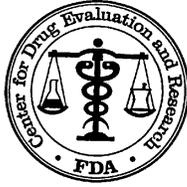


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125349Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ANIMAL EFFICACY AND SAFETY STUDIES

NDA/BLA #: 125349
Supplement #: 0025
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Indication(s): Treatment of inhalational anthrax caused by *Bacillus anthracis*
Applicant: Human Genome Sciences, Inc
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1 EXECUTIVE SUMMARY

This Biological Licensing Application (BLA) resubmission contains two animal studies, Study 1141-CG920871 and Study 1103-G923704, conducted by the Human Genome Sciences (HGS) to evaluate the efficacy and safety of raxibacumab (ABthrax, PA mAb) for the treatment of subjects with known or suspected exposure to *Bacillus anthracis*.

Study 1141-CG920871 tested the therapeutic efficacy of a single IV dose of 40 mg/kg raxibacumab when administered with 50 mg/kg levofloxacin once daily for 3 days in anthrax spore challenged rabbits. Treatment was initiated at about 84 hours post spore challenge in order to approximate a survival rate with antibiotic more similar to that observed during the anthrax attacks in humans in 2001 (~55%). At 28 days after the last levofloxacin dose, the survival rates were 32/39 (82.05%) in the raxibacumab plus levofloxacin combination group and 24/37 (64.86%) in the levofloxacin alone group. A single IV dose of 40 mg/kg raxibacumab given in combination with levofloxacin resulted in 17% (P-value=0.0874) improvement in survival over levofloxacin monotherapy. This study was not powered to produce a statistically significant ($p < 0.05$) result with an absolute difference in survival rate of 17%. A trial with 80% power to detect a statistically significant result with the 17% difference seen in the current study would require 116 animals per group to be treated (232 animals). With only 42% of the animals estimated to be alive at 84 hours post challenge, the total sample size of spore-challenged animals would be 552, with over 300 animals dying before having the opportunity to be treated. A study of this size may not be ethical or feasible. Although a positive, statistically significant 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 after inhalational anthrax exposure.

Study 1103- G923704 evaluated the histopathology in surviving and non-surviving animals after anthrax exposure and therapeutic treatment with placebo or raxibacumab. There was an increased incidence and severity of lesions in placebo-treated animals for all organs (eg, lung, bronchial and mediastinal lymph nodes, and spleen), except the brain. The brains of raxibacumab-treated non-survivors had a greater incidence and severity of lesions (bacteremia, inflammation, hemorrhage, and/or necrosis) than the placebo-treated animals. Within the raxibacumab-treated non-survivors, those with severe brain lesion appeared to have survived longer and died later. However, given the small sample sizes the differences are not statistically significant. Among raxibacumab-treated survivors, all of the microscopic findings were graded as minimal to mild (one animal with mild brain hemorrhage), except 1 instance each of hemosiderosis and of hyperplasia in the spleen which were graded as moderate. These results are consistent with previous raxibacumab monotherapy studies in anthrax-infected rabbits and monkey. It remains to be understood why raxibacumab-treated non-survivors exhibited greater incidence and more severe lesions in their brains compared to placebo-treated animals.

In conclusion, these two studies adequately address the added benefit of raxibacumab when administered concomitantly with antibiotics and its effect on central nervous system (CNS) in animals that survived to 28 days post anthrax spore exposure. However, the mechanism of action by raxibacumab on the brain is still not clear.

2 INTRODUCTION

2.1 Overview

Raxibacumab is a fully human monoclonal antibody developed by the Human Genome Sciences (HGS) for the treatment of subjects with known or suspected exposure to *Bacillus anthracis*. The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. Raxibacumab can be administered alone or in combination with antimicrobials. Due to the lethality of the anthrax infection, clinical trials in humans are not ethically feasible. The original BLA was submitted to the FDA on 14 May 2009 and contained four treatment studies: two studies (Study 682-G005758 in rabbits and Study 724-G005829 in cynomolgus monkeys) tested raxibacumab efficacy versus placebo and the other two (Study 781-G923701 and Study 789-G923702) evaluated the efficacy of raxibacumab plus antimicrobial versus antimicrobial alone. The animals were challenged with aerosolized *B. anthracis* spores at 200xLD₅₀ and treated following elevation of body temperature or a positive result on PA toxemia screen assay.

In raxibacumab monotherapy studies, raxibacumab treatment at 40 mg/kg IV single dose resulted in a statistically significant improvement in survival relative to placebo and raxibacumab-treated animals lived longer compared to placebo. However, an exaggerated inflammatory response in the CNS of the raxibacumab treated non-survivors compared to the placebo non-survivors was found on histopathological examination in the raxibacumab monotherapy animal studies. Additional studies to elucidate raxibacumab effect on CNS in survivors and non-survivors were recommended.

In raxibacumab combination therapy studies, raxibacumab at 40 mg/kg IV single dose was administered concomitantly with levofloxacin in rabbits or ciprofloxacin in monkey. The combination therapy resulted in similar observed efficacy as antimicrobial monotherapy in both rabbits and monkeys. The efficacy of the combination was high, but the efficacy of antimicrobials alone was also high, raising the question whether the animal models adequately represented advanced anthrax disease in humans, where high mortality was observed despite antimicrobial treatment.

Due to several limitations of the efficacy and safety findings in previous animal studies, the FDA issued a Complete Response Letter (CRL) to the sponsor on 14 November 2009. The FDA CRL recommended the sponsor conduct a study in an animal model of inhalational anthrax to demonstrate the added benefit of raxibacumab when used with an antimicrobial drug, for example, by showing that the outcome in the antimicrobial plus raxibacumab arm is higher than the outcome in the antimicrobial alone arm. At a Type A meeting held on 29 January 2010, FDA indicated that the added benefit study should have an antibiotic survival rate more similar to that observed during the anthrax attacks in humans in 2001 (~55%) rather than the survival rate (85-100%) observed when antibiotic was administered as soon as systemic anthrax disease was detected in rabbits and monkeys. FDA also indicated that a human equivalent dose of antibiotic be administered and that the antibiotic should be administered concomitantly with raxibacumab, and further, that the animals had to be symptomatic at the time of treatment for a therapeutic treatment claim.

The FDA CRL also recommended that the sponsor conduct a study to evaluate the effect of raxibacumab on the CNS in an animal model of inhalational anthrax and characterize the clinical course and histological appearance of the CNS in animals that survive and animals that die of anthrax.

The current resubmission dated 15 June 2012 represents the sponsor's effort to address the deficiencies identified during review of the original submission. The sponsor has thus additional studies (Study 1141-CG920871 and Study 1103-G923704) which will be subjects of this statistical review.

2.2 Data Sources

Data sets for the sponsor's Added Benefit Study (Study 1141-CG920871) and CNS Study (Study 1103-G923704) were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows:

\\cbsap58\M\CTD Submissions\STN125349\0025\m5\datasets

The electronic data sets generally represented the data described in the study report.

3 STATISTICAL EVALUATION

One Added Benefit study and one CNS study were conducted to address efficacy and safety issues identified in the FDA complete response letter. This section presents and discusses the details of these two studies.

Added Benefits Study 1141-CG920871 (Study 1141): Added Benefit of Raxibacumab with Levofloxacin vs. Levofloxacin as Post-exposure Treatment in the New Zealand White Rabbit Inhalational Anthrax Model

CNS Study 1103-G923704 (Study 1103): Evaluation of Raxibacumab as a Therapeutic Treatment against Inhalation Anthrax in the New Zealand White Rabbit Model

3.1 Data and Analysis Quality

The submitted data followed FDA guidance and were ready to be reviewed. No extra effort was needed to process the data.

3.2 Added Benefit Study

3.2.1 Study Design

The Added Benefit Study 1141-CG920871 (Figure 1) was a parallel-group, blinded, randomized, placebo-controlled Good Laboratory Practice (GLP) study in healthy male and female New Zealand White (NZW) rabbits to evaluate the added benefit of therapeutic treatment of raxibacumab combined with levofloxacin compared with levofloxacin alone. The primary objective was to evaluate the added benefit against lethality of raxibacumab treatment combined with levofloxacin treatment compared with levofloxacin treatment, when administered at a predetermined time-point following inhalational exposure to *B. anthracis* in NZW rabbits.

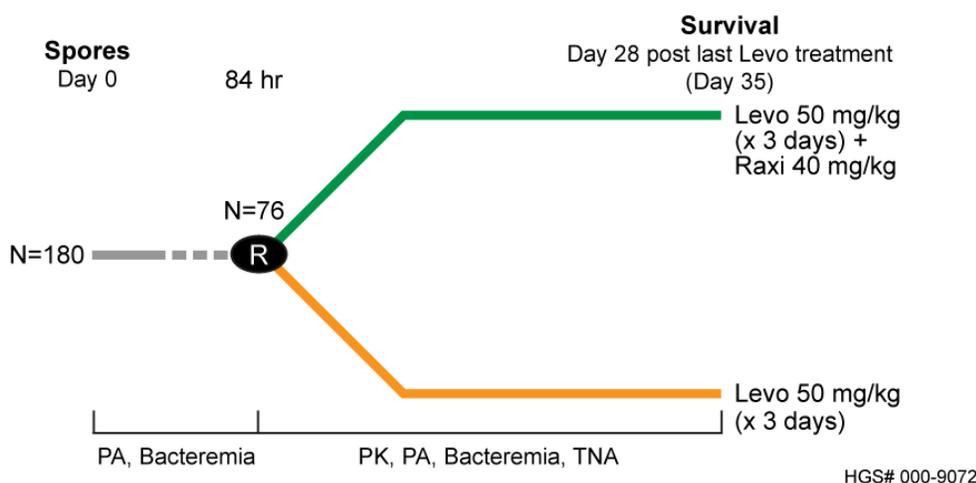


Figure 1 Study 1141-CG920871 Design

A total of 180 NZW rabbits were exposed to 200 x LD₅₀ of *B. anthracis* spores on Day 0. Rabbits that were alive at 84 hours after spore exposure received treatment; first with levofloxacin (50 mg/kg), followed by intravenous (IV) injection of raxibacumab (40 mg/kg) or raxibacumab buffer (0.8 mL/kg). Animals were treated with 3 doses of levofloxacin: initially once at 84 (± 4 of actual exposure time) hours and then every 24 (±1) hours thereafter for another 2 days if animals survived to receive each treatment. Raxibacumab or raxibacumab buffer was administered via the VAP or a marginal ear vein immediately after administration of the first levofloxacin dose. Animal observations and temperature monitoring occurred approximately every 6 hours between the time of spore challenge and 10 days post-challenge. Monitoring was twice daily on all other study days. Animals were observed until 28 days after last dose of levofloxacin and then euthanized.

The study was conducted in 3 phases (January, March, and May 2011) corresponding to 3 separate shipments of 60 rabbits each to the Battelle Biomedical Research Center. Rabbits from each shipment were randomized to 1 of 2 challenge days such that 30 animals were challenged

on each day (A, B, C, D, E, F). The challenge order within each challenge day was also randomized.

Randomization of animals to either the levofloxacin alone group or the raxibacumab plus levofloxacin group consisted of 2 procedures: randomization of dosing vials and assignment of animals to randomized dosing vials in numerical order. Dosing vials were filled by a technician that was not involved in the conduct of the treatments or observations of the animals that received treatment.

Treatments were blinded until the animal in-life portion of the study was complete and the study director signed Protocol Amendment 2 dated 03 June 2011. On 24 June 2011, the treatment assignments were released to the study director, but the study director did not release this information to the study pathologist. The study pathologist remained blinded until the peer review pathologist had completed a peer review of the microscopic slide readings of the study pathologist, indicating all histopathology slides had been read by the primary pathologist in a blinded manner. On 21 November 2011, the study director provided the study pathologist a file unblinding the treatment assignments to allow the study pathologist to complete the pathology narrative which contains treatment group comparisons.

Comment:

The original blinding language in the protocol was written with the assumption that the study director, technicians performing the dosing, technicians assessing the animals, study microbiologists, and study pathologist would be blinded until the study pathologist had completed review of the pathology slides. During the course of the trial, the sponsor determined that the study director could be unblinded following the completion of the in-life phase in order to complete the required documentation to ship the plasma samples to HGS to allow the PK and immunogenicity assays and subsequent analyses to progress. Consequently, the un-blinding language was changed as follows: "The treatment assignments to each vial will be blinded until the animal in-life portion of the study is complete. Once this is complete, the treatment assignments will be released to the study director, but the study director will not release this information to the pathologist. The study pathologist will remain blinded until the pathology narrative is ready for peer review, indicating all histopathology slides have been read by the primary pathologist in a blinded manner." The sponsor stated that there was no impact of this change on the study.

The primary efficacy endpoint of this study was 28-day survival, defined as the proportion of animals that survive to Day 28 after the last dose of levofloxacin treatment. The primary efficacy analysis was the comparison of the 28-day survival between the raxibacumab/levofloxacin combination group and the levofloxacin group using a 2-sided likelihood ratio chi-squared test. The analysis was performed in the Intent-to-Treat (ITT) population, defined as all rabbits that survived to 84 hours and were randomized to dosing vials. The ITT analysis was based on the planned treatment group rather than the actual treatment received and rabbits that died between randomization and the first dose of study agent would be analyzed as an event (death). However, all rabbits received the treatment to which they were assigned and no animals died between randomization and treatment.

Among the 180 rabbits that were challenged with *B. anthracis* spores, 76 (42%) rabbits survived to 84 hours after spore challenge and were treated. There were 37 in the levofloxacin group and 39 in the raxibacumab/levofloxacin combination group. All rabbits received the treatment to which they were assigned.

As shown in Table 2, the treatment groups were comparable with regard to sex, weight, age at randomization, toxemic and bacteremic status. None of the 76 animals was toxemic (with detectable PA) or bacteremic prior to spore challenge. No significant differences were observed between the 2 treatment groups for any of the demographic or baseline characteristics.

Table 2 Demographics and Baseline Characteristics in Study 1141

| | Levo N = 37 | Levo/ Raxi N = 39 | P-value* |
|--------------------------------------|------------------------|------------------------------|-----------------|
| Sex | | | 0.8276 |
| male | 18 (48.6%) | 18 (46.2%) | |
| female | 19 (51.4%) | 21 (53.8%) | |
| Pre challenge weight (kg) | | | 0.7609 |
| Mean ± SD | 3.1 ± 0.2 | 3.1 ± 0.2 | |
| Median | 3.1 | 3.1 | |
| (Min, Max) | (2.8, 3.5) | (2.8, 3.6) | |
| Age at randomization (months) | | | 0.8727 |
| Mean ± SD | 7.4 ± 1.5 | 7.4 ± 1.5 | |
| Median | 6.7 | 6.7 | |
| (Min, Max) | (6.0, 11.1) | (6.0, 10.9) | |
| Toxemic prior to challenge | 0 (0.0%) | 0 (0.0%) | |
| Bacteremic prior to challenge | 0 (0.0%) | 0 (0.0%) | |

*P-value for comparison across 2 treatment groups obtained from likelihood ratio chi-square test for categorical data, and 1-way ANOVA for continuous data.

Table 3 shows that while there is no difference in exposure dose between those died before randomization and those alive to be randomized at 84 hours post challenge, the mean exposure of 173.8 x LD50 in the levofloxacin group is significantly lower than the mean exposure of 197.4 x LD50 in the raxibacumab/levofloxacin combination group (p=0.0291). Animals randomized to raxibacumab/levofloxacin combination arm received higher average LD50 dose compared to those randomized to levofloxacin on all challenge days. A post hoc sensitivity analysis of the primary efficacy endpoint was performed with adjustment for baseline spore dose (see Section 3.2.3.2.3). There is not much difference in LD50 across challenge days for animals randomized in either group or for animals that died before randomization.

Table 3 Extent of Anthrax Exposure (LD₅₀) in Study 1141

| | Animals Randomized to Levo | Animals Randomized to Levo/Raxi | Randomized Animals | Animals Died before Randomization | All Animals |
|---|-----------------------------------|--|---------------------------|--|--------------------|
| N | 37 | 39 | 76 | 104 | 180 |
| Mean ± SD | 174 ± 43 | 197 ± 49 | 186±48 | 189±44 | 188±45 |
| Median | 162 | 198 | 183 | 183 | 183 |
| (Min, Max) | (83, 277) | (105, 348) | (83, 348) | (86, 305) | (83, 348) |
| P-value* | - | 0.0291 | - | 0.6948 | - |
| LD₅₀ by Challenge Day (N) Mean ± SD | | | | | |
| A | (5) 164±40 | (5) 182±20 | (10) 173±31 | (20) 178±38 | (30) 176±35 |
| B | (7) 153±39 | (7) 182±52 | (14) 168±47 | (16) 189±41 | (30) 179±44 |
| C | (7) 197±38 | (7) 208±27 | (14) 202±32 | (16) 213±43 | (30) 209±38 |
| D | (7) 164±40 | (8) 182±40 | (15) 174±40 | (15) 195±34 | (30) 184±37 |
| E | (7) 173±41 | (9) 211±53 | (16) 194±50 | (14) 194±48 | (30) 194±48 |
| F | (4) 199±66 | (3) 234±111 | (7) 214±81 | (23) 173±47 | (30) 182±58 |

* P-values are for the comparison between Levo vs Levo/Raxi and randomized animals vs animals died before randomization.

During the course of this study, all rabbits became toxemic (detectable PA) before treatment initiation. Table 4 shows that the average time to toxemia is 31 hours in the levofloxacin group and 29 hours in the raxibacumab/levofloxacin combination group. All but one rabbit (L34828) became bacteremic before treatment initiation, with mean time to bacteremia being 33 hours and 35 hours in the levofloxacin group and the raxibacumab/levofloxacin combination group, respectively. Rabbit L34828 was negative for bacteremia prior to treatment and at all times subsequent to treatment. There was no difference in the time to treatment initiation between the 2 treatment groups. The average time to treatment initiation was 85.2 hours and 85.8 hours in the levofloxacin group and the raxibacumab/levofloxacin combination group, respectively.

Table 4 Time to detectable PA, bacteremia and treatment initiation in Study 1141

| | Levo | Levo/ Raxi | P-value* |
|--|--------------|-------------------|-----------------|
| Time to toxemia (detectable PA) (hours) | | | 0.9737 |
| N | 37 | 39 | |
| Mean ± SD | 30.6±13.1 | 29.0±7.9 | |
| Median | 26.3 | 26.8 | |
| (Min, Max) | (12.6, 86.9) | (12.1, 47.4) | |
| Time to bacteremia (hours) | | | 0.2047 |
| N | 37 | 38 | |
| Mean ± SD | 32.9±14.1 | 35.2±13.0 | |
| Median | 27.5 | 34.2 | |
| (Min, Max) | (14.7, 86.9) | (20.3, 71.9) | |
| Time to treatment initiation (hours) | | | 0.4744 |
| N | 37 | 39 | |
| Mean ± SD | 85.2±2.1 | 85.8±1.9 | |
| Median | 85.1 | 85.9 | |
| (Min, Max) | (81.8, 89.2) | (82.4, 89.2) | |

*P-value based on Log-rank test for comparison of the 2 treatment groups.

3.2.3 Evaluation of Efficacy

3.2.3.1 Primary Efficacy Analysis

Table 5 presents the primary efficacy results in Study 1141. Twenty out of the 76 animals that received study agent died, 13 in the levofloxacin group and 7 in the levofloxacin/raxibacumab combination group. The survival rate in the raxibacumab/levofloxacin combination group (82.05%) was numerically higher than the levofloxacin group (64.86%), but the difference was not statistically significant ($p = 0.0874$). The odds ratio for the rabbits to survive at 28 days post treatment is 2.48 (95% CI: 0.86, 7.15; P -value=0.0937) in the raxibacumab/levofloxacin group compared with the levofloxacin alone group. The findings are consistent regardless of signs and symptoms at treatment initiation. Following spore challenge, all animals became toxemic so the analysis for toxemic animals is the same as that for the ITT animals. All animals became bacteremic, with exception of one (L34828) in the raxibacumab/levofloxacin group which was negative for bacteremia prior to treatment, or at any time subsequent to treatment. This animal had a positive result for plasma PA at 36, 48, 60, and 72 hours post challenge and prior to treatment, as well as all time points tested through 2 days post the third dose of levofloxacin. This animal was excluded from the analysis for animals bacteremic at or before treatment initiation.

Table 5 Survival at 28 days after last dose of levofloxacin in Study 1141

| Analysis Population | Levo | Levo/Raxi | Difference (Levo/Raxi – Levo) (95% CI)** | P-value* |
|--|----------------|----------------|--|----------|
| ITT animals | 24/37 (64.86%) | 32/39 (82.05%) | 17.19 (-2.35, 36.72) | 0.0874 |
| Bacteremic at or before treatment initiation | 24/37 (64.86%) | 31/38 (81.58%) | 16.71 (-3.00, 36.43) | 0.0998 |

*P-value based on a 2-sided likelihood ratio chi-square test.

**Difference in % survivors with 95% confidence interval (CI) based on normal approximation.

Comment: Note that the 17% difference in survival rates between the 2 treatment groups did not reach statistical significance ($p = 0.0874$). This study was not adequately powered (i.e., 80%) to produce a statistically significant ($p < 0.05$) result with an absolute difference in survival rate of 17%. A trial with 80% power to detect a statistically significant result with the 17% difference seen in the current study would require 116 animals per group to be treated (232 animals). With only 42% of the animals estimated to be alive at 84 hours post challenge, the total sample size of spore-challenged animals would be 552, with over 300 animals dying before having the opportunity to be treated. A study of this size may not be ethical or feasible.

*Comment: Note that in Study 1141, the antibiotic survival rate of 65% is more similar to that observed during the anthrax attacks in humans in 2001 (~55%). This is achieved by initiating treatment approximately 84 hours after aerosol challenge. Two previous studies (Study 781-G923701 and Study 789-G923702) had been conducted to evaluate the efficacy of raxibacumab when administered as a therapeutic agent in combination with antimicrobial against lethality due to *B. anthracis* inhalation. The survival rates were 95% to 100% in Study 781 and Study 789*

when antibiotic was administered as soon as systemic anthrax disease was detected in rabbits and monkeys (median treatment times 27 hours and 39 hours, respectively).

This high rate of survival on the antibiotic alone arm did not allow for the assessment of an added benefit of raxibacumab. The study results showed that there was no significant difference in survival rates between the antimicrobial plus raxibacumab combination arms and antimicrobial alone arms. The table below presents Day 28 survival rates from Study 781-G923701 and Study 789-G923702.

| Previous Study [@] | Anti | Anti/Raxi | Difference (Anti/Raxi - Anti) (95% CI) | P-value |
|-----------------------------|---------------|---------------|--|---------|
| Rabbit 781-G923701 | 19/20 (95.0%) | 16/17 (94.1%) | -0.88 (-23.9, 19.6) | 0.947 |
| Monkey 789-G923702 | 13/13 (100%) | 11/13 (84.6%) | -15.4 (-45.5, 11.4) | 0.222 |

[@] Levofloxacin was used in the rabbit study while Ciprofloxacin was used in the monkey study.

* P-value based on a 2-sided Fisher's exact test

** CIs are exact confidence intervals for comparison between anti/Raxi and antimicrobial.

3.2.3.2 Exploratory Efficacy Analysis

3.2.3.2.1 Survival Time from Spore Challenge or Treatment Initiation

As an exploratory efficacy analysis, time from the initiation of spore challenge to death was compared between the raxibacumab/levofloxacin combination group and the levofloxacin group. For animals that died on study, most deaths occurred within 8 days of spore challenge. The 13 deaths in the levofloxacin group happened between 3.67 days and 8.07 days following spore challenge while the 7 deaths in the levofloxacin/raxibacumab group happened between 3.64 days and 7.52 days following spore challenge. The average time from spore challenge to death is 4.9 days in the levofloxacin group and 4.7 days in the raxibacumab/levofloxacin combination group. No animals died beyond 3 days post the last dose of levofloxacin. According to the log-rank test, the probability of survival was numerically greater in the raxibacumab/levofloxacin combination group than in the levofloxacin group, but the difference was not statistically significant (Figure 2, P-value = 0.1016).

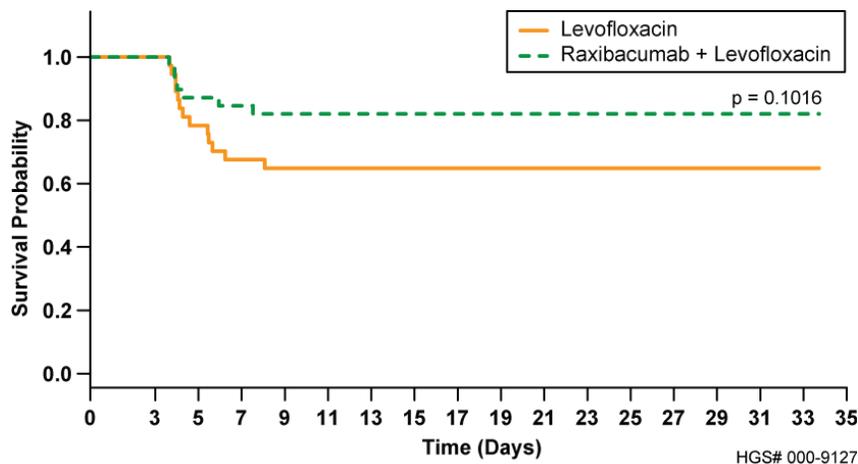


Figure 2 Survival time from spore challenge in Study 1141

Likewise, the survival time from the treatment initiation was compared between the raxibacumab/levofloxacin combination group and the levofloxacin group. The probability of survival was numerically greater in the raxibacumab/levofloxacin combination group than in the levofloxacin group, but the difference was not statistically significant (Figure 3, P-value = 0.1016). Both analyses were performed in the ITT population.

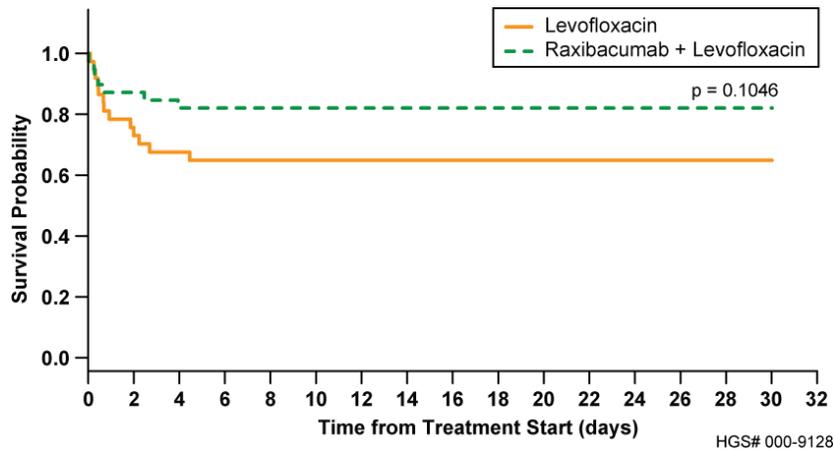


Figure 3 Survival time from treatment in Study 1141

3.2.3.2.2 Analysis by Day of Spore Challenge

Spore challenges were carried out in 3 sets of challenge days (A and B, C and D, E and F). Table 6 presents the proportion of animals alive at randomization and the 28-day survival by challenge day for the 76 animals that were randomized and treated. For animals challenged on Day B, C, and D, the raxibacumab/levofloxacin treatment had a higher 28-day survival rate than levofloxacin treatment, though the difference is not significant. Of note, there were fewer survivors at 84 hours post exposure for animals challenged on Day A and F, but these survivors all survived to Day 28 after being treated by levofloxacin or raxibacumab/levofloxacin combination therapy. Perhaps both the lower survival rates to 84 hours in groups A and F as well as the 100% survival in animals who were then treated in these groups point to a different, hardier type of animal that would be less likely to distinguish treatment effect. An exploratory analysis was conducted by excluding animals challenged on Day A and F to see how that affects the difference between the two treatment arms. In this analysis, the 28-day survival rates become 15/28 (53.6%) in the levofloxacin group and 24/31 (77.4%) in the raxibacumab/levofloxacin combination group, giving a difference of 23.8 and a corresponding p-value of 0.0521. The time from spore challenge to death is not significantly different between groups according to a log-rank test excluding animals challenged on Day A and F (P-value=0.0648).

Table 6 Day 28 Survival Rate by Day of Spore Challenge in Study 1141

| Challenge Day | Animals Alive at Randomization | Levo | Levo/Raxi | Total |
|---------------|--------------------------------|---------------|---------------|---------------|
| A | 10/30 (33.3%) | 5/5 (100%) | 5/5 (100%) | 10/10 (100%) |
| B | 14/30 (46.7%) | 4/7 (57.1%) | 6/7 (85.7%) | 10/14 (71.4%) |
| C | 14/30 (46.7%) | 2/7 (28.6%) | 5/7 (71.4%) | 7/14 (50.0%) |
| D | 15/30 (50.0%) | 4/7 (57.1%) | 7/8 (87.5%) | 11/15 (73.3%) |
| E | 16/30 (53.3%) | 5/7 (71.4%) | 6/9 (66.7%) | 11/16 (68.8%) |
| F | 7/30 (23.3%) | 4/4 (100%) | 3/3 (100%) | 7/7 (100%) |
| Overall | 76/180 (42.2%) | 24/37 (64.9%) | 32/39 (82.1%) | 56/76 (73.7%) |

3.2.3.2.3 Analyses Adjusting for Baseline Spore Level

Due to the difference in baseline anthrax spore exposure (LD50) observed between the 2 treatment groups, various post hoc sensitivity analyses were conducted to evaluate any effect of the LD50 doses on either survival to 84 hours for randomization, 28-day survival rate post treatment, and time to death post treatment.

Among the 180 animals exposed to anthrax spore, 104 died prior to randomization. There is no apparent relationship between LD50 dose level and survival status at 84 hours post challenge (see Table 3). Additionally, there is no association between the LD50 dose and time from initiation of spore challenge to death for the 104 deaths occurring prior to 84 hours (Pearson correlation = 0.133). Within each treatment arm, there is no apparent relationship between LD50 and either survival (P-values from logistic regression is 0.6196 for the levofloxacin group and 0.1352 for the levofloxacin/raxibacumab group) or time to death (Pearson correlation is -0.0735 for the levofloxacin group and -0.252 for the levofloxacin/raxibacumab group). Table 7 presents the 28-day survival rate with respect to quartiles of LD50 doses for the 76 animals that were randomized and treated. There is a clear imbalance by treatment group in the number of animals within the different quartiles of LD50 (as expected given results in Table 3). The 28-day survival appears to be lower in animals receiving greater than 220 LD50; but there is no clear association between range of LD50 and survival.

Table 7 Day 28 Survival Rate by Quartile of Anthras Spore Level (LD50) in Study 1141

| LD50 Dose | Levo | Levo/Raxi | % Difference (Levo/Raxi – Levo) |
|-------------|--------------|---------------|---------------------------------|
| 83 - 148 | 9/13 (69.2%) | 5/6 (83.3%) | 14.1% |
| 148 – 182.5 | 8/12 (66.7%) | 7/7 (100%) | 33.3% |
| 182.5 - 220 | 3/4 (75%) | 13/15 (86.7%) | 11.7% |
| 220 - 348 | 4/8 (50.0%) | 7/11 (63.4%) | 13.6% |

Despite the lack of a clear effect of LD50 on survival, given the imbalance of this baseline variable between treatment arms, a logistic regression model was used to compare the 28-day survival rate between the 2 treatments with adjustment for LD50 level. As expected there was no significant LD50 dose effect on the 28-day survival rate (P-value=0.1557). However, the adjusted odds ratio (OR) for the rabbits to survive at 28 days post treatment was 3.12 (95% CI:

1.002 – 9.715; P-value=0.0495) in the raxibacumab/levofloxacin combination group versus the levofloxacin alone group. In addition, a proportional hazard model was used to compare the survival time from the initiation of spore challenge between the 2 treatment groups. Anthrax spore exposure (LD50) does not have a clear effect on time from spore challenge to death (P-value=0.1686). After adjusting for baseline spore levels, the hazard ratio (HR) for the risk of dying was 0.41 (95% CI: 0.16 – 1.05; P-value=0.0624) in the raxibacumab/levofloxacin combination group compared with the levofloxacin alone group.

3.2.4 Evaluation of Safety

Complete necropsies were performed on all animals, including those that died prior to treatment and those surviving to terminal sacrifices on Day 28 post last dose of levofloxacin. Animals in both groups had clinical and microscopic findings consistent with those reported for rabbits dying from inhalational anthrax.

For animals in both groups that survived to Day 28 post last dose of levofloxacin, there was no evidence of central nervous system (CNS) effects, either clinically or microscopically.

For animals that died following treatment, brain lesions (meningeal and/or parenchymal hemorrhage and necrosis) were observed in 2 levofloxacin-treated animals (L23083 and L34864). There were no brain findings in the raxibacumab/levofloxacin-treated non-survivors. Three of 13 levofloxacin-treated animals (L23083, L34808, L34816) and 1 of 7 raxibacumab plus levofloxacin-treated animal (L33730) had large rod-shaped bacteria present in one or more organs, including the brain, lung, bronchial and mediastinal lymph nodes, and spleen. The remaining animals from both treatment groups lacked visible bacteria in any organs.

Comment: The above is just a brief summary of necropsy and histopathology findings. For details, please see the medical officer's review.

3.3 CNS Study

3.3.1 Study Design

The CNS Study 1103-G923704 was a parallel-group, blinded, randomized, placebo-controlled Good Laboratory Practices (GLP) study in healthy male and female NZW rabbits to evaluate the histopathology in surviving and non-surviving animals after anthrax exposure and therapeutic treatment with placebo or raxibacumab. The primary objective was to assess terminal pathology in both non-surviving and surviving rabbits after anthrax exposure and therapeutic treatment with placebo or raxibacumab. The secondary objective of the study was to evaluate the efficacy of raxibacumab when administered as a therapeutic treatment against lethality due to inhalation exposure to *B. anthracis* in NZW rabbits.

A total of 54 NZW rabbits were randomized by gender and body weight into each of 2 treatment groups (Placebo or Raxibacumab) with 6 animals serving as potential replacements. Rabbits were exposed to 200 x LD₅₀ of *B. anthracis* spores on Day 0. Following aerosol challenge, rabbits received either a single IV administration of 40 mg/kg raxibacumab or 0.8 mL/kg placebo. The treatment trigger was detectable plasma PA or after the results of the 48 hour electrochemiluminescence (ECL) assay were known (regardless of the result).

Animal observations and temperature monitoring occurred approximately every 6 hours between 18 and 168 hours post-challenge. Monitoring was twice daily on all other study days. Surviving animals were euthanized on Day 28 post challenge. If possible, cerebrospinal fluid (CSF) was collected from all rabbits prior to euthanasia or on animals found dead. Complete gross necropsies were conducted on all challenged rabbits, including survivors euthanized at the end of the study. Histopathology was conducted on gross lesions, brain, lungs, spleen, liver, kidney, and if possible, mediastinal and bronchial lymph nodes for all challenged rabbits.

The personnel administering study agent and evaluating the animals were blinded to the study agent treatment assignment. The group assignments were blinded until the animal in-life portion of the study was complete. Then the group assignments were released to the study director, but the study director did not release this information to the pathologist. The pathologist remained blinded until all histopathology slides had been read by the primary pathologist (and documentation was provided to the study director indicating this was complete).

Comment: *The original protocol stated that the study director, technicians performing the dosing, technicians assessing the animals, study microbiologists, and study pathologist would be blinded until the study end. The study started on 7-10-2010. Protocol Amendment 03 (dated 1-17-2011) added the provision that group assignments would be blinded until the animal in-life portion of the study was complete. Once this was complete, the group assignments were to be released to the study director, but the study director was not to release this information to the pathologist. The pathologist was to remain blinded to treatment assignment until all histopathology slides had been read by the primary pathologist and documentation had been provided to the study director indicating this was complete. The sponsor stated that there was no impact of this change on the study.*

The primary efficacy endpoint of this study was 28-day survival, defined as the proportion of animals that survive to Day 28 post-challenge. The primary efficacy analysis was the comparison of the 28-day survival between the placebo control group and the raxibacumab treatment group using a likelihood ratio chi-squared test or Fisher's exact test if more than 20% of the expected contingency table cell counts were less than 5. The analysis was performed in the Intent-to-Treat (ITT) population, defined as all rabbits that were randomized and challenged with anthrax spores. The ITT analysis was based on the intended treatment group rather than the actual treatment received.

Comment: *The protocol also defined a Modified Intent-to-Treat (mITT) population which included all animals that are assigned to randomized dosing vials and treated with at least one dose of study agent. Since all rabbits received their assigned treatment, the mITT population is the same as the ITT population.*

The secondary efficacy endpoint was animal's survival time from the initiation of spore challenge. Survival time was compared between the placebo group and the raxibacumab treatment group using a log-rank test. Survival times for animals surviving past Day 28 were censored at Day 28.

For exploratory analysis, a logistic regression model was used to describe the relationship between the survival probability and inhaled dose (LD50) among animals treated with raxibacumab, and a Cox proportional hazards model was used to describe the relationship between time to death and inhaled dose.

The sample size was chosen based on results observed in previous studies, to allow evaluation of a sufficient number of survivors (approximately 10 survivors). This design also provides 88% power to detect a survival benefit of 42% (10/24) from the raxibacumab-treated group compared with a 4% (1/24) survival rate in the placebo treatment group.

3.3.2 Animal Disposition, Demographic and Baseline Characteristics

Table 8 provides a summary of animal disposition in Study 1103- G923704. A total of 48 rabbits were randomized, 24 in the placebo group and 24 in the raxibacumab group. All rabbits received the treatment to which they were assigned.

Table 8 Animal Disposition in Study 1103

| | Placebo | Raxi | Total |
|---|-----------------|------|-----------------|
| Animals Randomized | 24 | 24 | 48 [@] |
| Animals Challenged and Treated | 24 | 24 | 48 [@] |
| Status at 28 days post Challenge | | | |
| Survived | 0 | 11 | 11 |
| Died | 24 | 13 | 37 |
| Analysis Population | | | |
| ITT | 24 | 24 | 48 |
| Toxemic at treatment initiation | 24 | 23* | 47 |
| Bacteremic at treatment initiation | 22 [†] | 23* | 44 |

[@]L35567 and L35572 were randomized to placebo, but not challenged due to non-functioning vascular access ports, and were replaced by L35557 and L35569 respectively.

*1 animal (L35541) was not toxemic or bacteremic during the entire study, survived.

[†] 2 animals (L35543 and L35563) not bacteremic at treatment initiation

Comment: Note that one animal (L35531) on raxibacumab arm had positive blood culture at 36 hours post exposure, missed a blood sample at the time of treatment administration but had a positive blood culture at 24 and 48 hours after treatment administration. This animal was considered bacteremic at treatment initiation.

As shown in Table 9, the treatment groups were comparable with regard to sex, weight, age at randomization, as well as toxemic or bacteremic status. No significant differences were observed between the 2 treatment groups for any of the demographic or baseline characteristics. Prior to spore challenge, 2 rabbits (L35553 in Raxi group and L35556 in placebo group) had a positive reading for PA (0.587 and 0.542 ng/mL, respectively) close to the lower limit of quantification (0.5ng/mL) in the quantitative ECL assay, but neither animal was positive for PA in the screening PA assay. None of the 48 animals were positive for bacteremia before challenge.

Table 9 Demographics and Baseline Characteristics in Study 1103

| | Placebo N = 24 | Raxibacumab N = 24 | P-value* |
|--------------------------------------|---------------------------|-------------------------------|-----------------|
| Sex | | | 1.0000 |
| male | 13 (54.2%) | 13 (54.2%) | |
| female | 11 (45.8%) | 11 (45.8%) | |
| Pre challenge weight (kg) | | | 0.3749 |
| Mean ± SD | 3.4 ± 0.3 | 3.5 ± 0.3 | |
| Median | 3.3 | 3.4 | |
| (Min, Max) | (2.9, 4.0) | (2.9, 4.2) | |
| Age at randomization (months) | | | |
| Mean ± SD | 7.7 ± 0.0 | 7.7 ± 0.0 | |
| Median | 7.7 | 7.7 | |
| (Min, Max) | (7.7, 7.7) | (7.7, 7.7) | |
| Toxemic prior to challenge | 1 (4.2%) | 1 (4.2%) | 1.0000 |
| Bacteremic prior to challenge | 0 (0.0%) | 0 (0.0%) | |

*P-value for comparison across 2 treatment groups obtained from likelihood ratio chi-square test for categorical data, and 1-way ANOVA for continuous data.

There was no significant difference in exposure dose between the two treatments. Table 10 shows that mean exposures were 137.8 x LD₅₀ and 153.8 x LD₅₀ in the placebo group and the raxibacumab group, respectively. A post hoc sensitivity analysis of the primary efficacy endpoint was performed adjusting for baseline spore dose (Section 3.3.3.3).

Table 10 Extent of Anthrax Exposure (LD₅₀) in Study 1103

| | Placebo | Raxibacumab | P-value |
|-------------------|----------------|--------------------|----------------|
| N | 24 | 24 | 0.1736 |
| Mean ± SD | 137.8 ± 38.9 | 153.8 ± 41.4 | |
| Median | 143.5 | 151.0 | |
| (Min, Max) | (70.0, 196.0) | (83.0, 240.0) | |

All of the placebo-treated animals (24/24, 100%) and 96% (23/24) of the raxibacumab-treated animals were toxemic at the time of treatment initiation. Animal L35560 was the sole animal that was not treated based on a positive ECL result but per evaluation by the Study Director. Table 11 presents the quantitative PA level prior to treatment initiation. The average PA level was 27.3 ng/mL in the placebo group compared to 60.2 ng/mL in the raxibacumab group (P-value=0.0393). A post hoc analysis was performed to evaluate possible relationship among baseline spore dose, quantitative PA prior to treatment, and time to toxemia (Section 3.3.3.3).

Table 11 Quantitative PA (ng/mL) prior to Treatment Initiation in Study 1103

| | Placebo | Raxibacumab | P-value |
|-------------------|----------------|--------------------|----------------|
| N | 24 | 24 | 0.0393 |
| Mean ± SD | 27.3 ± 29.8 | 60.2 ± 70.0 | |
| Median | 15 | 31.1 | |
| (Min, Max) | (3.3, 124.6) | (0.5, 252.8) | |

Table 12 shows that animals in the placebo treatment group were treated approximately 3 hours later than those in the raxibacumab group, on average 32.3 hours versus 28.6 hours after challenge (P-value= 0.0112) . This corresponded to the later time to positive PA (trigger event) for placebo versus raxibacumab-treated animals (on average 27.9 versus 23.9 hours after challenge, respectively; P-value=0.0122). Within Raxibacumab-treated animals, the time to positive PA or bacteremia were similar (about 23 to 24 hours post challenge) across the survivors and non-survivors and their mean time to treatment were 28.4 and 28.7 hours, respectively.

Table 12 Time (hours) to Treatment Trigger and Initiation (hours) post-challenge in Study 1103

| | Placebo | Raxi | P-value |
|---|----------------|--------------|----------------|
| Time to PA(scr) from challenge start | | | 0.0122 |
| N | 24 | 24 | |
| Mean ± SD | 27.9±5.9 | 23.9±5.1 | |
| Median | 26.8 | 22.6 | |
| (Min, Max) | (19.7, 39.3) | (16.3, 34.6) | |
| Time to bacteremia | | | 0.0721 |
| N | 24 | 23 | |
| Mean ± SD | 31.4±9.5 | 24.9±4.8 | |
| Median | 28.6 | 23.0 | |
| (Min, Max) | (21.3, 63.4) | (16.3, 36.7) | |
| Time to treatment initiation | | | 0.0112 |
| N | 24 | 24 | |
| Mean ± SD | 32.3±5.2 | 28.6±4.7 | |
| Median | 31.4 | 27.7 | |
| (Min, Max) | (24.8, 42.6) | (20.7, 38.3) | |

3.3.3 Evaluation of Efficacy

3.3.3.1 Primary Efficacy Analysis

Table 13 presents the primary efficacy results in Study 1103. The survival rate for the raxibacumab-treated group was significantly higher than placebo-treated (P-value < 0.0001). No placebo-treated animals survived to Day 28, and 45.83% (11/24) of raxibacumab-treated animals survived.

Table 13 Survival at 28 days after spore challenge in Study 1103

| Analysis Population | Placebo | Raxi | Difference (Raxi – Placebo) (95% CI) (%)** | P-value* |
|---------------------|--------------|----------------|--|----------|
| ITT animals | 0/24 (0.00%) | 11/24 (45.83%) | 45.83 (25.27, 67.18) | 0.0002 |

*P-values based on a 2-sided Fisher's exact test.

** Difference in % survivors between Raxibacumab vs. placebo with unconditional exact 95% confidence interval.

Comment: The survival benefit observed here replicated those seen in two previous pivotal studies.

| Previous Studies | Placebo | Raxi | Difference (Raxi – Placebo) (95% CI) | P-value |
|---------------------------------|--------------|--------------|--------------------------------------|---------|
| Rabbit 682-G005758 [©] | 0/13 (0.00%) | 6/17 (35.3%) | 35.3 (7.3, 59.6) | 0.0237 |
| Monkey 724-G005829 | 0/10 (0.00%) | 9/13 (69.2%) | 69.2 (31.1, 88.9) | 0.0016 |

[©]Survival measured at Day 14 instead of Day 28 as in Studies 1103 and 724.

Various sensitivity analyses were performed and the results showed consistent survival benefits of raxibacumab treatment. Table 14 presents Day 28 survival rate by signs and symptoms at treatment initiation. All animals were toxemic at treatment initiation with the exception of one animal (L35541) in the raxibacumab group, which was not toxemic or bacteremic during the entire study. This animal was excluded from the analysis for animals toxemic at treatment initiation. All but 3 animals (L35541 in raxibacumab group; L35543 and L35563 in placebo group) were positive for bacteremia at treatment initiation. These 3 animals were excluded from both the analysis for animals bacteremic at treatment initiation and the analysis for animals toxemic and bacteremic at treatment initiation. Animal L35531 on raxibacumab arm had positive blood culture at 36 hours post exposure, missed a blood sample at the time of treatment administration but had positive blood culture at 24 and 48 hours after treatment administration. This animal was considered as being bacteremic at treatment initiation. Furthermore, Animal L35568 had signs and symptoms often seen in unchallenged animals and had no positive brain culture for anthrax. The sponsor suggested that this animal did not die of anthrax.

Table 14 Survival at 28 days by signs and symptoms at treatment initiation in Study 1103

| | Placebo | Raxi | Difference (Raxi – Placebo) (95% CI) (%)** | P- value* |
|--|-------------|----------------|--|--------------|
| Toxemic animals | 0/24 (0.0%) | 10/23 (43.48%) | 43.48 (22.86, 65.51) | 0.0002 |
| Bacteremic animals | 0/22 (0.0%) | 10/23 (43.48%) | 43.48 (22.52, 65.51) | 0.0006 |
| Toxemic and bacteremic animals | 0/22 (0.0%) | 10/23 (43.48%) | 43.48 (22.52, 65.51) | 0.0006 |
| Toxemic or bacteremic animals | 0/24 (0.0%) | 10/23 (43.48%) | 43.48 (22.86, 65.51) | 0.0002 |
| Animals excluding non-anthrax death | 0/24 (0.0%) | 11/23 (47.8%) | 47.8 (26.64, 69.41) | <0.0001 |

* P-values based on a 2-sided Fisher’s exact test.

** Difference in % survivors between Raxibacumab vs. placebo with unconditional exact 95% confidence interval.

3.3.3.2 Secondary Efficacy Analysis

A secondary efficacy analysis of survival time from spore challenge to death showed that raxibacumab-treated animals survived significantly longer than placebo-treated animals. No animals treated with placebo survived to Day 7 and the 13 deaths in the raxibacumab group occurred between 1.69 days and 10.99 days following spore challenge. The median time from challenge to death of placebo-treated animals was 3.3 days versus 8.0 days in the raxibacumab-treated group (P-value < 0.0001).

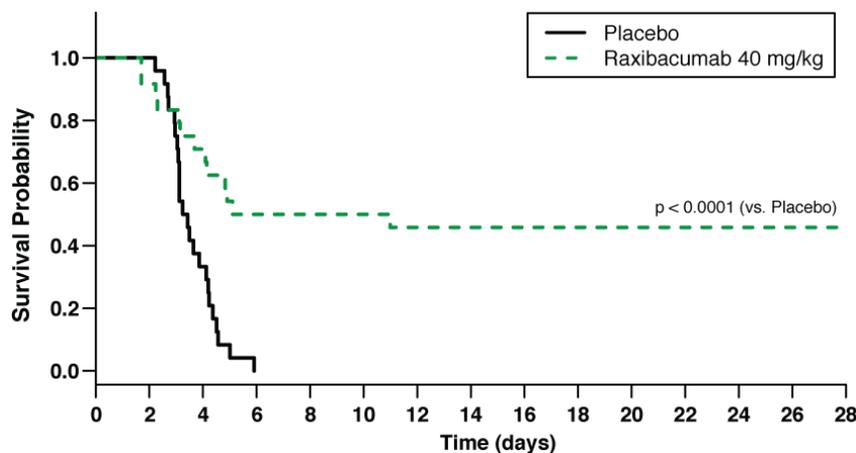


Figure 4 Survival time in Study 1103

P-value obtained from a log-rank test comparing survival time between placebo and raxibacumab-treated groups.

3.3.3.3 Exploratory Analysis

An exploratory analysis was conducted to evaluate the association between Day 28 survival in raxibacumab-treated animals and the inhaled dose exposure to *B. anthracis* spores. This analysis showed that there was no significant association between inhaled dose and survival (P-value = 0.3208). Animals treated with placebo were excluded from this analysis since none survived.

In addition, an analysis explored the association between time from spore challenge to death and inhaled dose exposure (LD50), including all placebo-treated and raxibacumab-treated animals. The analysis showed that there was no significant association between inhaled spore dose and the time to death. After adjusting for baseline spore levels, the hazard ratio for the risk of dying was 0.26 (95% CI: 0.12 – 0.58; P-value=0.0009) in the raxibacumab group compared with the placebo group.

Since animals in the placebo group had a later time to positive PA and were treated approximately 3 hours later than those in the raxibacumab group, a post hoc analysis was conducted to explore possible relationship among the inhaled dose exposure LD50, quantitative PA prior to treatment, and time to positive PA. There was no apparent relationship between LD50 dose and quantitative PA level prior to treatment (Pearson correlation = 0.0298), or between LD50 and time to positive PA (Pearson correlation = -0.198). Within the placebo group, there appeared to be a negative correlation between LD50 dose and time to positive PA, meaning the higher the dose the shorter time to positive PA (Pearson correlation = -0.594; P-value = 0.002). This is also similar to what was seen with the raxibacumab treated animal having a higher exposure and a shorter time to positive PA. However, the correlation between LD50 dose and time to positive PA was not statistically significant for animals in the raxibacumab group (Pearson correlation = 0.352; P-value = 0.091).

3.3.4 Evaluation of Safety

Complete necropsies were performed on animals found dead or euthanized, including those surviving to terminal sacrifice on Day 28. Gross observations of all animals showed that more remarkable findings were observed in the placebo-treated animals than raxibacumab-treated non-survivors, but the difference was not statistically significant (Table 15). There were 3 remarkable incidences in the brains (L35569 and L35575 in placebo group, and L35548 in raxibacumab death group) of animals that died on study. Among the 11 surviving animals (all raxibacumab-treated), two animals had remarkable gross findings (L35530 with mild enlargement of a mediastinal lymph node, and L35532 with a mass in the kidney on Day 28) but none of these findings was in brain.

Table 15 Gross observations in Study 1103

| | Placebo N = 24 | Raxi Deaths N = 13 | Raxi Survivors N=11 |
|--------------------------------|---------------------------|-------------------------------|--------------------------------|
| Remarkable findings | 11 (45.8%) | 4 (30.8%) | 2 (19.2%) |
| Non remarkable findings | 13 (54.2%) | 9 (69.2%) | 9 (81.8%) |

Table 16 presents the number of animals with microscopic observations by organ type. The raxibacumab-treated animals are separated out by those who died and those who survived to 28 days. There are higher incidences of inflammation and necrosis in the brains of raxibacumab-treated non-survivors than placebo-treated animal. The difference are statistically significant; for brain inflammation there were 8/24 (33.4%) raxibacumab-treated animals compared to 1/24 (4.2%) placebo-treated animals (P-value=0.0133) and for brain necrosis there were 8/24 (33.4%) raxibacumab-treated animals compared to 0/24 (0.0%) placebo-treated animals (P-value=0.002). In the placebo treatment group in which all rabbits died before study termination, bacteremia extravascular in all organ systems, except the brain, was more commonly observed than they were in raxibacumab-treated non-survivors. Hemorrhage and inflammation occurred more frequently in the lymph nodes of placebo-treated animals.

Among raxibacumab-treated survivors, all of the microscopic findings were graded as minimal to mild, except 1 instance each of hemosiderosis and of hyperplasia in the spleen which were graded as moderate. Note that one animal in the raxibacumab survivor group (L35566) had brain hemorrhage/meninges which was graded as mild (severity level=2).

Table 16 Number of animals with microscopic observations by Organ in Study 1103

| | Placebo N=24 | Raxi Deaths N=13 | Raxi Survivors N=11 |
|-------------------------|-----------------|---------------------|------------------------|
| Bacteria | | | |
| Brain | 9 (37.5%) | 7 (53.9%) | 0 (0.0%) |
| Kidney | 20 (83.3%) | 2 (15.4%) | 0 (0.0%) |
| Liver | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lung | 21 (87.5%) | 2 (15.4%) | 0 (0.0%) |
| Lymph Node, Bronchial | 22 (91.7%) | 3 (23.1%) | 0 (0.0%) |
| Lymph Node, Mediastinal | 24 (100.0%) | 4 (30.8%) | 0 (0.0%) |
| Spleen | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hemorrhage | | | |
| Brain | 11 (45.8%) | 10 (76.9%) | 1 (9.1%) |
| Kidney | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Liver | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lung | 5 (20.8%) | 3 (23.1%) | 0 (0.0%) |
| Lymph Node, Bronchial | 21 (87.5%) | 8 (61.5%) | 1 (9.1%) |
| Lymph Node, Mediastinal | 22 (91.7%) | 9 (69.2%) | 1 (9.1%) |
| Spleen | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Inflammation | | | |
| Brain | 1 (4.2%) | 8 (61.5%) | 0 (0.0%) |
| Kidney | 2 (8.3%) | 2 (15.4%) | 1 (9.1%) |
| Liver | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lung | 14 (58.3%) | 5 (38.5%) | 3 (27.3%) |
| Lymph Node, Bronchial | 21 (87.5%) | 6 (46.2%) | 5 (45.5%) |
| Lymph Node, Mediastinal | 1 (4.2%) | 1 (7.7%) | 0 (0.0%) |
| Spleen | 10 (41.7%) | 6 (46.2%) | 8 (72.7%) |
| Necrosis | | | |
| Brain | 0 (0.0%) | 7 (53.9%) | 1 (9.1%) |
| Kidney | 1 (4.2%) | 0 (0.0%) | 0 (0.0%) |
| Liver | 8 (33.3%) | 8 (61.5%) | 0 (0.0%) |
| Lung | 1 (4.2%) | 2 (15.4%) | 0 (0.0%) |
| Lymph Node, Bronchial | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lymph Node, Mediastinal | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Spleen | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Comment: Note in the pivotal rabbit study (682-G005758), among all necropsized animals there were higher rates of brain pathology in the raxibacumab treatment groups than in the placebo group.

| Study 682-G005758 (all necropsized animals) | Placebo N = 16 | Raxi death 20 mg/kg N=12 | Raxi death 40 mg/kg N = 11 |
|--|-------------------|--------------------------------|----------------------------------|
| Animals with brain pathology | 5 (31.3%) | 12 (100%) | 8 (72.7%) |
| p-value(vs Placebo) | - | 0.0003 | 0.0542 |

Table 17 shows the incidence of severe brain findings with severity level graded as moderate/marked or with acute neurodegeneration. A total of 9 animals had either high bacteria level, or severe hemorrhage or severe inflammation in their brains, 1 in the placebo-treated group and 8 in the raxibacumab-treated non-survivors group. Specifically, Animal L35576 had bacteria extravascular (grade=3) and severe hemorrhage and was the only animal in the placebo group that was graded with severe brain lesion. Among the 13 raxibacumab-treated non-survivors, 4 animals (L35553, L35561, L35562, L35582) had high bacteria level in the brain (graded=3), 2 animals (L35554 and L35560) had severe hemorrhage, and 5 animals (L35548, L35554 and L35560, L35561, L35575) had severe inflammation in the brain. When bacteria extravascular, severe hemorrhage, severe inflammation, and acute neurodegeneration with FluoroJade-C are considered for severe brain lesion, the incidence of animals with severe lesion are 1/24 (4.2%), 5/13 (38.5%), and 1/11 (9.1%) in placebo, raxibacumab deaths, and raxibacumab survivors, respectively. Note the one animal in the raxibacumab survivor group (L35581) who was counted as having a severe brain lesion had it due to acute neurodegeneration.

Table 17 Incidence of severe brain findings in Study 1103

| | Placebo N = 24 | Raxi Deaths N = 13 | Raxi Survivors N=11 |
|---|---------------------------|-----------------------------------|------------------------------------|
| Animals with high bacteria level, or severe hemorrhage or severe inflammation | 1 (4.2%) | 8 (61.5%) | 0 (0.0%) |
| Animals with high Bacteria level | 1 (4.2%) | 4 (30.8%) | 0 (0.0%) |
| Animals with Severe Hemorrhage | 1 (4.2%) | 2 (15.4%) | 0 (0.0%) |
| Animals with Severe Inflammation | 0 (0.0%) | 5 (38.5%) | 0 (0.0%) |
| Animals with Severe Lesion (Hemorrhage or Inflammation or Acute neurodegeneration) | 1 (4.2%) | 5 (38.5%) | 1 (9.1%) |

Comment: Note in the pivotal rabbit study (682-G005758), among all necropsized animals there were higher rates of bacteria meningitis in the raxibacumab treatment groups than in the placebo group. The rates of animals with bacteria meningitis were 9/12 in the raxi 20 mg/kg group (p -value=0.0061) and 7/11 in the raxi 40 mg/kg group (p -value=0.0402) compared to 3/16 in the placebo group, respectively.

| <i>Study 682-G005758 (all necropsized animals)</i> | <i>Placebo N = 16</i> | <i>Raxi death 20 mg/kg N=12</i> | <i>Raxi death 40 mg/kg N = 11</i> |
|--|---------------------------|---|---|
| <i>Animals with bacteria meningitis</i> | <i>3 (18.8%)</i> | <i>9 (75%)</i> | <i>7 (63.6%)</i> |
| <i>p-value (vs Placebo)</i> | <i>-</i> | <i>0.0061</i> | <i>0.0402</i> |

Comment: As in the pivotal rabbit study (682-G005758), the current study showed that there was an increased incidence and severity of lesions in placebo-treated animals for all organs except the brain. With the exception for Animal L35576, the placebo-treated rabbits had minimal or mild inflammation and hemorrhage in their brains. The brains of raxibacumab-treated non-survivors had a greater incidence and severity of brain lesions than the placebo-treated animals.

The raxibacumab-treated survivors did not exhibit clinical sequelae of adverse CNS effects, brain pathology, or the presence of bacteria or PA in the brain at sacrifice (Day 28).

Figure 5 and Table 18 present survival time in hours for animals that died prior to scheduled termination. There is no significant difference between placebo-treated and raxibacumab-treated animals, with an average time from spore challenge to death of 86 hours in placebo animals and 96 hours in the raxibacumab group. Excluding Animal L35568 which might not have died of anthrax, the average time from spore challenge to death in the raxibacumab group became 82 hours which is still not much different from that in the placebo group.

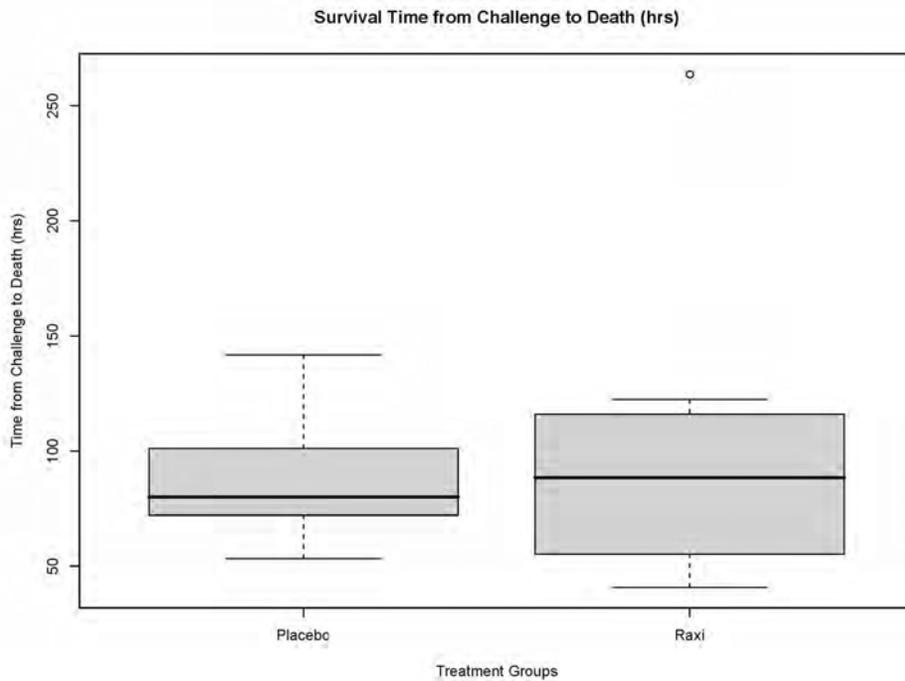


Figure 5 Survival time in placebo animals and raxibacumab-treated non-survivors in Study 1103

Table 18 Time (hours) from Challenge to Death in Non-survivors in Study 1103

| | Placebo | Raxi | P-value |
|----------------------------|---------------|---------------|---------|
| All deaths | | | 0.912 |
| N | 24 | 13 | |
| Mean ± SD | 86.2 ± 21.0 | 95.9 ± 57.9 | |
| Median | 80.1 | 88.5 | |
| (Min, Max) | (53.3, 141.8) | (40.7, 263.7) | |
| All Anthrax deaths* | | | 0.8028 |
| N | 24 | 12 | |
| Mean ± SD | 86.2 ± 21.0 | 81.9 ± 29.7 | |
| Median | 80.1 | 80.1 | |
| (Min, Max) | (53.3, 141.8) | (40.7, 122.4) | |

* Excluding L35568 which might not have died of anthrax per sponsor. L35568 did not have bacteria extravascular or severe brain lesion.

Comment: *The difference in CNS incidence and severity between placebo and treatment cannot be explained by the time to death since animals in the two groups died at similar times.*

Figures 6 and 7 display time from anthrax exposure to death in relation to bacteria level, severity of lesion, hemorrhage, and inflammation in the brain of non-surviving animals for each treatment group. All animals that died prior to scheduled termination (except L35568 which did not die of anthrax) were plotted, with one circle indicating one animal. Within the raxibacumab non-survivors, there appears to be a relationship between time course to death and histopathology findings. Animals with high levels of bacteria accrued in the brain or with more severe brain lesions had a longer survival time than those without severe observations; however, given the small sample sizes the differences are not statistically significant.

Comment: *Note there is no evidence that supports a claim by the sponsor at the time of the first submission of the BLA that the higher proportion of raxi-treated animals with CNS involvement compared to placebo is due to longer survival time of these animals. However, it might be hypothesized that among the raxibacumab deaths, those dying later have a higher likelihood of CNS involvement.*

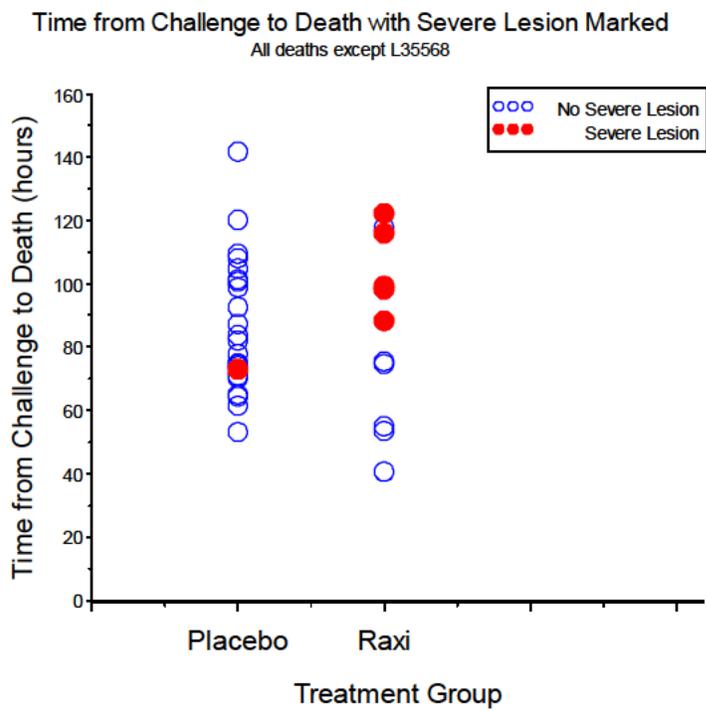
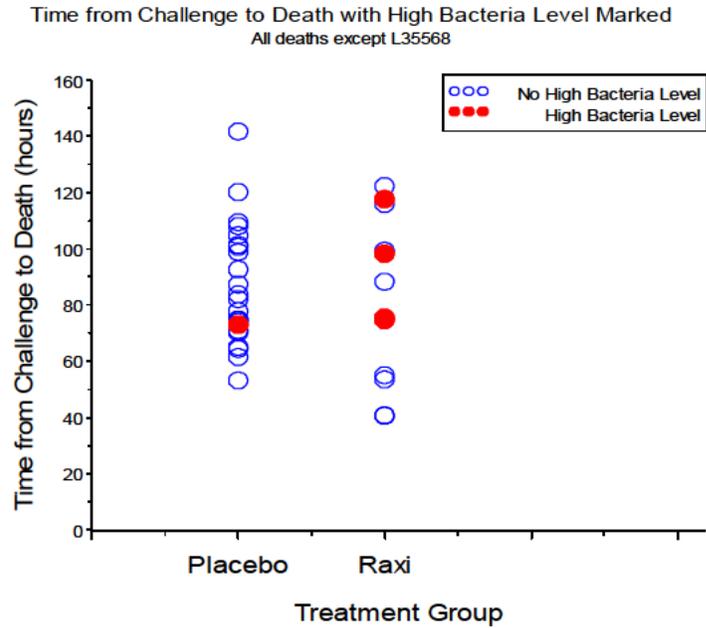


Figure 6 Time from anthrax exposure to death in relation to bacteria level and brain lesion in Study 1103

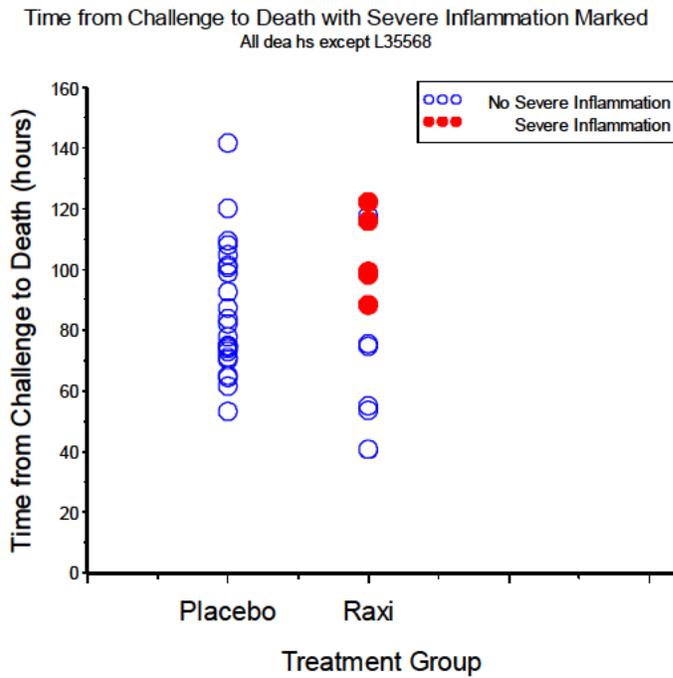
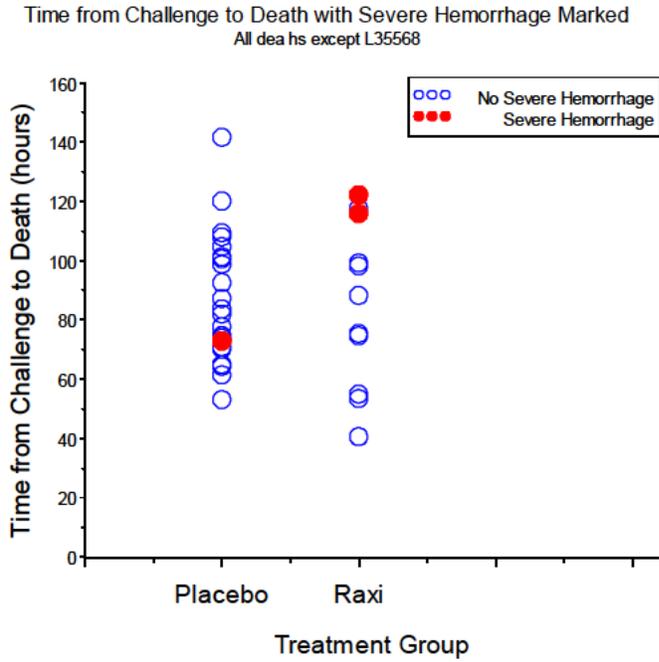


Figure 7 Time from anthrax exposure to death in relation to brain hemorrhage and inflammation in Study 1103

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Race is not applicable for the current studies. Given that there was very little variation in age of the rabbits in both studies, (in Study 1141 rabbits ages ranged from 6.0 – 11.1 months and in Study 1103 rabbits were all 7.7 months), age was not a factor to consider in the subgroup analyses.

Table 19 presents survival rates according to the sex of the rabbits in each treatment group for the added benefit study 1141. The survival rates were comparable between male and female rabbits within the same treatment group. The treatment effect of raxibacumab over levofloxacin is 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%).

Table 19 Survival Rate by Sex in Study 1141 Number of Survivors/Total Animals, n/N (%)

| | Levo | Levo/Raxi | P-value |
|---------------|---------------|------------------|----------------|
| Male | 11/18 (61.1%) | 15/18 (83.3%) | 0.2642 |
| Female | 13/19 (68.4%) | 17/21 (81.0%) | 0.4727 |

Comment: The findings are consistent with results from previous studies as below.

| <i>Previous Study[®]</i> | <i>Antimicrobial</i> | <i>Antimicrobial/Raxi</i> |
|-----------------------------------|----------------------|---------------------------|
| <i>Rabbit 781-G923701</i> | | |
| Male | 9/10 (90.0%) | 8/8 (100%) |
| Female | 10/10 (100%) | 8/9 (88.9%) |
| <i>Monkey 789-G923702</i> | | |
| Male | 7/7 (100%) | 4/6 (66.7%) |
| Female | 6/6 (100%) | 7/7(100%) |

[®]Levofloxacin was used in the rabbit Study 781 while Ciprofloxacin was used in the monkey Study 789.

In Study 1103, (Table 20) all 13 male and 11 female rabbits in the placebo group died. In the raxibacumab group, the survival rate for male rabbits was significantly lower than the female animals. The observed overall survival benefit of raxibacumab treatment was driven by female animals. Of note, compared to male animals in the raxibacumab group, male animals in the placebo group had significantly longer time from spore challenge to positive PA or bacteremia and were treated significantly later. There is not much difference in female animals between treatments in terms of time from challenge to positive PA or bacteremia and treatment were initiated at about the same time (Table 21).

Table 20 Survival Rate by Sex in Study 1103 Number of Survivors/Total Animals, n/N (%)

| | Placebo | Raxi | P-value* |
|---|-------------|--------------|----------|
| ITT | | | |
| Male | 0/13 (0.0%) | 2/13 (15.4%) | 0.4800 |
| Female | 0/11 (0.0) | 9/11 (81.8%) | 0.0002 |
| Animals toxemic at treatment initiation | | | |
| Male | 0/13 (0.0%) | 2/13 (15.4%) | 0.4800 |
| Female | 0/11 (0.0) | 8/10 (80.0%) | 0.0002 |
| Animals bacteremic at treatment initiation | | | |
| Male | 0/12 (0.0%) | 2/13 (15.4%) | 0.4800 |
| Female | 0/10 (0.0) | 8/10 (80.0%) | 0.0007 |
| ITT excluding non-anthrax death (L35568) | | | |
| Male | 0/13 (0.0%) | 2/12 (16.7%) | 0.2200 |
| Female | 0/11 (0.0) | 9/11 (81.8%) | 0.0002 |

* P-values based on a 2-sided Fisher's exact test.

Comment: Note that in previous pivotal studies, raxibacumab 40 mg/kg treatment led to a higher survival rate in male animals than female animals based on the sponsor's ITT populations.

| Previous Study | Placebo | Raxi 20 mg/kg | Raxi 40mg/kg |
|---------------------------|------------|---------------|--------------|
| Rabbit 682-G005758 | | | |
| Male | 0/9 (0.0%) | 2/10 (20.0%) | 6/10 (60.0%) |
| Female | 0/8 (0.0%) | 3/8 (37.5%) | 2/8 (25.0%) |
| Monkey 724-G005829 | | | |
| Male | 0/6 (0.0%) | 3/7 (42.9%) | 5/7 (71.4%) |
| Female | 0/6 (0.0%) | 4/7 (57.1%) | 4/7 (57.1%) |

Table 21 Anthrax exposure and time to signs and treatment by sex in Study 1103

| | Placebo | | Raxi | | P-value* |
|---|---------|------------|------|------------|----------|
| | N | | N | | |
| LD50 | | | | | |
| Male | 13 | 139.0±44.0 | 13 | 155.2±41.5 | 0.3432 |
| Female | 11 | 136.3±34.0 | 11 | 152.1±43.3 | 0.3532 |
| Time to PA(scr) from start of challenge (hours) | | | | | |
| Male | 13 | 29.5±6.5 | 13 | 23.9±4.4 | 0.0158 |
| Female | 11 | 26.0±4.6 | 10 | 23.9±6.1 | 0.4362 |
| Time to Bacteremia from start of challenge (hours) | | | | | |
| Male | 13 | 32.0±10.9 | 13 | 24.9±3.1 | 0.0064 |
| Female | 11 | 30.8±8.1 | 10 | 25.0±6.6 | 0.6330 |
| Time to Treatment from start of challenge (hours) | | | | | |
| Male | 13 | 33.7±5.8 | 13 | 28.7±3.8 | 0.0091 |
| Female | 11 | 30.7±4.2 | 10 | 28.5±5.8 | 0.4588 |

*P-value for comparison across 2 treatment groups obtained from 1-way ANOVA for LD50 and log-rank test for time to positive PA, Bacteremia or Treatment initiation.

Table 22 shows microscopic findings in brain by sex for Study 1103. For either male or female animals, raxibacumab-treated non-survivors had more CNS events than placebo animals. Within the raxibacumab-treated deaths, there is not much difference between males and females in terms of incidence of microscopic findings in brains.

Table 22 Microscopic observations in brains by sex in Study 1103

| | Placebo | Raxi Deaths | Raxi Survivors |
|-------------------------------|--------------|--------------|----------------|
| Bacteria Extravascular | | | |
| Male | 3/13 (23.1%) | 6/11 (54.6%) | 0/2 (0.0%) |
| Female | 6/11 (54.6%) | 1/2 (50.0%) | 0/9 (0.0%) |
| Hemorrhage | | | |
| Male | 6/13 (46.2%) | 8/11 (72.7%) | 1/2 (50.0%) |
| Female | 5/11 (45.5%) | 2/2 (100.0%) | 0/9 (0.0%) |
| Inflammation | | | |
| Male | 1/13 (7.7%) | 7/11 (63.6%) | 0/2 (0.0%) |
| Female | 0/11 (0.0%) | 1/2 (50.0%) | 0/9 (0.0%) |
| Necrosis | | | |
| Male | 0/13 (0.0%) | 5/11 (45.5%) | 1/2 (50.0%) |
| Female | 0/11 (0.0%) | 2/2 (100.0%) | 0/9 (0.0%) |

4.2 Other Special/Subgroup Populations

Analysis of other special/subgroup populations is not applicable.

5 SUMMARY AND CONCLUSIONS

Two animal studies, Study 1141-CG920871 and Study 1103-G923704 have been conducted by the sponsor to evaluate the efficacy and safety of raxibacumab for the treatment of subjects with known or suspected exposure to *Bacillus anthracis*.

Study 1141-CG920871 was a blinded, parallel-group, randomized, placebo-controlled Good Laboratory Practices (GLP) study to evaluate the therapeutic efficacy of a single IV dose of 40 mg/kg raxibacumab when administered with 50 mg/kg levofloxacin once daily for 3 days in anthrax spore challenged rabbits. The study objective was to demonstrate the added benefit of raxibacumab when used with an antimicrobial drug, by showing that the outcome in the antimicrobial plus raxibacumab arm is higher than the outcome in the antimicrobial alone arm when treatment is administered late in the course of disease. To approximate a survival rate with a human equivalent dose of levofloxacin administered to rabbits with systemic anthrax infection, rabbits were treated with raxibacumab and/or levofloxacin at about 84 hours post-spore exposure. The primary efficacy endpoint was survival at 28 days after the last dose of levofloxacin in the intent-to-treat population. The primary analysis was to compare the percent of animals alive at Day 28 post last dose of levofloxacin between the levofloxacin alone group and the levofloxacin plus raxibacumab combination treatment groups.

Study 1103-G923704 was a parallel-group, blinded, randomized, placebo-controlled GLP study in rabbits to evaluate the histopathology in surviving and non-surviving animals after anthrax exposure and therapeutic treatment with placebo or raxibacumab. The primary objective was to assess terminal pathology in both non-surviving and surviving rabbits after anthrax exposure and therapeutic treatment with placebo or raxibacumab. Evaluation of efficacy of raxibacumab treatment was a secondary objective.

5.1 Statistical Issues

There are two main statistical issues in the review of this BLA resubmission, statistical power of primary efficacy analysis in the added benefit study and interpretation of brain lesion in the CNS study, both of which were randomized well-designed Good Laboratory Practices (GLP) studies.

In the added benefits study, while the goal was to show that the outcome in the antimicrobial plus raxibacumab arm was higher than the outcome in the antimicrobial alone arm when treatment was administered late in the course of disease, the study was not power demonstrate a statistically significant difference at a medically important change in mortality. This study was not powered to produce a statistically significant ($p < 0.05$) result with an absolute difference in survival rate of 17%. A trial with 80% power to detect a statistically significant result with the 17% difference seen in the current study would require 116 animals per group to be treated (232 animals). With only 42% of the animals estimated to be alive at 84 hours post challenge, the total

sample size of spore-challenged animals would be 552, with over 300 animals dying before having the opportunity to be treated. A study of this size may not be ethical or feasible. The study protocol and statistical analysis plan were reviewed and agreed upon by the FDA per a special protocol agreement letter dated 14 October 2010 with understanding that the power to detect a significant effect would be low.

In the CNS study, raxibacumab-treated animals had a greater incidence and severity of brain lesions than placebo-treated animals as in the previous raxibacumab studies in the absence of antibiotics. Also consistent with previous monotherapy studies, severe brain lesions were associated with raxibacumab-treated animals dying later. The sponsor in the original BLA submission hypothesized that raxibacumab treatment led to longer survival time to allow anthrax toxin in brains causing more severe brain lesion. The analyses of histopathology data by this review as well as the previous statistical review indicate that an increased incidence and severity of CNS findings is related to increase survival time only within the raxibacumab group. The differences between raxibacumab and placebo could not be explained by increased survival time on the raxibacumab arm since the animals on the two treatment arms had very similar times to death.

5.2 Collective Evidence

In the Added Benefits study, 180 rabbits were entered and challenged, 76/180 (42%) remained alive at 84 hours post exposure to be treated with raxibacumab with or without levofloxacin. At Day 28 after the last dose of levofloxacin, the survival rate in the raxibacumab plus levofloxacin combination group was 32/39 (82.05%) compared to that of 24/37 (64.86%) in the levofloxacin alone group, although the approximate 17% difference did not reach statistical significance (P-value = 0.0874). This study was not designed to be adequately powered to detect a statistically significant difference between the study arms. There is no significant difference in survival time from spore challenge between the raxibacumab plus levofloxacin combination group and the levofloxacin alone group. Raxibacumab had no clear impact on survival time from spore challenge for non-surviving animals in both treatment groups (identical mean time to death of 4.7 to 4.9 days). The result is consistent in a post-hoc sensitivity analysis when imbalances in spore challenge dose between treatment groups were adjusted. Complete gross necropsies were conducted on all 76 animals, 2 of which had brain lesions and were treated with levofloxacin alone. None of the raxibacumab plus levofloxacin-treated animals had brain lesions and none of the surviving animals in either treatment group had evidence of central nervous system (CNS) effects, either clinically or microscopically.

In the CNS study, 48 rabbits were challenged and treated with raxibacumab or placebo. At Day 28 post spore challenge, the survival rate for the raxibacumab-treated group was 11/24 (45.83%) compared to 0/24 (0.0%) in the placebo group (P-value < 0.001). The raxibacumab-treated survivors did not exhibit clinical sequelae of adverse CNS effects, brain pathology, or the presence of bacteria or PA in the brain at sacrifice. There was an increased incidence and severity of lesions in placebo-treated animals for all organs (eg, lung, bronchial and mediastinal lymph nodes, and spleen), except the brain. The brains of raxibacumab-treated non-survivors had a greater incidence and severity of lesions (bacteremia, inflammation, hemorrhage, and/or necrosis) than the placebo-treated animals. Within the raxibacumab-treated non-survivors, those

with severe brain lesion appeared to have survived longer and died later. Specifically the 5 rabbits documented as having severe brain lesions had an average time to death of 104.9 hours while the average time to death for the 7 other raxibacumab-treated animals that died on study was 65.5 hours (excluding rabbit L55568 that did not die of anthrax). However, given the small sample sizes the differences are not statistically significant. There is no significant difference in time to death between placebo-treated and raxibacumab-treated non-survivors, with an average time from spore challenge to death of 86 hours in placebo animals and 96 hours (or 82 hours excluding Animal L35568 which might not have died of anthrax) in the raxibacumab group. These results are consistent with previous raxibacumab monotherapy studies in anthrax-infected rabbits and monkeys.

5.3 Conclusions and Recommendations

In the assessment of this review, a single intravenous dose of 40 mg/kg raxibacumab given in combination with levofloxacin resulted in 17% (P-value=0.0874) improvement in survival over levofloxacin monotherapy in Study 1141-CG920871 that was submitted as the added benefit study in this BLA resubmission. The point estimates of Day 28 survival rates for the raxibacumab plus levofloxacin combination group was 32/39 (82.05%) and 24/37 (64.86%) for the levofloxacin alone group, respectively. The observed survival rate with antibiotic is more similar to that observed during the anthrax attacks in humans in 2001 (~55%). Although a positive, statistically significant 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 after inhalational anthrax exposure.

Also as part of this BLA resubmission, Study 1103- G923704 was submitted to evaluate the histopathology in surviving and non-surviving animals after anthrax exposure and therapeutic treatment with placebo or raxibacumab. There was an increased incidence and severity of lesions in placebo-treated animals for all organs (eg, lung, bronchial and mediastinal lymph nodes, and spleen), except the brain. The brains of raxibacumab-treated non-survivors had a greater incidence and severity of lesions (bacteremia, inflammation, hemorrhage, and/or necrosis) than the placebo-treated animals. Within the raxibacumab-treated non-survivors, those with severe brain lesion appeared to have survived longer and died later. However, given the small sample sizes the differences are not statistically significant. Among raxibacumab-treated survivors, all of the microscopic findings were graded as minimal to mild (one animal with mild brain hemorrhage), except 1 instance each of hemosiderosis and of hyperplasia in the spleen which were graded as moderate. These results are consistent with previous raxibacumab monotherapy studies in anthrax-infected rabbits and monkeys. It remains to be understood why raxibacumab-treated non-survivors exhibited greater incidence and more severe lesions in their brains compared to placebo-treated animals.

In conclusion, these two studies adequately address the added benefit of raxibacumab when administered concomitantly with antibiotics and its effect on central nervous system (CNS) in animals that survived to 28 days post anthrax spore exposure. However, the mechanism of action by raxibacumab on the brain is still not clear.

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/s/

LAN ZENG
11/21/2012

KAREN M HIGGINS
11/21/2012
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125349 Applicant: Human Genome Sciences Stamp Date: 6/15/2012

Drug Name: Raxibacumab NDA/BLA Type: BLA Resubmission

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 | Subgroup analyses conducted by toxemia and/or bacteremia status |
| 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 | | | |

This is a resubmission with responses to the Complete Response Letter (CRL, dated 11/14/2009) on Raxibacumab BLA. Two main deficiencies were noted in the CRL: 1) No added benefit of Raxibacumab over antibiotics alone; and 2) CNS lesions observed in animals who died on Raxibacumab. To address these deficiencies, the sponsor conducted an added benefit study (Study 1141-CG920871) to evaluate the efficacy of levofloxacin given with or without concomitant administration of Raxibacumab in anthrax spore challenged rabbits and a CNS study (1103-G923704) to evaluate the histopathology in survivors and non-survivors, as well as the efficacy of raxibacumab to treat rabbits due to B. anthracis exposure.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

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 60-day (08/14/2012) letter.

| Content Parameter (possible review concerns for 60-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 | | | |
| 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 | |
| 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 | |

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

LAN ZENG
07/18/2012

KAREN M HIGGINS
07/18/2012

STATISTICAL REVIEW AND EVALUATION

| | |
|---------------------------------|----------------------------------|
| BLA | 125349 |
| Submission# (Stamp date) | SN0024 (02/16/2012) |
| Contains | Pre-resubmission Meeting Package |
| Drug | Raxibacumab |
| Sponsor | Human Genome Sciences, Inc. |
| Indication | Anthrax |
| Statistical Reviewer | Lan Zeng |
| Medical Reviewer | Yuliya Yasinskaya |
| Project Manager | Jane Dean |
| Meeting Date | 03/19/2012 |

The current submission contains a Type B meeting package about resubmission of BLA (STN 125349), which was originally submitted by Human Genome Sciences (HGS) on 05/13/2009 under 21 CFR 601, Subpart H for raxibacumab, a human monoclonal antibody to the protective antigen (PA) of *Bacillus anthracis*, for the treatment of inhalation anthrax. FDA issued a Complete Response Letter (CRL) to HGS on 11/14 2009 and had a meeting with the sponsor on 01/29/2010 to discuss deficiencies noted in the CRL. HGS has since conducted additional studies and requests this meeting to discuss the adequacy of these new data, along with the updated quality information, to support the resubmission of the BLA, as well as logistics of resubmitting the BLA in the eCTD format. HGS is currently targeting resubmission of the BLA in June 2012.

HGS states that the key topics for the resubmission meeting include efficacy in animals (per the Animal Rule), raxibacumab effects on the central nervous system (CNS), assay methods for pharmacokinetics (PK) in animals and humans, updated Chemistry, Manufacturing and Controls (CMC) information, and organization and submission of information in the electronic Common Technical Document (eCTD) format to the BLA. The efficacy, safety and eCTD portion of this briefing package are reviewed below.

Efficacy

CRL Recommendation

The FDA CRL recommended the sponsor conduct a study in an animal model of inhalational anthrax to demonstrate the added benefit of raxibacumab when used with an antimicrobial drug, for example, by showing that the outcome in the antimicrobial plus raxibacumab arm is higher than the outcome in the antimicrobial alone arm. At the Type A meeting (01/29/2010) it was indicated that the added benefit study should have an antibiotic survival rate more similar to that observed during the anthrax attacks in humans in 2001 (~55%) rather than the survival rate (85-100%) observed when antibiotic was administered as soon as systemic anthrax disease was detected in rabbits and monkeys (median treatment times 27 hours and 39 hours, respectively). FDA also indicated that a human equivalent dose of antibiotic be administered and that the antibiotic should be

administered concomitantly with raxibacumab, and further, that the animals had to be symptomatic at the time of treatment for a therapeutic treatment claim.

The briefing package discussed 3 NIH/Battelle studies (see table below) in terms of survival and proportion of rabbits alive for treatment at 72 or 96 hours post spore exposure. Survival with levofloxacin treatment ranged from 80% when treatment was initiated at 72 hours post spore exposure to 40-50% when treatment was initiated at 96 hours. These studies, along with previous HGS data (rabbit survival of 51.3%, 33.3%, and 23.2% at 72, 84, and 96 hours post placebo treatment), helped the sponsor select 84 hours following anthrax spore challenge as the time of treatment intervention in order to achieve a lower survival rate with antibiotic monotherapy for the Added Benefit Study (1141-CG920871).

| NIH/Battelle Study | Levofloxacin Treatment Time (post challenge) | #Treated/ #Challenged (% Surviving to be Treated) | # (%) Survivors at Day 30 (All Animals) | # (%) Survivors at Day 30 (Treated Animals) |
|--------------------|--|--|---|--|
| 1 | 48 h | 8/8 (100%) | 7/8 (88%) | 7/8 (88%) |
| | 72 h | 7/10 (70%) | 5/10 (50%) | 5/7 (71%) |
| | 96 h | 6/12 (50%) | 3/12 (25%) | 3/6 (50%) |
| 2 | 96 h | 5/16 (31%) | 2/16 (12.5%) | 2/5 (40%) |
| 3 | 72 h | 9/16 (56%) | 7/16 (44%) | 7/9 (80%) |

Added Benefit Study (1141-CG920871)

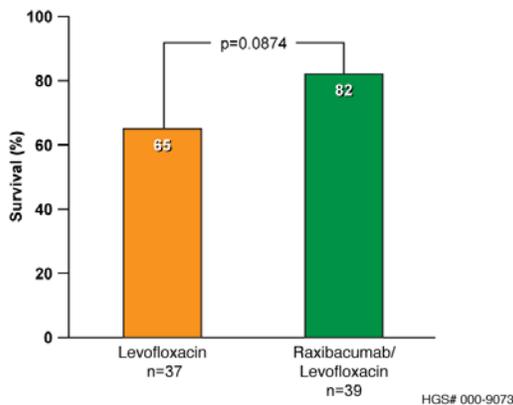
The Added Benefit study was a parallel-group, randomized, double-blind, placebo-controlled Good Laboratory Practices (GLP) study in healthy male and female New Zealand white (NZW) rabbits to evaluate efficacy of raxibacumab when administered in combination with levofloxacin as a therapeutic treatment against lethality due to inhalational anthrax. One hundred ninety-eight (198) NZW rabbits, approximately 50% male and 50% female were used: 180 were required for the study with 18 extra rabbits serving as replacements should a rabbit require removal from the study prior to spore challenge. Following aerosol exposure, treatments were initiated at 84 hours post-challenge. Animals surviving to 84 hours were randomized to receive levofloxacin (50 mg/kg/day for 3 days) plus raxibacumab (40 mg/kg single intravenous infusion; 0.8 mL/kg) or levofloxacin plus placebo. Raxibacumab or placebo was administered immediately following the first levofloxacin dose. Rabbits were to be monitored by laboratory animal personnel for abnormal clinical signs for 35 days post-challenge. The final protocol (Version 5.0, dated 10/14/2010) and Statistical Analysis Plan (SAP, dated 10/14/2010) received a Special Protocol Agreement letter on 10/14/2010 (see review in DARRTS on SN123, SN124, and SN125).

The primary endpoint of the study was survival at Day 28 post-spore exposure. The primary efficacy analysis was the comparison of the 28-day survival between the raxibacumab/levofloxacin combination group and the levofloxacin alone group. The analysis was performed in the intent-to-treat (ITT) population, defined as all animals that were assigned to the randomized dosing vials irrespective of the actual treatment the

animals received. A total of 76 animals survived to 84 hours post challenge, all of them received the treatment to which they were randomized, so the ITT population was the same as the as-treated population.

Figure 2-2 presents that the survival rate is 32/39 (82%) for the raxibacumab/levofloxacin group and 24/37 (65%) of the animals in the levofloxacin alone group. The 17% increase in survival due to raxibacumab treatment did not reach statistical significance ($p = 0.0847$), however, the sponsor claims that 17% is clinically meaningful and confirmed that raxibacumab does not interfere with antibiotics and may be additive to their effect.

Figure 2-2 Primary efficacy endpoint – survival at Day 28 (Added Benefit study)



According to HGS, to conduct a study with 80% power to demonstrate a 17% improvement in survival (65% to 82%) with statistical significance at $p \leq 0.05$ would require 276 animals per group or over 550 animals in total, of which it is estimated that 320 animals would already be dead before treatment at 84 hours post spore exposure. This study achieved a survival rate with antimicrobial treatment (65%) that was consistent with the survival rate of 55% observed in human subjects in 2001 and suggests that raxibacumab, even administered late in the course of the disease when over half of the animals have already succumbed, confers a survival benefit over antimicrobial alone.

The complete study report with supporting data for this study will be provided in the BLA resubmission. The following question is posed by the sponsor:

Sponsor's Question: Does the FDA agree that the added benefit study is sufficient to demonstrate that the outcome in the antimicrobial plus raxibacumab arm is higher than the outcome in the antimicrobial alone arm and supports resubmission of the BLA?

FDA Response: We agree.

Safety

CRL Recommendation

The FDA CRL recommended that the sponsor conduct a study to evaluate the effect of raxibacumab on the CNS in an animal model of inhalational anthrax and characterize the clinical course and histological appearance of the CNS in animals that survive and animals that die of anthrax.

CNS Study (1103-G923704)

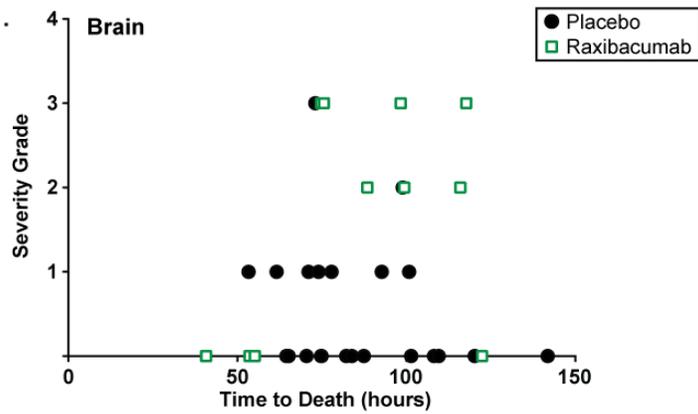
The CNS study was a parallel-group, randomized, double-blind, placebo-controlled GLP study in healthy male and female NZW rabbits to evaluate the histopathology in surviving and non-surviving animals after anthrax exposure and therapeutic treatment with placebo or raxibacumab. In total, 54 NZW rabbits were randomized by gender and body weight into each of 2 treatment groups (24 rabbits/group) with 6 animals serving as potential replacements. Following aerosol challenge, rabbits received either a single IV administration of 40 mg/kg raxibacumab or 0.8 mL placebo. The treatment trigger was detectable plasma PA or after the results of the 48 hour ECL assay were known (regardless of the result). The personnel administering study agent and evaluating the animals were blinded to the study agent treatment assignment. Animals were monitored for 28 days and those surviving on Day 28 post challenge were euthanized.

The primary efficacy analysis demonstrated that raxibacumab treatment significantly increased survival (45.8%, $p < 0.0001$) compared with placebo treatment (0%).

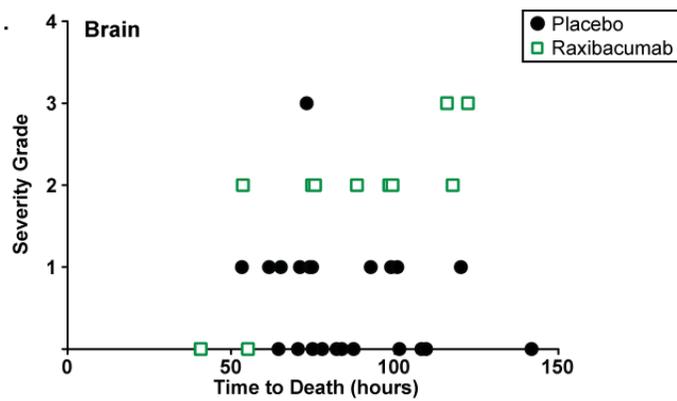
Complete necropsies were performed on animals found dead or euthanized, including the animals surviving to terminal sacrifice on Day 28. As in the pivotal rabbit study (682-G005758), there was an increased incidence and severity of lesions in placebo-treated animals for all organs except the brain. The brains of raxibacumab-treated non-survivors had a greater incidence and severity of brain lesions than the placebo-treated animals. The raxibacumab-treated survivors did not exhibit clinical sequelae of adverse CNS effects, brain pathology, or the presence of bacteria or PA in the brain or CSF at sacrifice (Day 28).

Microscopic findings consistent with anthrax were present in all rabbits that died or became moribund during the study except for 1 rabbit in the raxibacumab treatment group. All of the microscopic findings in the raxibacumab-treated survivors were graded as minimal to mild, except 1 instance graded as moderate.

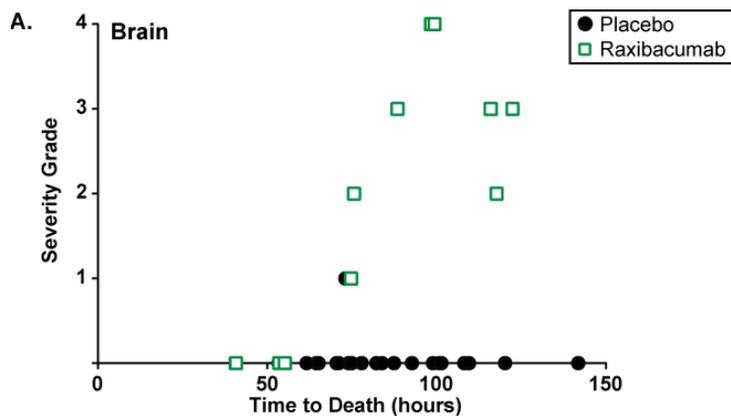
The following figures show a possible relationship between time course to death and the histopathology findings such as the severity of bacteria, hemorrhage and inflammation in the brain of non-surviving animals.



Severity of bacteria in brain by time of death in non-survivors



Severity of hemorrhage in brain by time of death in non-survivors



Severity of inflammation (heterophilic predominating) in brain by time of death in non-survivors

In the raxibacumab-treated group, the 5 rabbits documented as having severe brain lesions (ie, moderate to marked severity in hemorrhage or inflammation) had an average time to death of 104.9 hours, while the 7 other raxibacumab animals had an average time to death of 65.5 hours (excluding rabbit 55568 that did not die of anthrax). Similarly, raxibacumab-treated animals with greater severity in hemorrhage and inflammation in the brain died later, while those with less hemorrhage or inflammation died before 72 hours.

In the placebo-treated group, the mean time to death in the placebo animals, none of which had severe brain lesions, was 86 hours. The placebo-treated rabbits had minimal or mild inflammation and hemorrhage in their brains.

Comment: As was seen previously, the difference between placebo and treatment cannot be explained by the time to death as the animals in the two groups died at similar times. However, within the raxibacumab group those animals who died early did not show the CNS events while those who died later did.

Among raxibacumab-treated animals surviving to Day 28, none had raxibacumab staining in the brain; 3 had positive raxibacumab staining of plasma, although in 2 of these the staining was weak. The sponsor proposed that the increased incidence of brain involvement in anthrax-infected animals that die is not evidence of a safety finding for raxibacumab, but rather the consequence of continued progression of anthrax infection despite treatment. The sponsor also claims that raxibacumab does not prevent the development of brain lesions in those animals that die despite raxibacumab treatment.

Comment: The sponsor still does not explain, however, why the CNS events were not seen in the placebo animals.

Sponsor's Question: Does the FDA agree that the CNS study performed is sufficient to address the requirement the CRL to evaluate the effect of raxibacumab on the CNS in an animal model of inhalational anthrax and supports resubmission of the BLA?

FDA Response: Defer to clinical.

eCTD Format submission

HGS plans resubmission of the BLA in the eCTD format at the end of June 2012. HGS previously submitted the original BLA in eCTD format and will add and replace sections as necessary. A draft protocol for use in the event of raxibacumab administration in an emergency will be included in the resubmission. In order to link the BLA resubmission electronically to the original BLA, the resubmission be supplied as an amendment to the original BLA.

Because the data to support efficacy are provided by animal, rather than human, studies per the Animal Rule, HGS will include discussion of the CNS animal study in the

Clinical Pharmacology section (Module 2.7.2.4) and the Added Benefit animal study in the Clinical Efficacy section (Module 2.7.3), rather than in the nonclinical written summaries (Module 2.6), consistent with the format of the original BLA. PK data from both animal studies will be discussed in Clinical Pharmacology (Module 2.7.2). There will also be ample hyperlinking within the sections for easy navigation between the Nonclinical, Clinical, and Quality modules.

Previously HGS had submitted HGS (original non-CDISC) raw and analysis datasets for the animal studies, including the PK data. Summary tables and by-animal line listings were also provided. In the BLA resubmission HGS intends to submit the same type of datasets, definition files, summary tables, and animal line listings for the new studies as for the previously submitted studies in the original BLA.

Sponsor's Question: Does the Agency agree with the datasets and listings proposed for submission for the new animal studies?

FDA Response: We agree.

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

/s/

LAN ZENG
03/21/2012

KAREN M HIGGINS
03/21/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ANIMAL EFFICACY STUDIES

BLA/Serial Number: 125349

Drug Name: Raxibacumab (ABthrax, PA mAb)

Indication(s): Treatment of inhalational anthrax caused by *Bacillus anthracis*

Applicant: Human Genome Sciences, Inc

Date(s): Submission date: May 13, 2009.
PDUFA due date: November 13, 2009

Review Priority: Priority Review

Biometrics Division: IV

Statistical Reviewer: Lan Zeng, M.S.

Concurring Reviewers: Karen Higgins, Sc.D.

Medical Division: Division of Special Pathogen and Transplant Products

Clinical Team: Sue Lim, M.D., Medical Reviewer
Susan McCune, M.D., Medical Reviewer
Yuliya Yasinskaya, M.D., Medical Team Leader

Project Manager: Rebecca Saville, Pharm.D.

Keywords: Animal studies, combination.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In the assessment of this reviewer, a single intravenous dose of 40 mg/kg raxibacumab given in combination with antimicrobial therapy resulted in similar observed efficacy as antimicrobial monotherapy in both the rabbit (Study 781-G923701) and the monkey (Study 789-G923702) studies that were submitted as the combination efficacy studies. However, these studies did not rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with levofloxacin or ciprofloxacin against lethality due to inhalation exposure of *Bacillus anthracis* (*B. anthracis*). The point estimates of survival rates for the antimicrobial arms were 95% in rabbits and 100% in monkeys whereas the point estimates for the antimicrobial/raxibacumab combination arms were 94.1% in rabbits and 84.6% in monkeys. Given the high survival rate of the antimicrobial monotherapy, it is not possible to show an improved efficacy of raxibacumab over antimicrobial. Due to limited number of animals, it is not possible to conclude that raxibacumab did not interfere with the efficacy of antimicrobial, either. In terms of histopathology, the two combination trials did not provide much additional information to further investigate the CNS findings observed in previous two pivotal studies (Study 682-G005758 and Study 742-G005829). However, the results from the combination trial in monkeys were consistent with the pivotal studies.

Interpretation of the study results is limited by the animal models which demonstrated much higher efficacies ($\geq 95\%$) of antimicrobial than in humans. Extrapolation of efficacy is therefore difficult from the animal models to humans.

1.2 Brief Overview of Animal Efficacy Studies

Two animal studies, Study 781-G923701 and Study 789-G923702, have been conducted by the sponsor to evaluate the efficacy of raxibacumab when administered as a therapeutic agent in combination with antimicrobial against lethality due to inhalation exposure of *B. anthracis*. Both trials were parallel-group, randomized, double-blind, placebo-controlled Good Laboratory Practices (GLP) studies. There were 3 arms in each study, including placebo, antimicrobial alone, and the combination of antimicrobial plus raxibacumab. Study 781-G923701 tested levofloxacin and the levofloxacin plus raxibacumab combination in New Zealand White rabbits. Study 789-G923702 examined ciprofloxacin and the ciprofloxacin plus raxibacumab combination in cynomolgus monkeys. The study duration was 28 days, with an additional post-Day 28 observation period of 60 days in the monkey Study 789-G923702. The primary efficacy endpoint of both studies was survival at Day 28, defined as the percent of animals alive at Day 28.

1.3 Statistical Issues and Findings

The main statistical issues encountered during the review were pertinent to the primary efficacy analysis. Following two pivotal efficacy studies (682-G005758 and 724-G005829), Study 781-G923701 and Study 789-G923702 were specifically designed as combination trials to assess possible antagonism or possible benefit of raxibacumab plus antimicrobial compared with antimicrobial alone. Despite that the primary goal was to explore the comparison between the antimicrobial/raxibacumab combination versus antimicrobial alone, the sponsor performed the primary analysis as to compare the percent of animals alive at Day 28 post challenge between the placebo group and the antimicrobial/raxibacumab combination group. The comparison between the combination group and the antimicrobial group was considered by the sponsor as a secondary analysis in Study 781-G923701 and an exploratory analysis in Study 789-G923702. Furthermore, the sponsor defined the intent-to-treat (ITT) population as the primary analysis population. The Agency considers the animals that were bacteremic at treatment initiation as the primary analysis population, as conveyed to the sponsor numerous times in FDA comments prior to protocol submission (see fax to the sponsor dated November 17, 2006) and also in comments regarding the study protocol.

Details of study findings are summarized below.

A total of 52 rabbits were randomized and challenged with anthrax spores in Study 781-G923701. Forty-seven of the 52 rabbits had bacteremia at the time of treatment and hence constituted the FDA primary analysis population. None of the rabbits in the placebo group survived. There was 1 death in the levofloxacin group at 11 days post challenge and 1 death in the levofloxacin/raxibacumab group due to a dosing accident at 1.9 days post challenge. There was no significant difference ($p=0.947$) in survival rates between the levofloxacin and levofloxacin/raxibacumab combination groups (-0.88%, 95% CI [-23.9%, 19.6%]). The 28-day survival rates were 0%, 95.0%, and 94.1% in the placebo, levofloxacin, and levofloxacin/raxibacumab combination groups, respectively. Complete gross necropsies were conducted on all 52 rabbits, none of which in the active treatment groups had lesions attributable to anthrax at sacrifice, or any brain lesions on microscopic examination.

A total of 40 monkeys were randomized and challenged with anthrax spores in Study 789-G923702. Thirty-six of the 40 monkeys had bacteremia at the time of treatment and hence constituted the FDA primary analysis population. None of the monkeys in the placebo groups survived. There was 1 death in the ciprofloxacin group which happened from a non-study-related issue during the 60-day additional observation period. There were 2 deaths in the ciprofloxacin/raxibacumab combination group, including one that died at 9.95 days post challenge and another one that died at 3.69 days from a gavage error. There was no significant difference ($p=0.222$) in survival rates between the ciprofloxacin and raxibacumab/ciprofloxacin combination groups (-15.4%, 95% CI [-45.5%, 11.4%]). The 28-day survival rates were 0%, 100%, and 84.6% in the placebo, ciprofloxacin, and ciprofloxacin/raxibacumab combination groups, respectively. Microscopic exams were performed on 15 monkeys that were found dead or euthanized, out of which one animal

treated with ciprofloxacin/raxibacumab had evidence of hemorrhagic meningitis that affected the entire brain.

The above efficacy results are similar to those generated by the sponsor using the ITT population and are robust with various sensitivity analyses. Analysis excluding non-anthrax deaths does not alter the efficacy conclusion. The two combination trials did not provide much additional information to further investigate the CNS findings observed in the pivotal studies.

2. INTRODUCTION

2.1 Overview

Raxibacumab (ABthrax, PA mAb) is a fully human monoclonal antibody developed by the Human Genome Sciences (HGS) for the treatment of subjects with known or suspected exposure to *Bacillus anthracis*. The proposed dosage of raxibacumab is a single intravenous (IV) administration of 40 mg/kg. Raxibacumab can be administered alone or in combination with antimicrobials. Due to the lethality of the anthrax infection, clinical trials in humans are not ethically feasible. Under the Animal Rule and per agreement with FDA, the sponsor conducted two pivotal studies (Study 682-G005758 in rabbits and Study 724-G005829 in cynomolgus monkeys) in order to support the efficacy of raxibacumab against anthrax toxin over placebo. Data showed that while a single IV dose of 40 mg/kg raxibacumab was superior to placebo for the treatment of anthrax in both studies, the results for raxibacumab 40 mg/kg group in the rabbit study would change if one non-bacteremic (at the time of treatment) animal was excluded from the analysis. Furthermore, non-surviving animals in the raxibacumab-treated groups had higher rates of meningitis and/or higher rates of moderate/marked inflammation in the brain than animals in the placebo group in both studies. Detailed statistical discussion of the two pivotal studies can be found in the statistical review by Hongling Zhou in DARRTS.

In order to characterize the clinical progression of inhalation anthrax and to examine the efficacy of raxibacumab administered as pre or post-exposure prophylaxis and treatment, the sponsor has performed a number of studies in 2 relevant species, rabbits and cynomolgus monkeys. In addition, clinical trials in healthy human volunteers have been conducted for evaluation of the raxibacumab single and double dose pharmacokinetics and safety, alone and in combination with ciprofloxacin. Since raxibacumab may be administered concomitantly with antimicrobials, two animal studies (Study 781-G923701 and Study 789-G923702) were specifically designed as combination trials to assess possible antagonism or possible benefit of raxibacumab plus antimicrobial compared with antimicrobial alone. These two combination studies were submitted as part of BLA and will be reviewed here.

2.2 Data Sources

Data sets for the sponsor's combination studies 781-G923701 and 789-G923702 were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows: \\cbsap58\M\CTD_Submissions\STN125349\0000\m5\datasets

The original files did not contain adequate information for the variables in the datasets. Per Agency's request, the sponsor provided relevant information in the updated files (\\cbsap58\M\CTD_Submissions\STN125349\0007\m5\datasets). The electronic data sets generally represented the data described in the study report.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

One study in rabbits and another one in cynomolgus monkeys were conducted as the combination efficacy studies for the indication of treatment of anthrax. This section presents and discusses the details of these two studies.

Protocol 781-G923701: Evaluating the Efficacy of Raxibacumab in Combination with Levofloxacin for Post-exposure Treatment in the New Zealand White Rabbit Inhalational Anthrax Model

Protocol 789-G923702: Evaluation of the Efficacy of Raxibacumab in Combination with Ciprofloxacin for Therapeutic Treatment in the Cynomolgus Monkey Inhalation Anthrax Model

3.1.1 Objectives and Study Design

The study design for Studies 781-G923701 and 789-G923702 is summarized in Table 1.

Table 1 Summary of Study Design

| | 781-G923701 (rabbits) | 789-G923702 (monkeys) |
|----------------------------------|---|---|
| Design | double-blind, placebo controlled, randomized, parallel arms | double-blind, placebo controlled, randomized, parallel arms |
| Animals | New Zealand White rabbits | Cynomolgus monkeys |
| Total Number of Animals | 52 | 40 |
| Group (Number of Animals) | | |
| 1 | Placebo (12) | Placebo (12) |
| 2 | Levofloxacin (20) | Ciprofloxacin (14) |
| 3 | Levofloxacin/Raxibacumab (20) | Ciprofloxacin/Raxibacumab (14) |
| Treatment Trigger | Detection of serum PA or temperature increase* | Detection of PA in serum |
| Study Timeline | 6/9/2008 to 7/21/2008 | 3/17/2008 to 5/9/2008 |
| Study Period | 28 days post challenge | 28 days post challenge with an additional 60-day observation period |

**Either 1st positive PA result, or first 2 consecutive time points of a body temperature 2 or more °F higher than the baseline average (whichever occurred first); after 36 hours, only temperature was used as a trigger.*

Both Study 781-G923701 and Study 789-G923702 were parallel-group, randomized, double-blind, placebo-controlled GLP studies with similar design. The primary objective was to evaluate the efficacy of raxibacumab when administered in combination with antimicrobials (levofloxacin in Study 781-G923701 or ciprofloxacin in Study 789-G923702) against lethality due to inhalation exposure to *B. anthracis* in animal inhalational anthrax model. Fifty-two New Zealand White rabbits weighing 2.97 to 4.02 kg at randomization were used in Study 781-G923701 and 40 juvenile cynomolgus monkeys weighing between 2.0 to 6.0 kg at randomization were used in Study 789-G923702. Following a quarantine period, animals were randomized by sex to 1 of 3 treatment groups receiving either placebo, antimicrobial alone, or combination of antimicrobial and raxibacumab. All animals were subjected to an inhalation challenge with a target dose of 200 x LD₅₀ of *B. anthracis* spores at Day 0. Once trigger symptoms were detected, animals were administered 3 doses of levofloxacin (50 mg/kg) or control material in Study 781-G923701 and 6 doses of ciprofloxacin (75 mg) or control material in Study 789-G923702. In addition, a single IV dose of 40 mg/kg of raxibacumab or raxibacumab buffer was administered immediately after injection of the first antimicrobial dose. In Study 781-G923701, timing of treatment was based on either first positive serum protective antigen (PA) or first 2 consecutive time points of a body temperature $\geq 2^{\circ}\text{F}$ higher than the baseline average (whichever occurred first); after 36 hours, only temperature was used as a trigger. If an animal had not been treated by 72 hours, the animal was to be treated after its last hourly temperature. In Study 789-G923702, only detectable serum PA was used as treatment trigger and animals that didn't have a positive serum PA assay result by 54 hours post challenge were treated with their intended treatment. The study duration was 28 days, with an additional post-Day 28 observation period of 60 days in Study 789-G923702.

Comment:

The sponsor specified that the antimicrobial regimen chosen for the combination studies were human-equivalent doses required by FDA and was adequate to demonstrate sterilization of bacteremia in the animals.

The primary efficacy endpoint of both studies was survival at Day 28, defined as the percent of animals alive at Day 28. The sponsor's primary analysis of the primary efficacy endpoint was to compare the percent of animals alive at Day 28 post challenge between the placebo group and the antimicrobial/raxibacumab combination group. The comparison was performed using a 2-sided Fisher's exact test. The analysis was not subjected to multiple comparison adjustment. As an additional analysis of the primary efficacy endpoint, the point estimate for the difference in the survival at Day 28 between the antimicrobial group and the antimicrobial/raxibacumab combination group was presented with a 95% confidence interval (CI). The secondary efficacy endpoint was survival time from spore challenge to death during the study period. The log-rank test, without adjustment for multiple comparisons, was to be used to compare the animals' survival time between any two treatment groups.

Comment:

As previously conveyed to the sponsor, the FDA's primary goal for these combination studies was to explore the comparison of the combination (antimicrobial/raxibacumab) to antimicrobial alone. However, the sponsor's primary analysis (i.e., the comparison of the combination to placebo) will not lead to the conclusion that the efficacy of the combination arm, if confirmed, is due to raxibacumab or antimicrobial. Instead, the comparison between the combination group and the antimicrobial group was considered by the sponsor as secondary analysis in Study 781-G923701 and exploratory analysis in Study 789-G923702, respectively.

The analysis populations for this study were defined by the sponsor as follows:

- ITT population: all animals that were randomized and challenged with *B. anthracis* spores in the study. The ITT analysis was based on the intended treatment group planned at randomization rather than the actual treatment received.
- Modified ITT population: a subset of the ITT population that included all animals that received a study agent. The modified ITT analysis was based on the planned treatment group rather than the actual treatment received.
- As-treated population: the set of all animals that received a study agent with the assignment to treatment group that is based on the actual treatment that the animals received.

The sponsor's primary efficacy analysis was performed on the intention-to-treat (ITT) population. Animals that were spore-challenged, but died before receiving placebo or active treatment, were to be included in this population as treatment failures.

Comment:

*As with the two pivotal studies, the **FDA primary** analysis population is defined as all animals that were bacteremic (based on a positive blood culture) at the time of treatment and according to the actual treatment administered. FDA used this as its primary analysis population because both PA assays quantitative ELISA and ECL trigger for intervention exhibited high intra and inter animal variability as well as a significant operator-dependency. In order to test raxibacumab as a treatment of anthrax disease, it was important that the animal have confirmed anthrax disease. The FDA primary analysis using only animals that were bacteremic at the time of treatment was specified in order to clearly differentiate those animals that received treatment as opposed to post-exposure prophylaxis.*

In addition, FDA defined an analysis population of “toxemic at treatment” which includes all animals with detection of PA by quantitative ECL at the time of treatment. The analysis of “toxemic at treatment” population will be based on the intended treatment group planned at randomization rather than the actual treatment received.

The sample size for Study 781-G923701 was to detect an absolute improvement of 71.7% or more 28-day survival benefit in the levofloxacin/raxibacumab combination arm over placebo, assuming an 8.3% (1 of 12) survival at Day 28 in the placebo group and an 80% (16 of 20) survival at Day 28 in the levofloxacin/raxibacumab combination group. This design provided approximately 99% power at 5% overall significance level.

The sample size for Study 789- G923702 was to detect an absolute improvement of 56% or more survival at Day 28 survival benefit in the ciprofloxacin/raxibacumab combination arm over placebo, assuming an 8.3% (1 of 12) survival at Day 28 in the placebo control group and a 64.3% (9 of 14) survival at Day 28 in the ciprofloxacin/raxibacumab combination group. This study design provides approximately 85% power at 5% overall significance level.

Comment:

The sample size calculation was based on comparison between the placebo group and the antimicrobial/raxibacumab combination group. The study was not powered to show any difference between the antimicrobial and antimicrobial/raxibacumab combination groups.

3.1.2 Animal Disposition, Demographic and Baseline Characteristics

Table 2 provides a summary of animal disposition in Studies 781-G923701 and 789-G923702.

Table 2 Distribution of Animals in Studies 781-G923701 and 789-G923702

| | 781-G923701 (rabbits) | | | 789-G923702 (monkeys) | | |
|----------------------------|-----------------------|------|-----------------|-----------------------|-----------------|------------|
| | Placebo | Levo | Levo/Raxi | Placebo | Cipro | Cipro/Raxi |
| Animals Randomized | 12 | 20 | 20 ^a | 12 ^b | 14 | 14 |
| Survived | 0 | 19 | 19 | 0 | 14 ^c | 12 |
| Died | 12 | 1 | 1 | 12 | 0 | 2 |
| Analysis Population | | | | | | |
| Sponsor's ITT | 12 | 20 | 20 | 12 | 14 | 14 |
| FDA Primary | 10 | 20 | 17 | 10 | 13 | 13 |
| As-treated | 12 | 21 | 19 | 12 | 14 | 14 |
| Toxic at treatment | 12 | 19 | 18 | 11 | 13 | 14 |

^a One animal (K99251) was randomized to the Levo/Raxi group but received levofloxacin according to its PK data. This animal was included in the levofloxacin group for the as-treated and the FDA primary analyses.

^b One animal (C25576) was randomized to the placebo group but received 1 dose of ciprofloxacin according to its PK data. This animal remained in the placebo group for the as-treated and the FDA primary analyses since it received placebo throughout the majority of the ciprofloxacin dosing schedule.

^c One animal (C30988) died (survival time=36.17 days) from a non-study-related issue during the 60-day additional observation period after the 28-day study period.

In Study 781-G923701, a total of 52 rabbits were randomized and challenged with anthrax spores and constituted the ITT population. All rabbits received treatment according to their assigned group, with the exception of rabbit K99251 (randomized to the levofloxacin/raxibacumab group), for which the PK data suggested was not dosed with raxibacumab. Rabbit K99251 was thus assigned to the levofloxacin group in the as-treated population. Note that this animal did survive. As previously conveyed to the sponsor, the Agency considers the animals that were bacteremic at treatment initiation as the primary analysis population. Two rabbits in the placebo group, 1 in the levofloxacin group, and 2 in the levofloxacin/raxibacumab group did not have positive blood culture at the time of treatment and hence were excluded from the FDA primary analysis population. Three of the 5 non-bacteremic rabbits were also not toxic at treatment initiation (1 in the levofloxacin group and 2 in the levofloxacin/raxibacumab group) and were thus excluded from the further analysis of animals with toxemia at treatment initiation.

Comment:

Since the FDA primary analysis population is defined as all animals which were bacteremic at treatment initiation and according to the actual treatment administered, rabbit K99251 was thus assigned to the levofloxacin group. An additional sensitivity analysis was conducted by including K99251 in the levofloxacin/raxibacumab group as randomized (see Section 3.1.3.2).

In Study 789-G923702, a total of 40 monkeys were randomized and challenged with anthrax spores and constituted the ITT population. All monkeys received treatment according to their assigned groups; hence the as-treated population is the same as the ITT population. The 1 exception was that the PK data suggested that monkey C25576 was randomized to the placebo group but received 1 dose of ciprofloxacin at the 12 hour post challenge. This animal remained in the placebo group for the as-treated and the FDA primary analyses since it received placebo throughout the majority of the ciprofloxacin dosing schedule. The FDA primary population excluded 4 monkeys that were not bacteremic at treatment initiation, including 2 in the placebo group, 1 in the ciprofloxacin group, and 1 in the ciprofloxacin/raxibacumab group. Two monkeys (C24800 in the placebo group and C23064 in the ciprofloxacin group) were excluded from the analysis of animals with toxemia at treatment.

As shown in Table 3, the treatment groups were comparable with regard to sex, weight, and age at randomization. In Study 781-G923701, all rabbits in the active treatment groups tested negative for anti-PA and TNA at baseline except for one rabbit (K99234) in the levofloxacin group which tested positive for anti-PA antibodies. In Study 789-G923702, one monkey (C24792, 6.4 kg) in the ciprofloxacin group had a body weight at randomization that was slightly outside of the protocol-specified range of 2.0 to 6.0 kg. The number of monkeys that were anti-PA antibody positive at baseline (all borderline positive just above LOQ) was comparable between the ciprofloxacin group (1/14, 7.1%) and the ciprofloxacin/raxibacumab group (2/12, 16.7%). All of the monkeys in the active treatment groups tested negative for TNA at baseline.

**Table 3 Summary of Demographics and Baseline Characteristics
(Sponsor's ITT Population)**

| | 781-G923701 (rabbits) | | | 789-G923702 (monkeys) | | |
|---|-----------------------|----------------|---------------------|-----------------------|-----------------|----------------------|
| | Placebo N = 12 | Levo N = 20 | Levo/Raxi N = 20 | Placebo N = 12 | Cipro N = 14 | Cipro/Raxi N = 14 |
| Sex | | | | | | |
| male | 6 (50.0%) | 10 (50.0%) | 10 (50.0%) | 6 (50.0%) | 7 (50.0%) | 7 (50.0%) |
| female | 6 (50.0%) | 10 (50.0%) | 10 (50.0%) | 6 (50.0%) | 7 (50.0%) | 7 (50.0%) |
| Pre challenge weight (kg) | | | | | | |
| Mean ± SD | 3.5 ± 0.2 | 3.4 ± 0.2 | 3.5 ± 0.3 | 3.4 ± 0.8 | 3.6 ± 1.2 | 3.3 ± 0.7 |
| Median | 3.5 | 3.4 | 3.5 | 3.2 | 3.2 | 3.1 |
| Range | (3.3, 3.8) | (3.1, 3.9) | (3.0, 4.0) | (2.6, 4.8) | (2.6, 6.5) | (2.5, 5.3) |
| Age at randomization (days for rabbits, years for monkeys) | | | | | | |
| Mean ± SD | 274.5 ± 18.3 | 274.5 ± 18.0 | 274.5 ± 18.0 | 4.2 ± 0.3 | 4.2 ± 0.6 | 4.3 ± 0.5 |
| Median | 274.5 | 274.5 | 274.5 | 4.1 | 4.2 | 4.1 |
| Range | (257.0, 292.0) | (257.0, 292.0) | (257.0, 292.0) | (3.6, 4.7) | (2.9, 5.0) | (3.3, 5.1) |
| Anti-PA antibody positive at baseline* | - | 1/19 (5.3%) | 0/19 (0.0%) | - | 1/14 (7.1%) | 2/12 (16.7%) |
| TNA positive at baseline* | - | 0/19 (0.0%) | 0/19 (0.0%) | - | 0/14 (0.0%) | 0/12 (0.0%) |

* Data on anti-PA antibody and TNA was available for survivors only

Mean exposure to *B. anthracis* in the ITT population was $293.5 \pm 83.6 \times LD_{50}$ in Study 781-G923701 and $275.7 \pm 87.0 \times LD_{50}$ in Study 789-G923702, respectively (Table 4). There was no statistically significant difference in inhaled anthrax dose levels among the 3 treatment groups.

Table 4 Extent of Anthrax Exposure (LD_{50}) (Sponsor's ITT Population)

| | 781-G923701 | | | 789-G923702 | | |
|---------------------------------|-------------------|------------------|---------------------|-------------------|------------------|----------------------|
| | Placebo N = 12 | Levo N = 20 | Levo/Raxi N = 20 | Placebo N = 12 | Cipro N = 14 | Cipro/Raxi N = 14 |
| N | 12 | 20 | 20 | 12 | 14 | 14 |
| Mean \pm SD | 324.7 \pm 110.1 | 285.8 \pm 64.5 | 282.5 \pm 82.3 | 228.0 \pm 58.0 | 290.8 \pm 97.5 | 301.5 \pm 85.5 |
| Median | 317.4 | 284.0 | 285.2 | 212.5 | 254.0 | 321.8 |
| Range | (190.0, 625.8) | (167.3, 394.3) | (171.0, 469.5) | (166.1, 382.0) | (168.0, 450.0) | (146.0, 409.5) |

Table 5 outlines time to treatment and trigger event status, and summarizes the occurrence of toxemia or bacteremia among treatment groups. The 3 treatment groups had similar mean time to treatment, with a median time to treatment of 27.3 hours in Study 781-G923701 and 39.7 hours in Study 789-G923702. Across the 3 treatment groups there were no statistically significant differences in time to treatment, trigger event, or the onset of bacteremia or toxemia. In Study 781-G923701, 5 of 52 (9.6%) rabbits had their treatment triggered by body temperature increase within 54 hours post challenge. The groups were similar with respect to signs and symptoms around the time of treatment. The vast majority of animal in all groups (90.4% in Study 781-G923701 and 87.5% in Study 789-G923702) were toxemic and bacteremic at or before treatment initiation.

In Study 781-G923701, 47 of the 52 rabbits (90.4%) were bacteremic at or before treatment initiation. Two of the remaining 5 rabbits (K99255 and K99257, both in the placebo group) were bacteremic within 76 hours post challenge. The other 3 rabbits (K99254 in the levofloxacin group, K99202 and K99224 in the levofloxacin/raxibacumab group) did not test positive for bacteremia while on study. There were 3 rabbits (K99254, K99202, and K99224) which were not toxemic at or before treatment initiation. In Study 789-G923702, 4 of the 40 monkeys were not bacteremic at treatment initiation, including 2 in the placebo group (C24781 and C24879), 1 in the ciprofloxacin group (C30969) and 1 in the ciprofloxacin/raxibacumab group (C31127). There were 2 monkeys (C24800 in the placebo group and C23064 in the ciprofloxacin group) which were not toxemic at or before treatment initiation.

Table 5 Summary of Signs and Symptoms (Sponsor's ITT Population)

| | 781-G923701 (rabbits) | | | 789-G923702 (monkeys) | | |
|---|-----------------------|----------------|---------------------|-----------------------|-----------------|----------------------|
| | Placebo N = 12 | Levo N = 20 | Levo/Raxi N = 20 | Placebo N = 12 | Cipro N = 14 | Cipro/Raxi N = 14 |
| Time to treatment (hour)^a | | | | | | |
| Mean ± SD | 28.1 ± 5.7 | 26.9 ± 3.5 | 28.7 ± 8.7 | 41.5 ± 6.4 | 38.4 ± 8.2 | 38.2 ± 6.3 |
| Median | 27.4 | 27.4 | 26.9 | 40.9 | 35.4 | 39.7 |
| Range | (22.6, 44.2) | (22.4, 35.3) | (18.6, 54.4) | (33.9, 58.1) | (28.7, 56.3) | (28.8, 47.8) |
| Trigger event | | | | | | |
| Detectable PA | 11 (91.7%) | 19 (95.0%) | 17 (85.0%) | 11 (91.7%) | 13 (92.9%) | 14 (100.0%) |
| Significant temperature increase ^b | 1 (8.3%) | 1 (5.0%) | 3 (15.0%) | NA | NA | NA |
| Toxemia^c | 12 (100.0%) | 19 (95.0%) | 18 (90.0%) | 11 (91.7%) | 13 (92.9%) | 14 (100.0%) |
| Bacteremia^c | 10 (83.3%) | 19 (95.0%) | 18 (90.0%) | 10 (83.3%) | 13 (92.9%) | 13 (92.9%) |
| Toxemia and bacteremia | 10 (83.3%) | 19 (95.0%) | 18 (90.0%) | 10 (83.3%) | 12 (85.7%) | 13 (92.9%) |

^aTime to treatment was calculated relative to the start of challenge

^bFirst 2 consecutive timepoints of a body temperature $\geq 2^{\circ}\text{F}$ higher than the baseline average temperature.

^cToxemia was defined as detectable PA by quantitative ECL assay and bacteremia was determined by culture. Only postchallenge bacteremia and toxemia were counted. Reported here are results at the time of treatment initiation.

3.1.3 Efficacy Results

3.1.3.1 Primary Efficacy Endpoint

Table 6 presents the primary efficacy results in Study 781-G923701 by analysis population. None of the 12 rabbits in the placebo group survived. There was 1 death in the levofloxacin group (K99203) at 11 days post challenge and 1 death in the levofloxacin/raxibacumab group (K99246) due to a dosing accident at 1.9 days post challenge. According to the FDA primary analysis population, the 28-day survival rates were 0%, 95.0%, and 94.1% in the placebo, levofloxacin, and levofloxacin/raxibacumab combination groups, respectively. There was no significant difference ($p=0.947$) in survival rates between the levofloxacin and levofloxacin/raxibacumab combination groups (-0.88%, 95% CI [-23.9%, 19.6%]). Excluding rabbit K99246 from the above analyses does not change the study conclusion (see Section 3.1.3.2).

Table 6 Survival Rate at Day 28 in Rabbit Study 781-G923701

| Population | Treatment | N | No. of Survivors (%) [*] | 95% CI ^{**} of Levo/Raxi – Levo (%) |
|------------------------|--------------|----|-----------------------------------|--|
| Sponsor's ITT | Placebo | 12 | 0 (0.0%) | |
| | Levofloxacin | 20 | 19 (95.0%) | |
| | Levo/Raxi | 20 | 19 (95.0%) | (-20.4, 20.4) |
| FDA primary | Placebo | 10 | 0 (0.0%) | |
| | Levofloxacin | 20 | 19 (95.0%) | |
| | Levo/Raxi | 17 | 16 (94.1%) | (-23.9, 19.6) |
| As-treated | Placebo | 12 | 0 (0.0%) | |
| | Levofloxacin | 21 | 20 (95.2%) | |
| | Levo/Raxi | 19 | 18 (94.7%) | (-22.2, 18.7) |
| Toxicemic at treatment | Placebo | 12 | 0 (0.0%) | |
| | Levofloxacin | 19 | 18 (94.7%) | |
| | Levo/Raxi | 18 | 17 (94.4%) | (-22.2, 21.2) |

^{*}There is significant difference between each active group and placebo (all p -values <0.0001).

^{**}CI's are exact confidence intervals for comparison between levo/Raxi and levofloxacin.

Comment:

The results above were consistent regardless of analysis populations.

As previously conveyed to the sponsor, the primary interest for this study was to compare the combination of levofloxacin and raxibacumab versus levofloxacin alone. Although the analysis shows that levofloxacin/raxibacumab group is efficacious over placebo, it does not address whether the efficacy of the combination treatment is due to the effect of raxibacumab or antimicrobial. Additionally, while the survival rate is numerically higher in the levofloxacin arm compared to the levofloxacin/raxibacumab arm, the study was not powered to detect a difference of interest.

Table 7 presents the primary efficacy results in Study 789-G923702 by analysis populations. None of the 12 monkeys in the placebo group survived. There was 1 death in the ciprofloxacin group (C30988) which happened from a non-study-related issue during the 60-day additional observation period. There were 2 deaths in the ciprofloxacin/raxibacumab combination group, including C31142 which died at 9.95 days post challenge and C24791 which died at 3.69 days from a potential gavage error. According to the FDA primary analysis population, the 28-day survival rates were 0%, 100%, and 84.6% in the placebo, ciprofloxacin, and ciprofloxacin/raxibacumab combination groups, respectively. There was not a significant difference ($p=0.222$) in survival rates between the ciprofloxacin and raxibacumab/ciprofloxacin combination groups (-15.4%, 95% CI [-45.5%, 11.4%]). Excluding monkey C24791 from the above analyses does not change the study conclusion (see Section 3.1.3.2).

Table 7 Survival Rate at Day 28 in Monkey Study 789-G923702

| Population | Treatment | N | No. of Survivors (%) [*] | 95% CI ^{**} of Cipro/Raxi – Cipro (%) |
|--------------------|---------------|----|-----------------------------------|--|
| Sponsor's ITT | Placebo | 12 | 0 (0.0%) | |
| | Ciprofloxacin | 14 | 14 (100%) | |
| | Cipro/Raxi | 14 | 12 (85.7%) | (-42.8, 11.9) |
| FDA primary | Placebo | 10 | 0 (0.0%) | |
| | Ciprofloxacin | 13 | 13 (100%) | |
| | Cipro/Raxi | 13 | 11 (84.6%) | (-45.5, 11.4) |
| As-treated | Placebo | 12 | 0 (0.0%) | |
| | Ciprofloxacin | 14 | 14 (100%) | |
| | Cipro/Raxi | 14 | 12 (85.7%) | (-42.8, 11.9) |
| Toxic at treatment | Placebo | 11 | 0 (0.0%) | |
| | Ciprofloxacin | 13 | 13 (100%) | |
| | Cipro/Raxi | 14 | 12 (85.7%) | (-42.8, 12.1) |

^{*}There is significant difference between each active group and placebo (all p -values <0.0001).

^{**}CI's are exact confidence intervals for comparison between cipro/Raxi and Ciprofloxacin.

Comment:

The results above were consistent regardless of analysis populations.

As previously conveyed to the sponsor, the primary interest for this study was to compare the combination of ciprofloxacin and raxibacumab versus ciprofloxacin alone. Although the analysis shows that ciprofloxacin/raxibacumab group is efficacious over placebo, it does not address whether the efficacy of the combination treatment is due to the effect of raxibacumab or antimicrobial. Additionally, while the survival rate is numerically higher in the ciprofloxacin arm compared to the ciprofloxacin/raxibacumab arm, the study was not powered to detect a difference of interest.

3.1.3.2 Additional Analyses of the Primary Efficacy Endpoint

Analysis Excluding Non-anthrax Deaths

Studies 781-G923701 and 789-G923702 each had one animal whose death could not be attributable to anthrax. In Study 781-G923701, one rabbit K99246 in the levofloxacin/raxibacumab group died at 1.9 days as the result of a dosing accident (inadvertent intratracheal gavage of study agent). In Study 789-G923702, one monkey (C24791) in the ciprofloxacin/raxibacumab group died from pneumonia related to a potential gavage error. Sensitivity analyses with respect to the primary efficacy endpoint were performed on several populations by excluding the non-anthrax death animals (Tables 8 and 9).

Sensitivity analyses did not alter the conclusions of the primary efficacy analyses. There was no statistical difference in 28 day survival rate between antimicrobial and antimicrobial/raxibacumab groups for all populations analyzed. Statistically significant survival benefit for both antimicrobial and antimicrobial/raxibacumab was maintained as compared to placebo.

Table 8 Survival Rate at Day 28 Excluding Non-anthrax Death in Rabbit Study 781-G923701

| Population | Treatment | N | No. of Survivors (%) [*] | 95% CI ^{**} of Raxi/Levo – Levo (%) |
|-----------------------------|--------------|----|-----------------------------------|--|
| Sponsor's ITT | Placebo | 12 | 0 (0.0%) | |
| | Levofloxacin | 20 | 19 (95.0%) | |
| | Raxi/Levo | 19 | 19 (100%) | (-12.8, 25.7) |
| FDA primary | Placebo | 10 | 0 (0.0%) | |
| | Levofloxacin | 20 | 19 (95.0%) | |
| | Raxi/Levo | 16 | 16 (100%) | (-15.2, 25.6) |
| As-treated | Placebo | 12 | 0 (0.0%) | |
| | Levofloxacin | 21 | 20 (95.2%) | |
| | Raxi/Levo | 18 | 18 (100%) | (-14.1, 23.8) |
| Toxemic at treatment | Placebo | 12 | 0 (0.0%) | |
| | Levofloxacin | 19 | 18 (94.7%) | |
| | Raxi/Levo | 17 | 17 (100%) | (-13.9, 26.0) |

**There is significant difference between each active group and placebo (all p-values <0.0001).*

***CIs are exact confidence intervals for comparison between levo/Raxi and levofloxacin.*

Table 9 Survival Rate at Day 28 Excluding Non-anthrax Death in Monkey Study 789-G923702

| Population | Treatment | N | No. of Survivors (%)* | 95% CI** of Raxi/Cipro – Cipro (%) |
|---------------------------|---------------|----|-----------------------|------------------------------------|
| Sponsor's ITT | Placebo | 12 | 0 (0.0%) | (-36.3, 15.5) |
| | Ciprofloxacin | 14 | 14 (100%) | |
| | Raxi/Cipro | 13 | 12 (92.3%) | |
| FDA primary | Placebo | 10 | 0 (0.0%) | (-38.5, 16.2) |
| | Ciprofloxacin | 13 | 13 (100%) | |
| | Raxi/Cipro | 12 | 11 (91.7%) | |
| As-treated | Placebo | 12 | 0 (0.0%) | (-36.3, 15.5) |
| | Ciprofloxacin | 14 | 14 (100%) | |
| | Raxi/Cipro | 13 | 12 (92.3%) | |
| Toxic at treatment | Placebo | 11 | 0 (0.0%) | (-36.0, 18.9) |
| | Ciprofloxacin | 13 | 13 (100%) | |
| | Raxi/Cipro | 13 | 12 (92.3%) | |

*There is significant difference between each active group and placebo (all p-values <0.0001).

**CIs are exact confidence intervals for comparison between cipro/Raxi and Ciprofloxacin.

As-randomized Analysis

As defined in Section 3.1.1, the FDA primary analysis population includes all animals with bacteremia at treatment initiation and according to the actual treatment administered. In Study 781-G923701, one of the 52 rabbits did not receive its assigned treatment. Rabbit K99251 was randomized to the levofloxacin/raxibacumab group but was not dosed with raxibacumab according to its PK data. This animal was included in the levofloxacin/raxibacumab group in the sponsor's ITT analysis and in the levofloxacin group in the FDA primary analysis. A sensitivity analysis was conducted by including this animal as randomized and excluding those animals that had no bacteremia at the time of treatment initiation (Table 10). Analysis of all animals with bacteremia at treatment initiation and according to the randomized group did not change the conclusion of this study.

Table 10 Survival Rate at Day 28 in Rabbit Study 781-G923701

| Population | Treatment | N | No. of Survivors (%)* | 95% CI** of Raxi/Levo – Levo (%) |
|----------------------|--------------|----|-----------------------|----------------------------------|
| FDA primary | Placebo | 10 | 0 (0.0%) | (-23.9, 19.6) |
| | Levofloxacin | 20 | 19 (95.0%) | |
| | Raxi/Levo | 17 | 16 (94.1%) | |
| As-randomized | Placebo | 10 | 0 (0.0%) | (-22.8, 20.6) |
| | Levofloxacin | 19 | 18 (94.7%) | |
| | Raxi/Levo | 18 | 17 (94.4%) | |

*There is significant difference between each active group and placebo (all p-values <0.0001).

**CIs are exact confidence intervals for comparison between levo/Raxi and levofloxacin.

In Study 789-G923702, all monkeys received treatment according to their assigned groups. Although monkey C25576 randomized to the placebo group but received 1 dose of ciprofloxacin at the 12 hour post challenge, this animal remained in the placebo group

since it received placebo throughout the majority of the ciprofloxacin dosing schedule. Therefore, the FDA primary population is the same as the sponsor's ITT population except for the bacteremic status. No additional sensitivity analysis is performed for Study 789-G923702.

3.1.3.3 Secondary Efficacy Endpoint

The secondary efficacy endpoint was survival time defined as the time from spore challenge to death during the 28-day post challenge period. For animals that were alive at the end of the 28-day post challenge, survival times were to be censored on the date of study completion. As shown in Figure 1 for Study 781-G923701 and Figure 2 for Study 789-G923702, survival time was significantly longer in the antimicrobial group ($p < 0.0001$) and the antimicrobial/raxibacumab combination group ($p < 0.0001$) relative to the placebo group. The difference in survival times between the 2 active treatment groups was not statistically significant ($p = 0.891$ in Study 781-G923701 and $p=0.149$ in Study 789-G923702 as determined by log-rank test). The median survival time in the placebo group was 3.1 days for rabbits in Study 781-G923701 and 3.9 days for monkeys in Study 789-G923702. Median survival time could not be determined for the antimicrobial and antimicrobial/raxibacumab groups because the medians extended beyond 28 days. The results were consistent with the ITT population as presented by the sponsor in the study report.

Figure 1 Survival Probability of Rabbit Study 781-G923701 (FDA primary analysis population)

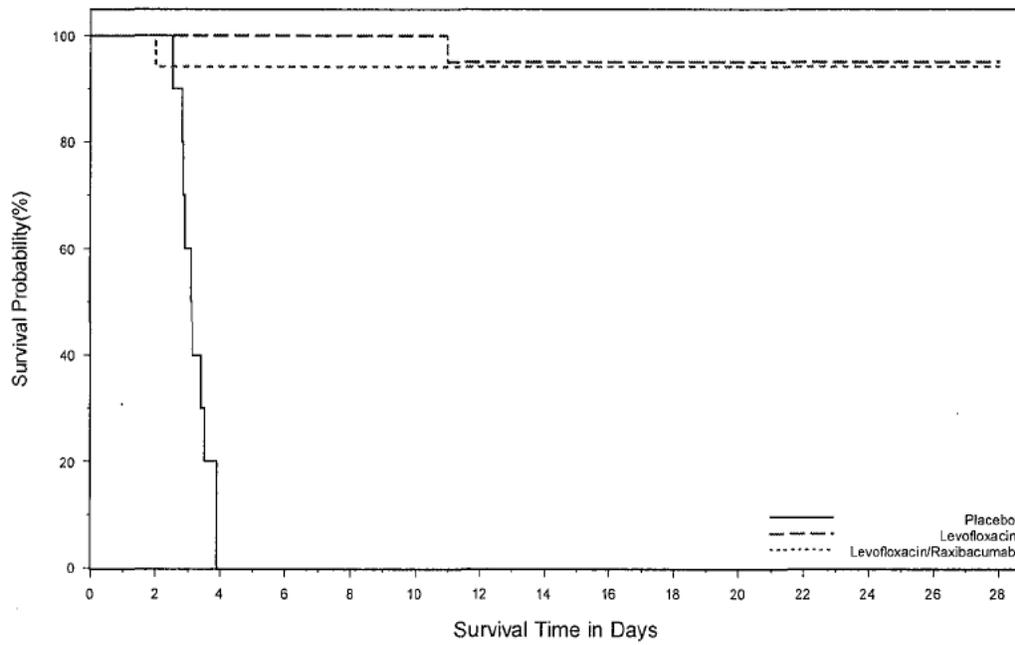
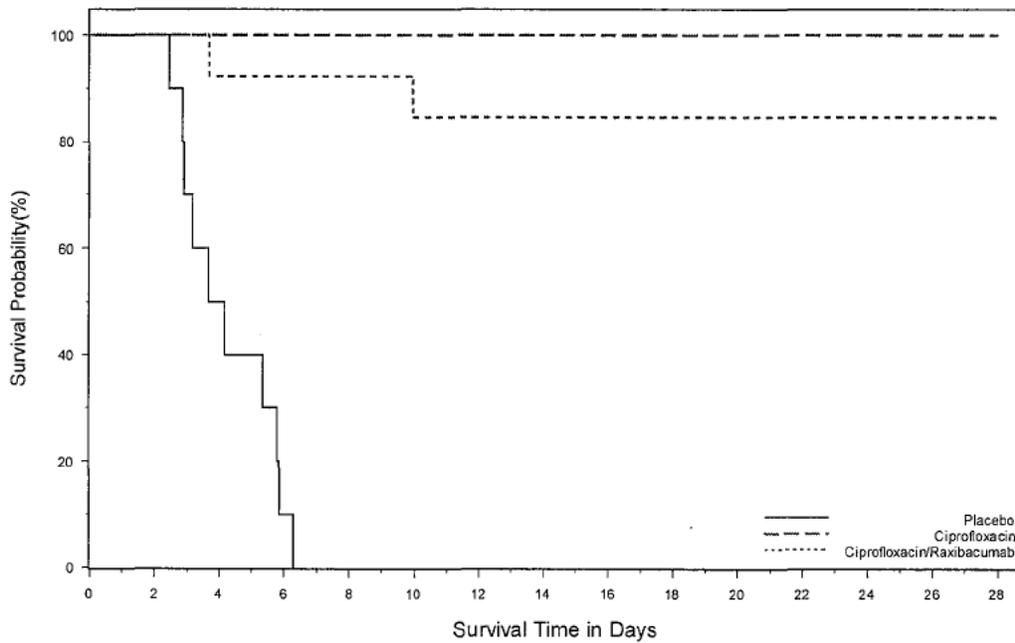


Figure 2 Survival Probability of Monkey Study 789-G923702 (FDA primary analysis population)



3.2 Evaluation of Safety

Limited safety information was collected during these studies. Complete gross necropsies were conducted on all 52 rabbits, survivors and non-survivors, in Study 781-G923701 while in Study 789-G923702, only the 15 monkeys that were found dead or euthanized had their tissues examined microscopically.

In Study 781-G923701, few gross lesions were evident in rabbits surviving to study termination, and these lesions did not correlate histologically with definitive evidence of anthrax. Gross lesions in rabbits dying prior to study termination included enlargement, discoloration and/or foci of the adrenal glands, appendix, brain, lung and multiple lymph nodes; fluid (effusion) in the pericardial and thoracic cavities, and fluid/thickening (edema) of the skin and thymus. These correlated histologically with necrosis, inflammation, hemorrhage, edema and anthrax bacteria. All 52 rabbits, survivors and non-survivors, had their tissues examined microscopically. On microscopic examination of the non-survivor animals that died of anthrax during study, moderate/marked hemorrhage and bacteria was seen in 1/12 placebo treated animal and 0/1 levofloxacin treated animal. The only death in the levofloxacin/raxibacumab group occurred due to a dosing accident not related to anthrax. All survivor animals also underwent necropsy and had no abnormal findings on histopathologic evaluation: 0/20 levofloxacin and 0/18 levofloxacin/raxibacumab treated animals.

In Study 789-G923702, lesions at necropsy consistent with anthrax included adrenal gland discoloration (indicating the presence of bacteria); brain/meningeal red-stained accumulation, discoloration or foci (hemorrhage and inflammation); abdominal and/or thoracic cavity fluid (effusion); enlargement of axillary, bronchial, mandibular and/or mediastinal lymph nodes (edema, fibrin exudation, and hemorrhage); and skin or thymic fluid (edema). Two monkeys died of non-anthrax causes, including one in the ciprofloxacin group that died of non-study-related issue and another in the ciprofloxacin/raxibacumab group that died of a gavage error. Microscopic findings consistent with anthrax were present in 13 of 15 dead monkeys. On microscopic examination of the brains of the animals that died of anthrax, 1/12 placebo animals and 1/1 ciprofloxacin/raxibacumab animals had moderate hemorrhagic meningitis. No animals in the ciprofloxacin group died due to anthrax.

Reviewer's comment: The above is just a brief summary of necropsy and histopathology findings. The CNS pathology rates in the monkey study are 1/12 in placebo, 0 in ciprofloxacin, and 1/1 in ciprofloxacin/raxibacumab group which is supportive of the CNS findings in previous pivotal studies. For details, please see the reviews of the medical officers.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Race is not applicable for the current studies.

Table 11 presents survival rates according to categories of sex and age of rabbits in each treatment group for Study 781-G923701. The survival rates were comparable between male and female monkeys within the same treatment groups. Rabbits in the study were either 257 or 292 days old at the time of randomization. The survival rates were also comparable between 257-day-old and 292-day-old rabbits within the same treatment groups.

**Table 11 Survival Rate by Sex and Age Categories in Rabbit Study 781-G923701
Number of Survivors/Total Animals, n/N (%)**

| | | Placebo | Levofloxacin | Levo/Raxi |
|----------------------|--------|-----------|---------------|---------------|
| Sponsor's ITT | N | 12 | 20 | 20 |
| Sex | | | | |
| | Male | 0/6 (0.0) | 9/10 (90.0) | 10/10 (100.0) |
| | Female | 0/6 (0.0) | 10/10 (100.0) | 9/10 (90.0) |
| Age (days) | | | | |
| | 257 | 0/6 (0.0) | 10/10 (100.0) | 9/10 (90.0) |
| | 292 | 0/6 (0.0) | 9/10 (90.0) | 10/10 (100.0) |
| FDA Primary | N | 10 | 20 | 17 |
| Sex | | | | |
| | Male | 0/6 (0.0) | 9/10 (90.0) | 8/8 (100.0) |
| | Female | 0/4 (0.0) | 10/10 (100.0) | 8/9 (88.9) |
| Age(days) | | | | |
| | 257 | 0/4 (0.0) | 10/10 (100.0) | 8/9 (88.9) |
| | 292 | 0/6 (0.0) | 9/10 (90.0) | 8/8 (100.0) |

Table 12 summarizes survival rates according to categories of sex and age of monkeys in each treatment group for Study 789-G923702. The survival rates were the same for male and female monkeys in the placebo and ciprofloxacin groups. The 2 deaths in the ciprofloxacin/raxibacumab group were both male monkeys leading to a lower survival rate. The age of monkeys ranged from 2.9 years to 5.1 years with a median of 4.1 years. The group of monkeys older than the median age had the lowest survival rate (80% in Sponsor's ITT and 77.8% in FDA primary) than the rest of the subgroups. The survival rate in this group of monkeys was also lower than the overall survival rate (85.7% in Sponsor's ITT and 84.6 in FDA primary) in the ciprofloxacin/raxibacumab group.

**Table 12 Survival Rate by Sex and Age Categories in Monkey Study 789-G923702
Number of Survivors/Total Animals, n/N (%)**

| | | Placebo | Ciprofloxacin | Cipro/Raxi |
|----------------------|------------------------|-----------|---------------|-------------|
| Sponsor's ITT | N | 12 | 14 | 14 |
| Sex | | | | |
| | Male | 0/6 (0.0) | 7/7 (100.0) | 5/7 (71.4) |
| | Female | 0/6 (0.0) | 7/7 (100.0) | 7/7 (100.0) |
| Age(years) | | | | |
| | Min(2.9) – median(4.1) | 0/5 (0.0) | 7/7 (100.0) | 4/4 (100.0) |
| | Median(4.1) – max(5.1) | 0/7 (0.0) | 7/7 (100.0) | 8/10 (80.0) |
| FDA Primary | N | 10 | 13 | 13 |
| Sex | | | | |
| | Male | 0/4 (0.0) | 7/7 (100.0) | 4/6 (66.7) |
| | Female | 0/6 (0.0) | 6/6 (100.0) | 7/7(100.0) |
| Age(years) | | | | |
| | Min(2.9) – median(4.1) | 0/4 (0.0) | 7/7 (100.0) | 4/4 (100.0) |
| | Median(4.1) – max(5.1) | 0/6 (0.0) | 6/6 (100.0) | 7/9 (77.8) |

4.2 Other Special/Subgroup Populations

Animal's weights may play a role in its response to challenge and treatment and hence are evaluated here (Tables 13 and 14).

The prechallenge weights of the rabbits in Study 781-G923701 ranged from 3.1 to 4.0 kg with a median and mean of 3.5 kg. None of the rabbits in the placebo group survived. In the both levofloxacin and levofloxacin/raxibacumab groups, the survival rates were comparable between rabbits with weights lower than the median weight and rabbits with weights greater than the median weight.

Table 13 Survival Rate by Weight Categories in Rabbit Study 781-G923701
Number of Survivors/Total Animals, n/N (%)

| | | Placebo | Levofloxacin | Levo/Raxi |
|------------------------|---|-----------|--------------|---------------|
| Sponsor's ITT | N | 12 | 20 | 20 |
| Weight (kg) | | | | |
| Min(3.1) – median(3.5) | | 0/7 (0.0) | 10/11 (90.9) | 10/10 (100.0) |
| Median(3.5) – max(4.0) | | 0/5 (0.0) | 9/9 (100.0) | 9/10 (90.0) |
| FDA Primary | N | 10 | 20 | 17 |
| Weight (kg) | | | | |
| Min(3.1) – median(3.5) | | 0/5 (0.0) | 10/11 (90.9) | 8/8 (100.0) |
| Median(3.5) – max(4.0) | | 0/5 (0.0) | 9/9 (100.0) | 8/9 (88.9) |

In Study 789-G923702, prechallenge weights of the monkeys ranged from 2.5 to 6.5 kg with a median of 3.1 kg. None of the monkeys in the placebo group survived while all monkeys in the ciprofloxacin group did. In the ciprofloxacin/raxibacumab group, the survival rates were 66.7% for the group with weights greater than the median weight (>3.1 kg) and 100% for the group with weights lower than the median weight (\leq 3.1 kg).

Table 14 Survival Rate by Weight Categories in Monkey Study 789-G923702
Number of Survivors/Total Animals, n/N (%)

| | | Placebo | Ciprofloxacin | Cipro/Raxi |
|------------------------|---|-----------|---------------|-------------|
| Sponsor's ITT | N | 12 | 14 | 14 |
| Weight (kg) | | | | |
| Min(2.5) – median(3.1) | | 0/6 (0.0) | 7/7 (100.0) | 8/8 (100.0) |
| Median(3.1) – max(6.5) | | 0/6 (0.0) | 7/7 (100.0) | 4/6 (66.7) |
| FDA Primary | N | 10 | 13 | 13 |
| Weight (kg) | | | | |
| Min(2.5) – median(3.1) | | 0/6 (0.0) | 6/6 (100.0) | 7/7 (100.0) |
| Median(3.1) – max(6.5) | | 0/4 (0.0) | 7/7 (100.0) | 4/6 (66.7) |

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two animal studies (781-G923701 in rabbits and 789-G923702 in monkeys) were submitted to support the combination use of raxibacumab and antimicrobial for the treatment of inhalation anthrax. They were specifically designed as combination trials to assess possible antagonism or possible benefit of raxibacumab plus antimicrobial compared with antimicrobial alone. The primary efficacy endpoint of both studies was survival at Day 28, defined as the percent of animals alive at Day 28. However, the sponsor performed the primary analysis as to compare the survival rates between the placebo group and the antimicrobial/raxibacumab combination group. The comparison between the combination group and the antimicrobial group was considered by the sponsor as a secondary analysis in Study 781-G923701 and an exploratory analysis in Study 789-G923702. Furthermore, the sponsor defined the intent-to-treat (ITT) population as the primary analysis population. The Agency considers the animals that were bacteremic at treatment initiation as the primary analysis population, as conveyed to the sponsor numerous times in FDA comments prior to protocol submission (see fax to the sponsor dated November 17, 2006) and also in comments regarding the study protocol.

There were 2 deaths in the active treatment groups of the rabbit Study 781-G923701, one in the levofloxacin group at 11 days post challenge and one in the levofloxacin/raxibacumab group at 1.9 days post challenge due to a dosing accident. There was no significant difference ($p=0.947$) in survival rates between the levofloxacin and levofloxacin/raxibacumab combination groups (-0.88%, 95% CI [-23.9%, 19.6%]). The 28-day survival rates were 0%, 95.0%, and 94.1% in the placebo, levofloxacin, and levofloxacin/raxibacumab combination groups, respectively. Complete gross necropsies were conducted on all 52 rabbits, none of which in the active treatment groups had lesions attributable to anthrax at sacrifice, or any brain lesions on microscopic examination.

There were 3 deaths in the active treatment groups of the monkey Study 789-G923702. One monkey in the ciprofloxacin group died from a non-study-related issue during the 60-day additional observation period. Two monkeys in the ciprofloxacin/raxibacumab combination group died, including one at 9.95 days post challenge and another one at 3.69 days from a gavage error. There was no significant difference ($p=0.222$) in survival rates between the ciprofloxacin and raxibacumab/ciprofloxacin combination groups (-15.4%, 95% CI [-45.5%, 11.4%]). The 28-day survival rates were 0%, 100%, and 84.6% in the placebo, ciprofloxacin, and ciprofloxacin/raxibacumab combination groups, respectively. Microscopic exams were performed on 15 monkeys that were found dead or euthanized, out of which one animal treated with ciprofloxacin/raxibacumab had evidence of hemorrhagic meningitis that affected the entire brain.

The above efficacy results are similar to those generated by the sponsor using the ITT population and are robust with various sensitivity analyses. Analysis excluding non-anthrax deaths does not alter the efficacy conclusion. The two combination trials did not

provide much additional information to further investigate the CNS findings observed in the pivotal studies. However, the results seen in the combination trial in monkeys were consistent with the pivotal studies.

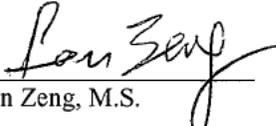
5.2 Conclusions and Recommendations

In the assessment of this reviewer, a single intravenous dose of 40 mg/kg raxibacumab given in combination with antimicrobial therapy resulted in similar observed efficacy as antimicrobial monotherapy in both the rabbit (Study 781-G923701) and the monkey (Study 789-G923702) studies that were submitted as the combination efficacy studies. However, these studies did not rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with levofloxacin or ciprofloxacin against lethality due to inhalation exposure of *B. anthracis*. The point estimates of survival rates for the antimicrobial arms were 95% in rabbits and 100% in monkeys whereas the point estimates for the antimicrobial/raxibacumab combination arms were 94.1% in rabbits and 84.6% in monkeys. Given the high survival rate of the antimicrobial monotherapy, it is not possible to show an improved efficacy of raxibacumab over antimicrobial. Due to limited number of animals, it is not possible to conclude that raxibacumab did not interfere with the efficacy of antimicrobial, either. In terms of histopathology, the two combination trials did not provide much additional information to further investigate the CNS findings observed in previous two pivotal studies (Study 682-G005758 and Study 742-G005829). However, the results from the combination trial in monkeys were consistent with the pivotal studies.

Interpretation of the study results is limited by the animal models which demonstrated much higher efficacies ($\geq 95\%$) of antimicrobial than in humans. Extrapolation of efficacy is therefore difficult from the animal models to humans.

SIGNATURES

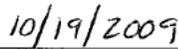
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Lan Zeng, M.S.


Date

Concurring Reviewer:


Karen Higgins, Sc.D


Date



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ANIMAL EFFICACY STUDIES

BLA/Serial Number: 125349

Drug Name: Raxibacumab (ABthrax, PA mAb)

Indication(s): Treatment of inhalational anthrax caused by *Bacillus anthracis*

Applicant: Human Genome Sciences, Inc

Date(s): Receipt Date: May 14, 2009
PDUFA Due Date: November 14, 2009

Review Priority: Priority

Biometrics Division: IV

Statistical Reviewer: Hongling Zhou, Ph.D.

Concurring Reviewers: Karen Higgins, Sc.D.
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Medical Division: Division of Special Pathogen and Transplant Products

Clinical Team: Susan McCune, M.D., Medical Reviewer
Sue Lim, M.D., Medical Reviewer
Yuliya Yasinskaya, M.D., Acting Medical Team Leader

Project Manager: Rebecca Saville, Pharm.D.

Keywords: Multiple comparisons, non-clinical studies.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In the assessment of this reviewer, a single intravenous dose of 40 mg/kg raxibacumab was shown to be superior to the placebo for the treatment of anthrax in the ITT and FDA primary analysis populations in both the monkey (Study 724-G005829) and the rabbit (Study 682-G005758) studies that were submitted as the pivotal efficacy studies. However, the results for raxibacumab 40 mg/kg group in the rabbit study would change if one rabbit, who was bacteremic 1/2 hour prior to treatment but was not bacteremic immediately before treatment initiation, was excluded, signaling that the evidence of there being a statistically significant difference between the raxibacumab 40 mg/kg group and the placebo group in the rabbit model is rather weak. In addition, the extrapolation from the animal to human use will depend on supportive evidence from pharmacokinetic information.

Two additional efficacy studies (Study 789-G923072 and Study 781-G923071) were conducted to evaluate the efficacy of raxibacumab in combination with antimicrobials. However, given the small sample size and the unexpectedly high survival rates in the antimicrobial alone arms, these studies cannot rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with levofloxacin or ciprofloxacin.

In both Study 724-G005829 and Study 682-G005758, non-surviving animals in the raxibacumab-treated groups were shown to have higher rates of high level of pathology in the brain than animals in the placebo group. The hypothesis stated by HGS that this difference was related to longer survival of the raxibacumab-treated animals rabbits compared to the placebo group was not found plausible. The analyses of histopathology data by this statistical reviewer indicate that an increased incidence and severity of CNS findings is related to increased survival time only within the raxibacumab group. In the combination studies (Study 781-G923701 and 789-G923702), there is no raxibacumab only treatment arm and only one animal in each study died of anthrax. These two studies contribute very little information regarding the CNS findings of the raxibacumab treatment. The CNS findings will need to be further investigated in the context of additional studies that are well designed to address this issue.

1.2 Brief Overview of Animal Efficacy Studies

A total of four animal efficacy studies were submitted to this BLA. Two animal studies (Study 682-G005758 and Study 724-G005829) conducted by the sponsor were used as pivotal efficacy studies to support raxibacumab for the treatment of inhalational anthrax. Two additional efficacy studies (Study 781-G923701 and Study 789-G923702) evaluated efficacy of raxibacumab with antimicrobials in cynomolgus monkeys and New Zealand White rabbits

Study 724-G005829 was a parallel-group, double-blind, randomized, placebo-controlled Good Laboratory Practices (GLP) study in healthy male and female cynomolgus monkeys to evaluate

the therapeutic efficacy of single intravenous (IV) doses of (20 mg/kg and 40 mg/kg) raxibacumab vs placebo in inhalation-challenged cynomolgus monkeys with symptomatic inhalation anthrax. The primary efficacy analysis was to compare the percent of animals alive at study Day 28 between the placebo group and each of the raxibacumab treatment groups.

Study 682-G005758 was an open-label, parallel-group, randomized, placebo-controlled GLP study in healthy male and female New Zealand White (NZW) rabbits to evaluate the therapeutic efficacy of single IV dose raxibacumab (20 mg/kg and 40 mg/kg) in anthrax spore inhalation-challenged rabbits experiencing symptoms of inhalation anthrax. The 14-Day survival rates of the two raxibacumab treatment groups were compared to that of the placebo group.

Study 789-G923702 was a parallel-group, double-blind, randomized, placebo-controlled study to evaluate the efficacy of raxibacumab in combination with ciprofloxacin as a therapeutic treatment in the cynomolgus monkey inhalation anthrax model. The primary efficacy analysis was to compare the survival at day 28 for the ciprofloxacin and ciprofloxacin/raxibacumab groups to the placebo group.

Study 781-G923701 was a parallel-group, randomized, double-blind, placebo-controlled GLP study to evaluate the efficacy of raxibacumab in combination with levofloxacin for therapeutic treatment in the NZW rabbit inhalational anthrax model. The primary efficacy analysis was to compare survival at Day 28 for the levofloxacin and levofloxacin/raxibacumab groups to the placebo group.

1.3 Statistical Issues and Findings

A statistical issue of both pivotal studies on the primary efficacy analysis was the adjustment for multiple comparisons. In protocol 724-G005829, the sponsor proposed to use a step-down sequential testing procedure. First, the 40 mg/kg raxibacumab group will be compared with the placebo group at a 2-sided $\alpha=0.05$ significance level. If the result is statistically significant, the 20 mg/kg group will be tested vs placebo at a two-sided $\alpha=0.05$ significance level. If the result for the 40 mg/kg group is not significant, superiority of neither raxibacumab group will be established. In the protocol for Study 682-G005758, the sponsor proposed that the primary efficacy analysis will be subject to a multiple comparison adjustment using the Hochberg procedure. The results will be considered statistically significant if: At least 1 of the pair-wise comparisons between raxibacumab and control achieves a p-value < 0.025 , or both pair-wise comparisons between raxibacumab and control achieve a p-value < 0.05 . The agency accepted the sponsor's proposals for multiplicity adjustments for both studies as defined in the relevant protocols. The sponsor did not discuss adjustment for multiple pairwise comparisons in the two study reports. However, the sponsor is only requesting approval of the 40 mg/kg dose which was found to be significant to placebo in the two pivotal efficacy studies even with adjustment for multiple comparisons.

In the two additional efficacy studies (Study 789-G923072 and Study 781-G923071) evaluating efficacy of raxibacumab with antimicrobials, the sponsor's primary analysis was to compare the survival at day 28 between the combination arm (raxibacumab/antimicrobial) to the placebo.

Both studies show that antimicrobial and raxibacumab/antimicrobial arms were superior to the placebo. In the protocol stage, the Division sent the comments to the sponsor that our primary goal for the combination studies is to explore the comparison of the combination (raxibacumab/antimicrobial) to antimicrobial alone and that the study's primary analysis (i.e., the comparison of the combination to placebo) will not lead to the conclusion that the efficacy of the combination arm, if confirmed, is due to raxibacumab or antimicrobial. However, the studies were not powered to detect a difference of our interest. The survival rates in the antimicrobial arms were very high in both studies, making it impossible to see any added benefit of raxibacumab to antimicrobial. Additionally, the survival rate was numerically higher in Ciprofloxacin arm than the raxibacumab/Ciprofloxacin arm in the monkey combination study (Study 789-G923072), leading to concern that raxibacumab may potentially reduce the efficacy of antimicrobials. However, given the small sample size and the unexpectedly high survival rates in the antimicrobial alone arms, these results are not very informative.

Given that the sponsor was exploring the efficacy of raxibacumab in the treatment of inhalational anthrax, it was very important that the animals in the study have active disease (i.e., be bacteremic) at the time of treatment. If they did not have active disease, the efficacy from the studies would be more relevant for an indication of post-exposure prophylaxis, which might be expected to yield higher survival rates. This was conveyed to the sponsor in the FDA comments numerous times prior to the submission of the study protocols and also in the comments on the study protocols. The FDA's primary analysis population, a type of modified intent to treat population with exclusion based on pre-treatment information only, includes only animals that were bacteremic at treatment initiation. The sponsor, however, considered the full intent to treat population as the primary analysis population.

The main statistical issue in this BLA review was regarding the histopathology finding that non-surviving animals in the raxibacumab-treated groups were shown to have higher rates of meningitis and/or higher rates of moderate/marked inflammation in the brain than animals in the placebo group in both Study 724-G005829 and Study 682-G005758. The sponsor claims that the higher proportion of raxibacumab-treated animals with evidence of CNS involvement is due to longer survival time of these animals. However, the histopathology data does not show the raxibacumab treated groups had longer duration of illness compared to the placebo group. Note that the two combination trials did not provide much additional information to further investigate the CNS findings observed in the pivotal studies, since there were very few deaths among the antimicrobial treated animals and no animal was treated with raxibacumab alone.

The details for each study are summarized below.

Study 742-G005829

Day 28 survival rates in both raxibacumab groups were shown to be superior to the rate in the placebo group for the FDA primary analysis population.

The rates of monkeys with moderate or marked brain inflammation were significantly higher in the raxibacumab 20 mg/kg group than the placebo group (6/7 [86%] compared with 1/12 [8%], $p = 0.0017$, Fisher's exact test) and numerically higher in the raxibacumab 40 mg/kg group than

the placebo group (2/5 [40%] compared with 1/12 [8%], $p=0.1912$). There is also a statistically significant difference between the raxibacumab 20 mg/kg group and the placebo in terms of proportion of monkeys with a high level of CNS pathology as determined by the medical reviewers (6/7 [86%] compared with 1/12 [8%], $p = 0.0017$) and a borderline significant difference between the raxibacumab 40 mg/kg group and the placebo group (3/5 [60%] compared with 1/12 [8%], $p=0.0525$).

Among the necropsized animals, there is no statistically significant difference in time to death (from the end of anthrax challenge) between the placebo and the raxibacumab groups ($p = 0.5895$ compared with the 20 mg/kg group and $p = 0.9586$ compared with the 40 mg/kg group). There is no credible evidence from the histopathology data for the sponsor's hypothesis that the length of survival led to the difference in the number of animals with moderate/marked level of bacteria presence and/or with moderate/marked brain inflammation in the 20 mg/kg raxibacumab group compared to the placebo group.

Study 682-G005758

Day 14 survival rates in both raxibacumab groups were higher than in the placebo group. Applying the Hochberg's procedure to the FDA primary analysis population, we conclude that the raxibacumab 40 mg/kg group showed a statistically significant survival benefit over the placebo group but the raxibacumab 20 mg/kg group did not show a significant survival benefit over the placebo. However, the results for raxibacumab 40 mg/kg group in the rabbit study would change if rabbit L08147 was excluded from the FDA primary analysis population. Rabbit L08147 was bacteremic 1/2 hour prior to treatment but was not bacteremic immediately before treatment initiation. This signals that the evidence of a statistically significant difference between the raxibacumab 40 mg/kg group and the placebo group shown in the FDA primary analysis population is rather weak.

The rates of rabbits with a high level of CNS pathology as determined by the medical reviewers were significantly higher in the raxibacumab treated groups, both 20 mg/kg (9/12 [75%]) and 40 mg/kg (6/11 [55%]), compared with placebo (2/16 [13%], p -values 0.002 and 0.033, respectively, Fisher's exact test).

Among the necropsized animals, there is no statistically significant difference for time to death between the placebo group and the raxibacumab groups ($p=0.5494$ compared with the 20 mg/kg group and $p=0.7877$ compared with the 40 mg/kg group, Wilcoxon two sample test). Again there is no credible evidence from the histopathology data for the sponsor's hypothesis that the length of survival led to the difference in the number of animals with meningitis in the raxibacumab groups compared to the placebo group.

Study 781-G923701

The 28-day survival rates were 0%, 95.0%, and 94.1% in the placebo, levofloxacin, and levofloxacin/raxibacumab combination groups, respectively. There was no significant difference ($p=0.947$) in survival rates between the levofloxacin and levofloxacin/raxibacumab combination groups (-0.88%, 95% CI [-23.9%, 19.6%]). However, given the small size of the study and the unexpectedly high survival rate in the antimicrobial alone arm, this study could not rule out

possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with levofloxacin. Complete gross necropsies were conducted on all 52 rabbits, none of which in the active treatment groups had lesions attributable to anthrax at sacrifice, or any brain lesions on microscopic examination.

Study 789-G923702

The 28-day survival rates were 0%, 100%, and 84.6% in the placebo, ciprofloxacin, and ciprofloxacin/raxibacumab combination groups, respectively. There was no significant difference ($p=0.222$) in survival rates between the ciprofloxacin and raxibacumab/ciprofloxacin combination groups (-15.4%, 95% CI [-45.5%, 11.4%]). However, given the small size of the study and the unexpectedly high survival rate in the antimicrobial alone arm, this study could not rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with ciprofloxacin. Microscopic exams were performed on 15 monkeys that were found dead or euthanized, out of which one animal treated with ciprofloxacin/raxibacumab had evidence of hemorrhagic meningitis that affected the entire brain.

2. INTRODUCTION

2.1 Overview

Raxibacumab (ABthrax, PA mAb) is a fully human monoclonal antibody to the Protective Antigen (PA) of *Bacillus anthracis* developed by the Human Genome Sciences. Anthrax disease is caused by infection with spore-forming *Bacillus anthracis* bacteria. Since the 2001 anthrax attack through the US mail system, there is increased emphasis on therapeutic treatments as a new anti-bioterrorism measure. Human Genome Sciences was contracted by BARDA (Biomedical Advanced Research and Development Authority) for developing therapeutic products for the treatment of inhalation anthrax disease for the Strategic National Stockpile (SNS). In 2009, the CDC's IND was deemed safe to proceed which allows for emergency use of raxibacumab.

Due to the lethality of the anthrax infection, clinical trials are not ethically feasible. The issue of animal efficacy studies required for licensure of raxibacumab under the Animal Rule was discussed with the leadership of the Center for Drug Evaluation and Research during a Regulatory Briefing in October 2006. A consensus was reached that the efficacy of the monoclonal antibody against anthrax toxin should be demonstrated in 2 animal species (rabbit and non-human primate). Both models must show a significant benefit of the monoclonal over placebo. In addition, both models should explore the magnitude of benefit of an antitoxin therapeutic when combined with an antimicrobial over antimicrobial alone. The Review Team had conveyed the agreement reached at the regulatory briefing to the sponsor in a letter dated November 17, 2006.

The two pivotal animal studies (Study 682-G005758 on rabbits and Study 724-G005829 on monkeys) conducted in support of the indication of therapeutic treatment of inhalation anthrax were first submitted to the Division by HGS (IND 11069 SN057, SN064 and SN067) as part of

the SNS application. The study reports and data for the rabbit and monkey therapeutic efficacy studies were included in that submission. The statistical review for the SNS application focused on these two pivotal animal studies (Study 682-G005758 on rabbits and Study 724-G005829 on monkeys). Two safety and pharmacokinetic studies were also submitted for the SNS application. Please see statistical review for the SNS applications (IND 11069 SN057) in DARRTS for more details.

Two additional studies evaluating efficacy of raxibacumab with antimicrobials were submitted in the BLA. Study 781-G923701 is entitled “Evaluating the Efficacy of Raxibacumab in Combination with Levofloxacin for Post-exposure Treatment in the New Zealand White Rabbit Inhalational Anthrax Model”, and Study 789-G923702 is entitled “Evaluate the Efficacy of Raxibacumab in Combination with Ciprofloxacin for Therapeutic Treatment in the Cynomolgus Monkey Inhalation Anthrax Model”. These two studies are part of the agreement between the sponsor and the agency that animal studies evaluating the efficacy of raxibacumab with antimicrobials were important to assess possible antagonism or possible benefit of raxibacumab plus antimicrobial compared with antimicrobial alone, as raxibacumab is likely to be used in combination with antimicrobials. The sponsor’s primary analysis was to compare the survival at day 28 between the combination arm (raxibacumab/antimicrobial) and the placebo. In the protocol stage, the Division sent the comments to the sponsor that our primary goal for the combination study is to explore the comparison of the combination (raxibacumab/antimicrobial) to antimicrobial alone and that the study’s primary analysis (i.e., the comparison of the combination to placebo) will not lead to the conclusion that the efficacy of the combination arm, if confirmed, is due to raxibacumab or antimicrobial. However, the studies were not powered to detect a difference of our interest. The survival rates in the antimicrobial arms were very high in both studies, making it impossible to see any added benefit of raxibacumab to antimicrobial. Additionally, the survival rate was even numerically higher in Ciprofloxacin arm than the raxibacumab/Ciprofloxacin arm in the monkey study, leading to concern that raxibacumab may potentially reduce the efficacy of antimicrobials. However, given the small sample size and the unexpectedly high survival rates in the antimicrobial alone arms, these results are not very informative.

2.2 Data Sources

Data sets for the four efficacy studies were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows:

\\Cbsap58\M\CTD_submissions\STN125349

For the SNS application, the original definition files did not provide adequate information for the variables in the datasets. The Agency requested the sponsor to provide clear definition for the variables. The updated definition files sent by the sponsor (SN064 for the raw datasets at \\FDSWA150\NONECTD\11069\O_064\2008-07-18 and SN067 for the analysis datasets at \\FDSWA150\NONECTD\11069\O_067\2008-07-30) provided the needed information for the review. With repeated requests from the agency, the histopathology data was provided by the sponsor in SN090 at \\FDSWA150\NONECTD\11069\O_090\2008-11-24. These updated data were provided in the BLA submission. The electronic data sets generally represented the data described in the study report.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

A total of four animal efficacy studies were submitted to this BLA. Two animal studies (Study 682-G005758 and Study 724-G005829) conducted by the sponsor were used as pivotal efficacy studies to support raxibacumab for the treatment of inhalational anthrax. Two additional efficacy studies (Study 781-G923701 and Study 789-G923702) evaluated efficacy of raxibacumab with antimicrobials in cynomolgus monkeys and New Zealand White rabbits.

Study 724-G005829: Evaluation of Raxibacumab Efficacy as Therapeutic Treatment against Inhalation Anthrax in the Cynomolgus Macaque

Study 682-G005758: Evaluation of raxibacumab Efficacy as Therapeutic Treatment against Inhalation Anthrax in the Rabbit Model

Study 789-G923702: Evaluation of the Efficacy of Raxibacumab in Combination with Ciprofloxacin for Therapeutic Treatment in the Cynomolgus Monkey Inhalation Anthrax Model

Study 781-G923701: Evaluating the efficacy of raxibacumab in combination with levofloxacin for post-exposure treatment in the New Zealand White Rabbit inhalational anthrax model

Study 724-G005829 and Study 682-G005758 were conducted as the pivotal animal efficacy studies for the indication of treatment of anthrax. This section presents and discusses the details of these two studies. Please see statistical review by Lan Zeng for details of study 789-G923702 and study 781-G923701.

3.1.1 Study 724-G005829

Objectives and Study Design

Study 724-G005829 was a parallel-group, double-blind, randomized, placebo-controlled GLP (Good Laboratory Practices) study in healthy male and female cynomolgus monkeys to evaluate the therapeutic efficacy of single intravenous (IV) doses of raxibacumab vs placebo in inhalation-challenged cynomolgus monkeys with symptomatic inhalation anthrax. The study was conducted from September 15, 2007 to January 11, 2008 at Battelle Biomedical Research Center (BBRC) in West Jefferson, OH.

The primary objective of this study was to evaluate the efficacy of raxibacumab when administered as a therapeutic treatment against lethality due to inhalation exposure to *B.*

anthracis in cynomolgus monkeys. Male and female, juvenile (< 5 years of age) naïve Chinese colony-bred cynomolgus monkeys (*Macaca fascicularis* (b) (4)) weighing 2.5 to 4.5 kg at randomization and free of malformations and clinical signs of disease were included in this study. The primary efficacy analysis was to compare the percent of animals alive at study Day 28 between the placebo group and each of the treatment groups.

The 28-Day survival rates of the two raxibacumab treatment groups were compared to that of the placebo group. According to the study protocol, the primary efficacy analysis will be performed using a 2-sided likelihood ratio test (or the Fisher's exact test, if any expected cell count in the contingency table is less than 5), and is subject to a multiple comparison adjustment using a step-down sequential testing procedure. First, the 40 mg/kg raxibacumab group will be compared with the placebo group at a 2-sided $\alpha=0.05$ significance level. If the result is statistically significant, superiority of 40 mg/kg vs placebo will be established, and the 20 mg/kg group will be tested vs placebo at a two-sided $\alpha=0.05$ significance level. If this is statistically significant, the superiority of 20 mg/kg vs placebo will also be established.

Monkeys were randomized to each of the 3 groups (50% males and 50% females). Each group received the dosages of raxibacumab or placebo as follows:

- Group 1 (14 monkeys): single IV dose of 40 mg/kg raxibacumab
- Group 2 (14 monkeys): single IV dose of 20 mg/kg raxibacumab
- Group 3 (12 monkeys): single IV dose raxibacumab buffer (control)

Monkeys were randomized by sex to 1 of 3 aerosol challenge days (9/18/07, 9/25/07 and 10/2/07) and a challenge order per day. On Study Day 0, monkeys were to be challenged with a targeted 200 x lethal dose (LD₅₀) (1.24 x 10⁷ spores) of *B. anthracis* spores (Ames strain) by a Collison nebulizer and delivered using a head-only inhalation exposure chamber. When an animal exhibited a positive serum PA level via the screening assay or at 54 hours post challenge, a single bolus IV injection of either 40 or 20 mg/kg raxibacumab, or 1 mL/kg raxibacumab buffer (dependent upon that animal's treatment assignment) was to be administered. Just prior to treatment intervention (\pm 5 minutes), monkeys were administered a single 1 mg/kg dose of diphenhydramine (or equivalent) intramuscularly (IM). Diphenhydramine was given to parallel the treatment paradigm for humans in Phase 2/3 studies. Staff administering the study agent were blinded to study agent preparation to preclude introduction of bias into the study following treatment.

The analysis populations for this study were defined as follows:

- ITT population: all monkeys that were randomized and challenged with anthrax spores in the study. The ITT analysis was based on the intended treatment group planned at randomization rather than the actual treatment received.
- Modified ITT population: A subset of the ITT population that included all animals that received a study agent. The modified ITT analysis was based on the planned treatment group rather than the actual treatment received.
- As-treated population: The set of all animals that received a study agent with the assignment to treatment group based on the actual treatment that the animals received.

The sponsor's primary efficacy analysis was performed on the intention-to-treat (ITT) population.

Note: The Medical Officer had the following comments to the sponsor regarding the primary efficacy population when the protocol was submitted (SN 033): For your study population to be sufficiently reflective of the human anthrax disease your primary study analysis should be conducted in all animals that were confirmed to have anthrax disease as evident by both PA toxemia and bacteremia at the time of treatment initiation.

In the review process for the SNS, it was found by the microbiology reviewer that Experimental Pathology Laboratories, Inc. (ECL) appears to be highly unreliable in the detection of B. anthracis. The decision was made to determine the status of bacteremia based on the culture. The FDA primary analysis population is, therefore, defined as all animals that were bacteremic (based on culture) at the time of treatment.

The motivation behind this FDA-defined analysis population was that treatment prior to development of anthrax disease would not parallel treatment of anthrax in humans and would be more reflective of a post-exposure prophylaxis model than of a treatment model. It is understood that treatment of active disease is much more difficult than treatment prior to development of anthrax disease. Therefore, in order to test raxibacumab as a treatment of anthrax disease, it was important that the animal have confirmed anthrax disease.

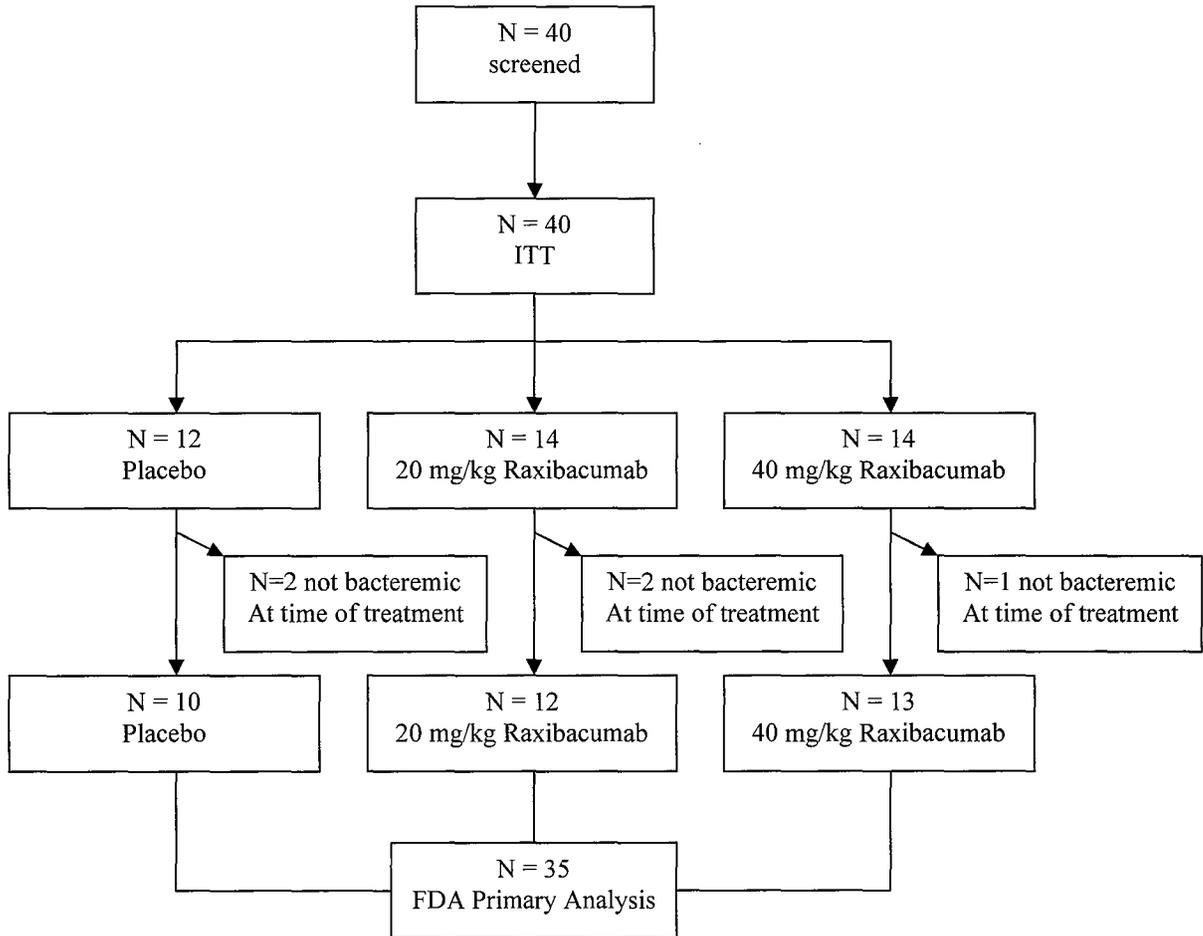
The sample size for the study is to detect an approximately 49% or more 28-day survival benefit from the 40 mg/kg raxibacumab group over the placebo at a 5% significance level, assuming a 8.3% (1 out of 12) survival at Day 28 in the placebo group and a 57.1% (8 of 14) survival at Day 28 in the 40 mg/kg raxibacumab group. This design provides 74% power at the 5% two-sided significance level.

Comment: The power calculation was based on comparison between the 40 mg/kg raxibacumab group and the placebo group.

Animal Disposition, Demographic and Baseline Characteristics

A total of 40 monkeys were screened, randomized, challenged with anthrax spores in the study and constituted the Intent-to-Treat (ITT) population (12 in the placebo group, and 14 in each of the 20 and 40 mg/kg raxibacumab groups). All monkeys received treatment according to their assigned groups, hence the as-treated population is the same as the ITT population. As conveyed to the sponsor numerous times in FDA comments prior to protocol submission (see fax to the sponsor dated November 17, 2006) and also in the comments regarding the study protocol, the Agency will consider the animals that were bacteremic at treatment initiation as our primary analysis population. A total of 5 monkeys (2 in the placebo group, 2 in the 20 mg/kg raxibacumab group and 1 in the 40 mg/kg raxibacumab group) were not bacteremic at treatment initiation and hence were excluded from the FDA primary analysis population. A diagram of animal disposition by treatment group is provided in Figure 1.

Figure 1: Animal Disposition and Analysis Groups for Study 724-G005829



As shown in Table 3.1.1A (from the Table on page 43 of the study report), the treatment groups were comparable with regard to sex, weight, and age at randomization. Three monkeys in the placebo group (C24784, 4.7 kg; C24853, 4.7 kg; C24858, 4.8 kg), 3 monkeys in the 20 mg/kg raxibacumab group (C21466, 2.3 kg; C24755, 5.1 kg; C24840, 4.7 kg), and 1 monkey in the 40 mg/kg raxibacumab group (C21474, 2.3 kg) had body weights slightly outside of the protocol-specified range of 2.5 to 4.5 kg.

**Table 3.1.1A Demographics and Baseline Characteristics, ITT population
(Study 724-G005829)**

| | Placebo N=12 | 20 mg/kg N = 14 | 40 mg/kg N = 14 | All Groups N = 40 |
|---------------------------------|-------------------------|----------------------------|----------------------------|------------------------------|
| Sex | | | | |
| n | 12 | 14 | 14 | 40 |
| Male | 6 (50.0%) | 7 (50.0%) | 7 (50.0%) | 20 (50.0%) |
| Female | 6 (50.0%) | 7 (50.0%) | 7 (50.0%) | 20 (50.0%) |
| Weight (kg) | | | | |
| n | 12 | 14 | 14 | 40 |
| Mean ± SD | 3.7 ± 0.8 | 3.4 ± 0.9 | 3.5 ± 0.7 | 3.5 ± 0.8 |
| Median | 3.6 | 3.3 | 3.6 | 3.5 |
| Range | 2.6 - 4.8 | 2.3 - 5.1 | 2.3 - 4.4 | 2.3 - 5.1 |
| Age at randomization (years) | | | | |
| n | 12 | 14 | 14 | 40 |
| Mean ± SD | 3.8 ± 0.4 | 3.5 ± 0.5 | 3.7 ± 0.4 | 3.7 ± 0.4 |
| Median | 3.9 | 3.6 | 3.8 | 3.8 |
| Range | 2.9 - 4.5 | 2.7 - 4.3 | 3.0 - 4.3 | 2.7 - 4.5 |

Efficacy Results

Primary Efficacy Endpoint

Table 3.1.1B summarizes the primary efficacy analysis results for the ITT population and the FDA primary analysis population. Day 28 survival rates in both raxibacumab groups were higher than the rate in the placebo group. The comparisons were made between each raxibacumab group and the placebo group. For the ITT population, the p-values were 0.0064 for the 20 mg/kg group and 0.0007 for the 40 mg/kg group compared with the placebo group based on a 2-sided Fisher's exact test. For the FDA primary analysis population, the p-values were 0.0396 for the 20 mg/kg group and 0.0016 for the 40 mg/kg group compared with the placebo group based on a 2-sided Fisher's exact test.

Table 3.1.1B Survival at Day 28, Study 724-G005829

| Population | Treatment | N | No. of Survivors (%) | P-value* | 95% CI** of Raxi - placebo (%) | 97.5% CI** of Raxi - placebo (%) |
|----------------------|----------------------|----------|-----------------------------|-----------------|---------------------------------------|---|
| Sponsor's ITT | Placebo | 12 | 0 (0.0%) | | | |
| | 20 mg/kg Raxibacumab | 14 | 7 (50.0%) | 0.0064 | (19.3, 73.7) | (13.2, 77.0) |
| | 40 mg/kg Raxibacumab | 14 | 9 (64.3%) | 0.0007 | (31.6, 84.7) | (27.0, 87.4) |
| FDA primary | Placebo | 10 | 0 (0.0%) | | | |
| | 20 mg/kg Raxibacumab | 12 | 5 (41.7%) | 0.0396 | (7.2, 68.7) | (1.5, 72.4) |
| | 40 mg/kg Raxibacumab | 13 | 9 (69.2%) | 0.0016 | (31.1, 88.9) | (25.7, 90.9) |

*P-values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.

**CIs are exact confidence intervals.

Reviewer's comment: The results for the sponsor's ITT population listed in the table above were consistent with the results from the sponsor's study report. The p-values in the table were based on a 2-sided Fisher's exact test. The 95% exact confidence intervals for the difference of survival rates (raxibacumab – placebo) excluded 0. The sponsor states that the primary efficacy endpoint was met for both raxibacumab doses with a survival at Day 28 that was statistically significantly higher in both the 40 mg/kg raxibacumab group and the 20 mg/kg raxibacumab group compared with the placebo group. Although the results of the primary efficacy analysis (both in ITT and in FDA primary analysis population) using the step-down sequential testing procedure did also show the superiority of raxibacumab groups over the placebo group, the sponsor did not discuss their conclusion using this pre-specified method for adjusting for multiple comparisons.

The sponsor presented the results in ITT population of an additional analysis, the Cochran-Armitage trend test, which indicated an increasing trend in survival at Day 28 across the placebo, the 20 mg/kg raxibacumab group, and the 40 mg/kg raxibacumab group ($p = 0.0011$). Note that though the trend test was significant, the difference in the survival at Study Day 28 between the two raxibacumab groups was not statistically significant ($p = 0.4441$).

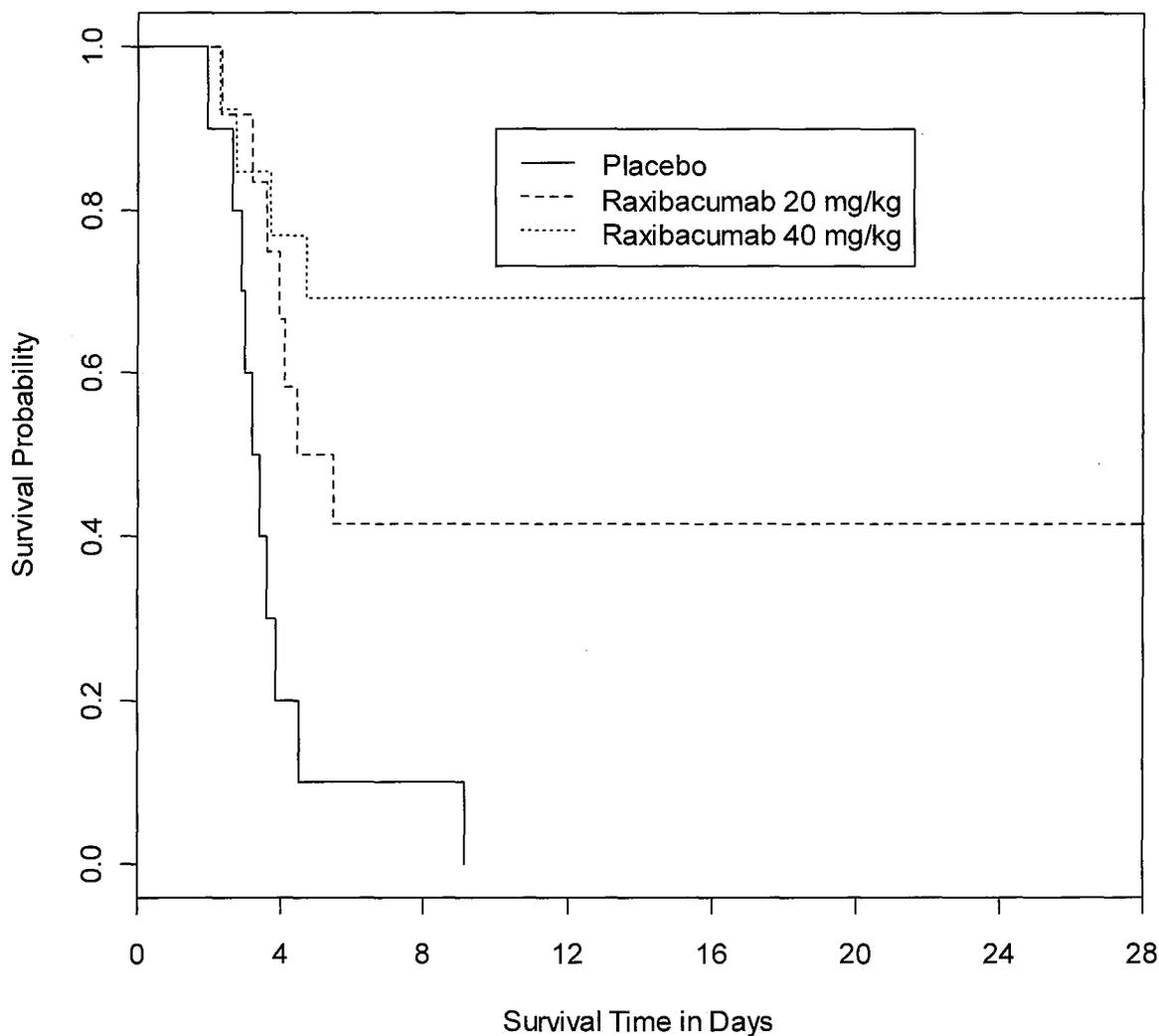
Secondary Efficacy Endpoint

The secondary efficacy endpoint was survival time defined as the time from the beginning of spore challenge to death during the 28-day study period. Figure 2 is a graph of the Kaplan-Meier survival curves for the three treatment groups of monkeys in the FDA primary analysis group. The median survival times were 3.3 days in the placebo group, 5.0 days in the raxibacumab 20 mg/kg group and beyond 28 days in the raxibacumab 40 mg/kg group because 69.2% of the animals survived at the end of the study. There was a statistically significant difference in terms

of survival time among the three groups (log rank test, $p=0.0006$). Pairwise comparisons also show statistically significant differences between each raxibacumab group and the placebo ($p = 0.0098 < 0.025$ for 20 mg/kg group vs placebo, and $p = 0.0005 < 0.025$ for 40 mg/kg group vs placebo) after a Bonferroni adjustment for multiple comparisons ($0.025=0.05/2$).

For the ITT population, the results were the same as the results presented by the sponsor in the study report. A significant difference among the three groups was shown in the ITT population ($p=0.0003$). Further pairwise comparisons for survival time were significant for the raxibacumab groups vs placebo ($p = 0.0029$ for 20 mg/kg and $p = 0.0004$ for 40 mg/kg) with a Bonferroni adjustment for multiple comparisons. However, the difference in the survival at Study Day 28 between the two raxibacumab groups was not statistically significant ($p = 0.4441$).

Figure 2 Survival Probability of Monkeys in the FDA primary analysis population



Anthrax Exposure Levels

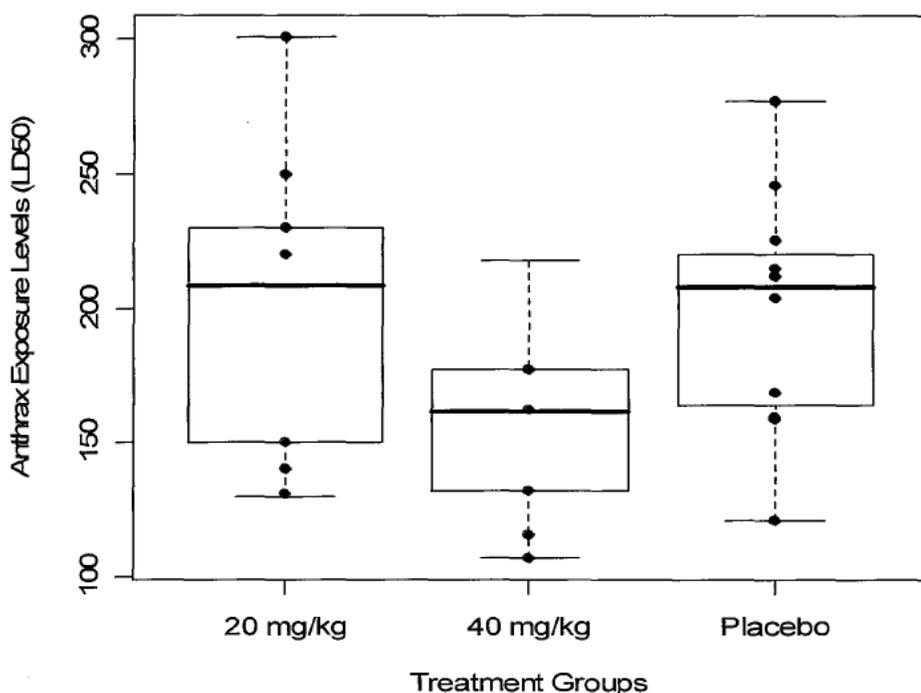
The anthrax exposure levels ranged from 106.9 to 301.0 LD₅₀ (1.24x 10⁷) (or 6.6 to 18.6 x 10⁶ cfu) with an overall mean of 184.0 and standard deviation of 46.8 LD₅₀. The table below summarizes the exposure level by treatment groups. There are statistically significant differences of mean anthrax exposure levels among the three treatment groups (F test, p=0.0255). Monkeys in the 40 mg/kg group received a lower mean dose of Ames strain anthrax spores than the other two groups. The p-values (t test) for further pair-wise comparisons are 0.9413 (20 mg/kg vs placebo group), 0.0123 (40 mg/kg vs placebo group) and 0.0176 (20 mg/kg vs 40 mg/kg group). Note that the difference of inhaled spores between the 40 mg/kg group and the placebo group is statistically significant even after the conservative Bonferroni multiplicity adjustment, i.e., 0.0123 < 0.0167 (=0.05/3).

Table 3.1.1C Anthrax Exposure Level by Treatment Group, Study 724-G005829

| | Placebo N=12 | 20 mg/kg N=14 | 40 mg/kg N=14 | P-value |
|-------|-----------------|------------------|------------------|---------|
| N | 12 | 14 | 14 | 0.0255 |
| Mean | 197.6 | 199.0 | 157.2 | |
| SD | 43.5 | 52.4 | 32.4 | |
| Range | 121.0-277.0 | 130.0-301.0 | 106.9-218.0 | |

The results of the sponsor's sensitivity analysis regarding this (excluding 3 animals in the 40 mg/kg group with exposure <120 LD₅₀) were confirmed by this reviewer. However, the mean exposure level of the placebo group remains much higher (197.57 ± 43.5) than that of the raxibacumab 40 mg/kg group (169.7 ± 23.8) after this exclusion. This reviewer performed other sensitivity analyses including an analysis excluding animals with anthrax exposure ≤150 LD₅₀. There were 11 animals in the placebo group, 10 in the 20 mg/kg raxibacumab group and 9 animals in the 40 mg/kg group which had anthrax exposure >150 LD₅₀. Fisher's exact test for comparing survival rates between the raxibacumab 20 mg/kg group and the placebo group returns a p-value of 0.0039 and has a p value of 0.0005 for comparison between raxibacumab 40 mg/kg and the placebo group. After adjustment for multiple comparisons, this sensitivity analysis still supports the survival benefit of raxibacumab treatment over placebo. Figure 3 shows the boxplot of anthrax exposure levels and deaths for each treatment group in the ITT population. Increased anthrax exposure levels do not seem to have negative impact on survival rates for the treatment groups.

Figure 3: Anthrax Exposure Level with Death Marked (dots) in Each Treatment Group



The monkeys were randomized to 1 of the 3 challenge days on 9/18/07, 9/25/07 and 10/2/07. Table 3.1.1D below summarizes the exposure level by the three challenge dates. There were statistically significant differences of mean anthrax exposure levels on three challenge dates (F test, $p=0.0257$). Animals challenged on 9/18/07 received a lower mean dose of anthrax spores than animals challenged on 9/25/07 and 10/2/07. The p-values (t test) for further pair-wise comparisons are 0.0544 (9/18/07 vs 9/25/07), 0.0119 (9/18/07 vs 10/2/07) and 0.5226 (9/25/07 vs 10/2/07). The largest difference is between the anthrax spores received on 9/18/07 and on 10/2/07. This difference is statistically significant even after the conservative Bonferroni multiplicity adjustment, i.e., $0.0119 < 0.0167 (=0.05/3)$. This trend of increasing exposures over the three challenge days is seen within the placebo and the raxibacumab 40 mg/kg treatment group as well. In the raxibacumab 20 mg/kg group, the mean anthrax exposure levels on the second and third challenge days were higher than the mean exposure level on the first challenge day, and the anthrax exposure level on the second challenge day was slightly higher than the exposure level on the third challenge day. Additionally, the trend with the 40 mg/kg group receiving the lowest exposure is seen in all three challenge days.

Table 3.1.1.D also reports the survival rate for each treatment arm by each exposure date. Note that given a very small sample size within treatment arm by exposure data ($n=4$ or 5), no rigorous comparisons can be made. The survival rate for animals challenged on 9/18/07 was higher than the overall survival rate in the 20 mg/kg group (60% vs 50%), and was slightly lower than the overall survival rate in the 40 mg/kg group (60% vs 64.3%). Both raxibacumab groups

have lower survival rates for the animals challenged on 9/25/07 than the overall survival rates (40% vs 50% in 20 mg/kg group and 25% vs 64.3% in 40 mg/kg group). Survival rate for the subgroup of animals challenged on 10/2/07 was the same as the overall rate in the 20 mg/kg group (50%) and was higher than the overall rate in the 40 mg/kg group (100% vs 64.3%). Note that for the 20 mg/kg group, the survival rates on 9/25/07 and 10/2/07 (when the mean exposure levels were higher, at 192.6 and 203.4 LD₅₀) were lower than the survival rate on 9/18/07 (when the mean exposure level was lower, at 157.9 LD₅₀). However, this trend does not continue with the 40 mg/kg group. Although the survival rate on 9/25/07 was lower than the rate on 9/18/07 (25% vs 60%), all monkeys challenged on 10/2/07 survived.

Table 3.1.1D Survival Rate (%) and Mean Exposure Level (±SD) by Challenge Date (Study 724-G005829)

| Challenge Date /mean exposure | Placebo | Raxibacumab 20 mg/kg | Raxibacumab 40 mg/kg |
|--------------------------------------|--------------------------|-----------------------------|-----------------------------|
| 9/18/07 157.9 (±45.4) | 0/4 (0) 192.3 (±67.7) | 3/5 (60) 156.0 (±29.6) | 3/5 (60) 132.4 (±19.9) |
| 9/25/07 192.6 (±43.6) | 0/4 (0) 194.4 (±30.2) | 2/5 (40) 225.1 (±34.5) | 1/4 (25) 150.0 (±30.3) |
| 10/2/07 203.4 (±41.4) | 0/4 (0) 206.0 (±35.9) | 2/4 (50) 220.1 (±65.7) | 5/5 (100) 187.9 (±18.3) |

In order to further explore the relationship of the anthrax exposure level and the probability of survival in animals in the study, the mean dose of anthrax exposure level in those animals who died was compared with animals who survived. The comparisons were carried out for the ITT population and also within each raxibacumab group. Sixteen animals who survived did have a lower mean exposure level (179.4 ± 37.4) than the 24 animals who died (187.0 ± 52.7). This pattern stays for the 20 mg/kg group with the mean exposure level $194.8 (\pm 42.1)$ for the survival subgroup and $203.2 (\pm 64.3)$ for the animals who died. For the 40 mg/kg group, the mean exposure level was higher in the animals survived (167.5 ± 30.5) than those died (138.9 ± 30.0). None of these differences were statistically significant.

Reviewer's comment: Note that since the study was not powered to detect if differences in exposure levels would lead to differences in survival rates in any of the groups and subgroups considered, we can not firmly conclude whether or not the higher level of anthrax exposure had a negative effect on the survival probability of the animals.

3.1.2 Study 682-G005758

Objectives and Study Design

Study 682-G005758 was an open-label, parallel-group, randomized, placebo-controlled Good Laboratory Practices (GLP) study in healthy male and female New Zealand White (NZW) rabbits to evaluate the therapeutic efficacy of single IV dose raxibacumab in anthrax spore

inhalation-challenged rabbits experiencing symptoms of inhalation anthrax. The study was conducted from February 26, 2007 to March 26, 2007 at Battelle Biomedical Research Center (BBRC) in West Jefferson, OH.

The primary objective of the study was to evaluate the efficacy of raxibacumab when administered as a therapeutic treatment against lethality due to inhalation of *B. anthracis* in rabbits. Male and female NZW rabbits that weighed 3 to 4 kg were to be placed on study. Rabbits were to be in good health and free of malformations and clinical signs of disease. The primary efficacy analysis was to compare the percent of rabbits alive at Study Day 14 between the placebo group and each of the treatment groups.

The primary efficacy endpoint of the study was survival at Day 14. The 14-Day survival rates of the two raxibacumab treatment groups were compared to that of the placebo group. According to the study protocol, the primary efficacy analysis will be performed using a 2-sided likelihood ratio test (or the Fisher's exact test, if any expected cell count in the contingency table is less than 5), and is subject to a multiple comparison adjustment using the Hochberg procedure. The results will be considered statistically significant if: At least 1 of the pair-wise comparisons between raxibacumab and control achieves a p-value < 0.025 , or both pair-wise comparisons between raxibacumab and control achieve a p-value < 0.05 .

Rabbits were randomized by gender and body weight into each of the 3 treatment groups. Each group received the dosages of raxibacumab or placebo as follows:

- Group 1 (18 rabbits): single IV dose raxibacumab buffer (control)
- Group 2 (18 rabbits): single IV dose of 20 mg/kg raxibacumab
- Group 3 (18 rabbits): single IV dose of 40 mg/kg raxibacumab

Rabbits were randomized to one of the challenge days on 3/5/07 and 3/12/07. Rabbits were to be placed individually into a plethysmography chamber and class III cabinet system and exposed to a targeted $200 \times LD_{50}$ (2.1×10^7 spores) dose of *B. anthracis* spores (Ames strain). The trigger for treatment with raxibacumab or placebo for individual rabbits was detectable serum PA (via qualitative screening ECL assay) or 1st rise in body temperature of 2 or more °F above the baseline average at 2 consecutive time points, whichever occurred first. For each rabbit, a single IV treatment of 20 or 40 mg/kg raxibacumab or placebo was administered immediately following detection of serum PA or body temperature increase. Beyond 36 hours post challenge, only temperature was to be used as a trigger for treatment, due to limitations on blood sample volumes.

The analysis populations for this study were defined by the sponsor as follows:

- ITT population: all rabbits that were randomized and challenged with anthrax spores in the study. The ITT analysis was based on the intended treatment group assignment rather than the actual treatment received.
- Modified ITT population: A subset of the ITT population that included all animals that received raxibacumab or placebo. The modified ITT analysis was based on the planned treatment group rather than the actual treatment received.

- As-treated population: The set of rabbits that received a study agent with the assignment to treatment group based on the actual treatment administered to the rabbits.

The sponsor's primary efficacy analysis was performed on the ITT population. The secondary analysis of the primary efficacy endpoint was performed in the modified ITT population.

Medical Officer's comment to the sponsor regarding primary efficacy population (SN 026): For your study population to be sufficiently reflective of human anthrax disease, your primary study analysis should be conducted in the population of all animals that were confirmed to have anthrax disease as evident by both PA toxemia and bacteremia at the time of treatment initiation.

In the review process for the SNS, it was found by the microbiology reviewer that ECL appears to be highly unreliable in the detection of B. anthracis. The decision was made to determine the status of bacteremia based on the culture. Therefore, the FDA primary analysis population is defined as all animals that were bacteremic (based on culture) at the time of treatment.

The sample size for the study was calculated to detect an approximately 45% or more 14-day survival benefit in one of the raxibacumab treatment groups compared with the placebo group at a 5% significance level, assuming a 5% survival at Day 14 in the placebo group (expecting that all placebo-treated rabbits would die, but allowing 5% deviation) and 50% survival at Day 14 in the raxibacumab treatment groups. This design provides 76% power at the 5% two-sided significance level.

Animal Disposition, Demographic and Baseline Characteristics

A total of 54 rabbits were screened and randomized into the three treatment groups. A diagram of animal disposition by treatment group is provided in Figure 5. One rabbit (L08129) which was originally randomized to the 20 mg/kg raxibacumab group was excluded due to death from a blood clot prior to challenge. The remaining 53 rabbits were challenged with anthrax spores in the study. Rabbit L08133, which was originally randomized to the placebo group, was randomly selected to replace rabbit L08129 and was assigned to the 20 mg/kg raxibacumab treatment group. The Intent-to-Treat population consists of 17 animals in the placebo group, and 18 in each of the 20 and 40 mg/kg raxibacumab groups. One rabbit (L08128) that was randomized to the 20 mg/kg raxibacumab group died during spore challenge without receiving any study agent (excluded from the FDA primary analysis population) and 1 rabbit (L08145) that was randomized to the placebo group actually received 40 mg/kg raxibacumab.

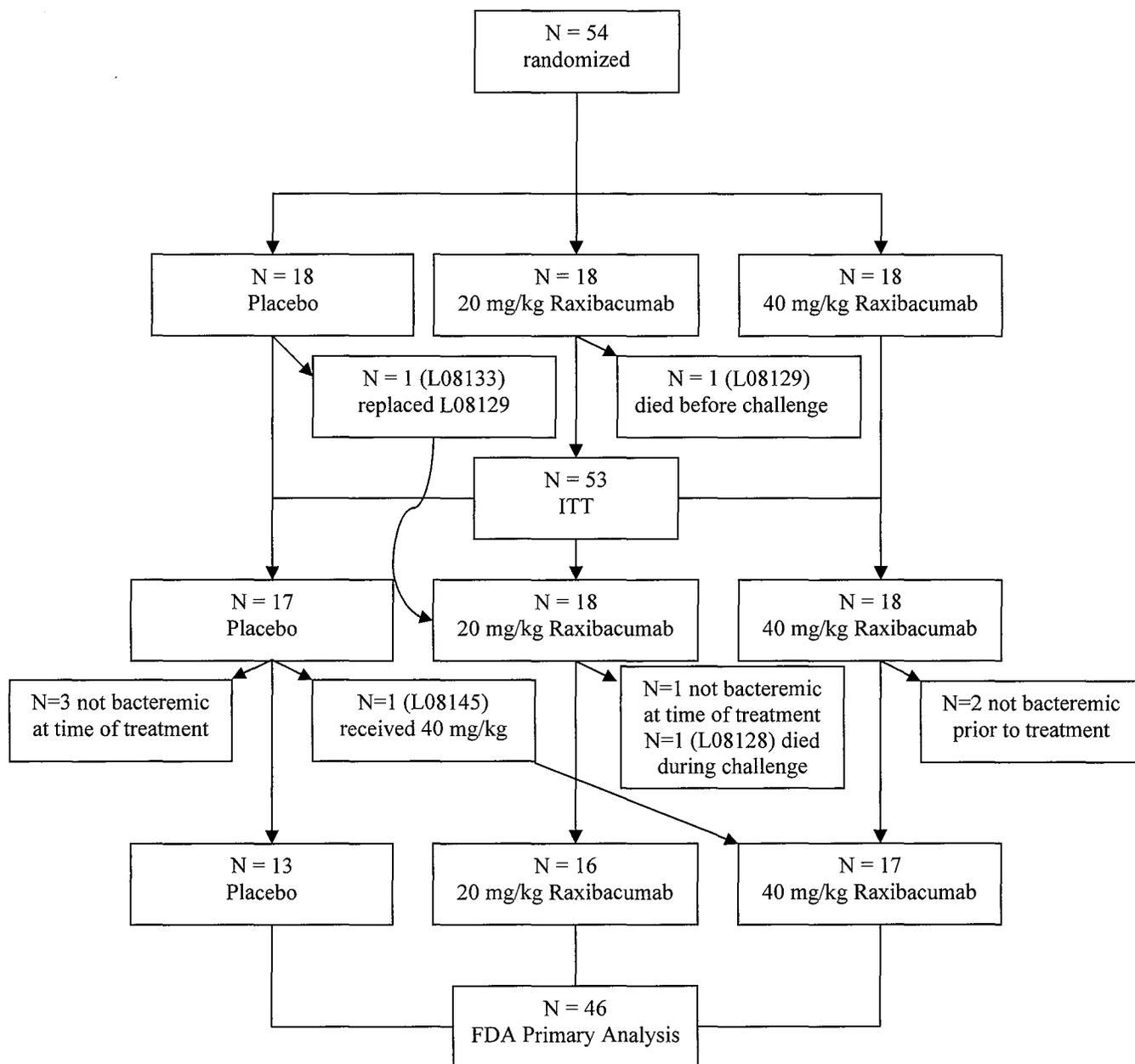
Reviewer's comment: There were conflicting information in section 5.6.5 and section 6.1. Rabbit L08129 was noted in section 6.1 as a screening failure. But section 5.6.5 states that rabbit L08129 was assigned to the 20 mg/kg raxibacumab. The information in the dataset also indicates that rabbit L08129 was randomized to the 20 mg/kg raxibacumab group.

The exclusion of rabbit L08129 from the ITT analysis was acceptable since the animal died before the challenge and this is consistent with the definition of the ITT population in the protocol. Rabbit L08133 was included in the 20 mg/kg raxibacumab group for the sponsor's ITT analysis. Although this replacement occurred before any rabbit had been challenged, this is not consistent with the definition of the ITT population. However, since this animal did not survive,

the sponsor's ITT analysis treating rabbit L08133 as in the 20 mg/kg group was actually more conservative than if it were included in the placebo group.

The Agency considers the animals that were bacteremic at treatment initiation as the primary analysis population. This was conveyed to the sponsor in the FDA comments numerous times prior to the submission of the study protocol (See fax dated November 17, 2006) and also in the comments on the study protocol. Three rabbits in the placebo group, one rabbit in the 20 mg/kg raxibacumab group and two rabbits in the 40 mg/kg raxibacumab group did not have positive blood culture prior to and at the time of treatment and hence were excluded from the FDA primary analysis population. Rabbit L08145 was analyzed as in the 40 mg/kg raxibacumab group in the FDA primary analysis based on the actual treatment that the animal received. This animal died and, therefore, including it in the 40 mg/kg group leads to a conservative analysis. Rabbit L08147 was shown bacteremic 1/2 hour prior to the treatment but was not shown bacteremic immediately prior to the treatment initiation. This animal was included in the FDA primary analysis since the animal was also febrile prior to the treatment.

Figure 5: Animal Disposition and Analysis Groups for Study 628-G005758



Demographics are summarized in the Table below (taken from Table 6-1 on page 42 in the study report). Ratios of males and females and mean values for weight were comparable among treatment groups. All of the rabbits were of the same age of 205 days at randomization.

**Table 3.1.2A Demographics and Baseline Characteristics, ITT population
(Study 628-G005758)**

| | Placebo N=17 | 20 mg/kg N = 18 | 40 mg/kg N = 18 | All Groups N = 53 |
|-------------|-------------------------|----------------------------|----------------------------|------------------------------|
| Sex | | | | |
| n | 17 | 18 | 18 | 53 |
| Male | 9 (52.9%) | 10 (55.6%) | 10 (55.6%) | 29 (54.7%) |
| Female | 8 (47.1%) | 8 (44.4%) | 8 (44.4%) | 24 (45.3%) |
| Weight (kg) | | | | |
| n | 17 | 18 | 18 | 36 |
| Mean | 3.0 | 3.1 | 3.1 | 3.1 |
| SD | 0.2 | 0.2 | 0.2 | 0.2 |
| Median | 3.0 | 3.1 | 3.1 | 3.1 |
| Range | 2.8 – 3.3 | 2.8 – 3.4 | 2.7 – 3.3 | 2.7 – 3.4 |

Note: The sponsor confirmed that all the rabbits in the study were born on Aug 5, 2006.

Efficacy Results

Primary Efficacy Endpoint

Table 3.1.2B summarizes the primary efficacy analysis results for the ITT population and the FDA primary analysis population. Day 14 survival rates in both raxibacumab groups were higher than the rate in the placebo group. The comparisons were made between each raxibacumab group and the placebo group. For the ITT population, the p-values were 0.0455 for the 20 mg/kg group and 0.0029 for the 40 mg/kg group compared with the placebo group based on a 2-sided Fisher's exact test. For the FDA primary analysis population, the p-values were 0.1067 for the 20 mg/kg group and 0.0237 for the 40 mg/kg group compared with the placebo group based on a 2-sided Fisher's exact test.

Table 3.1.2B Survival at Day 14 (Study 628-G005758)

| Population | Treatment | N | No. of Survivors (%) | P-value* | 95% CI** of Raxi-placebo (%) | 97.5% CI** of Raxi – placebo (%) |
|----------------------|----------------------|----------|-----------------------------|-----------------|-------------------------------------|---|
| Sponsor's ITT | Placebo | 17 | 0 (0.0%) | | | |
| | 20 mg/kg Raxibacumab | 18 | 5 (27.8%) | 0.0455 | (6.6, 52.5) | (1.4, 54.5) |
| | 40 mg/kg Raxibacumab | 18 | 8 (44.4%) | 0.0029 | (21.3, 66.7) | (16.1, 69.6) |
| FDA primary | Placebo | 13 | (0.0%) | | | |
| | 20 mg/kg Raxibacumab | 16 | 4 (25.0%) | 0.1067 | (-2.2, 50.9) | (-7.8, 53.4) |
| | 40 mg/kg Raxibacumab | 17 | 6 (35.3%) | 0.0237 | (7.3, 59.6) | (2.2, 62.3) |

*P-values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.

**CIs are exact confidence intervals.

Reviewer's comment: The sponsor proposed in the protocol that the Hochberg procedure would be used to adjust for multiple comparisons. However, the sponsor did not discuss the adjustment for multiple pairwise comparisons in the study report. The sponsor states that the primary efficacy endpoint was met for both raxibacumab doses with survival at Day 14 that was significantly higher in the 40 mg/kg raxibacumab group and the 20 mg/kg raxibacumab group compared with the placebo group. Note that in this case the results of the sponsor's primary efficacy analysis using the Hochberg procedure did show the superiority of raxibacumab groups over the placebo group. However, this claim should not be made without proper discussion of adjustment for multiple comparisons.

Applying the Hochberg procedure to the results of FDA primary analysis: Since $0.1067 > 0.05$, we conclude that the results for raxibacumab 20 mg/kg is not statistically significantly different compared with the placebo group. And since the next largest p-value $0.0237 < 0.025 (=0.05/2)$, the results for raxibacumab 40 mg/kg group is statistically significantly different compared with the placebo group. Therefore, we conclude that the raxibacumab 40 mg/kg group showed statistically significant survival benefit over the placebo group.

In addition, the sponsor presented the results in the ITT population using the Cochran-Armitage trend test, which indicated an increasing trend in survival at Day 14 across the placebo, the 20 mg/kg raxibacumab group, and the 40 mg/kg raxibacumab group ($p = 0.0027$). But the difference in the survival at Study Day 14 between the two raxibacumab groups was not statistically significant ($p = 0.2962$).

Sensitivity analyses using different inclusion criteria for the animals in the bacteremic population

Table 3.1.2C listed several scenarios with slightly different inclusion criteria for the bacteremic group. Rabbit L08147 was shown to have a positive culture a half hour prior to the treatment initiation but was not shown to be bacteremic immediately before the treatment initiation. The sponsor did not include this animal in their subgroup of animals that were bacteremic at treatment initiation. The clinical review team decided to include this animal in the FDA primary analysis group. When excluding rabbit L08147 from the FDA primary analysis group and applying the Hochberg method to adjust for multiple comparisons, there were still no statistically significant difference of survival rate between the raxibacumab 20 mg/kg group and the placebo group ($0.1067 > 0.05$), but the difference in survival rates between the raxibacumab 40 mg/kg group and the placebo group became not significant as well ($0.0476 > 0.025 = 0.05/2$). The same pattern holds for the bacteremic group defined by the sponsor. In this analysis group, there were no statistically significant differences of survival shown between each raxibacumab group and the placebo group. If adding rabbit L08147 to the sponsor's bacteremic-at-treatment-initiation group, the results for the raxibacumab 40 mg/kg group then became significant. As shown in the FDA primary analysis and the scenarios in Table 3.1.2C, the study conclusion for the raxibacumab 40 mg/kg group would be very different when including or excluding rabbit L08147. This signals that the evidence of statistically significant difference between the raxibacumab 40 mg/kg group and the placebo group shown in the FDA primary analysis population is rather weak.

Table 3.1.2C Survival Rates in Bacteremic Group, Study 628-G005758

| Bacteremic Population | Placebo | Raxibacumab 20 mg/kg | Raxibacumab 40 mg/kg |
|---------------------------------------|---------|-------------------------|-------------------------|
| FDA primary analysis excluding L08147 | | | |
| n | 13 | 16 | 16 |
| Number of Survivors (%) | 0 (0%) | 4 (25.0%) | 5 (31.3%) |
| P-value | | 0.1067 | 0.0476 |
| Sponsor's Definition* | | | |
| n | 14 | 16 | 15 |
| Number of Survivors (%) | 0 (0%) | 4 (25.0%) | 5 (33.3%) |
| P-value | | 0.1029 | 0.0421 |
| Sponsor's Definition* adding L08147 | | | |
| n | 14 | 16 | 16 |
| Number of Survivors (%) | 0 (0%) | 4 (25.0%) | 6 (37.5%) |
| P-value | | 0.1029 | 0.0185 |

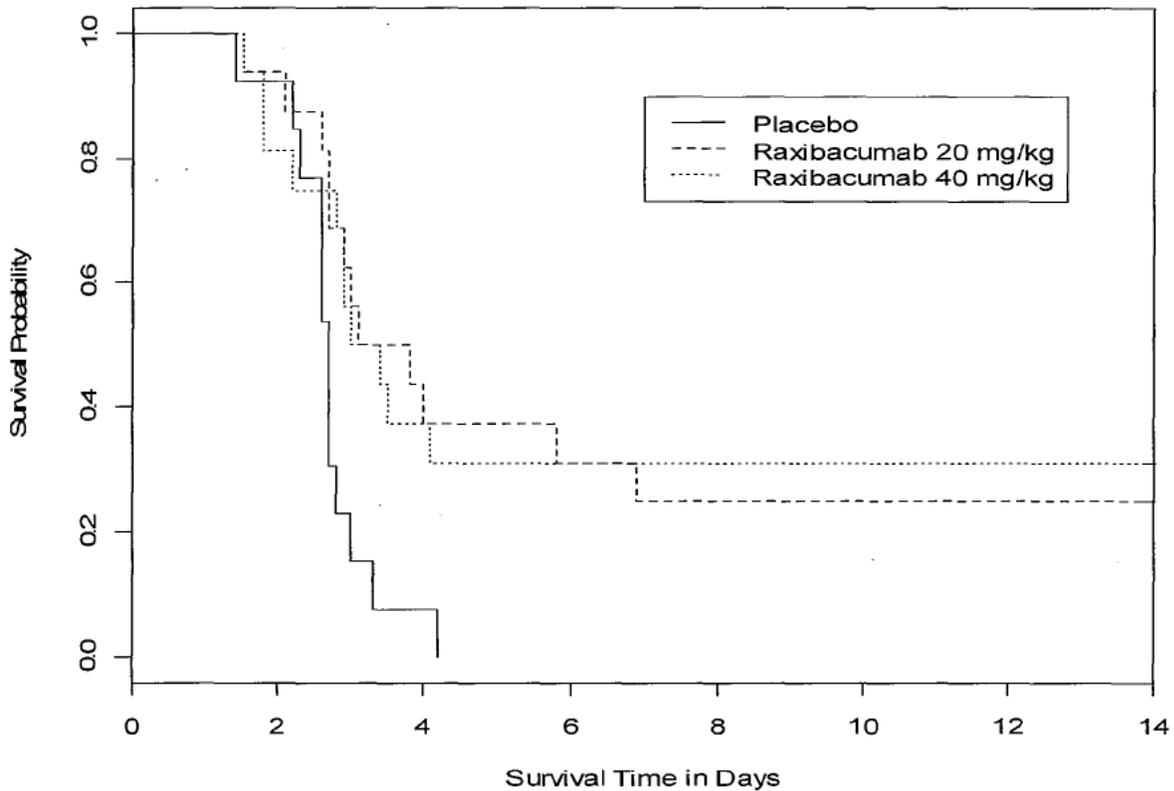
*Rabbit L08145 was randomized to placebo but was treated with raxibacumab 40 mg/kg. This animal was analyzed as placebo by the sponsor. The FDA analysis treated it as in 40 mg/kg group.

Secondary Efficacy Endpoint

The secondary efficacy endpoint was survival time defined as the time from the beginning of spore challenge to death during the 14-day study period. Figure 6 is a graph of the Kaplan-Meier survival curves for the three treatment groups of rabbits in the FDA primary analysis group. The median survival times were 2.7 days in the placebo group, 3.5 days in the raxibacumab 20 mg/kg group and 3.2 days in the raxibacumab 40 mg/kg group. There were statistically significant differences in terms of survival time among the three groups (log rank test, $p=0.0125$). Pairwise comparisons also show statistically significant differences between each raxibacumab group and the placebo ($p = 0.0065$ for 20 mg/kg group vs placebo, and $p = 0.0165$ for 40 mg/kg group vs placebo) with the Bonferroni correction for multiple comparisons. Note that the survival curves for the raxibacumab 20 mg/kg group and the 40 mg/kg group intertwined. There was no significant difference of survival time between the raxibacumab 20 mg/kg and 40 mg/kg group ($p=0.9547$).

For the ITT population, the results based on the submitted data sets were slightly different with the results presented by the sponsor in the study report. But the discrepancy did not change the conclusion. Significant difference among the three groups was shown in the ITT analysis population ($p=0.0040$). Further pairwise comparisons for survival time were significant for the raxibacumab groups vs placebo ($p = 0.0084$ for 20 mg/kg and $p = 0.0033$ for 40 mg/kg) with the Bonferroni adjustment for multiplicity.

Figure 6: Survival Probability of Rabbits in FDA Primary Analysis Population



Anthrax Exposure Level

The anthrax exposure level ranged from 144 to 352 LD₅₀ (1.24×10^7) with an overall mean of 228.1 LD₅₀ and standard deviation of 41.5 LD₅₀. Table 3.1.2D below summarizes exposure level by treatment groups. There was not a statistically significant difference of mean anthrax exposure levels among the three treatment groups ($P = 0.7134$). Rabbits in the 40 mg/kg group received a higher mean dose of Ames strain anthrax spores than the other two groups, but with a larger variation of the spore levels than the other two groups.

**Table 3.1.2D Anthrax Exposure Level by Treatment Group, ITT Population
(Study 628-G005758)**

| | Placebo N =17 | 20 mg/kg N = 18 | 40 mg/kg N =18 | P-value |
|-------|------------------|--------------------|-------------------|---------|
| n | 17 | 17 | 18 | 0.7134 |
| mean | 221.5 | 229.6 | 233.0 | |
| SD | 30.7 | 36.9 | 54.1 | |
| Range | 174.0–298.0 | 175.0-299.0 | 144.0-352.0 | |

The rabbits were randomized to one of the two challenge days on 3/5/07 and 3/12/07. Table 3.1.2E below summarizes the exposure level by the two challenge dates as well as the survival rates for the treatment groups on each day. There was a statistically significant difference of mean anthrax exposure levels between the two challenge dates ($P < 0.0001$). Animals challenged on 3/12/07 received a lower mean dose of anthrax spores than animals challenged on 3/5/07. Animals in each treatment group challenged on 3/12/07 also had lower mean dose of anthrax exposure than the corresponding treatment group challenged on 3/5/07. But the survival rates for each treatment group challenged on 3/5/07 were higher than the survival rates for the corresponding treatment group challenged on 3/12/07. The increased level of anthrax exposure did not seem to have negative impact on the survival rates.

**Table 3.1.2E Survival Rate (%) and Mean Exposure level (\pm SD) by Challenge Date
(Study 628-G005758)**

| Challenge Date /mean exposure | Placebo | Raxibacumab 20 mg/kg | Raxibacumab 40 mg/kg |
|----------------------------------|--------------------------------|-----------------------------------|-----------------------------------|
| | 3/5/07 248.6 (\pm 38.6) | 0/9 (0) 223.6 (\pm 25.7) | 3/9 (33.3) 256.7 (\pm 25.7) |
| 3/12/07 206.0 (\pm 32.7) | 0/8 (0) 219.3 (\pm 37.3) | 2/9 (22.2) 199.1 (\pm 18.9) | 3/9 (33.3) 200.4 (\pm 37.7) |

3.2 Evaluation of Safety

3.2.1 CNS Findings in Animal Efficacy Studies

The sponsor initially did not perform histopathology readings for this study. The agency requested in a teleconference with the sponsor on September 9, 2008 to submit histopathology data on all preserved tissues from monkeys that died in Study 724-G005829. Due to the findings of higher rate of meningitis in raxibacumab-treated animals compared with the placebo group in study 682-G005758, the key interest for histopathology findings in this study was the brain.

Note: The sponsor first presented to the Agency the summary of histopathology findings for Study 724-G005829 at the Raxibacumab pre-BLA meeting on October 21, 2008. The sponsor submitted the draft report and line listings of gross necropsy and histopathology findings for the study in SN088. The division requested the sponsor to provide the datasets and respective

definition files for both Study 724-G005829 and Study 628-G005758 that were used to generate the report in SN088. But the sponsor responded in SN089 that the datasets for the histopathology readings from both studies 628-G005758 and 724-G005829 were provided to HGS by Battelle as text documents, not as Excel spread sheets. No electronic datasets were submitted in SN089. After another request from the agency for the dataset used to generate the report in SN088, the sponsor submitted in SN090 an electronic dataset which contains the same information as the line listings submitted in SN088. The sponsor stated that the data requested by the agency did not exist as SAS files and was created only under FDA's request. However, a pathology listing (also submitted in SN090) with the severities of histopathology findings by-organ and by-animal with a footnote "program:listing-pathology.sas" contains the same information as the line listings in SN088. It is not clear why the sponsor did not submit this electronic file of the pathology listing but created another dataset to submit to the Agency. The analysis presented in this section of the review was based on the information extracted by this reviewer from the electronic dataset submitted in SN090.

Study 724-G005829 (Monkeys)

There were higher rates of monkeys which were found to have moderate or marked brain inflammation in the raxibacumab treatment groups (6/7 in the 20 mg/kg group and 2/5 in the 40 mg/kg group) than in the placebo group (1/12) based on all necropsized animals. The rates of monkeys with moderate or marked brain inflammation were significantly different between the placebo group and the raxibacumab 20 mg/kg group ($p = 0.0017$, Fisher's exact test) even with the Bonferroni correction ($0.05/2=0.025$). The difference between the placebo group and the raxibacumab 40 mg/kg group was not statistically significant ($p = 0.1912$, Fisher's exact test).

The sponsor reported that 11/12 animals in the placebo arm, 5/7 in the 20 mg/kg raxibacumab arm and 5/5 in the 40 mg/kg raxibacumab arm had bacteria in their brains. However, of the 11 monkeys who had bacteria in their brain in the placebo arm, only one monkey had moderate severity or amount of bacteria present, 9 had minimum or very slight degree or amount and 1 had slight degree or small amount of bacteria present. The rate of monkeys who had moderate or marked level of bacteria presence in their brain were higher in both the 20 mg/kg (5/7) and 40 mg/kg raxibacumab groups (2/5) than in the placebo group (1/12). There is a statistically significant difference between the raxibacumab 20 mg/kg group and the placebo in terms of proportion of monkeys with moderate or marked level of bacteria presence in the brain ($p = 0.0095$), even with Bonferroni correction ($0.05/2=0.025$) for multiple comparisons. The difference between the placebo group and the raxibacumab 40 mg/kg group was not statistically significant ($p = 0.1912$, Fisher's exact test).

For the BLA review, the review team defined the pathology level of CNS pathology findings for each necropsized animal based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low. There were higher rates of monkeys which were recorded to have high pathology level in the raxibacumab treatment groups (6/7 in the 20 mg/kg group and 3/5 in the 40 mg/kg group) than in the placebo

group (1/12) among the necropsized animals. The rates of monkeys with high pathology level were significantly different between the placebo group and the raxibacumab 20 mg/kg group ($p = 0.0017$, Fisher's exact test) even with the Bonferroni correction ($0.05/2=0.025$). The difference between the placebo group and the raxibacumab 40 mg/kg group was not statistically significant ($p = 0.0525$, Fisher's exact test). See table below.

Table 3.2.1A CNS findings in Necropsized Monkeys (Study 724-G005829)

| Treatment | Number of Necropsized Monkeys | No. (%) of CNS findings | P-value* |
|---|-------------------------------|-------------------------|----------|
| Moderate/Marked Brain Inflammation | | | |
| Placebo | n = 12 | 1 (8.3%) | |
| 20 mg/kg Raxibacumab | n = 7 | 6 (85.7%) | 0.0017 |
| 40 mg/kg Raxibacumab | n = 5 | 2 (40.0%) | 0.1912 |
| FDA CNS Pathology Level** | | | |
| Placebo | n = 12 | 1 (8.3%) | |
| 20 mg/kg Raxibacumab | n = 7 | 6 (85.7%) | 0.0017 |
| 40 mg/kg Raxibacumab | n = 5 | 3 (60.0%) | 0.0525 |

* P values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.

** The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

The table below lists the mean and median time to death for the treatment groups. For the all treated animals, the median survival times in the raxibacumab groups were higher than the median survival times in the placebo group since all animals in the placebo group died and some animals in the raxibacumab groups survived. Among the necropsized animals, there is no statistically significant difference in time to death (from the end of anthrax challenge) between the placebo and the raxibacumab groups ($p = 0.5895$ compared with the 20 mg/kg group and $p = 0.9586$ compared with the 40 mg/kg group, Wilcoxon two-sample test). Note that however, the time to death is longer on average in the placebo group (4.3 days) than in the raxibacumab-treated groups (3.8 days for the 20 mg/kg group and 3.7 for the 40 mg/kg group).

Only one monkey in the placebo group had moderate inflammation and moderate level of bacteria presence in the brain. The time to death (4.5 days) for this animal is longer than the mean (3.8 days) and median time to death (3.9 days) of the animals in the 20 mg/kg raxibacumab group with moderate/marked level of bacteria presence and is also longer than the mean (4.1 days) and median (4.0 days) time to death of the animals in the 20 mg/kg raxibacumab group with moderate/marked brain inflammation. As noted above, the rate of monkeys with moderate or marked level of bacteria presence in the brain is significantly higher in the 20 mg/kg raxibacumab group than the rate in the placebo group ($p = 0.0095$). The rate of monkeys with moderate or marked inflammation in the brain was also significantly higher for the raxibacumab 20 mg/kg group than the placebo group ($p=0.0017$). Therefore, the sponsor's claim (discussed in

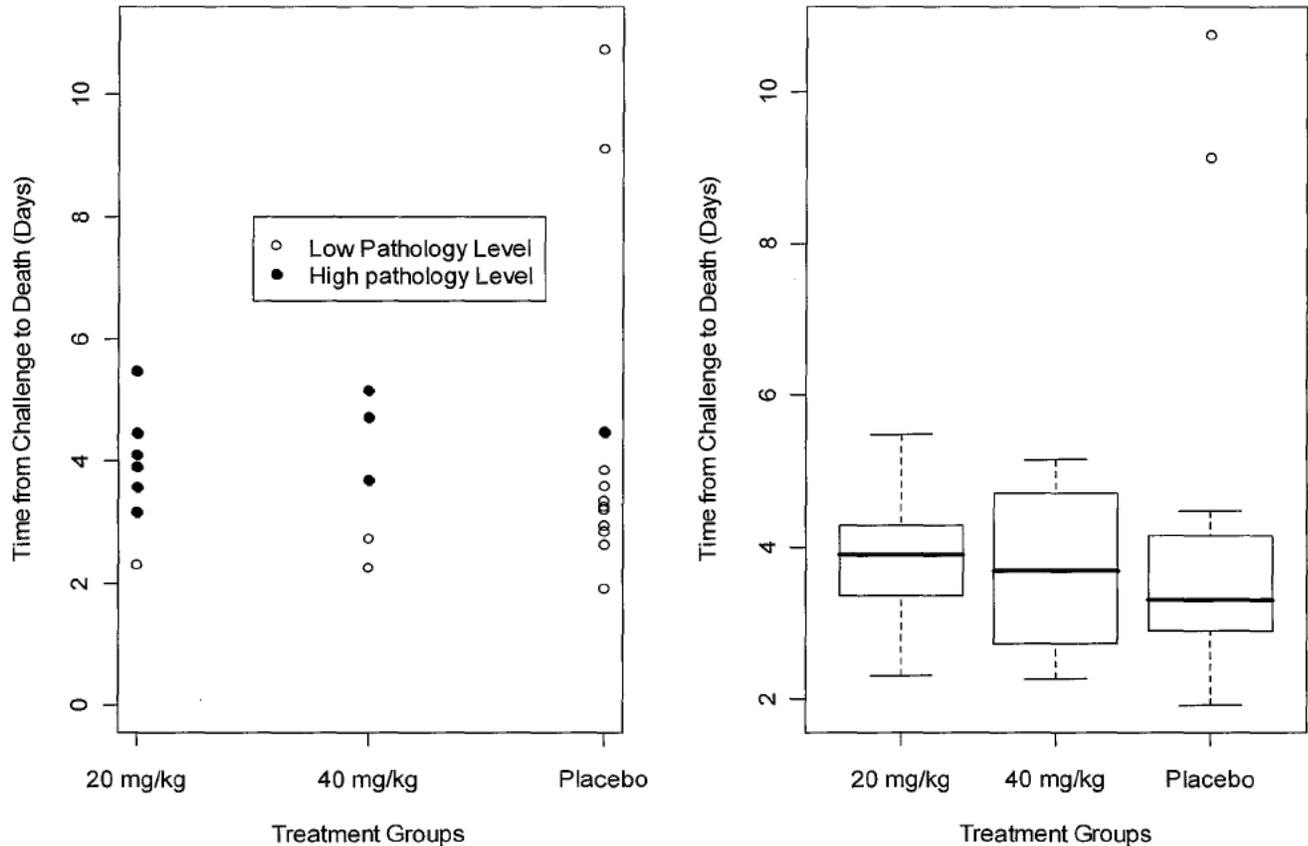
more detail below) that the higher proportion of raxibacumab-treated animals with evidence of CNS involvement is due to longer survival time of these animals is not supported by the data.

Table 3.2.1B Survival Time by Treatment Groups, ITT Population (Study 724-G005829)

| | Placebo | Raxibacumab 20mg/kg | Raxibacumab 40mg/kg |
|---|-----------|------------------------|------------------------|
| All treated animals (Sponsor's) | N=12 | N=14 | N=14 |
| Median | 3.3 | 5.0 | > 28 |
| All necropsized animals** | N=12 | N=7 | N=5 |
| Mean | 4.3 ± 2.7 | 3.8 ± 1.0 | 3.7 ± 1.2 |
| Median | 3.3 | 3.9 | 3.7 |
| Animals with bacterial meningitis | N=11 | N=5 | N=5 |
| Mean | 3.7 ± 1.9 | 3.8 ± 0.5 | 3.7 ± 1.2 |
| Median | 3.2 | 3.8 | 3.7 |
| Animals with moderate or marked level of bacteria presence in the brain | N=1 | N=5 | N=2 |
| Mean | 4.5 | 3.8 ± 0.5 | 4.9 ± 0.3 |
| Median | 4.5 | 3.9 | 4.9 |
| Animals with moderate or marked brain inflammation | N=1 | N=6 | N=2 |
| Mean | 4.5 | 4.1 ± 0.8 | 4.9 ± 0.3 |
| Median | 4.5 | 4.0 | 4.9 |
| Animals without moderate or marked brain inflammation | N=11 | N=1 | N=3 |
| Mean | 4.3 ± 2.8 | 2.3 | 2.9 ± 0.7 |
| Median | 3.2 | 2.3 | 2.7 |

A total of 10 animals were recorded to have high pathology level as defined by FDA in the brain (1 in the placebo group, 6 in the 20 mg/kg raxibacumab group and 3 in the 40 mg/kg raxibacumab group). Figure 4 shows the scatter plot and boxplot of time from challenge to death of monkeys who died of anthrax in the study by treatment groups. The monkeys who were found to have high pathology level were marked with dark circles in the respective graph. Note that the two outliers (C24784 and C23052) in the placebo groups are the monkeys who had the longest survival time among all dead animals but were recorded to have low pathology level. Animal C24784 survived 9.1 days and animal C23052 survived 10.7 days after the end of challenge. The median of the length of times to death in monkeys who died of anthrax in the study was very close across the treatment groups (see Figure 4). Monkeys who lived longer in the raxibacumab groups tended to have CNS findings, but monkeys who had comparable longer survival time in the placebo group still had no CNS events. The occurrence of CNS events appears to be related to raxibacumab treatment rather than just longer survival.

**Figure 4: Time from Challenge to Death by Treatment Groups
(Study 724-G005829)**



Under the Agency's request, the sponsor contracted a third party, Experimental Pathology Laboratories, Inc. (EPL) to perform an independent review of the histopathology slides from this study (724-G005829) and the pivotal rabbit study (682-G005758). The agency requested that this tissue analysis by EPL be blinded and assess the extent and severity of lesions. The results of the histopathology findings by EPL were submitted by the sponsor in SN093. Table 3.2.1C lists the proportion of necropsized animals with bacterial meningitis and inflammation. The EPL's histopathology findings in the brain were very similar to the findings previously presented by the sponsor. The EPL results also show significantly higher rates of moderate or marked level of bacteria presence (6/7 vs 1/12, $p=0.0017$) and moderate or marked level of brain inflammation (6/7 vs 1/12, $p=0.0017$) in the raxibacumab 20 mg/kg group compared to the placebo group.

Table 3.2.1C Proportion of Necropsized Monkeys with CNS Findings by Treatment Groups (Study 724-G005829)

| | Placebo | | Raxibacumab 20mg/kg | | Raxibacumab 40mg/kg | |
|--|---------|------|------------------------|-----|------------------------|-----|
| | N=12 | | N=7 | | N=5 | |
| | HGS | EPL | HGS | EPL | HGS | EPL |
| Bacterial meningitis | 11/12 | 9/12 | 5/7 | 6/7 | 5/5 | 5/5 |
| Moderate or marked level of bacteria | 1/12 | 1/12 | 5/7 | 6/7 | 2/5 | 2/5 |
| Inflammation | 1/12 | 2/12 | 6/7 | 6/7 | 3/5 | 2/5 |
| Moderate or marked level of brain inflammation | 1/12 | 1/12 | 6/7 | 6/7 | 2/5 | 2/5 |

Reviewer’s Comment: The question the review team seeks to answer in the histopathology data is why there are more frequent and severe CNS pathology findings in the raxibacumab treated groups compared to the placebo group. Although longer duration of illness would potentially cause more CNS pathology to develop in general, the data does not show the raxibacumab treated groups had longer duration of illness compared to the placebo group. As noted in Dr. Susan McCune’s clinical review, “the overall survival time and time from bacteremia to death based on treatment group would not seem to explain these differences. Based on the available analyses, the pathophysiologic basis for these differences is unclear.”

Note: The discussions regarding the CNS findings in this section are focused on the aspects of statistical interest, please see Dr. McCune’s clinical review on this study for more details on the histopathology findings.

Study 682-G005758 (Rabbits)

In discussion of the histopathology findings of this study in section 8.2.2 of the study report, the sponsor states that "The average time to death in rabbits with moderate inflammation in the brain was 4.5 days compared with 3.1 days in all rabbits that died, suggesting that the increased survival time allowed for additional pathology to develop in the brain." The review team was not able to replicate the sponsor’s claim with the information provided by the sponsor and requested the sponsor to clarify. The brain pathology status of the animals was not presented in the datasets in the original SNS submission (IND 11069 SN057) and the definition of moderate inflammation of the brain was not provided in the study report. In response to the Agency’s request, the sponsor later submitted the by-animal necropsy and histopathology listings (IND 11069 SN067). The clinical reviewer determined the brain pathology status for each animal in the study based on the information provided in SN067. The sponsor also identified 6 rabbits that were determined to have moderate or marked inflammation in the brain and listed time to death of these rabbits (IND 11069 SN076), still with no clear description of how the categorization was

made in terms of degree of brain inflammation. In the dataset submitted in SN090 under IND 11069, the sponsor removed Rabbit L08150 from and added Rabbit L08135 into the category of moderate or marked brain inflammation, indicating that the data summarized at least at the time of submission SN076 was still not finalized. Furthermore, the relatively longer survival time in the subgroup of rabbits with inflammation in the brain does not validate the sponsor's claim that all raxibacumab treated animals had on average "increased survival time allowed for additional pathology to develop in the brain". As shown below, the histopathology data does not support the sponsor's claim.

Based on the dataset provided by the sponsor, of all the necropsized animals, no animals (0/16) in the placebo group had moderate or marked inflammation in the brain. There were 3 animals in each of the raxibacumab treatment groups (3/12 in the 20 mg/kg group and 3/11 in the 40 mg/kg group) with moderate or marked brain inflammation. Although the rates of animals with moderate or marked brain inflammation in the raxibacumab groups were higher than that of the placebo group, the differences of the rates were borderline not statistically significant between the placebo and the raxibacumab-treated groups ($p=0.0672$ compared with the 20 mg/kg group and $p=0.0564$ compared with the 40 mg/kg group).

Based on the information provided in SN067, there were higher rates of rabbits which were found to have brain pathology in the raxibacumab treatment groups (12/12 in the 20 mg/kg group and 8/11 in the 40 mg/kg group) than in the placebo group (5/16) based on all necropsized animals. The rates of rabbits with brain pathology were significantly different between the placebo group and the raxibacumab 20 mg/kg group ($p = 0.0003$, Fisher's exact test) even with the Bonferroni correction ($0.05/2=0.025$). The difference between the placebo group and the raxibacumab 40 mg/kg group was not significantly significant ($p = 0.0542$, Fisher's exact test). Based on the dataset submitted in SN090, 19 animals were found to have bacteria in the brain. The rates of bacterial meningitis are 3/16 in the placebo group, 9/12 in the raxibacumab 20 mg/kg group and 7/11 in the raxibacumab 40 mg/kg group. The difference between the raxibacumab 20 mg/kg group and the placebo group with bacteria presence in the brain is still statistically significant ($p=0.0061$, Fisher's exact test). The p value is 0.0402 (Fisher's exact test) for the comparison between the 40 mg/kg group and the placebo.

For BLA review, the review team defined the pathology level of CNS pathology findings for each necropsized animal based on the same criteria as used for the Study 724-G005829 which is as follows: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low. There were higher rates of rabbits which were recorded to have high pathology level in the raxibacumab treatment groups (9/12 in the 20 mg/kg group and 6/11 in the 40 mg/kg group) than in the placebo group (2/16) among the necropsized animals. The rates of monkeys with high pathology level were significantly different between the placebo group and the raxibacumab 20 mg/kg group ($p = 0.0015$, Fisher's exact test) even with the Bonferroni correction ($0.05/2=0.025$). The p value is 0.0332 (Fisher's exact test) for the comparison between the 40 mg/kg group and the placebo. See table below.

Table 3.2.1D CNS findings in Necropsized Rabbits (Study 628-G005758)

| Treatment | Number of Necropsized Rabbits | No. (%) of CNS findings | P-value* |
|---|-------------------------------|-------------------------|----------|
| Moderate/Marked Brain Inflammation | | | |
| Placebo | n = 16 | 0 (0%) | |
| 20 mg/kg Raxibacumab | n = 12 | 3 (25.0%) | 0.0672 |
| 40 mg/kg Raxibacumab | n = 11 | 3 (27.3%) | 0.0564 |
| FDA CNS Pathology Level** | | | |
| Placebo | n = 16 | 2 (12.5%) | |
| 20 mg/kg Raxibacumab | n = 12 | 9 (75.0%) | 0.0015 |
| 40 mg/kg Raxibacumab | n = 11 | 6 (54.5%) | 0.0332 |

* P values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.

** The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

Table 3.2.1E lists the mean and median time to death by the treatment groups. For the all treated animals, the median survival times in the raxibacumab groups were higher than the median survival in the placebo group since all animals in the placebo group died and some animals in the raxibacumab groups survived. Among the necropsized animals, there is no statistically significant difference for time to death between the placebo group and the raxibacumab groups ($p=0.5494$ compared with the 20 mg/kg group and $p=0.7877$ compared with the 40 mg/kg group, Wilcoxon two sample test). Among the animals with brain pathology, the mean (3.4 days) and median (3.0 days) of time to death in the raxibacumab 20 mg/kg group are slightly longer than those values (mean 3.2 days and median 2.7 days) in the placebo group, but the difference is not statistically significant ($p=0.9577$). The time to death appears to be longer for the raxibacumab treated groups than the placebo group among the rabbits with bacterial meningitis, but was longer for the placebo group than the raxibacumab groups among the rabbits with aseptic meningitis. Although the study was not designed to detect any statistically significant difference between the treatment groups regarding the histopathology findings, there is no indication that the histopathology data supports the sponsor's claim that the higher proportion of raxibacumab-treated animals with evidence of CNS involvement is due to longer survival time of these animals.

**Table 3.2.1E Survival Time by Treatment Groups, As-treated Population*
(Study 628-G005758)**

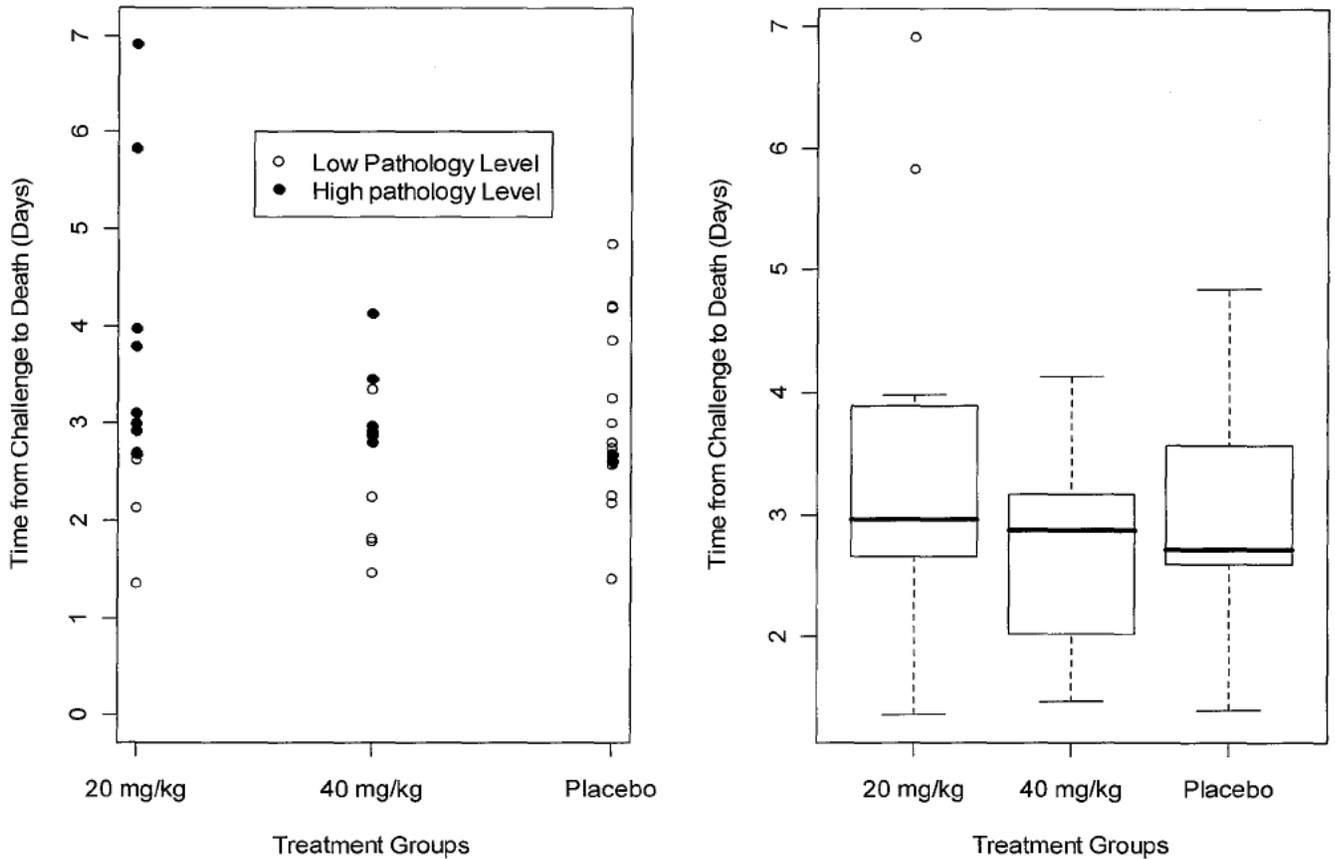
| | Placebo | Raxibacumab 20mg/kg | Raxibacumab 40mg/kg |
|-----------------------------------|-----------|------------------------|------------------------|
| All treated animals (Sponsor's) | N=16 | N=17 | N=19 |
| Median | 2.7 | 3.8 | 3.5 |
| All necropsized animals** | N=16 | N=12 | N=11 |
| Mean | 3.0 ± 0.9 | 3.4 ± 1.5 | 2.7 ± 0.8 |
| Median | 2.7 | 3.0 | 2.9 |
| Animals with brain pathology | N=5 | N=12 | N=8 |
| Mean | 3.2 ± 0.8 | 3.4 ± 1.5 | 3.1 ± 0.7 |
| Median | 2.7 | 3.0 | 3.0 |
| Animals with bacterial meningitis | N=3 | N=9 | N=7 |
| Mean | 2.7 ± 0.1 | 3.9 ± 1.5 | 3.2 ± 0.5 |
| Median | 2.7 | 3.1 | 3.0 |
| Animals with aseptic meningitis | N=2 | N=3 | N=1 |
| Mean | 4.1 ± 0.2 | 2.0 ± 0.6 | 1.8 |
| Median | 4.1 | 2.1 | 1.8 |
| Animals without brain pathology | N=11 | N=0 | N=3 |
| Mean | 3.0 ± 0.9 | - | 1.8 ± 0.4 |
| Median | 2.7 | - | 1.8 |

*Rabbit L08128 died during the challenge and was excluded from the as-treated population.

**Only animals died of anthrax were necropsized.

Figure 7 shows the scatter plot and boxplot of time from challenge to death of rabbits who died of anthrax in the study. A total of 17 rabbits were recorded to have high pathology level in the brain (2 in the placebo group, 9 in the 20 mg/kg raxibacumab group and 6 in the 40 mg/kg raxibacumab group). The rabbits who were found to have high brain pathology level were marked with dark circles in the graph. With the exception of the two outliers in the raxibacumab 20 mg/kg, the length of time to death in rabbits who died of anthrax in the study and time to death of rabbits with brain pathology were very close across the treatment groups. Rabbits who lived longer in the raxibacumab groups tended to have CNS findings, but rabbits who had comparable longer survival time in the placebo group still had no CNS events. The occurrence of CNS events appears to be related to raxibacumab treatment rather than just longer survival.

Figure 7: Time to Death due to Anthrax with Brain Pathology Marked, Study 628-G005758



As with the monkey study (724-G005829), the sponsor contracted Experimental Pathology Laboratories, Inc. (EPL) to perform an independent review of the histopathology slides from this study (682-G005758). The agency requested that this tissue analysis by EPL be blinded and assess the extent and severity of lesions. The results of the histopathology findings by EPL were submitted by the sponsor in SN093. The EPL review categorized 15/16 in the placebo arm, 9/12 in the raxibacumab 20 mg/kg group and 7/11 animals in the raxibacumab 40 mg/kg group to have CNS bacteria. This is different from the results provided by the sponsor. However, proportion of moderate or marked level of CNS bacteria as determined by EPL was similar to that of the sponsor and is higher in raxibacumab groups (4/12 in the 20 mg/kg group and 3/11 in the 40 mg/kg group) as compared to placebo treated animals (0/16) that underwent necropsy. The differences between the raxibacumab groups and the placebo group are statistically significant ($p=0.0242$ for 20 mg/kg group and $p=0.0188$ for 40 mg/kg group).

Reviewer's Comment: The question the review team seeks to answer in the histopathology data is why there are more frequent and severe CNS pathology findings in the raxibacumab treated groups compared to the placebo group. Although longer duration of illness would potentially

cause more CNS pathology to develop in general, the data does not show the raxibacumab treated groups had longer duration of illness compared to the placebo group. As noted in Dr. Yasinskaya's clinical review, "it does not appear that just the duration of illness alone could account for greater pathologic findings in the brain of animals treated with raxibacumab versus placebo"

Note: See more details for the histopathology findings for study 682-G005758 in Dr. Yuliya Yasinskaya's clinical review

Raxibacumab and antibacterial combination studies

In the combination studies (Study 781-G923701 and 789-G923702), there is no raxibacumab only treatment arm and only one animal in each study died of anthrax. One animal in Study 789-G923702 had CNS findings and this animal was in the Ciprofloxacin/Raxibacumab treatment arm. Study 781-G923701 was the only efficacy study that had CNS results for surviving animals. The sponsor reported that none of the rabbits had CNS findings. These two studies contributed very little information regarding the CNS findings of the raxibacumab treatment. On page 203, last paragraph, the sponsor states the results that none of the rabbits had evidence of brain lesions in study 781-G923701, "suggests that raxibacumab administration to animals with systemic anthrax disease does not increase the occurrence of brain lesions". There is no raxibacumab only treatment arm in the study to support this conclusion.

CNS findings and time of death

(b) (4)

- 1) Analysis of CNS inflammation: Time to death in animals with moderate to marked inflammation in the brain was significantly longer than for non-surviving animals without moderate to marked inflammation in the brain: 4.0 days with inflammation and 2.7 days without inflammation for rabbits and 4.5 days with inflammation and 3.2

days without inflammation for monkeys, $p=0.0017$ and $p=0.0171$ by Wilcoxon test (page 203 briefing document).

- 2) Analysis of survival time: In the pivotal therapeutic efficacy studies in both species, 20 mg/kg and 40 mg/kg raxibacumab significantly increased survival time compared with placebo and the trend to increased survival time was dose-dependent.

Based on our analyses below, we do not believe that the sponsor's above quotes are valid. The sponsor's conclusion that animals that died with moderate or marked inflammation had a significantly longer survival time compared to those who did not have moderate or marked inflammation is only true for the raxibacumab treatment groups (See Table 3.2.1F). Since we are looking for possible treatment effects of raxibacumab, it is not appropriate to pool the treatment groups with the placebo group (a major design of the study), as the sponsor has done. Note that to increase power for safety analyses, different doses of a test drug are often pooled; however, they are not then pooled with the control group. An analyses of time to death by brain inflammation without pooling placebo with the raxibacumab groups are given in the table below.

Table 3.2.1F: Median Time to death by Brain Inflammation Status

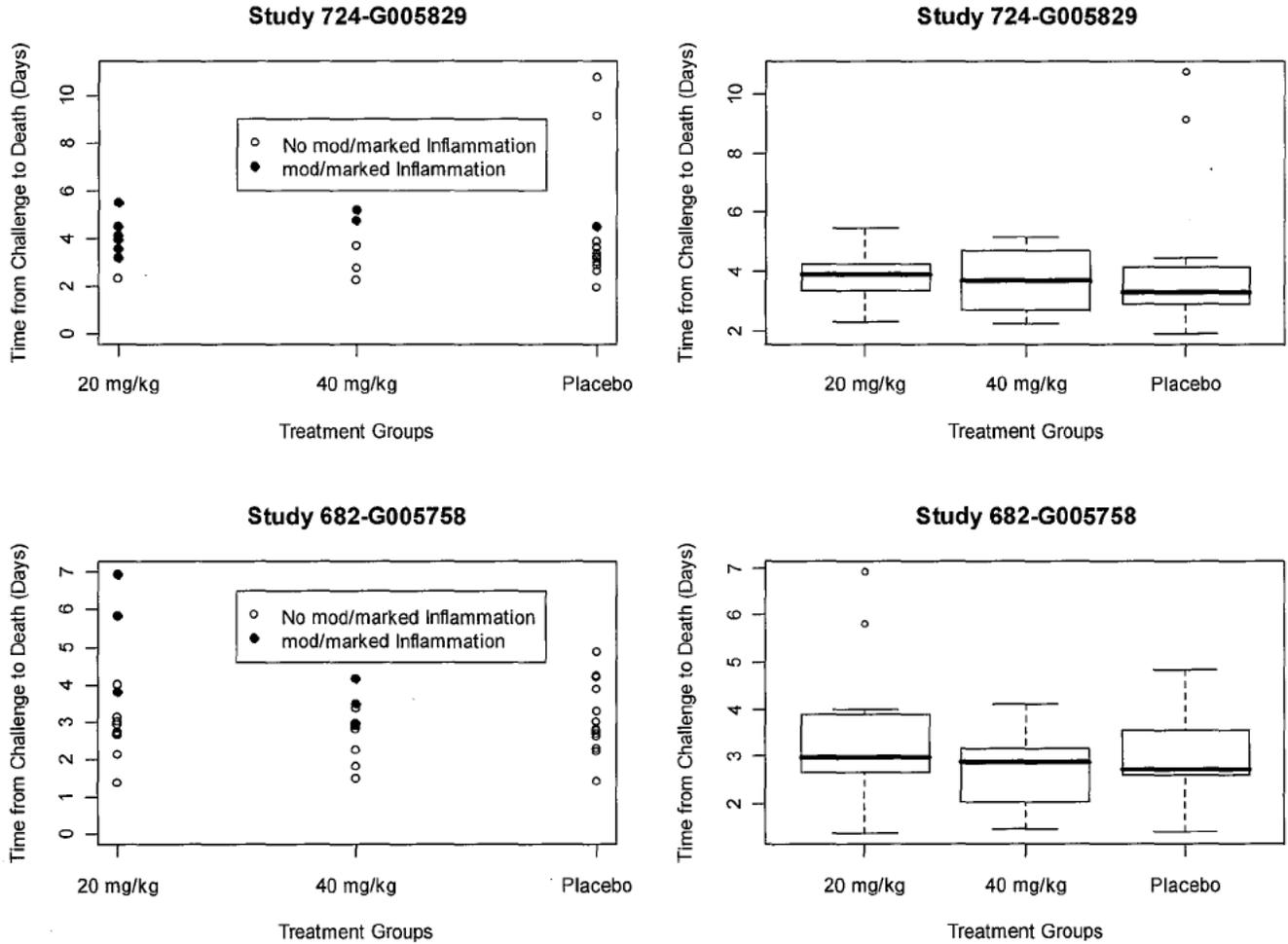
| | Moderate/Marked brain inflammation | No moderate/marked brain Inflammation | Wilcoxon p-value |
|---|---------------------------------------|--|------------------|
| Study 724-G005829 | | | |
| Pooled 3 groups (sponsor's analysis) | 4.5 (n=9) | 3.2 (n=15) | 0.0171 |
| Raxibacumab (pooled 20 and 40 mg/kg) | 4.3 (n=8) | 2.5 (n=4) | 0.0219 |
| Raxibacumab 40 mg/kg | 4.9 (n=2) | 2.7 (n=3) | 0.1489 |
| Raxibacumab 20 mg/kg | 4.0 (n=6) | 2.3 (n=1) | 0.2113 |
| Placebo | 4.5 (n=1) | 3.2 (n=11) | 0.3848 |
| Study 682-G005758 | | | |
| Pooled 3 groups (sponsor's analysis) | 4.0 (n=6) | 2.7 (n=33) | 0.0028 |
| Raxibacumab (pooled 20 and 40 mg/kg) | 4.0 (n=6) | 2.7 (n=17) | 0.0016 |
| Raxibacumab 40 mg/kg | 3.5 (n=3) | 2.5 (n=8) | 0.0313 |
| Raxibacumab 20 mg/kg | 5.8 (n=3) | 2.7 (n=9) | 0.0262 |
| Placebo | N/A | 2.7 (n=16) | N/A |

The sponsor's second conclusion is that the increased incidence and severity of brain findings is related to the increased survival time in the raxibacumab treatment groups (compared to placebo). Since only animals that died have brain histopathology assessed in the pivotal studies and since the sponsor's conclusion is regarding only non-surviving animals, we need to assess survival time (i.e., time to death) only in the animals that died. Our assessment of time to death across the treatment arms by numbers (Table 3.2.1G) and graphs (Figure 8) does not show an increased survival time in the raxibacumab treatment groups compared to the placebo for either the pivotal monkey or rabbit studies.

Table 3.2.1G: Time to death for Animals that died

| Study 724-G005829 | | Study 682-G005758 | |
|-------------------------------|------------|--------------------------------|-----------|
| Raxibacumab 40 mg/kg (n=5) | | Raxibacumab 40 mg/kg (n=11) | |
| Median | 3.7 | Median | 2.9 |
| Mean | 3.7 | Mean | 2.7 |
| Min - Max | 2.3 – 5.2 | Min - Max | 1.5 – 4.1 |
| Raxibacumab 20 mg/kg (n=7) | | Raxibacumab 20 mg/kg (n=12) | |
| Median | 3.9 | Median | 3.0 |
| Mean | 3.9 | Mean | 3.4 |
| Min - Max | 2.3 – 5.5 | Min - Max | 1.4 – 6.9 |
| Placebo (n=12) | | Placebo (n =16) | |
| Median | 3.3 | Median | 2.7 |
| Mean | 4.3 | Mean | 3.0 |
| Min – Max | 1.9 – 10.8 | Min - Max | 1.4 – 6.9 |
| p = 0.855, Krusal-Wallis test | | P = 0.655, Kruskal-Wallis test | |

Figure 8: Time to death by Treatment Group with Moderate/Marked Inflammation Marked (Study 724-G005829 and Study 682-g005758)



Based on the above analysis, we believe that the sponsor's statement that

(b) (4)

is misleading. There is no evidence that the

(b) (4)

(b) (4) The conclusions of our analyses, as well as, a request to clarify and correct inaccurate statements in their briefing document was relayed to the sponsor in a fax dated *September 17, 2009*.

3.2.2 Human Clinical Safety

For the assessment of human clinical safety of raxibacumab, the Agency relies on Studies HGS1021-C1064, HGS1021-C1063 and HGS 1021-C1069. The safety database consists of 323 subjects treated with the recommended dose of raxibacumab of 40 mg/kg manufactured by the M11 process, with 303 subjects receiving a single dose (studies HGS1021-C1064 and HGS1021-C1063), 23 subjects receiving a 2nd dose 2 weeks after their first dose (study HGS1021-1063), and 20 subjects from study HGS1021-C1064 who received a 2nd dose more than 4 months after their initial dose (study HGS1021-C1069).

Reviewer's comment: For details of safety assessment, please see Dr. Sue Lim's clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section presents and discusses subgroup analyses of the pivotal studies, study 724-G005829 and study 682-G005758. Please see statistical review by Lan Zeng for subgroup analyses of study 789-G923702 and study 781-G923701.

4.1 Gender, Race and Age

Study 724-G005829

Table 4.1 summarizes survival rates for the ITT population according to categories of sex and age of monkeys in each treatment group for the study. There were equal numbers of males and females in each treatment group. The survival rates were comparable between male and female monkeys within the same treatment groups. The age of monkeys in study 724-G005829 ranged from 2.71 years to 4.55 years with a median of 3.82 years. The group of monkeys older than the median age in the 40 mg/kg raxibacumab group had the highest survival rate (5/6) than the rest of the subgroups. The survival rate in this group of monkeys was also higher than the overall survival rate (9/14=64.3%) in the 40 mg/kg group.

Table 4.1 Survival Rates by Sex and Age Categories in ITT Population (study 724-g005829)

| | Placebo N = 12 | 20 mg/kg Raxibacumab N = 14 | 40 mg/kg Raxibacumab N = 14 |
|-----------------------------------|-------------------|--------------------------------|--------------------------------|
| Sex | | | |
| male | 0/6 | 3/7 (42.9) | 5/7 (71.4) |
| female | 0/6 | 4/7 (57.1) | 4/7 (57.1) |
| Age (years) | | | |
| min (2.71) - median (3.82) | 0/5 | 4/7 (57.1) | 4/8 (50.0) |
| median – max (4.55) | 0/7 | 3/7 (42.9) | 5/6 (83.3) |

Study 682-G005758

Given that all rabbits in the study were 205 days old at the time of randomization, age was not a factor to consider for subgroup analysis. All 9 male and 8 female rabbits in the placebo group died. The survival rate for male rabbits was lower than the female rabbits in the 20 mg/kg raxibacumab group (2/10=20% vs 3/8=37.5%), and the survival rate for male rabbits was higher than the female rabbits in the 40 mg/kg raxibacumab group (6/10=60% vs 2/8=25%).

4.2 Other Special/Subgroup Populations

Study 724-G005829

Another factor of potential interest is weight. Weights of the monkeys in the study ranged from 2.3 to 5.1 lbs with a median and mean of 3.5 lbs. Six monkeys in the placebo group were below the median weight (<3.5 lb) and 6 monkeys were above the median weight. As noted previously, none of these 12 monkeys survived. In the 20 mg/kg raxibacumab group, the survival rates were 4/7 (57.1%) for the group with weights lower than the median weight (<3.5) and 3/7 (42.9%) for the group with weights greater than the median weight (>3.5). In the 40 mg/kg raxibacumab group, the survival rates was 4/7 (57.1%) for the group with weight < 3.5 and was 5/7 (71.4%) for the group with weight >3.5 lbs.

Study 682-G005758

The weights of the rabbits in this study ranged from 2.7 to 3.4 lbs with a median and mean of 3.1 lbs. There were 13 rabbits in the placebo group with a weight below the median (3.1 lbs) and 4 rabbits in the placebo group with weight above the median weight. As noted previously, none of these 17 rabbits survived. In both raxibacumab treatment groups, the survival rates were higher for the group with weights lower than the median weight than the group with weights greater than the median weight (4/13=30.8% vs 1/5=20% for the 20 mg/kg group and 6/12=50% vs 2/6=33.3% for the 40 mg/kg group).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A statistical issue of both pivotal studies on the primary efficacy analysis was the adjustment for multiple comparisons. In protocol 724-G005829, the sponsor proposed to use a step-down sequential testing procedure. First, the 40 mg/kg raxibacumab group will be compared with the placebo group at a 2-sided $\alpha=0.05$ significance level. If the result is statistically significant, the 20 mg/kg group will be tested vs placebo at a two-sided $\alpha=0.05$ significance level. If the result for the 40 mg/kg group is not significant, superiority of neither raxibacumab group will be established. In the protocol for Study 682-G005758, the sponsor proposed that the primary efficacy analysis will be subject to a multiple comparison adjustment using the Hochberg

procedure. The results will be considered statistically significant if: At least 1 of the pair-wise comparisons between raxibacumab and control achieves a p-value < 0.025 , or both pair-wise comparisons between raxibacumab and control achieve a p-value < 0.05 . The agency accepted the sponsor's proposals for multiplicity adjustments for both studies as defined in the relevant protocols. The sponsor did not discuss adjustment for multiple pairwise comparisons in the two study reports. However, the sponsor is only requesting approval of the 40 mg/kg dose which was found to be significant to placebo in the two pivotal efficacy studies even with adjustment for multiple comparisons.

In the two additional efficacy studies (Study 789-G923072 and Study 781-G923071) evaluating efficacy of raxibacumab with antimicrobials, the sponsor's primary analysis was to compare the survival at day 28 between the combination arm (raxibacumab/antimicrobial) to the placebo. Both studies show that antimicrobial and raxibacumab/antimicrobial arms were superior to the placebo. In the protocol stage, the Division sent the comments to the sponsor that our primary goal for the combination studies is to explore the comparison of the combination (raxibacumab/antimicrobial) to antimicrobial alone and that the study's primary analysis (i.e., the comparison of the combination to placebo) will not lead to the conclusion that the efficacy of the combination arm, if confirmed, is due to raxibacumab or antimicrobial. However, the studies were not powered to detect a difference of our interest. The survival rates in the antimicrobial arms were very high in both studies, making it impossible to see any added benefit of raxibacumab to antimicrobial. Additionally, the survival rate was numerically higher in Ciprofloxacin arm than the raxibacumab/Ciprofloxacin arm in the monkey combination study (Study 789-G923072), leading to concern that raxibacumab may potentially reduce the efficacy of antimicrobials. However, given the small sample size and the unexpectedly high survival rates in the antimicrobial alone arms, these results are not very informative.

Given that the sponsor was exploring the efficacy of raxibacumab in the treatment of inhalational anthrax, it was very important that the animals in the study have active disease (i.e., be bacteremic) at the time of treatment. If they did not have active disease, the efficacy from the studies would be more relevant for an indication of post-exposure prophylaxis, which might be expected to yield higher survival rates. This was conveyed to the sponsor in the FDA comments numerous times prior to the submission of the study protocols and also in the comments on the study protocols. The FDA's primary analysis population, a type of modified intent to treat population with exclusion based on pre-treatment information only, includes only animals that were bacteremic at treatment initiation. The sponsor, however, considered the full intent to treat population as the primary analysis population.

The main statistical issue in this BLA review was regarding the histopathology finding that non-surviving animals in the raxibacumab-treated groups were shown to have higher rates of meningitis and/or higher rates of moderate/marked inflammation in the brain than animals in the placebo group in both Study 724-G005829 and Study 682-G005758. The sponsor claims that the higher proportion of raxibacumab-treated animals with evidence of CNS involvement is due to longer survival time of these animals. However, the histopathology data does not show the raxibacumab treated groups had longer duration of illness compared to the placebo group. Note that the two combination trials did not provide much additional information to further investigate

the CNS findings observed in the pivotal studies, since there were very few deaths among the antimicrobial treated animals and no animal was treated with raxibacumab alone.

The details for each study are summarized below.

Study 742-G005829

Day 28 survival rates in both raxibacumab groups were shown to be superior to the rate in the placebo group for the FDA primary analysis population.

The rates of monkeys with moderate or marked brain inflammation were significantly higher in the raxibacumab 20 mg/kg group than the placebo group (6/7 [86%] compared with 1/12 [8%], $p = 0.0017$, Fisher's exact test) and numerically higher in the raxibacumab 40 mg/kg group than the placebo group (2/5 [40%] compared with 1/12 [8%], $p=0.1912$). There is also a statistically significant difference between the raxibacumab 20 mg/kg group and the placebo in terms of proportion of monkeys with a high level of CNS pathology as determined by the medical reviewers (6/7 [86%] compared with 1/12 [8%], $p = 0.0017$) and a borderline significant difference between the raxibacumab 40 mg/kg group and the placebo group (3/5 [60%] compared with 1/12 [8%], $p=0.0525$).

Among the necropsized animals, there is no statistically significant difference in time to death (from the end of anthrax challenge) between the placebo and the raxibacumab groups ($p = 0.5895$ compared with the 20 mg/kg group and $p = 0.9586$ compared with the 40 mg/kg group). There is no credible evidence from the histopathology data for the sponsor's hypothesis that the length of survival led to the difference in the number of animals with moderate/marked level of bacteria presence and/or with moderate/marked brain inflammation in the 20 mg/kg raxibacumab group compared to the placebo group.

Study 682-G005758

Day 14 survival rates in both raxibacumab groups were higher than in the placebo group. Applying the Hochberg's procedure to the FDA primary analysis population, we conclude that the raxibacumab 40 mg/kg group showed a statistically significant survival benefit over the placebo group but the raxibacumab 20 mg/kg group did not show a significant survival benefit over the placebo. However, the results for raxibacumab 40 mg/kg group in the rabbit study would change if rabbit L08147 was excluded from the FDA primary analysis population. Rabbit L08147 was bacteremic 1/2 hour prior to treatment but was not bacteremic immediately before treatment initiation. This signals that the evidence of a statistically significant difference between the raxibacumab 40 mg/kg group and the placebo group shown in the FDA primary analysis population is rather weak.

The rates of rabbits with a high level of CNS pathology as determined by the medical reviewers were significantly higher in the raxibacumab treated groups, both 20 mg/kg (9/12 [75%]) and 40 mg/kg (6/11 [55%]), compared with placebo (2/16 [13%], p -values 0.002 and 0.033, respectively, Fisher's exact test).

Among the necropsized animals, there is no statistically significant difference for time to death between the placebo group and the raxibacumab groups ($p=0.5494$ compared with the 20 mg/kg group and $p=0.7877$ compared with the 40 mg/kg group, Wilcoxon two sample test). Again there is no credible evidence from the histopathology data for the sponsor's hypothesis that the length of survival led to the difference in the number of animals with meningitis in the raxibacumab groups compared to the placebo group.

Study 781-G923701

The 28-day survival rates were 0%, 95.0%, and 94.1% in the placebo, levofloxacin, and levofloxacin/raxibacumab combination groups, respectively. There was no significant difference ($p=0.947$) in survival rates between the levofloxacin and levofloxacin/raxibacumab combination groups (-0.88%, 95% CI [-23.9%, 19.6%]). However, given the small size of the study and the unexpectedly high survival rate in the antimicrobial alone arm, this study could not rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with levofloxacin. Complete gross necropsies were conducted on all 52 rabbits, none of which in the active treatment groups had lesions attributable to anthrax at sacrifice, or any brain lesions on microscopic examination.

Study 789-G923702

The 28-day survival rates were 0%, 100%, and 84.6% in the placebo, ciprofloxacin, and ciprofloxacin/raxibacumab combination groups, respectively. There was no significant difference ($p=0.222$) in survival rates between the ciprofloxacin and raxibacumab/ciprofloxacin combination groups (-15.4%, 95% CI [-45.5%, 11.4%]). However, given the small size of the study and the unexpectedly high survival rate in the antimicrobial alone arm, this study could not rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with ciprofloxacin. Microscopic exams were performed on 15 monkeys that were found dead or euthanized, out of which one animal treated with ciprofloxacin/raxibacumab had evidence of hemorrhagic meningitis that affected the entire brain.

Note: Please see the statistical review for Study 781-G923701 and Study 789-G923702 by Lan Zeng for the statistical issues of these two studies.

5.2 Conclusions and Recommendations

In the assessment of this reviewer, a single intravenous dose of 40 mg/kg raxibacumab was shown to be superior to the placebo for the treatment of anthrax in the ITT and FDA primary analysis populations in both the monkey (Study 724-G005829) and the rabbit (Study 682-G005758) studies that were submitted as the pivotal efficacy studies. However, the results for raxibacumab 40 mg/kg group in the rabbit study would change if one rabbit, who was bacteremic 1/2 hour prior to treatment but was not bacteremic immediately before treatment initiation, was excluded, signaling that the evidence of there being a statistically significant difference between the raxibacumab 40 mg/kg group and the placebo group in the rabbit model is rather weak. In addition, the extrapolation from the animal to human use will depend on supportive evidence from pharmacokinetic information.

Two additional efficacy studies (Study 789-G923072 and Study 781-G923071) were conducted to evaluate the efficacy of raxibacumab in combination with antimicrobials. However, given the small sample size and the unexpectedly high survival rates in the antimicrobial alone arms, these studies cannot rule out possible antagonism or demonstrate possible benefit of raxibacumab when used in combination with levofloxacin or ciprofloxacin.

In both Study 724-G005829 and Study 682-G005758, non-surviving animals in the raxibacumab-treated groups were shown to have higher rates of high level of pathology in the brain than animals in the placebo group. The hypothesis stated by HGS that this difference was related to longer survival of the raxibacumab-treated animals rabbits compared to the placebo group was not found plausible. The analyses of histopathology data by this statistical reviewer indicate that an increased incidence and severity of CNS findings is related to increased survival time only within the raxibacumab group. In the combination studies (Study 781-G923701 and 789-G923702), there is no raxibacumab only treatment arm and only one animal in each study died of anthrax. These two studies contribute very little information regarding the CNS findings of the raxibacumab treatment. The CNS findings will need to be further investigated in the context of additional studies that are well designed to address this issue.

SIGNATURES

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Hongling Zhou, Ph.D., 10/19/2009

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