positive staining in human skeletal muscle at both antibody concentrations was punctuate and multifocal within some, but not all, striated muscle fibers. Similar staining was not observed in monkey skeletal muscle tissue above background levels. However, monkey thyroid showed a stronger affinity for PA mAb with intense, punctuate cytoplasmic staining of follicular cuboidal epithelium, present in human tissue but to a lesser intensity. Human endometrium, monkey breast, and human and monkey prostate

tissue all showed weak, positive staining, in both initial and repeat experiments.

The study appears to have been conducted adequately and all controls produced expected results. However, triplicate samples were not all representative from the same portion of the tissue type, staining was not consistently observed in all analogous triplicate samples, and the small number of samples per tissue type (three) limits the strength of the finding.

2. Cross-reactivity study of HGS1021 – Raxibacumab with Normal Human, Cynomolgus Monkey, and New Zealand White Rabbit Tissues.

(b) (4) Study No. 1M1634; Final Cross-Reactivity Report: Sept. 4, 2008 (Complete Review)

BLA Number: 125,349

Sponsor: Human Genome Sciences, Inc.
14200 Shady Grove Rd., Rockville, MD 20850

Product: Human Monoclonal Antibody against the Protective Antigen Protein of *Bacillus anthracis*; **raxibacumab**; **PA mAb**

Indication: Treatment of *Bacillus anthracis* disease

Report Authors: Terry J. Miller, Ph.D., William H. Taylor, Ph.D.

STUDY OBJECTIVE

To evaluate the potential for cross-reactivity of HGS 1021 – raxibacumab with cryosections of normal cynomolgus monkey and New Zealand White rabbit tissues.

STUDY REVIEWED

Cross-reactivity study of HGS1021 – Raxibacumab with Normal Human Cynomolgus Monkey, and New Zealand White Rabbit Tissues. (b) (4)
(b) (4) Study No. 1M1634; Final Cross Reactivity Report, Sept. 4, 2008.

KEY FINDINGS

Positive cross-reactivity of PA mAb occurred in the thyroid tissue from humans and cynomolgus monkey, with no comparable staining detected in rabbit. No positive tissue staining was observed in any other tissues in any species evaluated.

The intense positive staining observed in the human and monkey thyroid sections was observed in all donor tissues examined (3/3 each). However, the number of replicate donor samples for each tissue successfully examined varied. In all cases, the small number of samples for many tissues (three) limited the strength of both the positive and negative findings. For the purposes of this application, the positive staining observed in the thyroid of human and monkeys should be considered a potential target for toxicity in humans administered this product. In addition, the absence of positive tissue cross-reactivity in rabbits as compared with humans and monkeys might indicate a difference in the affinity for off-target antibody binding sites, including thyroid, in rabbit tissue.

BACKGROUND

This study was conducted to evaluate target antigen specific (cross-reactive) binding of the human, anti-protective antigen (anti-PA) IgG1 antibody, HGS1021 (raxibacumab), to normal human, cynomolgus monkey, and New Zealand White rabbit tissues.

GLP: The study was conducted under GLP regulations except for the characterization of the test and control articles, which were analyzed under the sponsor's standard operating procedures (SOP) guidelines.

Testing facility: (b) (4)

Study Pathologist: (b) (4)

Dates: Initiation: 6/03/08; Completion: 7/10/08

Test article: HGS1021 – Raxibacumab (PA mAb), Lot. No. 71044

Control article: CAT-002, Lot. No. AB19337-MI (Human IgG1 antibody)

Positive control tissue: Cryosections of PA from *B.anthraxis* expressed by *E.coli* bacterial cell pellets

Negative control tissue: Cryosections of PA from *B.anthraxis* not expressed by *E.coli* bacterial cell pellet

Table 1. Normal Human, Cynomolgus Monkey and New Zealand White Rabbit Tissue from Three Separate Donors – Tissue List

Adrenal	Lung	Spinal Cord
Blood Cells ¹	Lymph Node	Spleen
Blood vessels (endothelium)	Ovary	Striated (skeletal) Muscle
Bone Marrow	Fallopian Tube (oviduct)	Testis
Brain - cerebrum (cortex)	Pancreas	Thymus
Brain - cerebellum	Parathyroid	Thyroid
Breast (mammary gland)	Peripheral Nerve	Tonsil
Eye	Pituitary	Ureter
Gastrointestinal Tract ²	Placenta	Urinary Bladder
Heart	Prostate	Uterus (endometrium)
Kidney (glomerulus, tubule)	Salivary Gland	Uterus (cervix)
Liver	Skin	

¹Blood cells include granulocytes, lymphocytes, monocytes, and platelets

²Gastrointestinal Tract includes colon, esophagus, small intestine, and stomach

Human, cynomolgus monkey, and New Zealand White rabbit tissues from at least three separate donors each were evaluated. After pathology review, if it was determined that the samples were unsuitable for evaluation due to tissue morphology or amount available, tissues from additional donors were stained and evaluated to obtain the required three evaluable tissue samples.

Deviation: In the cynomolgus monkey donor, (2/3) donors of adrenal gland and (1/4) donors of parathyroid gland were evaluated. In the New Zealand White rabbits, (2/3) donors of ovary and fallopian tube, and (1/3) donors of placenta were evaluated. In addition the mucosa was not present for evaluation in (1/3) human donors of urinary bladder and (1/4) human donors of uterus-cervix, and in (3/5) cynomolgus monkey donors of urinary

bladder. The epithelium was not present for evaluation in (2/4) New Zealand White rabbit donors of skin.

Concentration selection was determined using both (HGS1021)-raxibacumab and negative control antibody on both the positive and negative control cryosections (*E. coli* expressing PA from *B. anthracis* and *E. coli* not expressing PA from *B. anthracis*, respectively.) The optimal staining concentrations of 12.5 and 2.5 µg/mL were evaluated in the previous cross-reactivity study (b) (4) Study No. 1494-95) in human and cynomolgus monkey tissues.

To eliminate the requirement for labeling and to reduce non-specific binding to anti-human endogenous IgG in tissues, the biotin conjugated secondary antibody [F(ab')₂ donkey anti-human IgG (H+L) (DAHulgG)] was incubated with the unlabeled primary antibody (either test article or negative control antibody) for 1 hour prior to application to the tissue cryosection.

Tissue slides were rinsed and treated to preserve morphology, quench endogenous peroxidase activity, and block non-specific binding sites on tissues (avidin/biotin and protein solutions). Pre-complexed antibody (raxibacumab or negative control antibody) was incubated with tissues and control cells (*E. coli*) at 12.5 and 2.5 µg/mL and then incubated with streptavidin horseradish-peroxidase (HRP) and diaminobenzidine (DAB) chromagen substrate for microscopic visualization. Validation of tissue samples was evaluated by staining sections of all tissue samples with anti-β₂-microglobulin antibody. Presence of β₂-microglobulin positive staining was evidence of tissue adequacy. β₂-microglobulin antigen (a relatively ubiquitous epitope) is expressed on many cell types and is strongly expressed on endothelium.

All slides were evaluated to identify tissue or cell type stained as well as staining intensity (1+ [weak], 2+ [moderate], 3+ [strong], 4+ [intense], or Neg [negative]). Frequency of cell type staining was identified as follows: very rare (<1% of cells of a particular cell type); rare (1-5% of cells of a particular cell type); rare to occasional (> 5-25% of cells of a particular cell type); occasional (>25-50 % of a particular cell type); occasional to frequent (>50-75% of cells of a particular cell type); frequent (>75-100 % of cells of a particular cell type). Positive control or test tissue staining affinity was determined immunohistochemically by comparing the reactivity of raxibacumab at two concentrations of antibody and scored as follows: [High affinity] staining and reactivity was equivalent at both concentrations; [Low affinity] staining and reactivity observed only at the higher concentration; and [Intermediate affinity] minor decrease in intensity or frequency of staining at the lower concentration compared to the higher concentration.

RESULTS

Nearly all human, monkey, and rabbit tissues failed to show positive staining when treated with the PA mAb at either concentration. The only tissue determined to stain positive was thyroid tissue in the human and monkey at both concentrations, with no test article staining observed in any tissue in rabbit.

Various descriptions of non-specific background staining were present in sections treated with either the PA mAb or the human negative control IgG1 antibody, including macrophages, neutrophils, granulocytes, glandular secretion, cytoplasmic pigments (lipofuscin, hemosiderin, melanin, and/or bilirubin), interstitium, adipose tissues, hepatocytes, and kidney tubular epithelium. Non-specific staining was minimal and not considered positive staining in this study.

Positive staining of β_2 -microglobulin was detected in all control and test tissue sections (except blood cells) indicating tissue suitability for inclusion in this cross-reactive study. Raxibacumab produced intense staining of the positive control (PA from *B.anthraxis* expressed by *E.coli* bacterial cell pellets) and did not specifically react with the negative control (PA from *B.anthraxis* not expressed by *E.coli* bacterial cell pellets). The negative control antibody did not react with either the positive or negative control slides.

PA mAb Cross-Reactivity with Thyroid:

Raxibacumab (2.5 and 12.5 $\mu\text{g}/\text{mL}$) specifically stained cytoplasmic granules of follicular epithelial cells of thyroid from three of three human donors with variable frequency (very rare to occasional) at concentrations of 2.5 and 12.5 $\mu\text{g}/\text{mL}$. The staining was scored moderate to strong (2-3+) in all three thyroid donor tissues at both concentrations.

Raxibacumab (2.5 and 12.5 $\mu\text{g}/\text{mL}$) specifically stained cytoplasmic granules of follicular epithelial cells in three of three cynomolgus donors of thyroid with variable frequency (very rare to occasional) at concentrations of 2.5 and 12.5 $\mu\text{g}/\text{mL}$. The staining was scored moderate to intense (2-4+) in all three donated thyroid tissues at the antibody concentration of 12.5 $\mu\text{g}/\text{mL}$, and weak to strong (1-3+) at the lower antibody concentration of 2.5 $\mu\text{g}/\text{mL}$.

No rabbit tissues stained positive with the raxibacumab antibody at 12.5 or 2.5 $\mu\text{g}/\text{mL}$ antibody concentrations.

Control testing of human, cynomolgus monkey, and rabbit tissues:

Human, monkey, and rabbit tissues stained with the negative control antibody, CAT-002, stained minimally as non-specific background, as observed historically. Staining of tissue samples with the anti- β_2 -microglobulin antibody resulted in diffuse, positive immunohistochemical staining, with intense staining observed in endothelium, in nearly all human, monkey, and rabbit tissue tested. The results support the overall tissue suitability for inclusion in the cross-reactivity study.

E.coli (control) cell lines:

HGS1021 (raxibacumab) produced strong to intense staining (3-4+) of the positive control (*E.coli* expressing PA) and did not specifically react with the negative control (*E.coli* not expressing PA).

SUMMARY, DISCUSSION, AND CONCLUSION

Species specific cross-reactivity of raxibacumab was observed in donor thyroid tissue from human and cynomolgus monkeys at both staining concentrations (2.5 and 12.5 µg/mL), with no positive staining observed in rabbit. No positive staining was observed in any other tissues from any species. Comparison of PA mAb staining in human and cynomolgus monkey tissue showed similarity in cell type, subcellular localization, staining intensity, and frequency. In contrast with findings from the initial tissue cross reactivity study (2003), in this study there appeared to be a similar affinity between human and cynomolgus thyroid tissue. In addition, comparisons of raxibacumab non-specific staining in human and rabbit tissues indicated significant differences in thyroid staining patterns.

The intense positive staining observed in the human and monkey thyroid was observed in all donor tissue (3/3 each) examined. However, with other organs, the number of replicate donor samples for each tissue varied. In all cases, the small number of samples for many tissues (three) limits the strength of both the positive and negative findings.

The study appears to have been conducted adequately and all controls produced expected results and the conclusions discussed by the pathologists appear to be consistent with the individual observations.

Although the positive staining observed in the thyroid of human and monkeys should be considered a potential target for toxicity in humans administered this product, the clinical significance of the finding is presently unknown. The absence of positive tissue cross-reactivity in rabbits as compared with humans and monkeys indicates the limitations of the rabbit as an animal toxicity model.

4.3 Safety Pharmacology

In agreement with the Agency (reference pre-BLA meeting minutes of October 21, 2008) and in accordance with ICH S7A, Part II.1 (ie. Conditions Under Which Studies Are Not Warranted, 2000), HGS did not perform any safety pharmacology studies.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

A single pharmacokinetics study of raxibacumab in pregnant New Zealand white rabbits (Study No. AB50409.INF.038 to accompany Study No. 6962-

173) was submitted to IND 11,069 and is included in this BLA. A summary of findings can be found in the review for Study No. 6962-173 in Section 6.2.2. All other PK or ADME studies in rodents (listed in section 3.2) and submitted to IND 11,069 were not reviewed. HGS studied rodents during early product development and determined they were not adequate models of clinical anthrax disease.

5.2 Toxicokinetics (If Not Included In Toxicity Studies)

No toxicokinetic studies were submitted to this BLA. A single toxicokinetic study (Study No. AB50409.INF.034 to accompany Study No. 6962-140) evaluated samples obtained from the "120-day toxicity study with PA mAb in cynomolgus monkeys" was originally submitted to IND 11,069 and is referenced in this BLA. A summary of findings can be found in the review for Study No. 6962-173 in Section 6.2.2.

6 General Toxicology

6.1 Single-Dose Toxicity

There were no single-dose toxicity studies submitted by the applicant with this BLA.

6.2 Repeat-Dose Toxicity

Two repeat-dose toxicity studies were submitted to BLA 125349 and were previously reviewed under IND 11,069: A 120-day study of raxibacumab in cynomolgus monkeys, and an embryo-fetal reproductive developmental study in New Zealand White rabbits. For this BLA review summaries of these studies are provided below and under Section 9.2.

Study title: 120-Day Toxicity Study with PA mAb in Cynomolgus Monkey (Study No. 6962-140).

Conducting laboratory:	(b) (4)
Date of study initiation:	1/24/2003
GLP compliance:	Yes (except for dose formulation, analysis, immunogenicity, and complement activation)
QA statement:	Yes, Signed 8/18/23
Drug, lot #, and purity:	Lot#: 02A21109, purity: size-exclusion HPLC major peak 99.6%; stored at 2 to 8° C.

Objective:

The purpose of this study was to evaluate the toxicity, toxicokinetic profile, and immunogenicity of PA mAb in cynomolgus monkeys following

administration three times (once every 12 days) by subcutaneous or intravenous injection (Phase I) and when administered by intramuscular injection (Phase II).

Methods:

Three cynomolgus monkeys (2 – 3 years old; 2.0 – 3.0 kg males; 1.9 – 2.7 kg females) per sex per group were administered single doses of PA mAb (i.e., raxibacumab) or vehicle on Days 1, 13, and 25 according to the following study design:

Table 1. Study Design

Group	Animals		Dose mg/kg/day	Concentration mg/mL
	Male	Female		
1 (Vehicle Control)	3	3	0	0
2 (SC)	3	3	40	40
3 (IV)	3	3	40	40

Controls (Group 1) received vehicle (PA mAb diluent) both by subcutaneous and intravenous injection. On Day 69, Groups 1 and 3 were administered PA mAb in a single dose IM at 40 mg/kg.

Assessment of toxicity by the subcutaneous and intravenous routes was based on mortality, clinical observations (including qualitative food consumption), body weight, and clinical pathology evaluations. For assessment of toxicity by the intramuscular route, gross and microscopic pathology evaluations were also conducted. Blood samples were collected from all three groups for toxicokinetic (TK) analysis, immunogenicity assays, and complement activation studies. For TK evaluation, blood was collected 48 hours after each SC dose (Group 2) on days 1, 13, and 25, immediately prior to dosing on days 13 and 25, and on days 37, 50, and 69 (Table 2). Serum concentrations of PA mAb were determined using a sandwich type ELISA (SOP 01PAM-AB-21-1841) and non-compartmental analysis to determine C_{max} , t_{max} , $t_{1/2}$, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and $AUC_{(t-\infty)}$. For the immunogenicity study, blood was collected on days -4, 13, 25, 37, 50, 69 (prior to IM injection, Groups 1 and 3), and day 120 (Group 2, to determine delayed immunogenicity). Serum concentrations of anti-PA mAb antibodies were determined using a sandwich type ELISA (SOP 01PAM-AB-21-1966).

Table 2. Toxicokinetic Analysis of Blood

Route	Blood collection parameters for TK analysis
SC	48 hours after each dose on days 1, 13, and 25; immediately prior to dosing on days 13 and 25; and on days 37, 50, 69.
IV	15 minutes after each dose on days 1, 13 and 25; immediately before dosing on days 13 and 25, and on days 37, 50, 69.
IM	Immediately prior to and 48 hours after dosing on day 69.

No satellite groups for recovery or toxicokinetic analysis were included in this study. Toxicokinetic analysis was performed on sample collected from the main study animals.

Study Findings:

All monkeys survived with no test article effect on clinical observations, food consumption, body weights, or clinical pathology attributable to injection with PA mAb by any route of administration. Serum chemistry data (including creatinine kinase and thyroid hormones) and hematology values were generally unremarkable and comparable to control animals.

Histomorphologic findings were limited to minimal, nonspecific changes characteristic of trauma incurred at intramuscular injection sites. Minimal, non-specific findings including microcysts in the thyroid gland and minimal or slight chronic inflammation in the prostate were observed in both treated and control animals and were considered incidental and unrelated to treatment.

Toxicokinetics

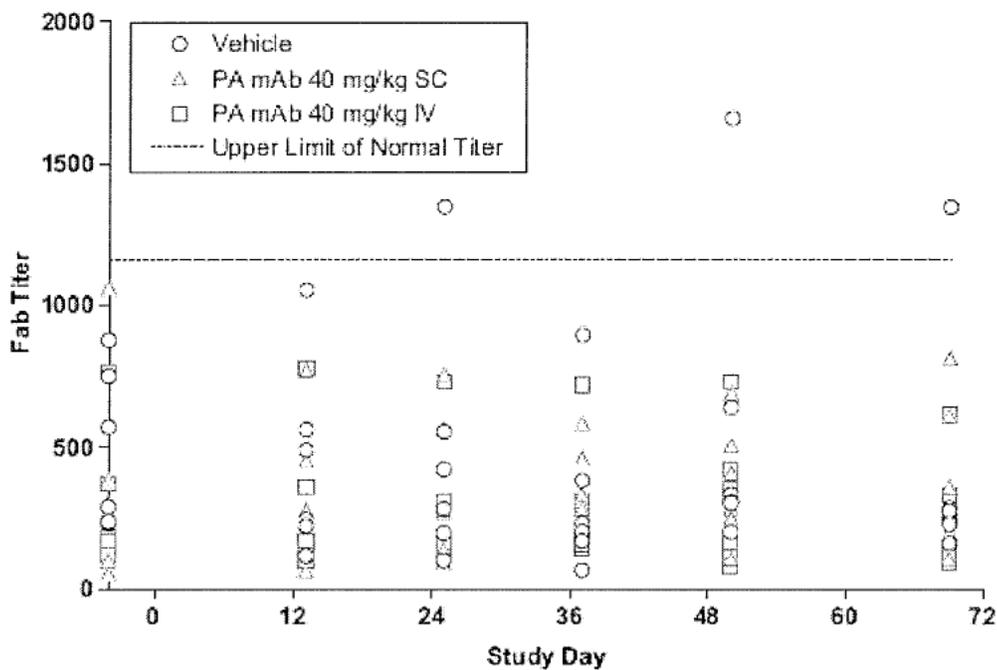
Samples from Study No. 6962-140 were analyzed for toxicokinetics and were reported under Study no. AB50409.INF.0.034. The toxicokinetic profile of raxibacumab in cynomolgus monkeys in Phase 1 showed a rapid increase in serum levels immediately after the I.V. injection, with a 2.5 times greater C_{max} value and only slightly greater AUC_(0-∞) exposure (1.2 times) compared to an S.C. dose, with near equal t_{1/2} of 12-14 days. Subsequent I.M. treatment on day 69 showed similar PK values as the first S.C. dose. AUC_(0-inf) values of 31,600 and 25,700 µg·day/mL and C_{max} values of 1088.8 and 417.8 µg/mL were achieved with IV or SC dose of 40 mg/kg respectively, with no significant serum retention or antibody neutralization after 3 repeat doses 12 days apart.

Toxicokinetic data were also compared with data from a previous single dose study (HGS AB50409.INF.0.017). Dose normalized serum concentrations were similar following single and repeat doses at 1, 10, and 40 mg/kg for both IV and SC administrations, indicating PAMAb is linear across a 40-fold range.

Immunogenicity

Samples from Study No. 6962-140 were analyzed for immunogenicity and reported under Study No. AB50409.INF.0.025. The study showed significant positive immunogenic responses to the Fab portion of the PA mAb (Figure 1) and to the Fc portion of the PA mAb (not shown) in all study groups. However, the applicant reported no positive responses to either the Fab or Fc portions of the antibody in any monkey treated over a 69-day time course because the titers fell below the applicant's established background levels (except for one vehicle control animal).

Figure 1. Individual titer values against the Fab portion of PA mAb in monkeys administered vehicle or PA mAb by the SC or IV routes on Days 1, 13, and 25.



Samples were collected on Days -4, 13, 25, 37, 50, and 69 for immunogenicity evaluation. The horizontal line represents the defined upper limit of normal based on values obtained in 50 normal monkey serum samples.

(Figure taken from study report, pg.9).

All animals of each sex within each dose group showed highly variable individual anti-Fab titer levels. Untreated male and female monkeys at day -4 showed variable anti-Fab antibody titers ranging from 52 to 878 and 290 to 1062 IU, respectively. Anti-Fc antibody titers were less variable in male and female monkeys ranging from 50-65 IU in both sexes. Fab and Fc titers were observed to both increase and decrease with repeated treatment of raxibacumab or vehicle control, with no statistically relevant differences or trends detectable in the data.

In 50 normal, untreated monkey sera, serum titers of ~ 1000 IU and ~ 150 IU were detected against the Fab and Fc portions of the PA mAb respectively. These values were used to define the "upper limit of normal"

to which all individual data analyzed in this study were compared, to determine a positive response. The background level of anti PA mAb antibodies detected in untreated animals is greater than any level of Fab or Fc titer observed in the raxibacumab treated animals. One female monkey (Animal ID. I54968) in the vehicle control group showed a positive response with a Fab titer as high as 1658.67 IU while all other animals had anti-Fab titers below the reported background level.

These results show that raxibacumab administration does not provoke an immunogenic response above the applicant's background levels in healthy cynomolgus monkeys. However, key deficiencies include: 1) high mean serum titers of anti-PA mAb detected in untreated animals, 2) absence of data used to generate positive baseline levels, and 3) possible interactions between the assay and serum raxibacumab and other circulating anti-PA mAb antibodies. These deficiencies cast suspicion on the reliability of the immunogenicity data in this study.

Conclusions

1. Raxibacumab treatment up to 40 mg/kg on multiple days by several routes of exposure (S.C., I.V., and I.M.) showed no significant test article related effects in healthy cynomolgus monkeys. The toxicity data collected in this 120-day toxicity study in healthy cynomolgus monkeys support a NOAEL of 40 mg/kg.
2. Anti-raxibacumab titers in raxibacumab-treated healthy cynomolgus monkeys were variable, were below 1100, and were similar to pre-dosing titer values. However, the quality of the assay used to measure the titers and the quality of the data obtained remain uncertain.

7 Genetic toxicology

No genotoxicity studies have been conducted with raxibacumab.

8 Carcinogenicity

No carcinogenicity studies have been conducted with raxibacumab.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No fertility or early embryonic development studies were conducted with raxibacumab.

9.2 Embryonic Fetal Development

Study title: Intravenous study for effects on embryo-fetal development and toxicokinetics with raxibacumab in rabbits (Study No. 6962-173).

Conducting laboratory:	(b) (4)
Date of study initiation:	5/17/2007
GLP compliance:	Yes (except for gestation day 0 body weights)
QA statement:	Yes. Signed 3/11/08
Drug, lot #, and purity:	Lot#: 71044, Purity: 100%.

Objective: The purpose of this study was to evaluate the effects on maternal health, toxicokinetics, immunogenicity, and embryonic development of raxibacumab when administered by twice by intravenous injections, on Gestation Days 7 and 14, at doses of 40 or 120 mg/kg on gestation days (GD) 7 and 14, in pregnant New Zealand White rabbits.

Key Study Findings

1. No mortality or overt signs of maternal toxicity (clinical observations, food consumption) were observed with raxibacumab I.V. doses up to 120 mg/kg.
2. While there was a significant decrease in body weight gain in treated animals late in gestation (GDs 21 to 24), there was no difference in the mean total weight gain. Additionally, this decreased weight gain did not translate into a reduction in fetal viability or fetal weights.
3. Mean uterine weights, pregnancy rates, numbers of corpora lutea, and implantation sites were comparable between treated and control animals.
4. There were no significant gross necropsy findings in the dams.
5. There were no significant differences in rates of pre-implantation loss and resorptions between treated and control animals.
6. There were no reports of fetal death, no abortions, and no early deliveries.
7. The ratios of male to female offspring and mean fetal weights were comparable to controls.
8. There were no significant reports of external variations in fetuses from dams treated with 40 mg/kg or 120 mg/kg; two skeletal variations (unossified 5th sternebra and presence of 13th rudimentary ribs)

exceeded the historical range but were not considered to be an adverse event.

9. The mean serum raxibacumab levels were proportionally higher for 120 mg/kg relative to 40 mg/kg at all time points.
10. Dose normalized serum levels were similar across doses and groups (3-fold dose range linearity).
11. There was a slight trend toward decreased serum PA mAb levels in rabbits with detectable anti-raxibacumab antibodies.
12. PA mAb concentration-time profiles were similar between pregnant and non-pregnant rabbits.
13. There was a low incidence of anti-raxibacumab antibody response, including one pre-dose animal casting suspicion on the assay reliability.
14. Serum levels of raxibacumab detected in several animals at both doses were sufficiently high to suspect decreased immunogenicity assay sensitivity.
15. The study results support the NOAEL of 120 mg/kg in healthy pregnant New Zealand White rabbits and their fetuses.

Samples from Study No. 6962-173 were analyzed for raxibacumab and reported under Study No. AB50409.INF.038.

Blood for PK analysis was collected at 5 minutes and 11 hours post-dose on GD 7, 9, 14, and 29, and serum was collected by centrifugation. Serum concentrations of PA mAb were determined using an electrochemiluminescence (ECL)-based assay. The raxibacumab concentration-time profiles presented for the pregnant rabbits in this study were similar to those obtained in healthy non-pregnant rabbits in another study (HGS AB50409.INF.0.016).. However, no derived PK values (e.g, C_{max} or AUC) were generated from this study. The PK data support a trend towards lower serum raxibacumab levels in animals with detectable anti-raxibacumab antibodies. However, the number of animals sampled was small and the immunogenicity assay has demonstrated limitations (see next paragraph).

Samples from Study No. 6962-173 were analyzed for immunogenicity and reported under Study No. AB50409.INF.0.037.

The overall incidence of anti-raxibacumab antibody response was low as only 5/138 samples were confirmed to be positive. However, one of the confirmed positives was from a pre-dose sample from an animal (F65974) in the 120 mg/kg PK study group, which casts doubt on the reliability of the assay. Additionally, one animal from the 40 mg/kg PK study group and 11 animals from the 120 mg/kg PK and main study groups had serum raxibacumab levels greater than 150 µg/mL – a concentration shown to decrease assay detection limits 20 fold. Another sample had a high raxibacumab concentration (1318.56 µg/mL) that would have reduced the assay's limit of detection to near 0. Of the 11 samples from the 120 mg/kg group that exceeded the 150 µg raxibacumab/mL limit, 7 were negative for anti-raxibacumab antibodies, 4 were potentially positive and only one of those was confirmed positive. These results indicate that a significant percentage of the high dose samples (11/23) contained sufficient raxibacumab to substantially reduce the performance of the

immunogenicity assay. The applicant stated that anti-raxibacumab antibody may affect raxibacumab PK, but the exposure (although apparently attenuated in some animals) was maintained throughout the study for anti-raxibacumab positive animals.

9.3 Prenatal and postnatal development

No prenatal and postnatal development studies were performed with raxibacumab.

10 Special toxicology studies

No special toxicology studies were performed with raxibacumab.

11 Integrated summary and safety evaluation

There were no significant toxicologic observations in the submitted toxicology studies of raxibacumab in healthy animals. The NOAEL values obtained in both studies were the high doses tested; i.e., 40 mg/kg in healthy cynomolgus monkeys and 120 mg/kg (3 times the clinical dose) in an embryo-fetal development study in pregnant New Zealand White rabbits. Based on comparisons of AUC in monkey and human, there is an approximately 2-fold safety margin; based on comparisons of C_{max} , there is a less than 2-fold safety margin. Based on comparisons of C_{max} in rabbits and humans (AUCs were not generated in the rabbits), there is a 2- to 4-fold safety margin.

Tissue cross-reactivity studies with raxibacumab show significant cross-reactive binding only to the thyroid of both non-human primates and human donor tissues; however the significance of this finding remains unknown.

Human safety studies of raxibacumab did not reveal any findings of sufficient concern to offset the significant potential shown for efficacy as demonstrated in increased survival of diseased animals.

Pivotal efficacy studies submitted to the BLA conducted under the "Animal Rule" clearly demonstrated a survival benefit of raxibacumab treatment in anthrax infected rabbits compared to placebo (0/17 placebo rabbits, 5/18 20 mg/kg in rabbits, and 8/18 40 mg/kg in rabbits). Animals euthanized or found dead showed similar pathologic findings in both treatment and placebo animals, with a notable exception of CNS tissues. Brain pathology, particularly meningitis, was observed in 4/16 of the placebo group, 12/12 in the 20 mg/kg group, and 8/11 of the 40 mg/kg group. Increased incidence and severity of findings in the brain (inflammation, hemorrhage, and necrosis) were greater with raxibacumab treatment compared to placebo. Additionally, efficacy data appear to suggest a trend

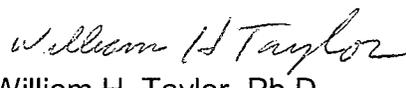
for longer survival time in non-surviving raxibacumab treated animals compared to placebo animals (all of which died), and animals that showed inflammation, necrosis, and/or cerebrovascular hemorrhage appear to have had a prolonged disease course. However comparisons of the time of death between treatment groups, particularly between euthanized moribund animals and animals found dead are difficult to interpret.

Similarly, clear survival benefit was shown in raxibacumab treated cynomolgus monkeys (0/12 placebo, 7/14 animals in the 20 mg/kg group, 9/14 animals in the 40 mg/kg group). Once again, CNS was the only organ afflicted with more severe pathologic findings in raxibacumab versus placebo group. CNS pathology in the brain and meninges was seen in 3/12 placebo group, 6/7 of the 20 mg/kg group, and 3/5 of the 40 mg/kg group. Dose dependent changes in the incidence and severity of the brain lesions were mirrored by more widespread bacterial infiltration throughout brain tissue, originally confined within blood vessels and perivascular space in placebo animals. Like in rabbits, a "delayed" death in animals that succumbed to the anthrax infection corresponded well with increased inflammation, hemorrhage, and necrosis observed in this tissue. However comparisons of the time of death between treatment groups, particularly between euthanized moribund animals and animals found dead were again difficult to interpret.

The etiology for the greater adverse CNS effects observed in raxibacumab treatment arms is unknown. CNS pathology is a common observation and complication in the pathophysiology of anthrax disease. The applicant hypothesized originally that animals in the placebo group died more quickly than animals in the raxibacumab treatment groups, suggesting that CNS pathology was a late appearing aspect of anthrax infection, and only animals that survive sufficiently long will exhibit this pathology. After careful analysis of the data, particularly the "time of death", these data appear not to support this hypothesis. Additionally, among the surviving monkeys in the raxibacumab treatment groups, no residual neurological symptoms were observed in general behavior.

Results of the placebo controlled animal studies appear to confirm a "superior" treatment benefit of intravenous raxibacumab over placebo alone in preventing anthrax-induced lethality. Although the CNS findings are concerning, the benefits of raxibacumab treatment in combination with antibiotics most likely will exceed any risk of CNS effects that may develop in humans. Any follow-up studies that may be recommended to further investigate the CNS findings in the various animal models of anthrax disease will most likely be addressed by clinicians under the "Animal Rule".

 10/19/09
Terry J. Miller, Ph.D.
Pharmacology/Toxicology Reviewer

 10/19/09
William H. Taylor, Ph.D.
Pharmacology/Toxicology Supervisor

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125,349

Applicant: Human Genome
Sciences, Inc.

Stamp Date: 5/14/09

Drug Name: raxibacumab
(Abthrax, PA mAb)

NDA/BLA Type: original

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	NA		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125349

Applicant: HGS

Stamp Date: 5/13/2009

Drug Name: Raxibacumab

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			x	Animal studies
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

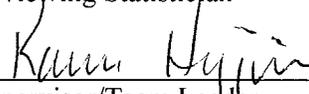
IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? x

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.		x		adjustment for multiplicity not applied
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	No interim analyses performed
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		x		
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			x	No dropouts

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

	6/10/2009
_____ Reviewing Statistician	_____ Date
	6/19/09
_____ Supervisor/Team Leader	_____ Date

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			<i>Pending discussions with CMC.</i>
11	Has the applicant addressed any abuse potential issues in the submission?	x		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	NA		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes X

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. *Considering additional requests.*

	<i>6/10/2009</i>
_____ Reviewing Pharmacologist	Date
<i>William H Taylor</i>	<i>6/10/2009</i>
_____ Team Leader/Supervisor	Date