Application Type	Original Application
STN	125562/0
CBER Received Date	March 10, 2014
PDUFA Goal Date	
Division / Office	DHCR/OBRR
Priority Review	Yes
Reviewer Name(s)	L. Ross Pierce, M.D.
Review Completion Date / Stamped Date	Dec 31, 2014
Supervisory Concurrence	
Applicant	Cangene
Established Name	Anthrax Immune Globulin Intravenous (Human)
(Proposed) Trade Name	Anthrasil
Pharmacologic Class	Hyperimmune immunoglobulin
Formulation(s), including Adjuvants, etc	The formulation contains purified human antibodies to Bacillus anthracis stabilized with 10 % maltose and 0.03% polysorbate 80.
Dosage Form(s) and Route(s) of Administration	Liquid for Intravenous Administration in 50 mL glass vials
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Anthrax Immune Globulin Intravenous (Human) [AIGIV] is indicated for the treatment of adult and pediatric patients with toxemia associated with inhalational anthrax. AIGIV is beneficial in combination with appropriate antibacterial drugs.
Orphan Designated (Yes/No)	Yes, for treatment of toxemia associated with inhalational anthrax (OP letter dated 29 July 2008 re: designation request # 08-2630)

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GLOSSARY

AE	Adverse event
AIGIV	Anthrax Immune Globulin Intravenous (Human)
AVA	Anthrax Vaccine Adsorbed
BMI	Body mass index
CFR	Code of federal regulations
CL	Drug clearance rate
C_{max}	Maximum serum concentration
CRF	Case Report Form
CRO	Contract research organization
CV%	Coefficient of variation
ECG	Electrocardiogram
(b) (4)	(b) (4)
GCP	Good Clinical Practices
GLP	God laboratory practice
GNS-POC	Glucose non-specific point-of-care device
GS-POC	Glucose specific point-of-care device
HBV	Hepatitis B virus
IV	Intravenous
NAT	Nucleic acid testing
NP-015	Cangene's Anthrax Immune Globulin Intravenous (Human)
PA	Protective Antigen
POC	Point-of-care [device]
SD	Standard Deviation
SAE	Serious adverse event
TNA	Toxin neutralization assay
Vd	Volume of distribution
WBC	White blood Cells

1. Executive Summary

Cangene Anthrax Immune Globulin Intravenous (Human) – AIGIV, code named NP-015 is a hyperimmune human polyclonal IgG, prepared from plasma from plasmapheresis donors vaccinated with Bioport's Anthrax Vaccine Adsorbed (AVA) and purified by lipoprotein removal and anion exchange chromatography using a (b) (4) (b) (4) column. Processing of the product includes solvent/detergent (S/D) treatment to inactivate potential lipid enveloped viruses and filtration with a 20 nM Planova virus filter to remove non-lipid enveloped viruses. (b) (4)

In IND amendment 03, the sponsor has stated its intention to amend the CMC section of the IND to switch to a liquid preparation containing (b) (4) total IGIV.

Donors at three FDA-licensed plasmapheresis centers had received a minimum of 3-4 doses of Anthrax Vaccine Adsorbed (AVA, Biothrax, Bioport). Two types of donors have been used. One was donors immunized with AVA under "an FDA licensed donor immunization program" and the other was from military personnel who had previously been immunized with AVA vaccine. Donors were required to meet the Source Plasma

donor eligibility criteria, including the International Quality Plasma Program (iQPP) standards, and the "anthrax antibody program" criteria and will be immunized with AVA according to the Biothrax package insert. Donors who mounted a suitable antibody response donated starting approximately 7-28 days post-vaccination after the 3rd and each subsequent dose of AVA vaccine. FDA guidances for plasma donation were to be met. Source plasma units were quantified for anti-protective-antigen (anti-PA) antibody using an (b) (4) at Cangene with an alternate backup site available. The reference standard for the (b) (4) was and is pooled serum derived from AVA-vaccinated human donors.

The pivotal study to support the proposed indication was conducted in rabbits under the Animal Rule. Animal efficacy model studies were conducted in two established models for inhalational anthrax: the rabbit and the rhesus macaque. These same animal models were also used to as the basis to extrapolate efficacy to humans for the 2012 FDA approval of the anti-anthrax monoclonal antibody product, raxibacumab, under the Animal Rule. The animal studies included in the present application assessed both efficacy and PK and were intended to establish a therapeutic level of AIGIV for treatment of inhalational anthrax when combined with antibiotic therapy. Studies in these two species also examined the efficacy of AIGIV as monotherapy without concomitant antimicrobial therapy. As monotherapy, AIGIV was shown to be effective in the treatment of inhalational anthrax resulting from standardized exposure to aerosolized anthrax spores in both animal models in comparison to saline control groups, according to the sponsor's analysis. However, the sponsor was unable to demonstrate statistically significant superiority of combined AIGIV plus antimicrobial therapy over antimicrobial therapy alone in its pivotal rabbit study, or in its pilot studies in (b) (4) macaques. The pivotal rabbit study did, however, suggest a trend toward superiority of combined antibiotic plus AIGIV therapy over antibiotic monotherapy.

Regarding the choice of animal species to provide substantial evidence of efficacy under the Animal Rule, FDA communicated to Cangene in a letter dated 14 January 2005 that the sponsor's choice of the animal models used to demonstrate efficacy of AIGIV against inhalational anthrax, the New Zealand White rabbit and the rhesus macaque, appeared reasonable, based on desirable characteristics of these animal models of inhalational anthrax disease, which include the following:

- Susceptibility to *Bacillus anthracis*

    - Disease pathogenesis and pathophysiology that recapitulates those of inhalational anthrax in humans, particularly with regard to the roles of anthrax toxins and microbial proliferation and dissemination

    - Pathologic findings that resemble those in human inhalational anthrax disease

    - An immunologic response (including cytokine responses) that is analogous to that in human inhalational anthrax disease

- The ability to adequately characterize the pharmacokinetics and pharmacodynamics of a potential therapeutic agent so as to allow selection of an effective dose in humans

- The ability to measure effects on clinically relevant endpoint(s), generally survival or prevention of major morbidity.

The letter went on to state that It was the preference of the Agency that definitive efficacy studies of therapeutics targeting anthrax toxin, for consideration under the Animal Rule, ultimately be performed in a relevant non-human primate (NHP) model of inhalational, established anthrax disease, as the sponsor had are proposed at that time. The Agency based this preference upon the evolutionary similarities between NHPs and humans, the similarities in the pathophysiological response to anthrax infection, and the relative degree of confidence that by which pharmacokinetic data obtained from NHPs can be bridged to pharmacokinetic information from humans, particularly when attempting to establish a comparable human dose for a product developed under the Animal Rule. Nevertheless, the sponsor, with FDA consent, conducted the pivotal rabbit efficacy model study in rabbits because a pilot study in NHPs showed only a very small incremental survival benefit of AIGIV plus antibiotic therapy over antibiotic therapy plus Immune Globulin Intravenous (Human), the latter used as a control for AIGIV lacking anthrax-specific antibodies.

The planned clinical development program originally comprised two human clinical trials to be conducted pre-licensure and one contingency protocol to be conducted post-licensure, as noted below, however trial AX-002 was never conducted. The sponsor stated in its 01 December 2014 amendment to this application that it removed trial AX-002 from its development plan because trial AX-001 had been revised to include more subjects receiving a "double" [single] dose of 840 U TNA.

- AX-001, a dose ranging study to examine the safety, PK, and dose proportionality of 3 single doses of AIGIV in healthy volunteers. Data from that trial was compared to the PK and effective dose data from the rabbit and rhesus macaque studies to determine a human dosing regimen. The design of AX-001 was revised to include both placebo-controlled and uncontrolled parts as detailed below.

- AX-002, a single and multiple dose safety and PK trial, was to have been conducted to confirm the proposed human dosing regimen, but, as noted above, was never conducted. This study was to have enrolled a total of 36 subjects: 12 to be given a single dose and 24 to be given a multi-dose regimen.

- AX-003, a phase IV contingency study, "to address the effectiveness of NP-015 in patients with symptomatic inhalational anthrax." The latter study is to be undertaken "in the event of the release of aerosolized anthrax (post-licensure commitment, in accordance to the animal rule)."

Randomized controlled trial (RCT) AX-001 enrolled 92 healthy human subjects. Study AX-001 was a 2 part study. In part 1, 72 subjects were each randomized into one of three dosage strata (cohorts A, B, and C) containing 24 subjects each to receive placebo (6 subjects per dose cohort) or single fixed doses of 210 U, 420 U, or 840 U of anthrax toxin neutralizing activity (TNA) (18 subjects per active dose cohort) at infusion rates up to 2 mL/min. In part 2 of the trial, 20 subjects were randomized in two cohorts of ten

each and administered single doses of 840 U of either of two lots of AIGIV different from the lot studied in part 1. No placebo was used in part 2 of the trial.

The randomization resulted in reasonably good balance between each of the active arms and the placebo arm in age, height, and body weight among the 92 subjects enrolled.

Pharmacokinetic analyses demonstrated dose-proportionality for Cmax and AUC across the studied fixed dosage range 210 U to 840U TNA. Of concern is the plausibility/likelihood that the observed PK parameters in healthy subjects may not predict the PK parameters of the product when administered to patients with inhalational anthrax who are likely to be hypermetabolic and who may exhibit multi-organ failure. For these reasons FDA has requested the draft package insert be revised to include consideration of upward adjustment of the recommended dose and/or repeated dosing.

No gender-related differences were observed using TNA for AUC or Cmax, but using anti-PA (b) (4) levels were slightly greater for females at the 420 IU dose. In aggregate, this difference appears unlikely to be clinically meaningful. The numbers of subjects enrolled in non-Caucasian racial subgroups and the Hispanic ethnicity subgroup were too small to permit meaningful analysis of these subgroups.

No deaths or SAEs were reported in the human safety and PK trial. One subject was withdrawn due to an adverse reaction (AR) consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache. Sixty-five of 74 (71%) subjects reported 251 AEs, of which 4 were severe (headaches) and 36 were moderate in intensity. The percentage of subjects experiencing AEs in active treatment groups was higher than in the placebo groups. The high dose (840U) active (AIGIV) cohort C had the greatest number of AEs.

The most frequently reported AEs (reported by 10% or more subjects) were headache, pharyngo-laryngeal pain, and nausea, all of which were reported more frequently in active randomization groups compared to corresponding placebo groups. Thirty-one subjects (34%) reported 50 headaches during the trial. The investigator considered that 20% of headaches were treatment-related, which may be an underestimate, given that a higher percentage of headaches were temporally related to prior AIGIV infusion and given that headache is the most common causally-associated AE in trials of IGIV products. Four headaches were severe, of which two (in subject Nos. (b) (6)) were deemed by the investigator to be treatment related. However the severe headaches in subjects (b) (6) occurred following dosing in the high dose cohort and may have been treatment related, despite not having been so classified by the investigator. Eleven percent of subjects reported nausea.

AEs considered treatment related by the investigator included tachycardia, vertigo, photophobia, abdominal discomfort, dyspepsia, lip swelling, salivary hypersecretion, vomiting, chest discomfort, chills, fatigue, feeling abnormal, feeling cold, feeling hot, infusion related reaction, pain, thirst, complication of device insertion, increased alanine aminotransferase, back pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity, disturbance in attention, dizziness, dysarthria, paresthesia, anxiety, hematuria, cough, dry throat, dyspnea, nasal congestion, rhinorrhoea, sneezing, throat tightness, erythema, pruritus, pruritic rash, urticarial, flushing, and infusion site reactions such as bruising, coldness, extravasation, induration, edema, pain, paresthesia, rash,

reaction, and swelling. Given that this was a study in healthy volunteers, many of the adverse reactions (ARs) so classified by the investigator may in fact have been treatment-related, however some or all of the ARs consisting of symptoms of upper respiratory infections may represent intercurrent illness not related to prior AIGIV administration.

As of the cutoff date for data inclusion in the BLA, 19 adult patients with clinical anthrax disease have received AIGIV under various mechanisms (FDA-authorized single-patient Expanded Access Investigational New Drug Applications (IND) for emergency use, CDC's contingency protocol -sponsored BB-IND 13026, or purchase directly from the manufacturer). Thirteen of the 19 patients who received AIGIV survived and six died. The breakdown of the route of infection for survivors and patients who died is given in the following table: The case fatality rate among patients with systemic anthrax treated with Cangene AIGIV was 6/19 = 32 percent.

Routes of Anthrax Infection among Patients who Survived or Died following AIGIV Administration

ROUTE OF INFECTION	NUMBER OF SURVIVING PATIENTS	NUMBER OF DEATHS
INHALATION	2	1
INTRAVENOUS INJECTION	10	5
GASTROINTESTINAL	1	0
ALL SITES COMBINED	13	6

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Anthrax is caused by the toxin producing gram positive spore-forming bacterial rod, Bacillus anthracis (BA). Anthrax disease exists in 4 forms according to the route of exposure: cutaneous, inhalational, intravenous, and gastrointestinal (GI). Systemic anthrax infection contracted by intravenous injection of contaminated heroin has been described only relatively recently. Sporadic natural infection occurs from direct contact with infected animals or direct on inhalation exposure to contaminated animal products. BA is considered an attractive agent for biological warfare or bioterrorism, because the spores are quite stable, the spores exist in a size distribution ideal for deep lung penetration and residence upon inhalation, and because of the very high case fatality rate of inhalational anthrax.

An accidental environmental exposure of presumably "weaponized" anthrax occurred in Sverdlovosk in 1979 in the former Soviet Union, which resulted in 70 deaths out of 79 reported cases of inhalational anthrax infection (case fatality rate 90 percent, Ref: Brookmeyer R, Blades N, Hugh-Jones M, et al. Biostatistics. 2001;2(2):233-47.). It should be noted however that the literature of this incident varies in the number of reported deaths and inhalation anthrax infection cases, and it has been suggested that the number of surviving cases has been underreported [Refs: Meselson M, Guillemin J, Hugh-Jones M, et al. Science. 1994;266(5188):1202-8.]. Antibiotic treatment and modified live anthrax vaccination by authorities was delayed approximately two weeks following exposure in this incident.

In the 2001 U.S. anthrax attack, anthrax spores were sent through the mail causing 11 known cases of inhalational anthrax, none of which were treated with an anthrax immunoglobulin product, but all of whom were treated with antibiotic therapy using ciprofloxacin and supportive measures. Five of the 11 cases of inhalational anthrax

died, giving a case fatality rate of 45 percent. [Ref: Jernigan JA, Stephens DS, Ashford DA, et al. Emerg Infect Dis. 2001;7(6):933-44 and Barakat LA, Quentzel HL, Jernigan JA, et al. JAMA. 2002;287(7):863-8.] In the same incident, post-exposure prophylaxis with doxycycline and/or ciprofloxacin appeared to be 100 percent effective in preventing clinical anthrax disease.

The minimal infectious dose (MID) of B.A. is unknown, but is estimated from primate studies to be 8000 to 50,000 spores by the inhalation route. The interplay of host and strain factors on the MID is not well understood, but one could anticipate that the MID would be reduced for the elderly, for the very young, and for immunocompromised individuals. The incubation period following aerosol exposure of B.A. spores ranges from 1 to 43 days. It is believed that inhaled spores can reside in alveolar spaces for weeks before being taken up by alveolar macrophages and eventually germinating.

Cutaneous anthrax results from direct contact/inoculation with B. anthracis spores and evolves over days to weeks to a black necrotic lesion with disproportionate surrounding edema. The characteristic black color of the necrotic tissue gives anthrax its name. Recognized reasonably early, the prognosis of cutaneous anthrax with antimicrobial chemotherapy is excellent. However, if specific therapy is delayed such that B.A. bacteremia occurs, the prognosis is grave.

The incubation time of GI and inhalational anthrax tends to be shorter than for cutaneous anthrax, but can range up to 1.5 months. This reviewer hypothesizes a possible inverse correlation between inoculum size and incubation period, other factors being equal. GI anthrax results in bacteremia. Inhalational anthrax leads in ~ 50% of cases to a widened mediastinum, visible on chest x-ray (CXR), due to hemorrhagic mediastinitis. Curiously, pneumonia and pulmonary consolidation are not typical features of inhalational anthrax, but toxemia and pulmonary edema complicated terminal cases. Historically, treatment with penicillin or tetracyclines initiated at the point when the anthrax infected patient manifests a widened mediastinum has generally been unsuccessful. This is particularly problematic because the characteristic widened mediastinum as seen on CXR is a key clinical feature that often leads to the diagnosis of inhalational anthrax.

Two exotoxins, lethal toxin (LT) and edema toxin (ET), are responsible for symptoms of anthrax disease. LT is formed by the combination of anthrax protective antigen (PA) with anthrax lethal factor (LF). ET is formed when PA combined with anthrax edema factor (EF). LT is a protease that causes macrophage death. ET causes edema when injected into animals.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The only product currently approved in the U.S. as an adjunct to antibiotic therapy in the treatment of inhalational/systemic anthrax is a monoclonal antibody product, raxibacumab. The safety and efficacy of this product is discussed in section 2.3.

Wild-type strains of anthrax are sensitive in vitro to antibiotics from a wide range of pharmacologic classes. Antibiotics approved for post-exposure prophylaxis and for treatment of anthrax in humans include doxycycline, ciprofloxacin, and levofloxacin.

Ciprofloxacin is an antibiotic indicated to reduce the incidence or progression of inhalational anthrax following aerosol exposure. Non-human primate studies combining AVA with ciprofloxacin have suggested efficacy of the combination in a post-exposure setting. Penicillin and doxycycline are labeled by FDA as indicated for treatment of symptomatic anthrax. Antibiotics are ineffective against the spore form of the organism. The current recommendation for post-exposure chemoprophylaxis in the absence of prior AVA administration is 60 days of antimicrobial therapy.

Anthrax Vaccine Adsorbed (AVA) (Bioport) was licensed for pre-exposure prophylaxis of anthrax. The vaccine is produced from a toxinogenic nonencapsulated [nonvirulent] strain of B. anthracis and contains primarily Protective Antigen (PA), along with some contaminating proteins. Based on animal studies and a single textile mill human study, it is believed that the AVA vaccine is effective for prevention of cutaneous anthrax and, more likely than not, effective for prevention of inhalation anthrax. The vaccination schedule of AVA is to give subcutaneous (SC) doses at 0, 2, and 4 weeks, then at 6, 12, and 18 months, followed by annual boosters. The vaccine was primarily available for military personnel and not generally available for the U.S. population, other than specific high risk individuals, such as veterinarians.

2.3 Safety and Efficacy of Pharmacologically Related Products

Anthrax hyperimmune globulin made from horses was commonly used in the U.S. for anthrax disease (mostly cutaneous) in the early 1900s, and its use continues to this day in Russian and China. Efficacy and safety data for equine anti-anthrax globulin are not readily available. Doses were typically 100-150 mL infused initially into the lesion and intravenously, followed by additional doses every 24-48 hours depending on clinical response. No information on antibody titers/potency is available. This reviewer is not aware of any published dose-ranging studies or clinical trials involving equine anti-anthrax globulin.

According to its package insert, the monoclonal antibody product, raxibacumab is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to Bacillus anthracis in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Raxibacumab has the following limitations of use:

• The effectiveness of raxibacumab is based solely on efficacy studies in animal models of inhalational anthrax.

• There have been no studies of raxibacumab in the pediatric population. Dosing in pediatric patients was derived using a population pharmacokinetic (PK) approach.

• Raxibacumab does not cross the blood brain barrier and does not prevent or treat meningitis. Raxibacumab should be used in combination with appropriate antibacterial drugs.

The safety of raxibacumab has been evaluated in 326 healthy subjects aged 18 – 88 years treated with a dose of 40 mg/kg in three clinical trials:

      a) a drug interaction trial with ciprofloxacin

b), a repeat – dose trial of 20 subjects with the second raxibacumab dose administered ≥4 months after the first dose
c)), and a placebo – controlled trial evaluating single doses with a subset of subjects receiving 2 raxibacumab doses 14 days apart.

Twenty-three subjects received 2 doses two weeks apart and 20 subjects received two doses more than 4 months apart. Four subjects (1.2%) had raxibacumab infusions discontinued due to adverse reactions: two due to mild urticaria, one due to moderate dyspnea, and one due to mild clonus. The most frequently reported ARs were rash in 2.8% of subjects, pain in extremity in 2.1% of subjects, prurit5is in 2.1% of subjects, and somnolence in 1.5% of subjects. Anti-raxibacumab antibodies were not detected in the trials.

Efficacy of raxibacumab as monotherapy and combined with was determined in New Zealand White (NZW) rabbits and cynomolgus macaques receiving 40 mg/kg IV. This dose produces similar or greater systemic exposure in humans.

The package insert for raxibacumab states:

Treatment with raxibacumab alone [i.e., without concomitant antibiotic therapy] resulted in a statistically significant dose dependent improvement in survival relative to placebo when administered at the time of initial manifestations of anthrax disease in the rabbit and monkey infection models…

In other animal studies evaluating antibacterial drug alone and raxibacumab - antibacterial drug combination, the efficacy of an antibacterial drug alone (levofloxacin in rabbits and ciprofloxacin in monkeys) was very high (95 - 100%) when given at the initial manifestations of inhalational anthrax disease…

The efficacy of raxibacumab administered with levofloxacin as treatment of animals with systemic anthrax disease (84 hours after spore challenge) was evaluated in New Zealand White rabbits (study 1). The dose of levofloxacin was chosen to yield a comparable exposure to that achieved by the recommended doses in humans. Levofloxacin and raxibacumab PK in this study were unaffected by product co - administration. Forty - two percent of challenged animals survived to treatment. Treatment with antibacterial drug plus raxibacumab resulted in 82% survival compared to 65% survival in rabbits treated with antibacterial drug alone, P = 0.0874.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Other than the U.S. IND trial in healthy subjects, the only use of the product in humans has been the administration of Cangene AIGIV on a compassionate use basis through the CDC to 19 patients with systemic anthrax.

As of May 2012, when raw data for compassionate use of AIGIV in human systemic anthrax cases was provided to Cangene, 19 adult patients with clinical anthrax disease have received AIGIV under various mechanisms (FDA-authorized single-patient Expanded Access Investigational New Drug Applications (IND) for emergency use, CDC's contingency protocols -sponsored BB-IND 13026, or purchased directly from the

manufacturer). Thirteen of the 19 patients who received AIGIV survived and six died. The breakdown of the route of infection for survivors and patients who died is given in the following table: The case fatality rate among patients with systemic anthrax treated with Cangene AIGIV was 6/19 = 32 percent.

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ALL SITES COMBINED	13	6

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Cangene held a pre-IND meeting with CBER regarding the development plan for Anthrax Immune Globulin on 26 August 2004, and received considerable input from CBER regarding product development at that time. Following submission of Cangene's IND for AIG, the CDC submitted an IND for a contingency use protocol for Cangene AIG with the aim of getting Cangene AIG into the Strategic National Stockpile. A number of human anthrax cases in the U.S. and in the U.K. have been treated with Cangene AIGIV distributed by the CDC and obtained from the U.S. Strategic National Stockpile.

The sponsor held several meetings and teleconferences with FDA regarding the design and progress of their animal efficacy model studies, given the intention of the sponsor to submit a BLA under the Animal Rule.

In a letter to the sponsor dated 14 January 2005, FDA wrote in part:

> We do not necessarily agree with your statement made on p 30 of the submission that "…clinical trials in a population exposed to inhalational anthrax are not ethical or feasible." If your product is eventually approved for treatment of toxemia associated with inhalational anthrax, you will be required to commit to conducting and reporting to FDA the results of one or more phase IV field trials of your product in the event that a sufficient number of human cases of inhalational anthrax occurs to make the conduct of such studies feasible. *We recommend such trial(s) be designed to verify the appropriateness of the recommended dose(s) and to validate the efficacy of the product in humans using a dose-regimen-controlled design [Emphasis added because it is not clear from the submitted synopsis that the design of the sponsor's proposed phase 4 post*

marketing requirement (PMR) contingency "field study" protocol would be adequate either to verify the appropriateness of the recommended dose or to validate the efficacy of the product in humans].

To the above the sponsor replied "*We do agree that clinical trials with NP-015 are feasible in the event of a sufficient number of human cases of inhalational anthrax, such as that which may occur after a bioterrorism event or an accidental release of anthrax spores. Phase IV post-licensure studies of NP-015 to treat inhalational anthrax and confirm the recommended dosing regimen are planned.*"

The FDA Guidance for Industry – Product Development Under the Animal Rule states that "…the determination that human efficacy trials are not feasible may be challenging. The feasibility issues to be considered will vary with the disease or condition to be studied and may change over time. For example, there may be circumstances that affect the feasibility of planning and execution of human efficacy studies for the disease or condition, such as: (1) a low prevalence and/or incidence, (2) an unpredictable incidence rate from year to year, (3) an inability to predict geographic locations where outbreaks may occur, (4) occurrences limited to areas lacking critical infrastructure, and/or (5) occurrences limited to areas in which there is some extraordinary threat to subject or investigator safety. In addition, other challenges, such as the inability to obtain permission from foreign governments, may preclude the conduct of clinical investigations." This reviewer considers that, *depending on the particular circumstances* of one or more mass exposures in the future with a sufficient number of inhalational anthrax cases, a field trial designed to compare the efficacy and safety of two or more different dosing regimens of AIGIV *may be feasible*. While patient-level randomization may present technical challenges in such scenarios, careful advance planning and consideration of options such as randomizing different dosage regimens across different treatment facilities or geographic regions represent, in this reviewer's opinion, the best and perhaps the only feasible option to confirm in humans the efficacy of the product for its intended use.

2.6 Other Relevant Background Information

Hyperimmune globulin preparations have been used in the treatment of bacterial infections in which the symptoms of the disease are due to a circulating toxin: botulism, diphtheria, and tetanus. Hyperimmune globulin products are also licensed for a variety of mostly viral infections: varicella-Zoster, HBV, CMV, rabies, RSV, and for certain complications from Vaccinia vaccination.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

3.2 Compliance With Good Clinical Practices And Submission Integrity

A BiMo inspection was performed for the single clinical sites of healthy volunteer trial AX-001 and did not raise concerns impacting the integrity of the submitted clinical data from that trial. No FDA-483 was issued.

Four submitted animal studies were the subject of a Good Laboratory Practice (GLP) inspection of (b) (4) and did not reveal significant problems impacting the animal treatment model data submitted in this Animal Rule BLA. Please see BiMo report by Anthony Hawkins dated 15 December 2014 for further details.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Not indicated on form, but presumably AX-001, the only human clinical trial included in the application.		
Was a list of clinical investigators provided:	Yes X☐	
Total number of investigators identified: 3, including 2 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): Not explicitly addressed in submission.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None.		
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None.		

There were no issues related to financial disclosures that would be expected to affect the reliability of the clinical information reviewed.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The product is a sterile solution of immune globulin intravenous (human) containing polyclonal antibodies that neutralize anthrax lethal toxin, which is composed of lethal factor combined with protective antigen. It is prepared from plasma collected from healthy screened donors previously immunized with Anthrax Vaccine Adsorbed (BioThrax) demonstrating at least a minimum "high" titer specification for antibody titer. During manufacture, the product undergoes two dedicated viral clearance/inactivation steps using tri-n-butyl phosphate and Triton X-100 (solvent/detergent) treatment and nanofiltration using a Planova 20N filter. The product is stabilized with 10% maltose and 0.03% polysorbate 80 at pH 5.0 to 6.5. Each vial contains > 60 U of anthrax toxin neutralizing activity (TNA) and contains 40 to 70 mg total protein in a maximum fill volume of (b) (4) in a 50 mL vial.

4.2 Assay Validation

4.3 Nonclinical Pharmacology/Toxicology

[This section is abstracted from the Clinical Phamacology Review Memo and from discussions with the Clinical Pharmacology Reviewer.]

The effective human dose of NP-015 (AIGIV) is currently unknown and was estimated/projected based on pre-clinical efficacy studies and human dose scaling techniques. An initial estimate of 420 U TNA for the theoretical human effective dose was proposed by Cangene based on literature data from animal studies and vaccination data in humans, but was considered likely sub-optimal when rabbit and non-human primate (NHP) studies were re-evaluated and dose-response modeling conducted by the sponsor at FDA request was reviewed. An 840 U human dose (equivalent to 30 U/kg in rabbits and NHPs) is predicted to be associated with improved survival compared to a 420 U human dose (equivalent to 15 U/kg in rabbits and NHPs).

Since the evaluation of human efficacy of NP-015 in randomized placebo-controlled trials is unethical and not feasible, Cangene Corporation is using the "Animal Rule" (Title 21 Code of Federal Regulation (CFR) 601 Subpart H) to seek approval for its human immunoglobulin antitoxin product. Although the NHP model of inhalational anthrax has been considered superior to the rabbit model, studies to evaluate the incremental benefit of adding AIGIV to appropriate antimicrobial therapy suggested that the benefit in NHPs was so small that an impractically large number of NHPs would be required to demonstrate the small incremental benefit. Thus, the pivotal added benefit over antibiotic therapy study was conducted in rabbits. At FDA suggestion, the sponsor conducted an interim analysis of the pivotal rabbit added benefit study and concluded that it was impractical to expand the study to the number of animals needed to show statistical significance for the observed trend of greater survival in the AIGIV plus antibiotic arm compared to the antibiotic monotherapy arm. Thus, the study was terminated without demonstrating a statistically significant benefit of AIGIV plus antibiotics vs. antibiotics plus polyclonal IGIV, though a trend toward higher survival with combined therapy was evident.

Survival Among Bacteremic and Toxemic Animals in Added Benefit Rabbit Pivotal GLP Study 1182-100011472 treated at 96 hours post anthrax aerosol exposure with AIGIV + levofloxacin vs. IGIV + levofloxacin (MITT)

Treatment	Survival
AIGIV + Levofloxacin	18/31 (58%)
IGIV + Levofloxacin	123/33 (39%)

The 19% absolute difference in survival rate between the AIGIV and IGIV groups did not reach statistical significance (p=0.1353; Z-test); however, that observed difference would be clinically meaningful if it were to pertain to humans.

A post-hoc analysis suggested statistically significant benefit among a subset of animals with Protective Antigen (PA) levels between 200 and 800 ng/mL. Great caution should be exercised in interpreting these findings due to the post-hoc nature of the analysis and potential inter-species in response to infection, the likely wide range of spore exposure and toxin burden in human exposure scenarios, etc.

Although AIGIV is intended to be administered in combination with appropriate antibiotic therapy, consistent with the CDER review of raxibacumab, weight was given during the nonclinical pharmacology review to AIGIV monotherapy studies comparing the efficacy of the product against IGIV which lacks antibodies against anthrax antigens. The latter

studies provided statistically significant evidence of activity of the product in improving survival. The likely mechanism of survival enhancement in monotherapy with AIGIV without antibiotics in animal studies likely involves amelioration of anthrax toxin-mediated effects until such time that the animal's own immune system can clear the infection, in the opinion of this reviewer.

There are a number of considerations and unknowns that come into play when attempting to project an effective dose of AIGIV in inhalational anthrax models in animals to an effective dose in humans. These include differences in immunogenicity of the product in animals vs. humans which were shown to have an effect on the PK in rabbits, differences in the clearance in the product between species, differences between the clearance in healthy animals/healthy volunteers and animals or humans with systemic anthrax, potential differences in anthrax spore exposure level, differences in anthrax tissue and blood/compartmental fluid body burdens, etc. It appeared from a review of the data and dose scaling projections that the difference in clearance between diseased and healthy animals may not be the same as the difference between diseased and healthy humans. In addition, procedures are employed in the care of humans with systemic anthrax, such as repeated thoracentesis and/or paracentesis removing large quantities of body compartmental fluids known to contain significant quantities of the previously-administered AIGIV (as well as anthrax toxin), which accelerate clearance. Such fluid drainage procedures were not employed in the animal experiments.

Whereas the sponsor elected to choose a fixed dose of 420 U (6 U/kg for a 70 kg human) as the human dose corresponding to 15 U/kg in rabbit efficacy model studies, FDA concluded that it was more appropriate to scale the human dose from 30 U/kg in rabbits and monkeys. This was based on a higher survival in both monkey and rabbit monotherapy studies in which survival was compared among animals surviving to particular time points post inhaled anthrax spore exposure, which were then treated with AIGIV vs. IGIV control, as well as the sponsor's dose-mortality response modeling done at FDA request.

The following graph depicts survival rates among 64 NHPs (four groups of 16 animals each) with inhalational anthrax in GLP study (b) (4) 828-G005780 who were treated with one of three different single doses of AIGIV (7.5 U/kg, 15 U/kg, or 30 U/kg) or IGIV control:
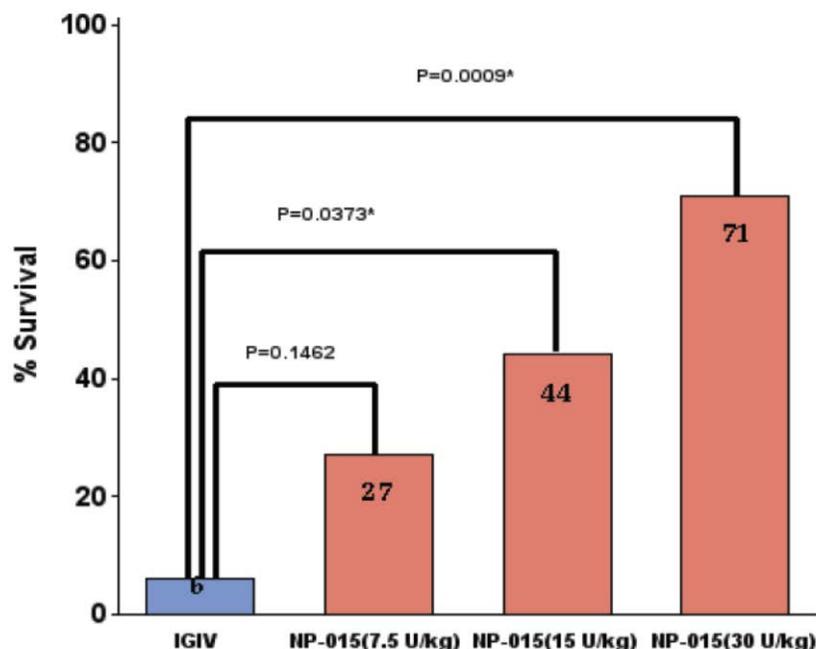
It can be seen that an absolute increase in survival of 27% (71% minus 44%) was obtained in the 30 U/kg group compared to the 15 U/kg group and that the level of statistical significance in the high dose group was much greater than obtained in the mid-dose group. Fatal toxin recurrence was observed in 2/15 (13%) of animals treated with 15 U/kg AIGIV compared to 0/14 (0%) in the 30 U/kg AIGIV group of NHPs in this study. Reportedly, the sponsor chose to do their pivotal studies using 15 U/kg rather than 30 U/kg because the difference in survival between these two arms was not statistically significant in a corresponding rabbit study. However, given the observed trend in further improved survival at the higher dose of 30 U/kg and its high degree of statistical significance, in retrospect, based on this NHP study, it would have been preferable to have performed the pivotal animal efficacy studies at 30 U/kg rather than at 15 U/kg as the sponsor did.

Improved survival was also observed in rabbits treated with 30 U/kg compared to 15 U/kg when treatment was initiated 20 hours post-exposure, but when treatment was delayed to 30 hours post- anthrax spore exposure, there was modestly lower survival at 30 U/kg compared to 15 U/kg (36% vs. 43%).

Compounding the aforementioned uncertainties in projecting an effective dose of AIGIV from animals to humans is the sponsor's decision to recommend a fixed dose of the product in humans vs. a body mass-based dosing regimen. The clinical pharmacology reviewer had particular concern in this regard and recommended a PK study be performed in healthy obese subjects. It was not possible to obtain data on the PK of polyclonal IGIV from the literature to help inform a dosing recommendation in obese subjects. DHCR management did not accept the clinical pharmacologist's

recommendation to conduct a PMC PK trial post-licensure in obese healthy volunteers. The draft label of the product was amended by the sponsor initially to state that the efficacy and safety of the product has not been established in obese subjects. FDA has requested this be changed to state that the safety and efficacy of the product have not been studied in obese subjects. While it would appear reasonable to empirically increase the dose of the product in morbidly obese subjects, we are not aware of data that would inform a specific recommendation in this regard.

It should be noted that a direct comparison of AUCs of anti-PA TNA levels obtained in healthy rabbits, healthy monkeys, and healthy human volunteers is not valid for determining the projected human dose in humans with inhalational anthrax. This is because the increase in clearance due to anthrax infection may be quantitatively different across species.

4.4 Clinical Pharmacology

See Clinical Pharmacology Memo. Dose proportionality in PK measurements was observed in the healthy volunteer PK trial AX-001 across the fixed doses of 210 U, 420 U, and 840 U.

4.4.1 Mechanism of Action

AIGIV is a passive immunizing agent that neutralizes anthrax toxin. The sponsor states that AIGIV binds to protective antigen (PA) "and other potential antigens in anthrax vaccine adsorbed (BioThrax) to neutralize the pathogenic effects of anthrax toxin."

4.4.2 Human Pharmacodynamics (PD)

No PD data are available from controlled clinical trials.

4.4.3 Human Pharmacokinetics (PK)

The clinical pharmacology reviewer does not agree with the sponsor's algorithm for pediatric dosing. The clinical pharmacology reviewer recommends that sparse PK sampling be undertaken should pediatric patients receive the product in the Phase 4 PMR contingency protocol.

The clinical pharmacology reviewer has raised the question of whether different doses may be appropriate for obese patients, particularly morbidly obese subjects. I concur with the clinical pharmacology reviewer that it is desirable to obtain PK data with the product in obese subjects, as the systemic exposure may be very different in such patients.

4.5 Statistical

See FDA Statistical Review Memo.

4.6 Pharmacovigilance

Ongoing capture of safety and survival data from both compassionate use of AIGIV in sporadic cases of systemic anthrax as well as from its use in any mass exposure scenarios is recommended as a two-component PMR (required under the Animal Rule).

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical review described herein emphasizes the safety review of the single clinical trial in humans conducted by the sponsor under IND 11982, Protocol AX-001, "Safety and Pharmacokinetics of Anthrax Immune Globulin Intravenous (Human), NP-015, in Healthy Volunteers," as well as review of the human cases of systemic anthrax for which the patients received the sponsor's AIGIV product on a compassionate use basis. No efficacy data were obtained in trial AX-001 as the subjects were not exposed to anthrax. Subjects who received AIGIV distributed from the National Strategic Stockpile to treat systemic anthrax received the product under an IND held by the CDC.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- Module 1 – Financial Disclosure
- Module 1 – Meetings
- Module 2 – Nonclinical Overview
- Module 2 – Clinical Overview
- Module 2 – Summary of Clinical Pharmacology Studies
- Module 2 – Summary of Clinical Efficacy
- Module 2 – Summary of Clinical Safety
- Module 2 – Literature References
- Module 5 – Tabular Listing of All Clinical Studies
- Module 5 – AX-001 Clinical Study Report (CSR)
- Module 5 - AX-001 Protocol, Audit Certificates, Protocol Deviations, Data listings
- Module 5 – Literature References

5.3 Table of Studies/Clinical Trials

Sponsor's Table 3 Listing of Human Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Formulation; Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	AX-001	5.3.3.1	1) To assess the PK of three doses of AIGIV in healthy volunteers 2) To evaluate the safety of AIGIV based on adverse events and laboratory assessments, and to determine the pharmacokinetic dose proportionality relation of three different doses of AIGIV	1) Phase 1 double blind, randomized, placebo-controlled, dose-ranging study; saline placebo control 2) Randomized, open-label; no placebo control group	1) Liquid AIGIV (10% maltose and 0.03% polysorbate 80), single intravenous dose of 210, 420 or 840 U TNA 2) Liquid AIGIV (10% maltose and 0.03% polysorbate 80), single intravenous dose of 840 U TNA	1) 72 (24/group) 2) 20 (10/group)	Healthy subjects	Single dose

5.4 Consultations

No consultations were obtained during the course of this review.

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was held regarding this BLA.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed (if applicable)

Several papers were reviewed that describe the experience with the use of the product in the U.S. and in the U.K. in treating sporadic systemic anthrax cases in humans on a compassionate use basis. These are listed in the submission.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

AX-001

"Safety and Pharmacokinetics of Anthrax Immune Globulin Intravenous (Human), NP-015, in Healthy Volunteers"

This Cangene-sponsored trial was conducted under IND by a single investigator, Alan Marion, M.D., Ph.D. of MDS Pharma Cervices, Lincoln, NE, USA. It was conducted between July 2007 and August 2008.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective:

- To assess the pharmacokinetics of three doses of NP-015 (210 U, 420 U and 840 U by TNA) in healthy volunteers.

Secondary Objectives:

- To evaluate the safety of NP-015 based on adverse events and laboratory assessments.

- To determine the pharmacokinetic dose proportionality relation of three different doses of NP-015.

6.1.2 Design Overview

This was a two-part single-dose trial. The first stage was a phase 1, double-blind, randomized, placebo controlled, dose ranging trial to assess PK and safety of three doses of the hyperimmune immunoglobulin product and comprised 72 healthy volunteer subjects. Subjects in part 1 were enrolled sequentially, starting with the lowest dose of test product or corresponding volume of placebo. There were three placebo control cohorts of six subjects each. Each cohort of subjects receiving AIGIV comprised 18

subjects at a given dose level. Subjects were randomized within cohorts of 24 subjects within each dosage level 3:1 to receive single doses in part 1 as follows:

- AIGIV 210 U by TNA (3 vials) or saline placebo
- AIGIV 420 U by TNA (6 vials) or saline placebo
- AIGIV 840 U by TNA (12 vials) or saline placebo

Subjects were monitored over 28 days with safety laboratory tests, AE monitoring, and were sampled for PK measurements.

In the 2nd stage (cohort 4), subjects (n = 20) were randomized in an open-label trial examining the safety of a single dose 840 U of AIGIV in two cohorts of 10 subjects each, each receiving a different lot of AIGIV which was also different from the single lot used in part 1 of the trial. (It is common in phase 3 trials of biologics to employ a minimum of three different lots of the investigational product to help ensure that the results will be generalizable across different product lots). The lot numbers and number of vials of AIGIV or saline in both stages of the trial are depicted in the table below reproduced from the submission:

Cohort	Treatment	Drug Administration
1	A	NP-015 (210 U by TNA, 3 vials - LotNumber 24906011) or saline placebo
2	B	NP-015 (420 U by TNA, 6 vials - LotNumber 24906011) or saline placebo
3	C	NP-015 (840 U by TNA, 12 vials - LotNumber 24906011) or saline placebo
4	D	NP-015 (840 U by TNA, 14 vials - LotNumber 10804812)
4	E	NP-015 (840 U by TNA, 14 vials - LotNumber 10804816)

U = Units by Toxin neutralization assay (TNA).

Cohort 4 subjects received 14 vials, due to a fill change in potency from (b) (4) TNA/vial to $\geq$ 60 TNA/vial. No PK measurements were made in Part 2.

Subjects were stratified at randomization according to gender and race (Caucasian or other) for cohorts 1-3 and gender only for cohort 4.

Blinding in stage 1 was limited to the subject and caregivers not knowing whether they received active AIGIV or placebo, but study staff presumably would have known to which dosage cohort subjects would belong because dosing cohorts were enrolled sequentially at a single center and the number of vials and volume of AIGIV or placebo infused differed between dosage cohorts. In the second stage, subjects and caregivers were blind as to which lot the subject received. The pharmacist or designate provided product in a semi-opaque IV bag labelled with subject ID number, subject initials, and protocol number.

Safety assessments included vital signs, physical exam, ECG, adverse events, concomitant medications, and routine laboratory assessments for CBC with differential, PT, PTT, fibrinogen, serum creatinine, BUN, total protein, albumin, ALT, AST, total and direct bilirubin, LDH, alkaline phosphatase, electrolytes, Mg, phosphate, urinalysis including microscopic, serology for HBV, HIV 1 & 2, and HCV. Hematology, urinalysis, and routine chemistries were obtained at baseline and on days 1, 3, 7, 14, 28, and 84. Blood for parvovirus B19 by NAT was obtained at day 14 and at the final visit. Blood for serology and NAT for the other viruses was obtained at baseline and at the final study

visit. Haptoglobin and free hemoglobin were obtained at baseline and day 1 following dosing. Anti-PA antibody and TNA assessments were made in cohorts 1-3 only in stage 1 at hours 1, 3, 8 and at days 1, 3, 5, 7, 9, 11, 14, 21, 28, 42, 56, and 84 days (or at early withdrawal) following infusion. The test product or saline control was warmed to room temperature prior to IV administration, which began at a rate of 0.5 mL/min for the first 30 min. The protocol permitted incremental increases in the infusion rate every 15-30 min up to a maximum of 2 mL/min if well tolerated. AEs could prompt slowing or temporary cessation of the infusion. Interrupted infusions resumed at half the last tolerated rate. Total infusion times as well as any change or stoppage in the infusions were recorded. In stage 1, blood glucose was tested at 1 hour _ 10 min after the start of test product infusion by both glucose-specific point-of-care (GS-POC) and glucose-non-specific point-of-care (GNS-POC) monitoring devices using finger pricks to obtain capillary blood, as well as on a venous sample run by the lab, due to the presence of maltose stabilizer in the product which is known to be misread as glucose by some test meters depending on the enzyme used in the associated strips. Subjects remained in the clinic for at least 24 hours after the end of the infusion. A Data Monitoring Committee/DSMB monitored safety on an interim basis during the trial.

The schedule of events showing the monitoring/testing/assessments schedule for the trial is reproduced below from the final protocol.

Schedule of Events (Cohorts 1-3)

	Screen	Baseline	D 0 - time 0	D 0 - 1 h	D 0 - 2 h	D 0 - 3 h	D 0 - 8 h	D 1	D 3	D 5	D 7	D9	D 11	D 14	D 21	D28	D 42	D 56	D 84	Early d/c
Informed consent	X																			
Admission criteria	X	X																		
Medical history	X	Update																		
Physical exam	X[1]	X[2]																	X[1]	X[1]
Vital signs[5]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)	X																			
Hematology	X	X[7]						X[7]	X		X			X		X			X	X
Blood Chemistry	X	X &X[8]	X[9]	X[8,10]	X[8]			X	X		X			X		X			X	X
Urinalysis	X	X	X[6]					X	X		X			X		X			X	X
Drug Screen	X	X																		
Alcohol Screen	X	X																		
Pregnancy Test	X	X														X			X	X
Markers of Viral Infection	X[3]	X[3,4]												X[4]					X[3,4]	X[3,4]
Dosing		X																		
Serum for anti-PA	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] General medical exam. [2] Brief medical exam. [3] Serological test. [4] NAT test. [5] Temperature, sitting blood pressure, respiratory rate and pulse. [6] At end of infusion.
[7] Assessment of haptoglobin and free hemoglobin levels in additional to normal hematology. [8] Finger prick glucose test. [9] Finger prick glucose test at 1 hr after the start of dosing and at the end of dosing. [10] Blood glucose lab test only.

Schedule of Events (Cohort 4)

	Screen	Baseline	D 0 -time 0	D 0 - 1 h	D 1	D 3	D 7	D 14	D28	Early d/c
Informed consent	X									
Admission criteria	X	X								
Medical history	X	Update								
Physical exam	X[1]	X[2]							X[1]	X[1]
Vital signs[5]	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)	X									
Hematology	X	X[7]			X[7]	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X[6]		X	X	X	X	X	X
Drug Screen	X	X								
Alcohol Screen	X	X								
Pregnancy Test	X	X							X	X
Markers of Viral Infection	X[3]	X[3,4]						X[4]	X[3,4]	X[3,4]
Dosing			X							
Adverse events			X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

[1] General medical exam. [2] Brief medical exam. [3] Serological test. [4] NAT test. [5] Temperature, sitting blood pressure, respiratory rate and pulse. [6] At end of infusion.
[7] Assessment of haptoglobin and free hemoglobin levels in additional to normal hematology.

6.1.3 Population

Key Inclusion Criteria:

☐ Male or female
☐ Age 19 – 55 years.
☐ Body mass index of 19 to 29.
☐ Normal and healthy as determined by medical history, physical exam, ECG, vital signs and laboratory tests of liver, kidney and hematological functions.
☐ Written informed consent.

Key Exclusion Criteria:

☐ Heavy smokers (>10 cigarettes/day) or individuals using smokeless tobacco or nicotine containing products.

☐ Use of any investigational product within the past 30 days.
☐ Recipient of any blood product within the past 12 months.
☐ Plasma donation within 7 days or blood donation within 56 days of baseline.
☐ Females with a hemoglobin level < 12 g/dL.
☐ Males with a hemoglobin level < 13 g/dL.
☐ History of hypersensitivity to blood products.
☐ History of allergy to latex or rubber.
☐ History of IgA deficiency.
☐ Pregnancy or lactation.
☐ Positive serology test for HIV or HCV, positive test for HBV as determined by HBsAg.
☐ History of, or suspected substance abuse problem (including alcohol).
☐ Failure of drug test at screening or baseline.
☐ Failure of alcohol test at baseline or consumption of alcoholic beverages within 48 hours
of baseline.
☐ History of anthrax vaccination with AVA or any other anthrax vaccine.
☐ Use of prescription medications within 7 days prior to baseline, or anticipated use during
the study (with the exception of hormonal contraceptives for females).
☐ Use of over-the-counter or herbal medications within 7 days of study admission.

6.1.4 Study Treatments or Agents Mandated by the Protocol

AIGIV 3 to 14 vials or saline placebo. See design overview above in section 6.1.2.

6.1.5 Directions for Use

The test product or saline control was warmed to room temperature prior to IV administration, which began at a rate of 0.5 mL/min for the first 30 min. The protocol permitted incremental increases in the infusion rate every 15-30 min up to a maximum of 2 mL/min if well tolerated. AEs could prompt slowing or temporary cessation of the infusion. Interrupted infusions resumed at half the last tolerated rate.

6.1.6 Sites and Centers

Single site at a contract research organization (CRO) in NE.

6.1.7 Surveillance/Monitoring

See design overview above in section 6.1.2 .

6.1.8 Endpoints

The protocol did not identify a primary efficacy endpoint or specify which of the several pharmacokinetic (PK) endpoints were considered key.

PK Endpoints

The following non-compartmental pharmacokinetic parameters were calculated using the serum anti-PA levels determined using the anti-PA (b) (4) and the TNA assay:

AUC_{0-t}: The area under the serum concentration versus time curve,
from time 0 to the last quantifiable concentration (anti-PA or TNA), as calculated by the linear trapezoidal method.

C_{max}: Maximum measured serum concentration over the time span specified.
T_{max}: Time of the maximum measured serum concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.

K_{el}: Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the serum concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero serum concentrations).

$t_{1/2}$: Apparent first-order terminal elimination half-life will be calculated as $0.693/\lambda_Z$.
AUC_{0-inf}: AUC_{0-t} plus the additional area extrapolated to infinity, calculated using the terminal elimination rate constant.

AUC_{0-t}: The ratio of AUC_{0-t} to AUC_{0-inf}.

AUC_{0-inf}

$AUC_{0-day\ 7}$: The area under the serum concentration versus time curve from time 0 to day 7.

Cl: Clearance as calculated by dose divided by AUC_{0-inf}.

V_{ss}: Initial volume of distribution as calculated by Cl divided by λ_Z.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The protocol states "As this study is to assess the pharmacokinetics of NP-015 and the relative safety of NP-015 to saline, no formal sample size calculation was performed."

No statistical analyses were planned for safety endpoints, except for testing of differences in AE rates, temporally associated AE rates, and blood glucose reading differences between the analytical methods used at the 5% alpha level. The placebo group was analyzed both as a single cohort as well as 3 separate cohorts by dose group.

A dose proportionality analysis of PK data was planned based on the power model approach.

Safety Endpoints

A comparison of the adverse events and laboratory values between the 4 arms of the study were conducted. Shift tables were constructed to compare any difference between the laboratory values from the 4 arms of the study.

The differences in blood glucose levels measured using GS-POC versus GNSPOC glucose monitoring devices were compared at specified time points prior to, during, and after dosing with NP-015.

6.1.10 Study Population and Disposition

A total of 92 healthy volunteers were studied in the two-state trial, AX-001 as follows:

The first stage of AX-001 enrolled 72 subjects, randomized into three cohorts of 24 subjects each. Each cohort was randomized to AIGIV (18 subjects) or saline placebo (6 subjects).

In the second stage, 20 subjects were randomized to receive either of two AIGIV lots not studied in the first stage (10 subjects per lot).

6.1.10.1 Populations Enrolled/Analyzed

All 92 subjects were adults. Eighty-seven subjects completed the trial. No pediatric or adolescent subjects were enrolled. Eighty-eight received the entire planned infusion volume and four subjects received partial infusions.

- Two subjects (Nos. (b) (6) had their infusions stopped after 50.5 and 5 minutes, respectively, due to IV infiltration. These two subjects were withdrawn from the study "by the sponsor" but continued to have data collection through day 28.

- Two subjects (Nos. (b) (6)) had their infusions stopped after 23.25 and 2.72 minutes, respectively, due to adverse events judged by the investigator to be related to study treatment. Subject (b) (6) completed study procedures, but did not have serum product concentration drawn. Subject (b) (6) was removed from the study by the investigator due to chest discomfort, flushing, tachycardia, and throat tightness.

Two additional subjects were discontinued prematurely during the follow-up observation period for non-compliance: Subject (b) (6) did not return for visits starting on day 28 and was withdrawn from the study due to non-compliance. Subject (b) (6) did not return for visits starting on day 42 and was withdrawn from the study due to non-compliance.

Refer to Sponsor's Fig 10-1, Flow Chart of Subject Disposition, in section 6.1.10.1.3 below.

6.1.10.1.1 Demographics

For the 92 enrolled subjects, the mean age was 31 years, the mean height was 171.4 cm, and the mean weight was 72.7 kg. Age, weight, and height were fairly evenly distributed across randomization groups, as shown in the table below reproduced from the submission. There were more Asians in the 210 U low dose group A. Blacks were fairly evenly distributed among the dose-comparison groups A, B, and C and the pooled placebo group.

Sponsor's Table 11-1: Demographics Summary

Characteristic	A Active (N= 18)	B Active (N= 18)	C Active (N= 18)	Active D (N= 10)	E Active (N= 10)	All Placebo (N= 18)
Gender						
Female	8	9	9	5	6	7
Male	10	9	9	5	4	11
Age (Years)						
Mean	30	29	32	29	34	32
Median	27	26	28	23	25	29
SD	10	10	13	12	15	11
Minimum	20	19	19	19	20	20
Maximum	55	52	55	55	55	52
Race						
American Indian or Alaska Native	0	0	2	0	0	1
Asian	3	1	0	1	0	2
Black or African American	3	4	3	0	1	2
White	12	13	13	9	9	13
Ethnicity						
Hispanic or Latino	1	1	1	0	0	0
Not Hispanic or Latino	17	17	17	10	10	18
Weight (kg)						
Mean	73.2	71.5	74.6	71.0	68.1	75.0
Median	73.1	67.6	73.7	71.0	70.9	74.6
SD	7.6	12.1	12.1	11.6	10.6	11.0
Minimum	58.5	49.9	52.6	54.4	50.3	55.8
Maximum	92.1	96.6	91.2	92.5	79.4	94.8
Height (cm)						
Mean	171.4	170.6	173.3	170.6	166.0	173.6
Median	170.0	170.0	173.0	168.5	161.5	173.0
SD	8.7	11.6	8.5	10.6	12.9	9.2
Minimum	157	142	160	157	151	157
Maximum	191	193	188	186	187	188

Source: Table 14.1.3
Treatment A Active = 210 U Anthrax Immune Globulin (Human) Lot Number 24906011
Treatment B Active = 420 U Anthrax Immune Globulin (Human) Lot Number 24906011
Treatment C Active = 840 U Anthrax Immune Globulin (Human) Lot Number 24906011
Treatment D Active = 840 U Anthrax Immune Globulin (Human) Lot Number 10804812
Treatment E Active = 840 U Anthrax Immune Globulin (Human) Lot Number 10804816

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All subjects were healthy volunteers. See inclusion/exclusion criteria.

6.1.10.1.3 Subject Disposition
All 92 subjects received at least partial doses. Eighty-seven subjects completed the trial.
Eighty-eight received the entire planned infusion volume and four subjects received
partial infusions as follows:

- Two subjects (Nos. (b) (6) had their infusions stopped after 50.5 and 5 minutes, respectively, due to IV infiltration. These two subjects were withdrawn from the study "by the sponsor" but continued to have data collection through day 28.

- Two subjects (Nos. (b) (6)) had their infusions stopped after 23.25 and 2.72 minutes, respectively, due to adverse events judged by the investigator to be related to study treatment. Subject (b) (6) completed study procedures, but did not have serum product concentration drawn. Subject (b) (6) was removed from the study by the investigator due to chest discomfort, flushing, tachycardia, and throat tightness.

Two additional subjects were discontinued prematurely during the follow-up observation period for non-compliance: Subject (b) (6) did not return for visits starting on day 28 and was withdrawn from the study due to non-compliance. Subject (b) (6) did not return for visits starting on day 42 and was withdrawn from the study due to non-compliance.

A flow chart showing the disposition of subjects is reproduced below from the submission.

Sponsor's Fig. 10-1: Flow Chart of Subject Disposition
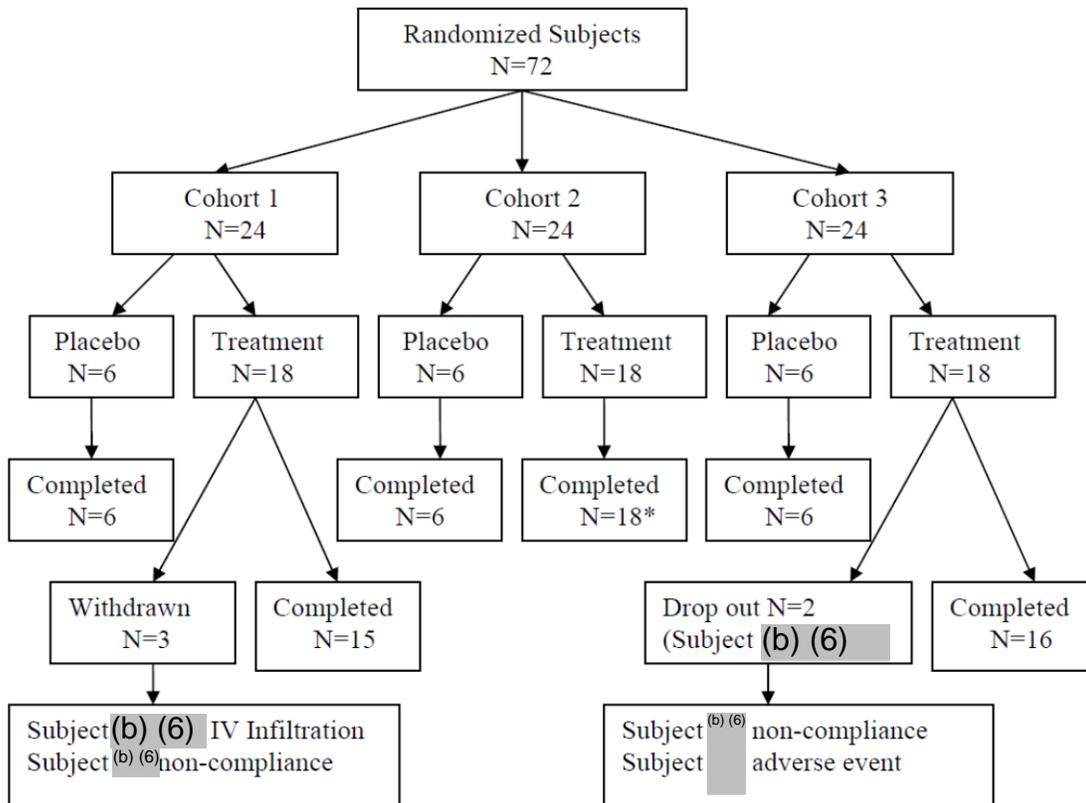
* No serum concentration data was collected for Subject (b) (6)

6.1.11 Efficacy Analyses

No efficacy data were collected in this trial because the healthy subjects were not exposed to or infected with anthrax.

6.1.11.1 Analyses of Primary Endpoint(s)

The protocol did not identify a primary efficacy endpoint or specify which of the several pharmacokinetic (PK) endpoints were considered key.

Please also refer to the FDA Clinical Pharmacology Review Memo for a more complete discussion of PK outcome measures related to this application.

Section 11.4.1 of the study report states:

> Pharmacokinetic analysis was performed using both the (b) (4) and TNA data. However, Cangene and the FDA concurred that TNA would be the primary assay for product potency, dosing and PK analysis, as it measures neutralizing antibodies as opposed to the anti-PA (b) (4), which measures only binding. This decision was based upon the fact that the TNA and (b) (4) assays did not correlate 100% for all lots. Use of the TNA data to establish the primary endpoint is not implicitly stated in the protocol; however, (b) (4) data are intended only to be supportive.

PK parameters were computed by the sponsor from the serum product concentration-time PK data set using actual PK serum collection times. The following graph of mean TNA activity following dosing for the three active treatment groups uses nominal PK sampling times and no baseline correction.

Sponsor's Fig. 11-2: Mean TNA Activities for Cohorts A-C
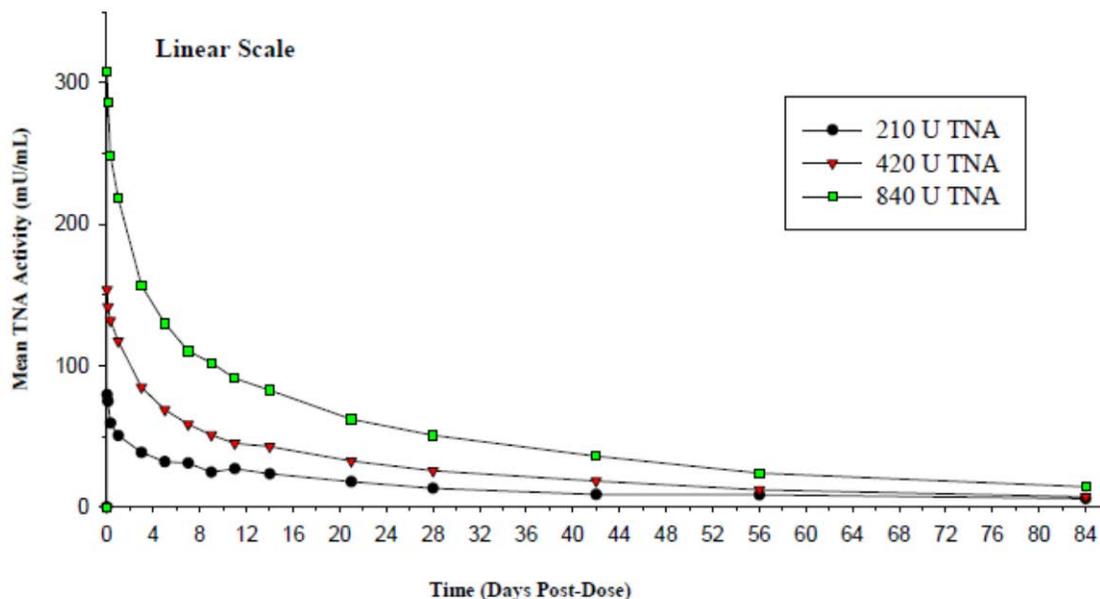
In the sponsor's analysis, mean TNA activity remained detectable over the 84-day period studied. The sponsor's calculated PK parameters from trial data for cohorts A – C are shown in the table below:

Sponsor's Table 11-4: Summary of Mean PK Results by Treatment (TNA)

PK Parameters	Dose Levels		
	210 U TNA	420 U TNA	840 U TNA
Geometric Mean (CV%)			
AUC_{0-t} (mU·d/mL)	1008.0 (22.2)	2133.7 (21.8)	4164.0 (24.1)
AUC_{inf} (mU·d/mL)	1239.4 (26.5)	2507.5 (16.4)	4624.2 (28.5)
$AUC_{0-day\ 7}$ (mU·d/mL)	279.5 (13.6)	596.2 (23.1)	1133.7 (16.3)
C_{max} (mU/mL)	82.3 (13.7)	152.9 (22.4)	311.8 (18.2)
Arithmetic Mean (CV%)			
$t_{1/2}$ (d)	24.3 (33.3)	28.3 (19.9)	28.0 (25.2)
CL (mL/d)	174.2 (24.1)	169.7 (17.9)	188.6 (29.5)
V_d (mL)	5714.8 (11.4)	6837.2 (20.4)	7238.2 (19.4)
Median (Min-Max)			
T_{max} (d)	0.116 (0.109-1.068)	0.120 (0.120-0.412)	0.169 (0.165-0.459)

Inspection of the various AUC and C_{max} values in the table above demonstrate dose-proportionality for TNA levels following dosing across the range of 210 U to 840 U TNA fixed doses among the studied cohort of healthy volunteers whose BMIs ranged up to 29. The mean half-life of TNA ranged from 24 to 28 days. It should be pointed out that the PK of the product in patients with systemic anthrax may be different. In particular, this reviewer would expect the half-life to be shorter in such patients due to their hypermetabolic state. *In order to maintain adequate blood and tissue levels of TNA for a sufficient duration to effect maximum efficacy in the actual intended use setting, the possible need for repeated dosing of the product should be considered.*

6.1.11.2 Analyses of Secondary Endpoints

The protocol did not identify secondary efficacy or PK endpoint(s). Safety endpoints are discussed in section 6.1.12.

6.1.11.3 Subpopulation Analyses

No gender-related differences were observed using TNA for AUC or C_{max}, but using anti-PA (b) (4) levels were slightly greater for females at the 420 IU dose. The numbers of subjects enrolled in non-Caucasian racial subgroups and the Hispanic ethnicity subgroup are too small to permit meaningful analysis of these subgroups.

6.1.11.4 Dropouts and/or Discontinuations

A total of 3 subjects were withdrawn from the trial. See section 6.1.10.1 for details.

6.1.11.5 Exploratory and Post Hoc Analyses

6.1.12 Safety Analyses

No statistical significance analyses of safety data were planned. Comparisons of AEs and laboratory values between the 4 arms of the placebo-controlled part of the trial were planned, as was a comparison of differences in reported blood glucose levels using glucose-specific and glucose-non-specific point-of-care glucose meters. A data monitoring committee (DMC) examined interim safety data during the trial.

6.1.12.1 Methods

Severity of adverse events (AEs) was to be assessed as follows:

> *Mild*: awareness of a sign or symptom but subject can tolerate.

> *Moderate:* discomfort enough to cause interference with normal daily activity.

> *Severe:* resulting in an inability to do work or do usual daily activity.

Investigators used the following definitions to assess causality of AEs:

> *Related:* There is a reasonable possibility that the AE was caused by the product in question. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

> *Not-related / No relationship:* The AE is clearly or most probably caused by other etiology such as the patient's underlying condition, therapeutic intervention or concomitant therapy, or the delay between the administration of the product and the onset of the AE is incompatible with a causal relation, or the AE started before the administration of the product.

6.1.12.2 Overview of Adverse Events and Adverse Reactions

No deaths or SAEs were reported in the human safety and PK trial. One subject was withdrawn due to an adverse reaction (AR) consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache. Sixty-five of 74 subjects (71%) reported 251 AEs, of which 4 were severe (headaches) and 36 were moderate in intensity. AEs were more frequent in active groups than with placebo. The high dose (840 U TNA) active cohort C had the greatest number of AEs. The AEs in the 2 lowest dose groups were approximately equal and about half as frequent as those in the high dose group.

The most frequently reported AEs (reported by 10% or more subjects) were headache, pharyngo-laryngeal pain, and nausea, all of which were generally reported more frequently in active randomization groups compared to corresponding placebo groups. Thirty-one subjects (34%) reported 50 headaches during the trial. The investigator considered that 20% of headaches were treatment-related, which may be an underestimate. Four headaches were severe, of which two (in subject Nos. (b) (6) were deemed by the investigator to be treatment related. However the severe headaches in subjects (b) (6)   occurred following dosing in the high dose cohort and may have been treatment related, despite not having been so classified by the investigator. Eleven percent of subjects reported nausea.

AEs considered related to test product infusion by the investigator were reported for up to 4.6% of subjects for any particular type of AE. AEs considered treatment related by the investigator included tachycardia, vertigo, photophobia, abdominal discomfort, dyspepsia, lip swelling, salivary hypersecretion, vomiting, chest discomfort, chills, fatigue, feeling abnormal, feeling cold, feeling hot, infusion related reaction, pain, thirst, complication of device insertion, increased alanine aminotransferase, back pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity, disturbance in attention, dizziness, dysarthria, paresthesia, anxiety, hematuria, cough, dry throat, dyspnea, nasal congestion, rhinorrhoea, sneezing, throat tightness, erythema, pruritus, pruritic rash, urticarial, flushing, and infusion site reactions such as bruising, coldness, extravasation, induration, edema, pain, paresthesia, rash, reaction, and swelling. Given that this was a study in healthy volunteers, many of the adverse reactions (ARs) so classified by the investigator may in fact have been treatment-related, however some or all of the ARs consisting of symptoms of upper respiratory infections may represent intercurrent illness not related to prior AIGIV administration. Vertigo and increased ALT were reported in the placebo group and were considered product-related by the investigator.

Review of the sponsor's list of concomitant medications used to treat AEs in Table 12-3 did not reveal unusual patterns of concern. Two active group subjects and two placebo group subjects were treated with antibiotics for infections.

Infusion site pain was reported more frequently in active groups pooled compared to the incidence in the placebo groups pooled, however there was no apparent dose-response relationship. When examining the incidences of AEs grouped into system organ class in active vs. placebo groups, only the "general disorders and administration site conditions" system organ class demonstrated a notably higher incidence with active treatment. When high dose cohorts C, D, and E were pooled, the incidence rate for nervous system disorders (mostly headaches) was higher than in the pooled placebo groups. Headaches were higher in incidence in the 420 and 840 U treatment groups (50% and 44% respectively) compared to in the 210 U group, in which the incidence was the same as with placebo (17%) Headaches are one of the most common causally-related adverse reactions considered to be associated with administration of Immune Globulin Intravenous (Human) products. Pharyngo-laryngeal pain was more frequent in AIGIV than placebo groups and more frequent at the two higher doses than at the 210 U dose.

The sponsor has been asked to analyze adverse reactions by dosage cohort and vs. placebo. These data will be reviewed in an addendum to this memo following submission by the sponsor.

6.1.12.3 Deaths
No deaths were reported in the trial.

6.1.12.4 Nonfatal Serious Adverse Events
No serious adverse events (SAEs) were reported during the trial.

6.1.12.5 Adverse Events of Special Interest (AESI)
One subject was withdrawn due to an adverse reaction (AR) consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache. Some of these symptoms may have represented an allergic reaction.

6.1.12.6 Clinical Test Results

No clinically significant chemistry laboratory abnormalities were identified in the trial. The only clinically significant hematology abnormality in the trial noted by the sponsor was a case of leukopenia at 3.3 x 103/microL in subject[(b) (6)] at day 85. This abnormality persisted upon repeat, and the subject was subsequently lost to follow up. The long latency of this AE reduces the likelihood that it was product related. *There was a dose-related finding of glycosuria in urinalysis on day 1, which was observed in 28% of the low dose active group with measurements, 94% of mid and high dose (cohorts B and C) active groups, and 100% of subjects with measurements in high dose D and E active cohorts.* This may likely be due to the maltose content of the product, which is misread as glucose by certain glucose test strips. The sponsor hypothesized that maltose from the product was being metabolized in the kidney to glucose and that glucose was spilling into the urine. Reviewer Comment: The finding of dose-related frequent glycosuria on urinalysis on day 1 following infusion should require a precaution in this regard in the WARNINGS AND PRECAUTIONS section of the draft package insert. There was a tendency for hemoglobin and hematocrit to drop from normal to low that was more frequent in mid- an high-dose groups compared to low dose groups and placebo. This may at least in part represent hemodilution from the oncotically active product. Shifts from normal to high reticulocyte counts were somewhat more frequent in active groups compared to placebo. Total protein values shifted from normal to high in 44% of the high dose active group on day 4, then declined to 11% of group C active subjects as of day 8.

Glucose

Since the product is formulated with 10% maltose as a stabilizer, the protocol called for simultaneous determinations of glucose by 3 different methodologies at day -1, 1 hour after the start of dosing, the end of dosing, and at 1 hour post-dosing. This was done because test strips in glucose meter point-of-care (POC) devices using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods give falsely high readings in the presence of maltose. Note that the draft package insert for AIGIV states in WARNIINGS AND PRECAUTIONS section 5.2 "Due to the potential for falsely elevated glucose readings, only use testing systems that are glucose-specific to test or monitor blood glucose levels in patients receiving maltose-containing parenteral products, including ANTHRASIL." The three methods used at this two time points for glucose measurement involved finger-stick capillary glucose determinations using GS-POC and GNS-POC glucose meters and venous serum glucose determination by the clinical laboratory. The sponsor analyzed the data using an ANCOVA model including reading method, treatment group, time point, and "all the interaction effects." For cohort 1, the time, method, and time-by-method interaction effects were significant, but the treatment effect was not significant at the 5% alpha level. For Cohorts 2 and 3, the time by method by treatment interaction effect is significant at the 5% alpha level, indicating that the reading methods give different results over time by treatment. Inspection of sponsor's Table 12-9 on pp 64-65 of the clinical study report (CSR), shows that the magnitude of difference between the higher readings of the glucose non-specific point-of-care device (GNS-POC) compared to either the glucose specific point-of-care device (GS-POC) or the serum glucose by the clinical lab was dose-related with the largest differences seen at the highest dose of the product, with comparatively much smaller differences seen with placebo. Thus the study confirms that administration of the product may result in falsely high readings by the GNS-POC

method in comparison to the clinical laboratory glucose determinations on venous serum as a gold standard. Sponsor's Table 12-9 corresponding to cohorts 2 and 3 glucose data is reproduced below to illustrate this point.

Sponsor's Table 12-9. Comparison of Reading Methods of Glucose at Each Time Point

Cohort	Comparison (Method 1 vs Method 2)	Treatment Group	Time Point	Least Square Means		Difference	P-value
				Method 1	Method 2		
1	GNS-POC vs GS-POC		Day -1	94.266	80.497	13.769	<.0001
			1 h post-dose	107.038	85.690	21.348	<.0001
	GS-POC vs Serum Glucose		Day -1	80.497	86.497	-6.000	0.0509
			1 h post-dose	85.690	85.937	-0.247	0.9387
	GNS-POC vs Serum Glucose		Day -1	94.266	86.497	7.769	0.0119
			1 h post-dose	107.038	85.937	21.101	<.0001
2	GNS-POC vs GS-POC	Active	Day -1	96.722	83.889	12.333	0.0005
		Placebo	Day -1	104.000	93.167	10.833	0.0823
		Active	1 h post-dose	128.111	85.111	43.000	<.0001
		Placebo	1 h post-dose	88.667	71.833	16.833	0.0075
	GS-POC vs Serum Glucose	Active	Day -1	83.889	89.000	-5.111	0.1547
		Placebo	Day -1	93.167	95.333	-2.167	0.7265
		Active	1 h post-dose	85.111	82.833	2.278	0.5244
		Placebo	1 h post-dose	71.833	81.833	-10.000	0.1084
	GNS-POC vs Serum Glucose	Active	Day -1	96.722	89.000	7.722	0.0325
		Placebo	Day -1	104.000	95.333	8.667	0.1635
		Active	1 h post-dose	128.111	82.833	45.278	<.0001

		Placebo	1 h post-dose	88.667	81.833	6.833	0.2711
3	GNS-POC vs GS-POC	Active	Day -1	93.384	80.289	13.095	0.0013
		Placebo	Day -1	91.333	84.833	6.500	0.3823
		Active	1 h post-dose	148.389	83.556	64.833	<.0001
		Placebo	1 h post-dose	97.500	83.167	14.333	0.0555
	GS-POC vs Serum Glucose	Active	Day -1	80.289	86.955	-6.667	0.0950
		Placebo	Day -1	84.833	85.333	-0.500	0.9403
		Active	1 h post-dose	83.556	96.444	-12.889	0.0032
		Placebo	1 h post-dose	83.167	92.500	-9.333	0.2104
	GNS-POC vs Serum Glucose	Active	Day -1	93.384	86.955	6.429	0.1073
		Placebo	Day -1	91.333	85.333	6.000	0.4198
		Active	1 h post-dose	148.389	96.444	51.944	<.0001
		Placebo	1 h post-dose	97.500	92.500	5.000	<.5012

Sponsor's discussion of differences in glucose readings between GS-POC and GNS-POC for Cohorts 2 and 3 is excerpted below:

> The significant time by treatment interaction effect indicates that the difference in readings are [sic] different for NP-015 treatment groups and placebo groups over time. The results of pairwise comparisons are presented in Table 12-10. The difference between the GS-POC and GNS-POC readings was not statistically different from the placebo difference at baseline (Day -1) and 1 hour after the start of dosing (Hour 1). However, the difference became significant at the end of dosing (Hour 1.88) and at 1 hour after the end of dosing (Hour 2.88). The difference in readings between the GS-POC and GNS-POC devices has dissipated by 2 hours after the end of dosing (Hour 3.88) and is no longer significant.

Sponsor's Table 12-11. Differences in Glucose Readings between GS-POC and GNS-POC – Cohort 2

Time Point	Least Square Means		Difference	P-value
	Active	Placebo		
Day -1	-12.83	-10.83	-2.000	0.8625
Hour 1	-36.59	-15.17	-21.42	0.0680
Hour 1.88	-81.28	-16.83	-64.44	**<.0001**
Hour 2.88	-43.00	-16.83	-26.17	**0.0255**
Hour 3.88	-30.72	-10.67	-20.06	0.0851

> The comparisons [for Cohort 3] indicate that there is a significant difference in readings between the GS-POC and GNS-POC devices by the end of dosing (Hour 3) for cohort 3. The difference declines in magnitude at 1 hour and 2 hours post-dosing (Hour 4 and 5, respectively) but remains statistically significant.

Sponsor's Table 12-11. Differences in Glucose Readings between GS-POC and GNS-POC – Cohort 3

Time Point	Least Square Means		Difference	P-value
	Active	Placebo		
Day -1	-13.24	-6.500	-6.742	0.5546
Hour 1	-30.33	-33.33	3.000	0.7966
Hour 3	-88.56	-12.17	-76.39	**<.0001**
Hour 4	-64.83	-14.33	-50.50	**<.0001**
Hour 5	-44.56	-13.17	-31.39	**0.0078**

Reviewer's Comment: The glucose methodology study results indicate a potential for clinically significant falsely high glucose readings by the GNS-POC method lasting up to several hours after infusion of the product, with higher doses having a greater and more prolonged effect. The boxed warning and other precautions in the draft package insert concerning the important of using a glucose test methodology specific for glucose are appropriate and justified.

Virology

Out-of-range virology results were not considered clinically significant by the investigator.

Subject (b) (6), a 20 year-old female in treatment cohort E, tested positive for Parvovirus B-19 on day 15 with a negative result on day 29. If the day 15 value were a true positive, the possibilities of either community-acquired or product-transmitted infection exist.

Subject(b) (6) a 21 year old female in active cohort C, had high hepatitis B RNA of 2.2 log IU./mL on day 85. The investigator graded this abnormality not clinically significant because true positives are usually associated with significantly higher values. The test was rechecked at day 303 and was normal at 0.00 log IU/mL. Other markers for HGV were negative and remained negative upon retesting.

6.1.12.7 Dropouts and/or Discontinuations

Not counting 2 subjects who were removed from the study by the sponsor due to infiltration of their IV during product administration, a single subject (No (b) (6) was withdrawn prematurely due to adverse events. Four subjects had infusions stopped early due to AEs. Two of these were due to IV infiltration; one (subject (b) (6) was stopped after 23 min after the start of a 420 U dose of AIGIV due to urticaria, pruritis, lip swelling (angioedema) and dry/sore throat; one subject (No. (b) (6) had his infusion stopped 2.7 min after the start of an 840 U dose of AIGIV due to mild chest discomfort, flushing, tachycardia, and throat tightness. Both of the latter cases' AEs resolved, the former after administration of diphenhydramine, application of an ice bag, and saline gargle, and the latter spontaneously without therapy.

6.1.13 Study Summary and Conclusions

Given the high mortality associated with systemic anthrax, the observed safety profile in healthy volunteer RCT AX-001 appears acceptable. In contrast to the monoclonal antibody product, raxibacumab, no repeat dose safety data are available in humans with AIGIV. A multi-dose safety and PK trial in healthy volunteers was originally planned but never conducted. This reviewer recommends that repeat dose safety and efficacy data be obtained in the phase 4 PMR contingency protocol.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

"Anthrax Immune Globulin Intravenous (Human) [AIGIV] is indicated for the treatment of adult and pediatric patients with toxemia associated with inhalational anthrax. AIGIV is beneficial in combination with appropriate antibacterial drugs."

No clinical efficacy trials in humans have been conducted with the AIGIV, due to ethical concerns. Human efficacy data are available, however, from a series of 19 patients with inhalational, intravenous, and gastrointestinal anthrax treated on a compassionate use in the U.S. and the U.K.   The Cangene AIGIV product in these cases was

distributed through the U.S. Center for Disease Control (CDC), in some cases through its Expanded Access IND 13026.

7.1.1 Methods of Integration

At FDA request, the sponsor compiled data from the compassionate use experience with the product into a report contained in the BLA.

7.1.2 Demographics and Baseline Characteristics

Of the 19 systemic anthrax human cases in which Cangene AIGIV was administered on a compassionate use basis, three were inhalational, 15 resulted from injection of heroin contaminated with anthrax spores, and one case involved gastrointestinal (GI) anthrax. All cases were laboratory-confirmed.

Of the three inhalational cases, two involved makers of African drums working with animal hides imported from Africa and one apparently resulted from natural environmental exposure while driving through Minnesota, North Dakota, Montana, Wyoming, and South Dakota. One of the African drum-source inhalational cases occurred in the U.S. and one occurred in the U.K.

The systemic anthrax cases that resulted from unknowing injection of anthrax spores contaminating heroin occurred in the U.K.

The gastrointestinal case occurred in a member of a drum circle in the U.S. His drumming environment was documented to have anthrax spore contamination.

The human anthrax cases ranged in age from 24 to 61 years (median 38 years) and comprised 14 males and five females treated with AIGIV.

Individual subjects who received AIGIV on a compassionate use basis are listed in Sponsor's Table 7 below:

Sponsor's Table 7: Anthrax patient Population Treated with AIGIV

CDC Patient ID[a]	Cangene Patient ID	Age (years)	Sex	Date of AIGIV Administration[b]	Survival Status
Inhalational Anthrax					
(b) (6)	(b) (6)	44	M	2006 Feb 23	Lived
(b) (6)	(b) (6)	34	M	2008 Oct 27	Died
(b)	(b) (6)	61	M	2011 Aug 8	Lived
Gastrointestinal Anthrax					
(b) (6)	(b) (6)	24	F	2009 Dec 25	Lived
Injectional Anthrax					
(b)	(b) (6)	34	M	2009 Dec 19	Died
(b)	(b) (6)	44	M	2009 Dec 21	Died
(b)	(b) (6)	39	F	2009 Dec 29	Lived
(b)	(b) (6)	35	F	2010 Jan 2	Died
(b)	(b) (6)	26	F	2010 Jan 17	Lived

	(b) (6)	40	M	2010 Jan 18	Lived
	(b) (6)	47	M	2010 Feb 5	Lived
	(b) (6)	43	M	2010 Feb 5	Lived
	(b) (6)	24	M	2010 Feb 16	Died
	(b) (6)	44	M	2010 Feb 26	Lived
	(b) (6)	31	M	2010 Feb 26	Lived
	(b) (6)	41	M	2010 Apr 10	Lived
	(b) (6)	36	M	2010 Apr 29	Lived
	(b) (6)	30	M	2010 Jan 20	Died
	(b) (6)	38	F	2010 Jul 3	Lived

[a] CDC patient ID refers to patient numbering in CDC dataset.

7.1.3 Subject Disposition

Six of the 19 treated subjects (32%) died despite treatment with AIGIV.

7.1.4 Analysis of Primary Endpoint(s)

Routes of Anthrax Infection among Patients who Survived or Died following AIGIV Administration

ROUTE OF INFECTION	NUMBER OF SURVIVING PATIENTS	NUMBER OF DEATHS
INHALATION	2	1
INTRAVENOUS INJECTION	10	5
GASTROINTESTINAL	1	0
ALL SITES COMBINED	13	6

7.1.5 Analysis of Secondary Endpoint(s)

7.1.6 Other Endpoints

Exposure was not quantified in any of the human anthrax cases.

Sponsor's Table 9: Summary of Time Course for Presentation of Symptoms, Hospital Admission and AIGIV Administration

	Gastrointestinal			Inhalational			Injectional		
	N	Median	Range	N	Median	Range	N	Median	Range

Symptom Onset to Hospital Admission (days)									
Lived	1	9.0	–	2	2.0	2–2	10	2.0	0–5
Died	–	–	–	1	2.0	–	5	3.0	0–4
Hospital Admission to AIGIV Administration (days)									
Lived	1	11.0	–	2	5.5	4–7	10	2.0	1–10
Died	–	–	–	1	6.0	–	5	1.0	1–4
Symptom Onset to AIGIV Administration (days)									
Lived	1	20.0	–	2	7.5	6–9	10	4.0	1–11
Died	–	–	–	1	8.0	–	5	4.0	2–6

Sponsor's Table 10: Summary of Time Course for Patients who Died

	Symptom Onset to Death Median Days (Range)	Hospital Admission to Death Median Days (Range)	AIGIV Administration to Death Median Days (Range)
Inhalational (N=1)	14.0	12.0	6 .0
Injectional (N=5)	7.0 (6–9)	4.0 (3–7)	3.0 (2–5)

In the three inhalational anthrax cases treated with AIGIV, peak anti-PA blood levels ranging from 132 to 160 mcg/mL (mean 144.8 mcg/mL) were observed at the first time point after administration, as shown in the sponsor's table below. This compares to a median C_{max} in the healthy volunteer RCT AX-001 of 192 mcg/mL (range 135 – 250 mcg/mL) following the 420 U TNA dose. Although each of the peak anti-PA levels in the three inhalational anthrax cases lay within the range of C_{max} values observed in RCT AX-001, the comparison of the medians suggests the possibility that levels achieved in patients with inhalational anthrax may be somewhere in the range of ~ 25% lower than seen in the healthy volunteer trial.

Sponsor's Table 64 Summary of Serum Anti-PA levels in Inhalational Anthrax Patients Treated with AIGIV

Patient ID	Pre-dose Anti-PA		Peak Anti-PA Post-AIGIV		Trough Anti-PA (Days 1–5 post-dose)		Highest Anti-PA (Days 4–6 post-dose)	
	Value[a]	Time[b]	Value[a]	Time[b]	Value[a]	Time[b]	Value[a]	Time[b]
(b) (6)	2.35 17.9	-132 h -12 h	141.45	0 h	70.95	36 h	168	138 h
	8.1	0.8 h	132.5	5.7 h	88.2	89 h	92.3	99.9 h
	1.186	0.6 h	160.514	3.8 h	80.047	92.6 h	193.329	133 h

[a] Anti-PA values expressed in µg/mL

[b] Time in hours relative to AIGIV administration where negative values refer to prior to AIGIV administration and 0 is immediately post-infusion

The following graph in surviving inhalational anthrax patient (b) (6) demonstrates that the serum LF level was falling prior to therapy, with an apparent acceleration in the rate of serum LF decline following administration of the product. It is noteworthy that the pleural fluid LF levels in this patient were considerably higher than the serum levels, and that the post-AIGIV infusion serum levels of anti-PA IgG remain steady

over a period of 20 days in this subject, which was not always the case with the treated injectional anthrax cases summarized below.
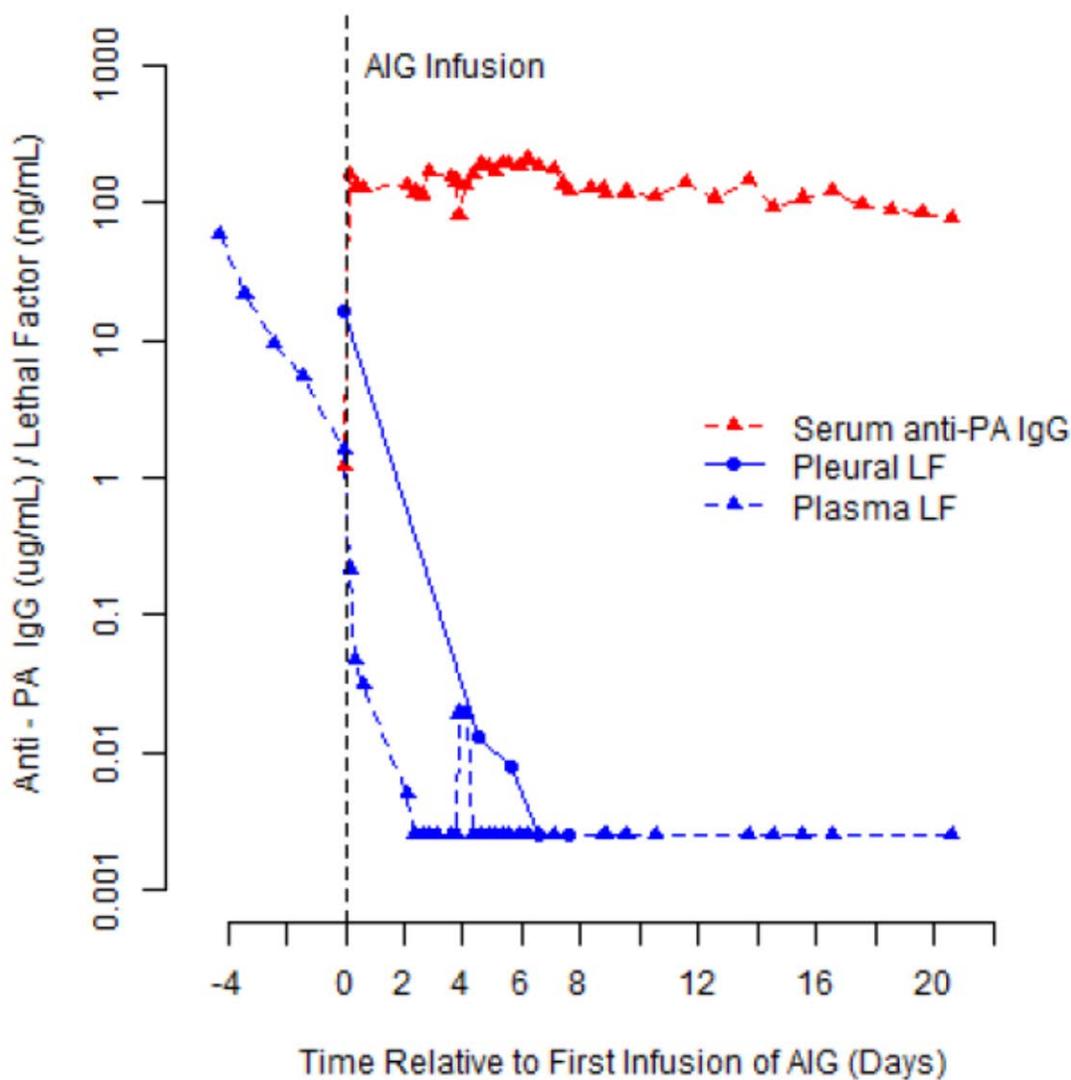
The following graph showing the time course of serum LF levels in inhalational anthrax patients treated with AIGIV.

Sponsor's Figure 4 - Declining Levels of LF in Inhalational Anthrax Patients
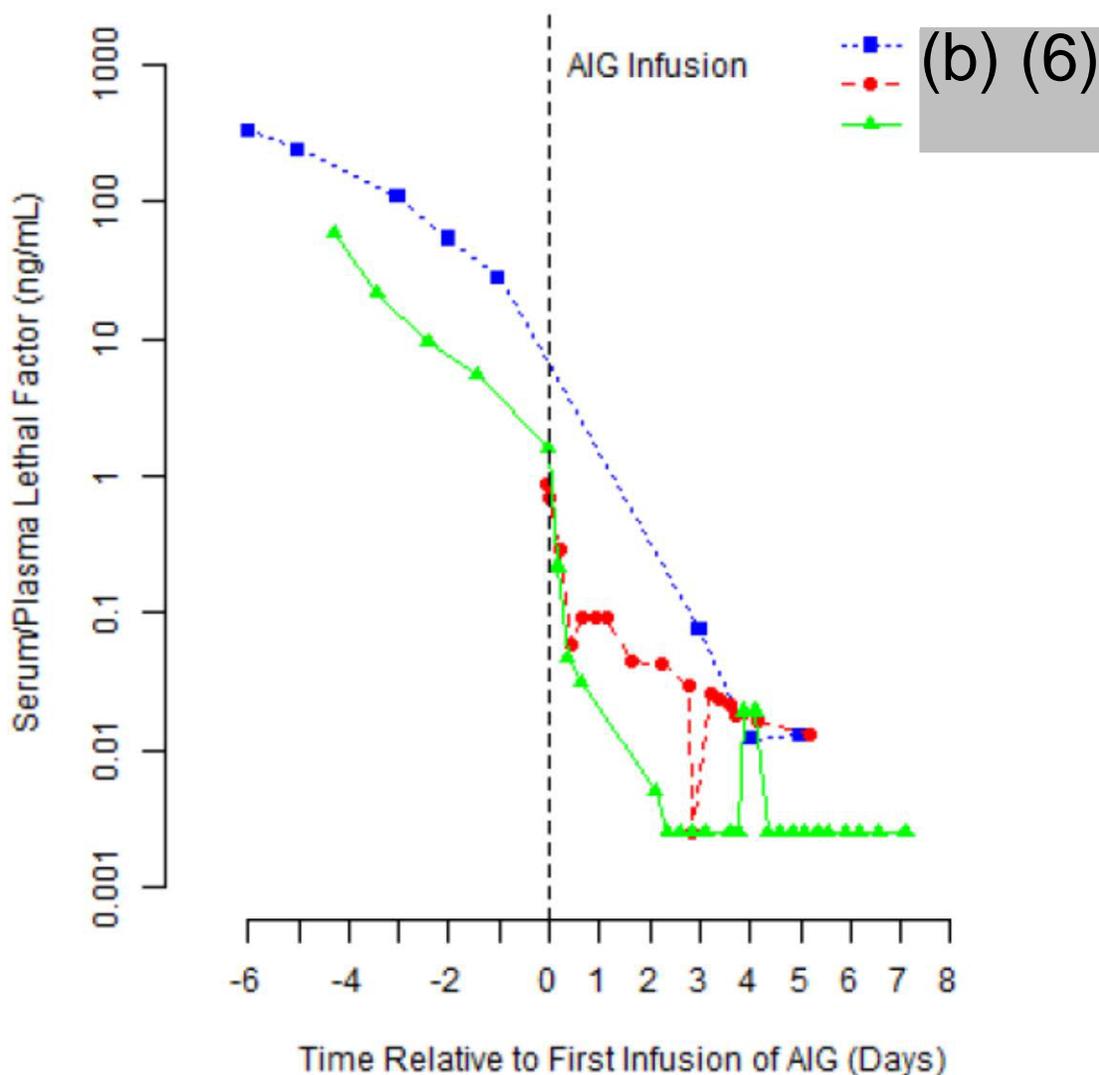
Examination of the anti-PA blood concentration – time curves of individual subjects suggests the comparative "steadiness" of anti-PA levels in the treated inhalational anthrax cases may have resulted from simultaneous rises in endogenous anti-PA levels from seroconversions while exogenously administered anti-PA from AIGIV declined. It is noteworthy that some of the exposure-by-injection systemic anthrax cases treated with AIGIV who died exhibited more substantial declines in anti-PA blood levels than were seen among the three inhalational anthrax treated cases. For example, in injectional anthrax patient (b) (6) , the peak anti-PA antibody blood level of 113 mcg/mL following the single 420 U TNA of AIGIV declined by more than 90% by 1.75 days following administration. In this subject, as shown in the figure below, serum LF fell during the first half-day following AIGIV, but then

stabilized/rose over the next few sampling points through 1.75 days following administration.

Sponsor's Figure 6- Changes in LF Protein and Anti-PA IgG Levels for Patient (b) (6)
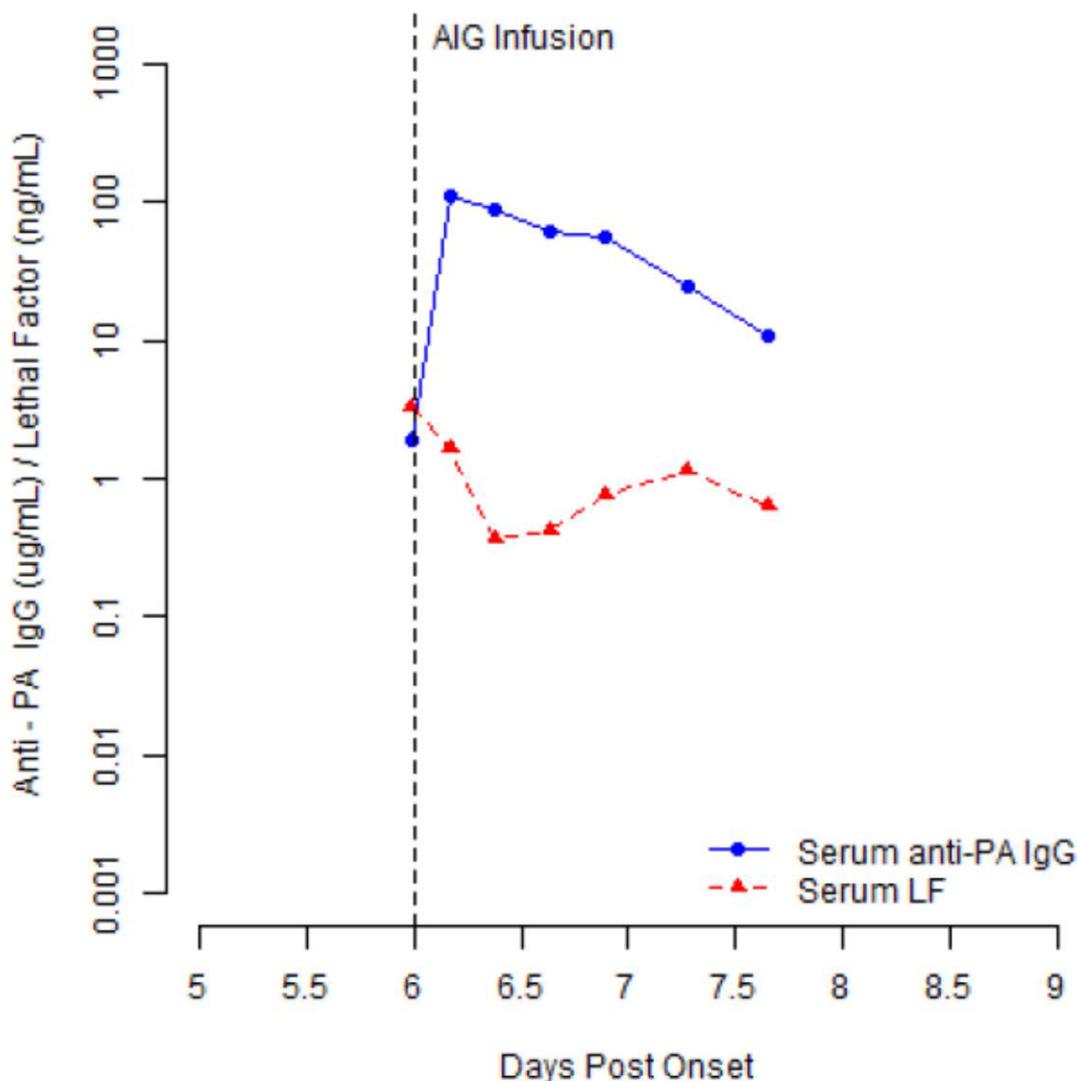
Because some chronic heroin addicts may be immunosuppressed and lack a robust capacity for seroconversion with sufficient endogenous anti-PA synthetic capability, this may explain the more rapid disappearance of anti-PA from the circulation among some of the injectional anthrax cases. Because the number of treated inhalational anthrax cases is very small, this data set is inadequate to determine whether some patients with inhalational anthrax, such as those with pre-existing immunosuppression, may benefit from additional repeated doses of AIGIV. This reviewer recommends that, in the absence of short-turn-around anti-PA and/or LF

blood level assay capability, strong consideration should be given to pre-emptive redosing of subjects who are known to have pre-existing conditions associated with significant immunosuppression, such as cancer patients who have recently received chemotherapy and patients receiving immunosuppressives for treating autoimmune diseases, prevention of transplanted organ rejection, or other conditions.

7.1.7 Subpopulations

Among 14 male patients, 5 (36%) died and 9 lived.
Among five female patients, one (20%) died, and four lived.

7.1.8 Persistence of Efficacy

As noted above, in some of the sampled injectional anthrax patients, anti-PA Ab levels fell by as much as 90% within 24 hours. This fall was likely aggravated by repeated large volume removal of pleural/peritoneal fluid into which anti-PA Abs have been demonstrated to distribute.

7.1.9 Product-Product Interactions

As the only clinical trial was conducted in healthy subjects, no drug-drug or drug-disease interactions were assessed.

7.1.10 Additional Efficacy Issues/Analyses

As discussed in section 65.1.11.1 of this memo, it is expected that the half-life of the product as measured by TNA may be shorter in patients with systemic anthrax due to their hypermetabolic state. *In order to maintain adequate blood and tissue levels of TNA for a sufficient duration to effect maximum efficacy in the actual intended use setting, the possible need for repeated dosing of the product cannot be excluded.*

7.1.11 Efficacy Conclusions

Substantial evidence of efficacy in humans in this application is extrapolated from animal efficacy model studies as per the Animal Rule. Please refer to the pharmacology-toxicology, statistical, and clinical pharmacology review memos for in-depth discussion of animal efficacy model for inhalational anthrax findings. As previously noted and, like in the case with raxibacumab, efficacy of AIGIV monotherapy compared to saline controls was demonstrated in rabbits and monkeys, but the trend suggesting improved survival with the combination of AIGIV and antibiotic therapy over antibiotic therapy alone did not reach statistical significance. No demonstration of efficacy in humans has been demonstrated due to ethical concerns and the scarcity and infrequency of sporadic human cases of naturally occurring inhalational anthrax. The uncontrolled nature and tiny size (n = three) of the series of compassionate use/expanded use inhalational anthrax cases precludes any conclusions regarding efficacy of the product. The observed mortality rate of 6/19 (32 percent) of the current series of systemic (inhalational, GI, and injectional) anthrax cases is lower than what was observed during the Soviet and U.S. 2001 anthrax incidents [see references section 2.1 of this review], but differences in route of exposure, lack of detailed data in the application regarding comparability of pre-existing co-morbidities across the historical and current AIGIV-treated cohort, and ongoing advances in intensive unit supportive care since the times of

the earlier incidents preclude definitive conclusions regarding efficacy from the human cases summarized in this review.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Only a single clinical trial has been conducted with the product in healthy volunteers. It is not appropriate to pool the safety data from this trial with that from the series of 19 subjects with systemic anthrax who received Cangene AIGIV on a compassionate use basis because the underlying rates of intercurrent events are expected to be vastly different in the two populations.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

- AX-001 – healthy volunteer RCT

- Patient Experience Report regarding compassionate use treatment of 19 patients with severe systemic anthrax

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

No pooling of safety data was performed.

8.2.3 Categorization of Adverse Events

Adverse events reporting was incomplete for patients with systemic anthrax treated with AIGIV.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

No pooling was performed because subjects in RCT AX-001 were not infected with anthrax.

8.4 Safety Results

8.4.1 Deaths

See section 7.1 for a discussion of mortality among the 19 patients with severe systemic anthrax treated on a compassionate use/expanded use basis with AIGIV.

8.4.2 Nonfatal Serious Adverse Events

Multi-organ system failure involving respiratory and kidney function was frequently present in systemic anthrax cases before and after administration of AIGIV.

8.4.3 Study Dropouts/Discontinuations

All subjects with systemic anthrax reportedly received the full single 420 U TNA dose of AIGIV. Not all subjects who were reported as having survived had been discharged

from the hospital as of the date that information on their clinical course had been collected and compiled.

8.4.4 Common Adverse Events and Adverse Reactions

No adverse reactions (product-related AEs) were reported for the systemic anthrax cases. Given the complexity and severe pre-existing illness of the systemic anthrax cases in which AIGIV was administered and the limitations of the safety data sets for these patients, it is not possible for this reviewer to determine whether any of the AEs compiled by the sponsor for the systemic anthrax human cases may have been product-related.

The CDC has summarized these cases succinctly in IND 13026 amendments 21 and 26 as follows:

Inhalational Anthrax

"Under the FDA-authorized emergency use BB-IND 12953, one dose of AIGIV was administered to a patient with laboratory-confirmed, naturally acquired inhalation anthrax on February 23, 2006. The AIGIV was administered on approximately day 10 of illness and day 7 of antimicrobial agent therapy. The patient survived and tolerated the infusion without any evidence of product-associated AEs."

"Under the FDA-authorized emergency use BB-IND 13867, one dose of AIGIV was administered to a patient with laboratory-confirmed, naturally acquired inhalation anthrax on October 27, 2008. The patient tolerated the infusion without any evidence of product-associated AEs and died with multi-organ failure on November 3, 2008."

"Under this protocol [IND 13026 expanded access], one dose of AIGIV was administered to a patient with laboratory-confirmed, naturally acquired inhalation anthrax on August 8, 2011. The AIGIV was administered on approximately day 6 of illness and day 4 of antimicrobial agent therapy. The patient survived and tolerated the infusion without any evidence of product associated AEs."

Gastrointestinal Anthrax

"Under the FDA-authorized emergency use BB-IND 14249, one dose of AIGIV was administered to a patient with laboratory-confirmed ingestion anthrax on December 25, 2009. The AIGIV was administered on approximately day 11 of illness and day 10 of antimicrobial agent therapy. The patient survived and tolerated the infusion without any evidence of product-associated AEs."

Injectional Anthrax

"From December 2009 to December 2010, an outbreak of anthrax occurred in the United Kingdom in heroin users due to contaminated heroin or a contaminated cutting agent. This type of anthrax has been termed "injection" anthrax. Out of the 15 patients who received AIGIV, 5 patients died and 10 patients survived. All doses were infused without any evidence of product associated AEs."

8.4.5 Clinical Test Results

Leucocytosis, thrombocytopenia, and perturbations of prothrombin time and or aPTT were frequently described among systemic anthrax cases treated with AIGIV.

8.4.6 Systemic Adverse Events and Adverse Reactions

No infusional adverse reactions were described among the 19 systemic anthrax cases treated with AIGIV. Systemic Adverse Events were not always reported.

8.4.7 Local Reactogenicity

Not described.

8.4.8 Adverse Events of Special Interest

Patients with systemic anthrax were frequently transfused with blood products. While bleeding may adequately explain the need for transfusions in many cases, It is possible that immunoglobulin-associated hemolysis may have occurred in some cases and gone undetected.

The sponsor describes 11 SAEs were reported among the patients who received AIGIV under compassionate use (8 injectional and 3 inhalational cases). Six of these SAEs had fatal outcomes. These SAEs were consistent with progression of anthrax or co-morbidities and were not considered related by the treating physicians for by the CDC. Causes of death in these patients is presented in sponsor's Table 21, presented below:

Table 21 Summary of Deaths in Severe Systemic Anthrax Patients Treated with AIGIV

Age/Sex	Patient ID	Route of Anthrax Exposure	Date of AIGIV Administration	Date of Death	Cause of Death/Narrative
34/Male	(b) (6)	Inhalational	Oct 27, 2008	(b) (6)	Death was caused by fulminant multi-organ failure developed post candidiasis sepsis.
34/Male		Injectional	Dec 19, 2009		Death was caused by worsening anthrax infection complicated with septic shock, DIC and acute renal failure.
44/Male		Injectional	Dec 21, 2009		The cause of death is unknown and no other safety information is available. It is assumed that the patient died from anthrax progressive deterioration.
35/Female		Injectional	Jan 3, 2010		The cause of death is unknown and no other safety information is available. It is assumed that the patient died from anthrax progressive deterioration.
24/Male		Injectional	Feb 16, 2010		Death was caused by worsening anthrax infection, complicated with bacteremia, coagulopathy and acute renal failure.
30/Male		Injectional	Jan 20, 2010		The cause of death is unknown and no other safety information is available. It is assumed that the patient died from anthrax progressive deterioration.

DIC = Disseminated intravascular coagulopathy

Elsewhere in the report, the sponsor describes 34 SAEs reported for 11 patients including the following:

coagulopathy,
disseminated intravascular coagulation (DIC),
cardiac arrest (n=2),
ascites (n=2),
rectal hemorrhage,
death otherwise unspecified (1),
multiorgan failure (n=2),
oedema, oedema peripheral,
septic shock (n=2),
systemic Candida,
hyperkalemia,
metabolic acidosis,
renal failure,
renal failure acute (n=3),
renal impairment
(n=3), acute respiratory distress syndrome (ARDS) (n=2),
haemothorax,
pleural effusion (n=2),

pulmonary congestion,
pulmonary oedema,
respiratory failure,
circulatory collapse,
hypotension

As noted above, from the information provided in the BLA, it is not possible for this reviewer to determine the possible relatedness of the above SAEs to treatment with AIGIV.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable in the human anthrax cases.

8.5.2 Time Dependency for Adverse Events

In the uncontrolled portion of AX-001, AEs occurring within 72 hours of product infusion will be considered by this reviewer to be at least possibly product-related.

8.5.3 Product-Demographic Interactions

No pediatric subjects or subjects over 65 years of age have received AIGIV either in the healthy volunteer safety and PK trial or in compassionate use settings for the treatment of severe systemic anthrax. No morbidly obese subjects were included in the AX-001 clinical trial.

8.5.4 Product-Disease Interactions

The observed mortality rate in the three inhalational anthrax cases (33%) was lower than in the injectional anthrax cases, but the numbers are too small to permit definitive conclusions.

8.5.5 Product-Product Interactions

These were not examined in AX-001 because it was a healthy volunteer RCT.

8.5.6 Human Carcinogenicity

Not applicable due to the short-term period of observation.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdosing was reported.

8.5.8 Immunogenicity (Safety)

No immunogenicity testing was performed, which is typically the case for trials of immunoglobulin products.

8.6 Safety Conclusions

The data from AX-001 in healthy volunteers indicates an adequate safety profile, given the risks of inhalational anthrax and the potential benefits of therapy. *The safety profile of the product may be different in patients with severe inhalational/systemic anthrax. For example, the risk of thrombosis may be different in patients with DIC due to anthrax, and the risk of renal insufficiency may be greater in patients with systemic anthrax who may be in shock and/or have pre-existing renal dysfunction and be receiving aminoglycosides and other nephrotoxic drugs. The sponsor will be requested to include a statement to this effect in the package insert.*

The safety of the product in the series of compassionate use/expanded use cases is difficult to determine, given that many of the patients had already developed significant organ dysfunction by the time AIGIV was administered.

It is necessary to perform glucose measurements using glucose-specific methodology, given the maltose content of the product and the demonstration in AX-001 that glucose non-specific methods of glucose determination may produce clinically significant falsely high readings. The sponsor has appropriately included a boxed warning in this regard in the draft package insert.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

The safety (and efficacy) of the product have not been studied in pediatric, geriatric, or obese subjects.

9.1.1 Human Reproduction and Pregnancy Data

None available.

9.1.2 Use During Lactation

No data available.

9.1.3 Pediatric Use and PREA Considerations

Given its orphan designation for "treatment of toxemia associated with inhalational anthrax" (letter dated 29 July 2008 re: designation request # 08-2630), the product is exempt from PREA.

As the only clinical trial with AIGIV was conducted in adults age 19 to 55 years, there are no safety data available for the pediatric age range. Given the seriousness and high mortality rate associated with inhalational anthrax, it may be reasonable to extrapolate safety for this product/indication from an adult population to the pediatric population, with additional supporting pediatric safety data from the sponsor's other hyperimmune immunoglobulin products made by very similar manufacturing methods. To this end, FDA requested on 03 October 2014 that the sponsor submit to this file safety data for from the sponsor's other hyperimmune immunoglobulin products made by very similar manufacturing methods and to discuss the rationale, pros and cons of extrapolating safety in pediatric patients from those products to AIGIV.

The sponsor submitted in the amendment to this BLA dated 24 October 2014 pediatric safety data for its other hyperimmune products WinRho SDF, HepaGam B, VARIZIG, and VIGIV in response to the above FDA information request. The sponsor noted that "currently all Cangene licensed hyperimmune products are manufactured with typically 5 to 6% protein in a liquid formulation that contains 10% maltose and 0.03% polysorbate 80. Previously, both WinRho® SDF and VARIZIG® were produced using a lyophilized formulation that contained 0.1 M glycine and 0.01% polysorbate 80. Lyophilized product was reconstituted in a sterile diluent containing 0.8% sodium chloride and 10 mM sodium phosphate. For WinRho® SDF, the lyophilized and liquid formulations were demonstrated to be pharmacokinetically bioequivalent following intravenous (IV) administration, and pharmacokinetically comparable after intramuscular (IM) administration... The liquid formulation of VARIZIG® was approved on September 30, 2014 based on manufacturing comparability with the lyophilized formulation, clinical data with the lyophilized formulation of VARIZIG® and supporting pharmacokinetic data from other Cangene hyperimmune products."

A summary of pediatric dosing and safety data as submitted for each of the above Cangene hyperimmune immunoglobulin products is presented below.

WinRho (ITP indication – initial dose 250 IU/kg IV)

"The safety profile for WinRho SDF for acute ITP, chronic ITP and ITP secondary to HIV in both adults and pediatrics were similar... In the ITP studies overall, related AEs were reported by 31% (27/87) of the adults and 26% (19/74) of the pediatric patients. The most common related AEs in children with ITP were headache (experienced by 11% of patients) and fever (experienced by 7% of patients) and in adults with ITP were headache (experienced by 12% of patients) and chills (experienced by 10% of patients)."
Reviewer Comment: Based on inspection of the sponsor's table of the six more frequent adverse reactions following WinRho administration for ITP in adults and children from the sponsor's clinical trials, I agree that the pattern of most frequent AEs reported with an incidence of >5% in ITP subjects treated with WinRho was similar for adults and children.

VARIZIG (*IM dose provided in table below taken from the 24 October 2014 amendment*)

Weight of Patient		VARIZIG Dose		Volume to Administer[a] (milliliters)
Kilograms	Pounds	IU	Number of Vials	
≤2.0	≤4.4	62.5	0.5	0.6
2.1–10.0	4.5–22.0	125	1	1.2
10.1–20.0	22.1–44.0	250	2	2.4
20.1–30.0	44.1–66.0	375	3	3.6
30.1–40.0	66.1–88.0	500	4	4.8
≥40.1	≥88.1	625	5	6.0

[a] Volume of VARIZIG to be administered: extractable volume for liquid formulation or after reconstitution for lyophilized formulation.

The sponsor concluded that "the low dose IM administration of VARIZIG compared to the higher dose IV administration of AIGIV make direct extrapolation of safety data difficult to justify." *Reviewer Comment: I agree that the different routes of administration*

in combination with the greater-than-order-of-magnitude difference between recommended VARIZIG doses and recommended AIGIV doses in pediatric patients do not justify extrapolation of pediatric safety data with VARIZIG to pediatric patients who would be administered AIGIV.

The expanded access protocol for VARIZIG included 374 pediatric patients, for whom 57 adverse reactions were reported in 19 patients (5.1%). Injection site pain, headache, and nausea were among the most commonly reported adverse reactions among both adults and children treated with VARIZIG*. Reviewer Comment: I agree with the sponsor's conclusion that the pattern of adverse reactions reported for VARIZIG was similar for pediatric patients and adults.*

HepaGam B (For post-exposure prophylaxis, HepaGam B is administered intramuscularly to newborn infants after perinatal exposure and to infants less than 12 months of age after household exposure at a dose of 0.5 mL.)

Of 253 infants treated with HepaGam B, only 1 adverse reaction of induration of thighs was reported. In 42 adults exposed to hepatitis B and treated prophylactically with HepaGam B, adverse reactions of headache (21%), nausea (9.5%), pyrexia (9.5%), arthralgia (7.1%), and myalgia (7.1%) were reported. *Reviewer Comment: The data described by the sponsor suggest that the incidence of adverse reactions following HepaGam B administration may be lower among infants than among adults, notwithstanding the inability of infants to articulate certain complaints.*

VIGIV (Vaccinia Immune Globulin Intravenous (Human) (Usual dose: 6000 U/kg)

VIGIV was administered to only one pediatric patient (in a case report) – age 28 months, weight 10 lbs; subject received 11 doses of 24000 U/kg over 20 days. No adverse reactions to VIGIV were mentioned in the case report [Ref: Vora S et al. Clinical Infectious Diseases 2008; 46:1555–61*]. Reviewer Comment: A single pediatric patient has been reported to receive VIGIV and this is grossly insufficient to characterize the pediatric safety of the product.*

The sponsor prepared the following table to compare the dosing recommendations for two example pediatric body weights and a 70 kg adult for its hyperimmune immunoglobulin products. The most pertinent unit of comparison is the volume, not the total units as the activity assays for these diverse products are different, but each of the products has a similar total protein and total (polyclonal) IgG concentration (b) (4)

Table 3 Comparative Dose levels of Cangene Hyperimmune Products for Pediatrics and Adults

Hyperimmune Product (Indication)	Max Dose (Max Volume) of Hyperimmune Administered Based on Weight			Comment
	Pediatric 10 kg	Pediatric 30 kg	Adult Dose (70 kg)	
AIGIV (Treatment of toxemia)	120 U (90 mL)	240 U (180 mL)	420 U (315 mL)	Adult dose administered for pediatrics ≥60 kg. Maximum dose volume of (b) (4) per vial containing >60 U TNA.
VIGIV (Treatment of vaccinia vaccine complications)	240,000 Units (61 mL)	720,000 Units (183 mL)	1,680,000 Units (427 mL)	Maximum dose of 24,000 Units/kg. Maximum extractable volume of (b) (4) per 50,000 Unit vial
WinRho SDF (ITP)	3000 IU (2.6 mL)	9000 IU (8 mL)	21,000 IU (18 mL)	Maximum dose of 300 IU/kg. Volume calculated base on target fill volumes from prescribing information
VARIZIG (Post-exposure prophylaxis)	125 IU (1.2 mL)	375 IU (3.6 mL)	625 IU (6 mL)	Adult dose administered for pediatrics ≥ 40.1 kg. Each 125 IU vial has an extractable volume of (b) (4)
HepaGam B (Post-exposure prophylaxis)	>156 IU (0.5 mL)	>562 IU (1.8 mL)	>1300 IU (4.2 mL)	The minimum dose of 0.5 mL or >156 IU listed for 10 kg applies to newborn infants and infants less than 1 year of age. Maximum dose is 0.06 mL/kg, with a potency of (b) (4)

As can be seem from the above table, only VIGIV is dosed in the same order of magnitude as the sponsor recommends for AIGIV and, as noted above, only a single pediatric patient has received VIGIV. Note that the 420 U AIGIV dose in a 70 kg adult is equivalent to 225 mg/kg total IgG, assuming 5% total IgG (50 mg/mL total IgG).

Although not requested to compare the safety in pediatric and adult subjects receiving Immune Globulin Intravenous (Human) (IGIV) in clinical trials, the sponsor also summarized information from the package inserts of U.S.-licensed IGIV products and concluded that there "is little differentiation in the safety profiles in pediatric and adult populations for marketed intravenous immune globulins in indications where dosing is more similar to or greater than AIGIV dose levels." However, the sponsor did note that vomiting was more frequently reported among pediatric subjects in the Gamunex primary humoral immunodeficiency trial, and that fever was more frequently reported among pediatric subjects in the Gamunex ITP trial. Otherwise, safety and efficacy in adults and pediatric subjects were similar in the Gamunex licensure trials. The Gamunex trial in primary humoral immunodeficiency, which enrolled 87 subjects to the Gamunex arm and 85 subjects to the Gamumune N arm, was the largest [active] controlled clinical trial reported to date for any IGIV product studied for that indication. The Gamunex trials in ITP evaluated 12 pediatric subjects. The sponsor points out in its response to the October 3 information request that the adverse reaction profiles for its hyperimmune immunoglobulins are consistent with the immune globulin class of products. In considering the safety of immune globulin products in neonates, the incidence and types of adverse reactions were similar in IGIV and placebo treated low-birth-weight neonates in a randomized, placebo-controlled, double blind trial in 287

subjects who received 500 mg/kg IGIV and 297 subjects who received placebo [Ref: Baker CJ et al, N Engl J Med 1992;327:213-219]. The rate of infusional adverse reactions in this study was 1% in both IGIV and placebo groups. In a randomized, double-blind, placebo-controlled trial of Staphyloccus aureus immune globulin intravenous (human) conducted in 1983 premature infants, there was no difference in mortality (7% vs. 6%), and no significant differences between treatment arms in the total numbers of adverse events, serious adverse events, adverse events considered related to treatment, or adverse events leading to interruption of infusion or permanent discontinuation of study drug [Ref: DeJonge M et al. J Pediatrics 2007;151:232-234]. The pattern of individual adverse events was quite similar between both treatment arms in this trial. *Reviewer Comment: I agree that the spectrum of adverse reactions and adverse events reported for Cangene's hyperimmune immunoglobulin products falls within the range of ARs and AEs observed for the Immune Globulin Intravenous (Human) class.*

In conclusion, although the doses, in terms of total IgG/total protein, of Cangene's hyperimmune products for which it has submitted pediatric safety data from clinical trials are too low to permit extrapolation of pediatric safety of those products to AIGIV, the submitted data do suggest a similar safety profile for the hyperimmune immunoglobulin products in adults and pediatric patients. It is noted that the sponsor did not break down the pediatric safety data by pediatric age groups, but given the large difference in doses between these products and AIGIV, such a breakdown would not likely be contributory. *Given the serious and life-threatening nature of inhalational anthrax, I conclude that it is reasonable to extrapolate the AIGIV safety data in adults from trial AX-001 to pediatric subjects. In addition to extending the indication to all pediatric patients, another option, given the additional uncertainty in defining the pediatric dose as discussed in the Clinical Pharmacology review, would be to administer the product to any pediatric patients with inhalational anthrax under the existing Emergency Use Authorization if activated, and to limited the indication for the to-be-licensed product to adults and adolescents.*

9.1.4 Immunocompromised Patients

While it is possible that some of the heroin addicts who developed injectional anthrax and were treated with AIGIV may have already been immunocompromised, which would explain some of these subject's apparent lack of an adequate endogenous anti-PA antibody response, data regarding the immunocompetence of these patients at the time of anthrax exposure are not available.

9.1.5 Geriatric Use

No clinical trial data from subjects aged > 65 (or > 55) years old are available. The only clinical trial with AIGIV, AX-001, was conducted in healthy adults age 19 to 55 years. No safety or efficacy data in humans over age 65 years of age treated for systemic anthrax are available. The human anthrax cases treated with AIGIV on a compassionate use/expanded use basis ranged in age from 24 to 61 years

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Repeated Dosing

The rationale for studying the efficacy of repeated dosing in the intended population and for recommending in the dosage and administration section of the package insert that

prescribers should consider the option of pre-emptive repeated dosing for selected patients can be summarized as follows:

- The experience with the product in the treatment of inhalational anthrax is limited to three patients, all of whom received a single 420 U TNA dose of the product. One of these three patients died. This experience is too small to permit generalization of the observed mortality rate to a larger population and too small to confirm efficacy of the product. [In the subject who died, pleural and serum LF gradually declined but were still detectable at 4 and 5 days, respectively following AIGIV administration, while serum and pleural anti-PA IgG rose following treatment and remained at a plateau, with serum levels in the range of 30 – 40 mcg/mL. This subject's course was complicated by systemic candidiasis, multi-organ failure and DIC.]

- Mean peak anti-PA blood levels among the three treated inhalational anthrax cases were 25% lower than the C_{max} observed for the 420 U TNA dose cohort of healthy volunteer RCT AX-001. This, and the fact that patients with systemic anthrax are expected to be hypermetabolic/catabolic, suggest that the pharmacokinetics of AIGIV in patients with inhalational anthrax may be altered compared to that observed in healthy volunteers.

- Inspection of the LF blood concentration – time curves in patients with systemic anthrax, including inhalational anthrax, who were administered a single 420 U TNA dose of AIGIV reveals that circulating LF levels do NOT plummet to zero shortly following administration of the product, but rather persist at detectable levels for several days. This may represent ongoing release of LF into the circulation from anthrax bacteria not yet eliminated by antimicrobial therapy. In some patients, particularly those whose own humoral antibody immune response to anthrax infection is slow in onset/inadequate, one (or more) additional AIGIV doses may be required to block the toxic effects due to the ongoing release of LF into the circulation.

- It is especially noteworthy that some of the exposure-by-injection systemic anthrax cases treated with AIGIV who died exhibited more substantial declines in anti-PA blood levels than were seen among the three inhalational anthrax treated cases. For example, in injectional anthrax patient (b) (6) , the peak anti-PA antibody blood level of 113 mcg/mL following the single 420 U TNA of AIGIV declined by more than 90% by 1.75 days following administration. In this subject, serum LF fell during the first half-day following AIGIV, but then stabilized/rose over the next few sampling points through 1.75 days following administration. This patient also had significant bleeding from his site of surgical debridement requiring large transfusion requirements and had ascites removal by laparotomy, which likely contributed to the rapid decline observed in anti-PA blood levels.

- Patients with ongoing blood loss requiring substantial blood and fluid replacement, as well as patients requiring evacuation of large quantities of plural or ascitic fluid are expected to have accelerated removal of anti-PA antibody from the body. The data from sampling of plural and ascitic fluid in multiple subjects treated with AIGIV are sufficient to establish that anti-PA antibody distributes well into pleural and ascetic fluid with levels approaching those in the blood. The sponsor acknowledges on p 39 of 286 of the Patient Experience Report in the submission that in the injectional anthrax patients who died "Anti-PA may have been more rapidly consumed due to accumulation of toxin in tissues, or it may have been cleared more rapidly due to fluid loss."

- Because some chronic heroin addicts may be immunosuppressed and lack a robust capacity for seroconversion with sufficient endogenous anti-PA synthetic capability, this may also help to explain the more rapid disappearance of anti-PA from the circulation following administration of a single dose of AIGIV among some of the injectional anthrax cases.

- Patients with pre-existing immunosuppression, such as those who are taking immunosupressives for autoimmune disease or prevention of transplanted organ rejection, as well as cancer patients who recently have received chemotherapy, may have an impaired humoral response to anthrax and require additional dose(s) of AIGIV in order to maintain adequate anti-PA levels for the duration of the period of LF production/release/circulating LF detection.

10. CONCLUSIONS

The potential benefits of AIGIV administration in conjunction with appropriate antibiotic therapy exceed the known risks in inhalational anthrax. The recommended dosage range is 420 to 840 U as a fixed (not-body-weight-based) initial dose. The totality of animal studies suggests that survival is projected to be higher using the 840 U dose. Public health considerations in large exposure scenarios may be taken into consideration in choosing the initial dose. The maximum single dose studied for safety in humans is 840 U. Repeated dosing has not been studied. Nevertheless, repeated administration may be considered on an individualized basis depending on clinical response, especially in patients with substantial ongoing hemorrhage or large compartmental fluid losses, as well as in patients who may be delayed or impaired in mounting an adequate immune response.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Inhalational anthrax is a serious condition associated with high mortality. The mortality rate with inhalational anthrax treated with antibiotics and intensive supportive care was 45% during the 2001 U.S. anthrax attack. The activity of AIGIV without concomitant antibiotic therapy in inhalational anthrax has been demonstrated in animal efficacy models in both rabbits and monkeys. The addition of AIGIV to appropriate antimicrobial

therapy has the potential, though unproven in the added benefit studies in rabbits and NHPs (and not studied in humans), to lower the mortality from this serious, life-threatening disease. Like in the pivotal animal efficacy model study in inhalational anthrax that supported the FDA approval of the monoclonal antibody therapeutic, raxibacumab, survival was higher among rabbits who received both the specific immunoglobulin product (AIGIV) and appropriate antibiotic therapy than in rabbits receiving antibiotic therapy plus non-specific IGIV, but the survival difference did not reach statistical significance. The safety profile of single doses of the product up to 840 U TNA as observed in the healthy adult volunteer RCT, AX-001 and, as inferred for pediatric patients from review of safety data for other immunoglobulin products (particularly IGIV), was acceptable, given the potential benefits. The safety of a single dose of 840 U TNA is expected to be comparable to the safety of two separate doses of 420 U TNA. The safety profile of the product may be different in patients with severe inhalational/systemic anthrax from that seen in healthy volunteer trial AX-001. For example, the risk of thrombosis may be different in patients with DIC due to anthrax, and the risk of renal insufficiency may be greater in patients with systemic anthrax who may be in shock and/or have pre-existing renal dysfunction and be receiving aminoglycosides and other nephrotoxic drugs. These risks, together with the other known risks of IGIV products including hemolysis, hypersensitivity reactions, and the very low risks of viral transmission and transfusion-associated lung injury (TRALI), will be addressed in the package insert. The product will carry a boxed warning for the risk of thrombosis and the risk of hypoglycemia from inappropriate administration of hypoglycemic in response to falsely elevated glucose readings if glucose non-specific test strips/devices are used to monitor blood sugar. This reviewer considers that the potential benefit of the product, as inferred from the submitted animal efficacy model studies, exceeds the known and expected risks of the product when used in conjunction with appropriate antimicrobial therapy to treat symptomatic inhalational anthrax disease. If a field trial becomes feasible, the sponsor is required by regulation as a post-marketing requirement to verify the safety and efficacy of the product in humans with inhalational anthrax and has agreed to design the field trial to verify the appropriateness of the recommended dosing regimen.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Inhalational anthrax carries a high (~ 45%) mortality rate despite appropriate antibiotic and supportive therapy.	• Same as column two. Inhalational anthrax is serious and life-threatening condition.
Unmet Medical Need	• No polyclonal antibody product against anthrax toxin is licensed. • The supply of the monoclonal antibody product, raxibacumab, is finite.	• There is a need for more effective products to treat inhalational anthrax. AIGIV would be a potentially useful addition to available therapy for inhalational anthrax.
Clinical Benefit	• Unknown and unproven in humans • Product beneficial in monotherapy studies vs. IGIV in rabbits and NHPs. • Potential benefit is suggested from animal studies, but add on study in rabbits was inconclusive as to added benefit over antibiotic therapy. • Product to be administered as add-on therapy to appropriate antibiotic therapy and supportive care.	• AIGIV might further reduce mortality when administered with appropriate antimicrobials in inhalational anthrax.
Risk	• Thrombosis. Some inhalational anthrax patients develop DIC which might be aggravated by the product. • Lots of the product vary in activated clotting factor content – some lots are presently quarantined. • Same as IGIV, namely: hemolysis, aseptic meningitis, TRALI, hypersensitivity, infection transmission	• Risks are more than balanced by potential benefit., but this requires outcomes monitoring in actual use.
Risk Management	• PMR to confirm clinical benefit is required under Animal Rule. • Thrombosis risk in this setting poorly defined.	• The PMR should be designed with two components: mass exposure and sporadic compassionate use.

11.2 Risk-Benefit Summary and Assessment

See Section 11.1

11.3 Discussion of Regulatory Options

Options include (1) approval, (2) a CR letter requesting the sponsor perform an added benefit study in rabbits at 30 U/kg, and (3) a CR letter requesting further exploration of the feasibility of evaluating added benefit over antibiotic therapy in the NHP. The latter two options would further delay licensure of this product, which has taken 13 years to develop (counting from the 2001 U.S. Anthrax attack). Note that the product currently resides in the Strategic National Stockpile for emergency distribution by the CDC under an Emergency Use Authorization (EUA) if activated. In addition, the CDC holds an active Expanded Use protocol for administration of the product in systemic anthrax, including inhalational anthrax.

11.4 Recommendations on Regulatory Actions

1.   I recommend approval of this BLA with revision of the INDICATIONS AND USAGE section of the draft package insert as detailed below.

2. Regarding your submitted synopsis of contingency postmarketing requirement (PMR) field study protocol AX-003:
    a. Please submit a draft protocol within 30 days of receipt of this request.
    b. Please submit a draft case report form (CRF) within 60 days of receipt of this request.
    c. Please submit with the draft protocol proposed relative timelines at this time in relation to initiation of the protocol for completion of enrollment, completion of data collection, and for submission of the final study report.
    d. Please include in the study design a mechanism for studying the use of more than one dose of the product in comparison to use of a single dose.
    e. Please consider including international healthcare providers who may administer AIGIV to patients with inhalational anthrax located overseas.
    f. Please consider sampling a subset of patients for lethal factor (LF) before and after administration of AIGIV and explore the relationship between changes in LF levels in relation to the time of administration of AIGIV and to changes in PA levels in individual patients.
    g. Serious adverse events (SAEs), adverse reactions, and suspected adverse reactions should be recorded, analyzed, and reported. Recording and reporting of adverse events that do not fall into one or more of the aforementioned categories need not be reported.
    h. Please change the secondary endpoint to the frequency of serious suspected adverse reactions plus serious adverse reactions.
    i. Please add exploratory endpoints consisting of cause-specific mortality, duration of ICU stay, duration of mechanical ventilation, need for dialysis, maximum increase from baseline in SOFA score, and duration of hospitalization.
    j. Please include in the protocol provision for independent assessment by the sponsor of the relatedness of all serious adverse events.

     k. Please define the total of serious suspected adverse reactions plus serious adverse reactions as all SAEs for which any one or more of the following criteria are met:

          i. SAEs for which the onset was during or within 24 hours of the end of AIGIV infusion.

          ii. SAEs considered by the healthcare provider or the sponsor to be possibly, probably, or definitely related to administration of AIGIV.

          iii. SAEs for which the healthcare provider's causality assessment was missing or indeterminate.

     l. Please include plans to compare the observed mortality rate to historical controls and to compare the demographics and other pertinent patient characteristics to historical controls.

     m. Please analyze both efficacy and safety outcomes by age, sex, race, and ethnicity.

11.5 Labeling Review and Recommendations

I agree with the sponsor's inclusion of a boxed warning regarding the risks of serious and potentially fatal hypoglycemia that could result from using glucose non-specific glucose meters/strips to measure blood glucose following administration of this maltose-containing product. The glucose data measured using various methods from RCT AX-001 confirm that the maltose content of the proposed dose of the product is sufficient to produce clinically significant false elevations in point-of-care device glucose determinations using glucose non-specific methodology.

Letter-ready comments:

Please respond to the following and make the following changes to the draft package insert:

General

1. Ensure that the PI is proof-read for editorial errors.

2. Use command language whenever possible.

3. The FULL PRESCRIBING INFORMATION should contain only headings and subheadings. We recommended revising the 5 WARNINGS AND PRECAUTIONS and 13 NONCLINICAL TOXICOLOGY sections to remove the sub-subheadings under the subheadings. In any case, do not separately number subsections of subsections (e.g. use 5.11 but not 5.11.1, 5.11.2, etc.).

4.

Highlights

5. Please ensure that the HIGHLIGHTS, excluding the Boxed Warning section, are limited in length to one-half page.

6. Please add the following language to the boxed warning in both HIGHLIGHTS and the FPI sections:

> WARNING: THROMBOSIS
>
> • Thrombosis may occur with immune globulin products, including Anthrasil. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
>
> • For patients at risk of thrombosis, administer Anthrasil at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration.
>
> • Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

7. Replace the second bullet under WARNINGS AND PRECAUTIONS in the HIGHLIGHTS section with the bulleted statement "Thrombosis may occur following treatment with immune globulin products including Anthrasil. (5.3)" Change the fourth bullet to read "Acute intravascular hemolysis may occur. Monitor for clinical signs and symptoms of hemolysis and hemolytic anemia. (5.5)" Move the fifth bullet down to be the next-to-the-last bullet in this section. Move the eighth bullet down to be the last bullet in this section.

Highlights (and, for some items, also Full Prescriber Information)

8. Please change the first paragraph of the INDICATIONS AND USAGE sections in HIGHLIGHTS and the full prescribing information (FPI) to read:

> ANTHRASIL is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.

9. Following the second paragraph in the INDICATIONS AND USAGE sections in HIGHLIGHTS and the FPI please add the following statement:

> Although survival in rabbits and monkeys with inhalational anthrax was greatest among animals that received AIGIV plus antibiotic therapy, a statistically significant independent contribution to efficacy (survival) of

ANTHRASIL above and beyond that conferred by appropriate antibiotic therapy was not demonstrated in animal efficacy trials (13.2). Although the efficacy of ANTHRASIL monotherapy was demonstrated with animal treatment models of inhalational anthrax, ANTHRASIL should be administered in combination with appropriate antibiotic therapy.

10. Please delete the first sentence in the third paragraph under the INDICATIONS AND USAGE sections in HIGHLIGHTS. Please move the second sentence in the third paragraph in the INDICATIONS AND USAGE sections in HIGHLIGHTS to the DOSAGE AND ADMINISTRATION section and change it to read "Pediatric dosing was derived using from allometric scaling. Please add this modified sentence to the beginning of the fourth bullet in to the DOSAGE AND ADMINISTRATION section of the FPI. Please add the statement "There have been no studies of ANTHRASIL in the pediatric, geriatric, or obese populations to the INDICATIONS AND USAGE section in the FPI. Please add the following statement to the DOSAGE AND ADMINISTRATION section in HIGHLIGHTS: "See section 2.1 for considerations regarding repeat dosing."

11. In the boxed warning in the HIGHLIGHTS and FPI sections, please spell out IGIV as Immune Globulin Intravenous (Human).

12. In the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS, please state the adult dosage range and indicate that the dose in pediatric patients under age 13 (corresponding to a body weight of approximately 60 kg or less) is determined by body weight.

13. In the dosing table showing infusion rates in the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS and the FPI, please change the Dose column entries to 7-14 vials for adults and 1-14 vials for Pediatric <1 year to < 16 years, and correct the fourth column to reflect for pediatric subjects incremental infusion rates if tolerated of 0.02 mL/kg/min. Eliminate the separate row for pediatric subjects <1 year.

14. In the CONTRAINDICATIONS section in HIGHLIGHTS, please revise the first bullet to include the word "immune" before globulins.
15. In the USE IN SPECIFIC POPULATIONS section in HIGHLIGHTS, change the last bullet to read "Pediatric dosing is based on allometric scaling."

Full Prescriber Information (FPI)

16. In the Full Prescriber Information please change the recommended dose for adults from 420 U to the following language:

> The minimum dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 U (7 vials). Animal data suggest that administration of the human equivalent of approximately 840 U (14 vials) may result in improved survival. It may be necessary to take into account the condition of the patient and/or availability of the product in relation to the size of the inhalational anthrax outbreak in determining the appropriate initial dose from a public health perspective.

17. Change the fifth bullet under DOSAGE AND ADMINISTRATION to read as follows:

> Consider repeat dosing depending on the severity of symptoms and the response to treatment, especially in patients experiencing substantial hemorrhage as reflected in large transfusion requirements, patients with significant compartmental fluid losses, such as from large volume and/or repeated therapeutic thoracentesis and/or abdominal paracentesis, and in patients whose own immune response may be impaired/ delayed.

18. Consider adding the following statement to the DOSAGE AND ADMINISTRATION section:

> The patient's clinical status and, where available, results of testing for serum/pleural/peritoneal levels of anti-protective antigen and of anthrax lethal factor following dosing with ANTHRASIL may be taken into account in evaluating the adequacy of dosing.

19. Please modify your dosing algorithm for pediatric patients as follows:

Table 2 Pediatric Dosing Guide for ANTHRASIL[1]:

Body wt (kg)	Number of ANTHRASIL Vials[2]
<5	1
5-<10	1 - 2
10-<18	2 - 4
18-<25	3 - 6
25-<35	4 - 8

35-<50	5 - 10
50-<60	6 - 12
>60	7 – 14

[1] The pediatric dosing in Table 2 is derived from allometric scaling based on observed adult exposure to ANTHRASIL at 420 or 840 Units by TNA dose.
[2] The lower number in each range is based on a 420 U adult dose and the higher number is based on an 840 U adult dose.

Please correct the exposure to protein in pediatric patients in section 5.4 accordingly.

20. Under DRUG INTERACTIONS in HIGHLIGHTS, change the first bullet to read "Based on animal studies, ANTHRASIL did not interfere with therapy with the antibiotics levofloxacin or ciprofloxacin."

21. Change the last bullet in HIGHLIGHTS under WARNINGS AND PRECAUTIONS to read "Interference with blood and urine glucose testing (5.11)."

22. Please change the statement in section 2.2 Preparation to read "Once punctured, the thawed vials should be used to prepare the infusion bag within 6 hours."

23. Change the first sentence in section 5.1 Hypersensitivity Reactions to read "Acute systemic allergic reactions were not seen in the clinical trial with ANTHRASIL"

24. In section 5.2 Interference with Blood Glucose Testing, change the second sentence to read "Maltose in ANTHRASIL and in Immune Globulin Intravenous (Human) products has been shown…"

25. In section 5.4 Aseptic Meningitis Syndrome (AMS), move the 2nd and 3rd sentences in the third paragraph to the top of section 5.2 and change them to read "For ANTHRASIL at the recommended adult dosages of 420 Units (seven vials) and 840 U (14 vials), an adult patient may be exposed to up to 0.368 g or 0.736 g protein per kg body weight, respectively. Exposure to protein in pediatric patients due to ANTHRASIL administration may range from 0.378 g per kg to 2.0 g per kg, depending on the pediatric dose (for body weight-dependent pediatric dosing; see Table 2 in 2.1 Dosage and Administration)." Precede these sentences at the top of section 5.2 with the statement, "The incidence and/or severity of some adverse reactions to ANTHRASIL and other Immune Globulin Intravenous

(Human) products may be related to the total protein/polyclonal antibody load administered."

26. In section 5.5 Hemolysis, change the second sentence in the third paragraph to read "Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours, and again approximately 7-10 days post infusion."

27. In section 6 ADVERSE REACTIONS, change the second sentence to read "This includes those adverse events (AEs) with an incidence of 5% or greater which were dose-dependent, and/or considered related by the Clinical Investigator, and/or which demonstrated a temporal relationship (within 72 hours of ANTHRASIL administration)." *Please provide the data listing and SAS code for identifying the most common adverse reactions as defined above and as included in Table 3 in section 6.1. What criteria were applied to determine if AEs were dose-dependent?*

28. In section 6.1 Clinical Trials experience:

    a. Change the first sentence in the fifth paragraph of section 6.1 to read "No serious adverse reactions were reported during the clinical study. Change the second sentence in this paragraph to read "Infusion of ANTHRASIL was stopped for four subjects due to adverse reactions (ARs). Change the next sentence to read "One subject was withdrawn due to an AR consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache."

    b. Replace the adverse drug reaction (ADR) with adverse reaction (AR).

    c. Strike the sentence in the 7th paragraph which begins "This includes all dose dependent AEs…"

    d. Change the first sentence in the 8th paragraph to read "Headache, pain (including back pain and pharyngolaryngeal pain), and cough were reported in a dose-dependent fashion. In addition, nasal congestion, rhinorrhea, and neck pain occurred more frequently with higher doses of

ANTHRASIL." *Please clarify the criteria used to determine these two categories of [possibly] dose-related ARs.*

e. Please redesign Table 3 to provide the numbers of subjects and events which occurred in the placebo group for the corresponding rows. Limit the data for the active subjects to the randomized, double-blind portion of the study. Include a narrative or separate tabular listing of the cumulative incidence by subject and event type for common ARs using all 74 subjects exposed to AIGIV for only those additional ARs not included in Table 3. Change the title of Table 3 to read "Adverse Reactions Observed in >5% of Subjects Administered AHTHRASIL or Placebo in Healthy Volunteer Clinical Trial." Please note that healthy volunteers were not "treated" with ANTHRASIL because they did not have anthrax.

f. Change the last sentence to read "In addition to the reported ARs, dose-related elevations in urine glucose were noted transiently following dosing *[see 5.11 Elevated Glucose in Urine]*.

29. Change the last sentence in subsection 7.1 Ciprofloxacin and Levofloxacin to read "Concomitant administration of ANTHRASIL with levofloxacin or ciprofloxacin in exposed rabbits and cynomolgus macaques, respectively, did not reduce the efficacy of antibacterial therapy."

30. Change subsection 8.4 Pediatric Use to read as follows:

Safety and effectiveness of ANTHRASIL in the pediatric population (<16 yrs of age) have not been studied. Allometric scaling was used to derive dosing regimens to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 420 to 840 Units. The dose for pediatric patients is based on body weight.

31. Change subsection 8.5 Geriatric Use to read as follows:

Safety and effectiveness of ANTHRASIL in the geriatric population (>65 yrs of age) have not been studied. No safety data are available in elderly patients from either the AX-001 healthy volunteer study or from the compassionate use of AIGIV in patients with systemic anthrax.

32. Change subsection 8.7 Use in Obese Population to read as follows:

Safety and effectiveness of ANTHRASIL in the obese population have not been studied. Although empirically-based guidance for dosing for Immune Globulin Intravenous (Human) in morbidly obese patients has been reported in the medical literature, pharmacokinetic data for ANTHRASIL or IGIV in obese patients are lacking.

33. Add the following statement to section 12.1 Mechanism of Action:

ANTHRASIL is administered in combination with appropriate antibiotic therapy as the product by itself is not known to have bactericidal activity against anthrax bacteria which otherwise may continue to grow and produce anthrax toxins.

34. In section 12.3 Pharmacokinetics:

   a. In Table 5, delete $AUC_{(0-7d)}$ and provide all PK parameters as arithmetic means with the exception of T_{max}.

   b. Insert a new paragraph under Table 5 which reads "It is expected that the clearance of anti-PA antibodies from ANTHRASIL administration will be greater and the AUC will be lower in patients with inhalational anthrax compared to healthy subjects."

   c. Change the next paragraph to read as follows:

      Mean PK results (TNA data) were evaluated by sex and revealed no sex-related differences over the dose range studies. Systemic exposure of ANTHRASIL increased in a dose-proportional manner over the dose range studied. ANTHRASIL has a serum elimination half-life of 24 to 28 days in humans.

   d. Change the next paragraph to read as follows:

In compassionate use/ expanded access programs [see 14.2 Compassionate Use/Expanded Access Program], inhalational anthrax patients concomitantly treated with antibiotics and a single ANTHRASIL dose of 420 Units TNA exhibited increases in serum and pleural anti-PA levels; these levels remained at >50% of the peak anti-PA levels over the next five days. The peak anti-PA levels in these patients following ANTHRASIL administration (132 to 160 mcg/mL, mean 145 mcg/mL) overlapped with those obtained with the 420 Units ANTHRASIL dose in healthy volunteers (135 to 250 mcg/mL, median 192

mcg/mL), although mean levels were approximately 25% lower in the inhalational anthrax patients. In the three inhalational anthrax patients, serum and pleural levels of lethal factor declined after initiation of antibiotics and further decreased over the period of five days following ANTHRASIL administration. Unlike the situation in the animal treatment model studies, plasma levels of lethal factor remained detectable 1 to 2 days following ANTHRASIL administration, despite their decline.

> e. Change the last paragraph to read as follows:

Because the effectiveness of ANTHRASIL cannot ethically be tested in placebo-controlled trials in humans, a comparison of ANTHRASIL exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax in therapeutic efficacy studies is necessary to support the dosage regimen of 420 Units to 840 Units IV as a single (or initial) dose for the treatment of inhalational anthrax in humans.

35. Change the heading for section 13 to NONCLINICAL TOXICOLOGY AND PHARMACOLOGY. Change the second paragraph in this section to read as follows:

The evaluation of new treatment options for anthrax using placebo controlled human trials is unethical and infeasible. Therefore, the effectiveness of ANTHRASIL for treatment of inhalational anthrax is based on controlled efficacy studies conducted in rabbits and cynomolgus macaques.

36. Change the second sentence in sub-subsection 13.2.2 to read "No significant difference between the control (normal immune globulin [IGIV] plus levofloxacin) and treatment groups (ANTHRASIL plus levofloxacin) was seen when combination treatment was delayed up to 60 hours post-challenge.

37. Change the third sentence in the third paragraph of sub-subsection 13.2.2 to read "Of the animals that survived to be treated (19% of those challenged), antibacterial drug plus ANTHRASIL (15 Units per kg) resulted in (58%) [sponsor fill in (number of surviving animals/number of animals surviving to be treated)] survival compared to 39% [sponsor fill in (number of surviving animals/number of animals surviving to be treated)] survival in rabbits treated with antibacterial drug and IGIV placebo (p = 0.21)." Round off the p value in the next paragraph to 0.02.

38. Please add the p value in parentheses for the survival difference in the cynomolgus macaque combination treatment study in the paragraph under Table 7 in sub-subsection 13.2.2.

39. Please modify the paragraph presently under 13.2.3 ANTHRASIL in Post-exposure prophylaxis to include the results to those in animals who were determined to be anti-PA positive, and both anti-PA positive and bacteremia at the time of dosing. Exclude the presentation of data from challenge dosing at 20 hours.

40. In section 14, please change the first sentence to read "Because it is not ethical or feasible to conduct placebo-controlled clinical trials in humans with inhalational anthrax.." Change the last sentence in this paragraph to read "The safety has been tested in healthy adults and evaluated in a limited number of patients with anthrax who were treated with ANTHRASIL under compassionate use or CDC's expanded use programs."

41. Strike the last sentence in section 14.1 which begins "The data collected in this study demonstrated…" as it is promotional in tone.

42. Change the title of subsection 14.2 to read Patient Experience (Compassionate Use/Expanded Access Program). (Note that not all human cases of systemic anthrax treated with AIGIV received the product under the Expanded Access Program.)

43. Strike the sentence in the first paragraph of section 14.2 which reads "To provide additional support…"

44. Change the second paragraph of section 14.2 to read "For the ANTHRASIL indication of inhalational anthrax, two out of three patients treated with ANTHRASIL plus appropriate antimicrobial therapy survived and one died from progression of anthrax disease. In all three patients, therapy included aggressive supportive measures including mechanical ventilation and pulmonary fluid drainage.'

45. Change the third paragraph of section 14.2 to read "In the three inhalational patients, the ANTHRASIL dose of 420 Units by TNA resulted in increased anti-PA levels (correlating with increased TNA activity); these levels remained comparatively stable up to 7 to 20 days post-administration, probably reflecting

rising antibody production by the patient at the same time that the exogenously-administered antibody was being cleared."

46. Add a fourth paragraph to section 14.2 to read as follows:

> Unlike the case in animals, serum lethal factor remained detectable in patients' serum following administration of ANTHRASIL, although substantial declines following product administration were observed. In some injectional anthrax cases complicated by substantial hemorrhage and pleural and/or peritoneal fluid losses from thoracentesis and/or paracentesis, serum anti-PA antibody levels fell as much as approximately 90% from their post-ANTHRASIL peak levels by 24 hours following ANTHRASIL administration.

47. In section 17 PATIENT COUNSELING INFORMATION change the term "legal guardian" to "legally authorized representative" in the first sentence. In the last bullet in this section, change the last sentence to read "The safety of ANTHRASIL has been tested in healthy adults, but no safety data are available in the pediatric population, the elderly, or pregnant women [*see 8 USE IN SPECIFIC POPULATIONS*].

Please make the following changes to the draft carton and container labels:

48. The proper name of the product on the carton and container label shall be placed above any trademark or trade name identifying the product.

11.6 Recommendations on Postmarketing Actions

According to the Animal Rule, the sponsor is required to conduct a postmarketing requirement (PMR) study to establish the efficacy and safety of the product in humans should such a study become feasible. In amendment 01 dated 04 September 2014, the sponsor has submitted a protocol synopsis for protocol AX-003 for this purpose. It is recommended that the sponsor's PMR obligation to confirm benefit in humans be split into two subparts as follows:

1. Protocol AX-003 with modifications to be requested by FDA to cover a "broad [anthrax] exposure event scenario."
2. A requirement to periodically submit and analyze data from use of AIGIV in sporadic systemic anthrax cases.

In addition, I concur with the clinical pharmacology reviewer who has recommended that sparse PK sampling for pediatric patients administered AIGIV under either of the above

scenarios be undertaken and the data eventually analyzed and submitted using a population PK approach.

See Appendix 1 for a summary and review of the proposed AX-003 contingency protocol and see letter-ready comments on recommendations on regulatory actions regarding this protocol synopsis in section 11.4 of this memo

APPENDICES

Appendix 1 – Review of AX-003 Contingency PMR Protocol Synopsis

Title of Protocol:

> AIGIV field study for the evaluation of clinical benefit and safety in the treatment of patients with inhalational anthrax in a broad exposure event scenario.

Objectives:
> The primary objective is to verify clinical benefit and evaluate safety of AIGIV for the treatment of inhalational anthrax in a broad exposure scenario such as intentional anthrax release during a bioterror attack.

Patient Population:

> Patients with inhalational anthrax who are treated with AIGIV. The patient population is anticipated to include pediatric, adult and geriatric patients.

Primary Endpoint: Mortality rate

Secondary Endpoint: Frequency of safety related adverse reactions

Additional Endpoints:

> Serum anti-PA levels, pre- and post-dose, especially in patients having large fluid loss, edema, requirement for blood products, or fluid replacement/drainage.

Inclusion Criteria:

- Confirmed or suspected inhalational anthrax patients in the USA treated with AIGIV provided by the CDC SNS.

- Informed consent/assent (as applicable) is required for provision of a serum sample for anti-PA testing.

Exclusion Criteria: N/A

Assessments:

> **Baseline, demographic and exposure history**

- Demography (date of birth, sex, race, ethnicity)
- Relevant medical history
- Details of exposure (including date of suspected exposure, if known)
- Clinical signs of inhalational anthrax at presentation with date and time of onset and severity for each clinical sign, and including Sequential Organ Failure Assessment (SOFA) score.
- Diagnostic indicators of inhalation anthrax including chest x-ray, CT scan and confirmatory laboratory results.

Treatment and supportive care data

- Details of AIGIV administration(s), lot number, date and time of administration, dose, infusion rate(s) and related adverse reactions.
- Details of supportive care provided to the patient, including hospitalization and/or Intensive Care Unit (ICU) admission and discharge date(s) and use/duration of mechanical ventilation, requirement for surgery or pleural or abdominal fluid drainage.
- Concomitant medications, including antibiotic therapy, blood products, vasopressors, hemodynamic support or corticosteroids.
- When available, pre- and post- AIGIV serum samples will be collected for anti-PA analysis. Sampling schedule guidelines will be provided, but any available samples will be collected for analysis.

Clinical outcomes
- All-cause mortality including date and cause of death.
- Adverse events.
- Date of discharge and location (home, rehabilitation or other care facility).
- Presentation (improvement or progression) of clinical signs post-AIGIV administration.
- Time course of disease, treatment and supportive care.

Statistical Methods

- Primary endpoint of mortality rate with 95% Cis.
- No formal statistical comparisons
- Exploratory analyses to determine predictors of outcome/treatment success to examine the relationship between survival and the disease/treatment course.
- Incidences of ARs overall and by age category (pediatric, adult, geriatric).
- Anti-PI levels will be listed and plotted to determine relationship to outcome if sufficient data are available.