



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

To: To File (BLA STN 125562/0)

From: Michael C. Kennedy, Ph.D., LPD/DHRR/OBRR,

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Applicant: Emergent BioSolutions (Former Cangene Corporation)

Product: Anthrax Immune Globulin Intravenous (Human)
Trade name: Anthrasil™

Subject: Final Review: Rabbit Inhalational Anthrax studies

Recommendation

This BLA is recommended for approval.

Executive Summary

Three rabbit studies were conducted by Cangene in order to support the efficacy of NP-015 Anthrax Immune Globulin Intravenous (AIGIV) for the treatment of inhalational anthrax under the Animal Rule. These studies were performed at (b) (4) under Good Laboratory Practices (GLP) using New Zealand White Rabbits (*Oryctolagus cuniculus*).

The pivotal efficacy study (1207-100005104) consisted of 110 rabbits (55 male, 55 female) challenged with *Bacillus anthracis* (Ames strain) spores via aerosol exposure (average challenge dose = $194 \pm 33 \times LD_{50}$). After the occurrence of a temperature spike and a positive test for circulating protective antigen (PA), 100 of the randomized animals were treated with either NP-015 (50 animals, 15 U/kg) or normal Immune Globulin Intravenous (Human) (IGIV) as control (50 animals). The remaining 10 challenged rabbits were used as untreated controls. All rabbits except for 2 control animals were later confirmed to be bacteremic prior to treatment. Of the NP-015 treated animals 26% survived as compared to 2% in the IGIV controls, with an average time to death of 148.5 hours post-challenge for non-survivors in the NP-015 treatment group as compared to 75.8 hours for the IGIV controls. Both the increase in survival and time to death for the NP-015 treatment group were statistically significant.

An earlier dose ranging study (677-G005681) treated 6 groups of Ames spore aerosol challenged rabbits (14 animals/group, average dose of $265 \pm 37 LD_{50}$) were treated with NP-015 dosed at either, 7.5 U/kg, 15 U/kg, or 30 U/kg, and treated at either 20 or 30 hours post-challenge. Additionally, two post-challenge IVIG treatment control groups (20 hour and 30 hour) and an untreated control group were included in the study. While the 20 hour post-challenge groups treated with NP-015 showed good dose responses to the drug, none of the animals in these groups were bacteremic or PA positive so this data is only relevant to

post-exposure prophylaxis (not the indication sought for the BLA). The 30 hour post-challenge NP-015 treatment groups did have a number of bacteremic and PA positive animals at the time of treatment. If only these animals are taken into consideration the 7.5 U/kg treatment group had 2 out of 10 survive (20%), the 15 U/kg treatment group had 2 out of 8 (25% survival), and the 30 U/kg group had 4 out of 12 (30% survival). No animals in the IGIV control groups or no treatment group survived so the survival numbers comparing NP-015 treatment groups to the IGIV groups are statistically significant but the numbers between the 30 hour NP-015 groups are not.

The third study was a combined therapy with Levofloxacin and either NP-015 or IGIV used in combination. Treatment was initiated 96 hour post-challenge (average of 238 x LD₅₀) with a large number of animals being used (336) because of the narrow therapeutic window with antibiotics treatment in this model. Of the 64 animals who survived long enough to be treated with both Levofloxacin and either NP-015 (n=31) or IGIV (n=33). All animals were bacteremic and PA positive at the time of treatment. Animals infused with IGIV exhibited a 39% (13/33) survival rate compared to the animals infused with NP-015 that exhibited a 58% (18/31) survival rate. This increase in survival following treatment with NP-015 was not statistically significant compared to IGIV.

Background Summary

Cangene Corporation of Winipeg, Canada (Cangene) (now Emergent Biosolutions) submitted a Biologics License Application (BLA) on July 25, 2014 for Anthrax Immune Globulin Intravenous (AIGIV). AIGIV is an intravenous immune globulin product obtained from fractionated pooled source plasma from donors immunized with Anthrax vaccine adsorbed (AVA) vaccine (BioThrax). This application was submitted electronically and represents the second BLA submitted to CBER requesting approval under the “Animal Rule” 21 CFR 601 (subpart H). Much of the product development was funded by the U.S. government under the Biomedical Advanced Research and Development Authority (BARDA) and many of the developmental studies for the rabbit inhalational anthrax model were supported through the National Institute of Allergy and Infectious Diseases. This product has previously been made available under a CDC held IND and the entire available product is stored at the Strategic National Stockpile.

Three bacterial polypeptides, protective antigen (PA), lethal factor (LF), and edema factor (EF), interact to form the two primary B. anthracis toxins which generate disease. PA and LF combine to produce anthrax lethal toxin (LT), and the PA and EF combine to produce edema toxin (ET). PA binds to a host cell receptor and is cleaved by a furin-like protease. The activated PA then forms a heptameric complex which competitively binds three molecules of LF and/or EF. The holotoxin is taken up by the cell via receptor-mediated endocytosis and produces cell death. This hyperimmune product contains polyclonal antibodies that are primarily directed against PA but some low level of antibodies against LF and/or EF may be present. Clearance of circulating PA to undetectable levels was seen in NP-015 treated animals shortly after the product was administered and this clearance is believed to be the primary mechanism of action. NP-015 will be indicated for the treatment of toxemia associated with inhalational anthrax.

NP-015 is manufactured and formulated with the same method as for other Cangene’s hyperimmune intravenous hyperimmune products, i.e., WinRho SDF, HepaGam B and VIGIV. The final product is supplied in 50 ml (b) (4) glass vials with no less than 60 Units/Vial activities based on Tissue Neutralization Assay, and is frozen and stored at ≤ - 15° C. However, since all the available NP-015 lots were manufactured before Cangene modified its manufacturing process (b) (4)

[REDACTED] this product does contain the potential for high prothrombotic activity.

Supplement Review Summary

The following final study reports for the rabbit based studies performed at (b) (4) (b) (4) under Good Laboratory Practices (GLP) using New Zealand White Rabbits were submitted in this BLA:

FINAL REPORT on Therapeutic Efficacy of Anthrax Immune Globulin Intravenous, NP-015 in Rabbit Model of Inhalation Anthrax:

GLP Study Conducted under (b) (4) Study No. 1207-100005104

February 2013

Study Design:

The primary objective of this study was to determine the efficacy of Anthrax Immune Globulin Intravenous (NP-015) in comparison to normal human Immune Globulin Intravenous (IGIV) when treatments were administered after the first detection of PA in serum. One hundred and ten (110, 55 male, 55 female) were challenged with *Bacillus anthracis* (Ames strain) spores via aerosol exposure. The average challenge dose received by the animals was $194 \pm 33 \times LD_{50}$. The exposed animals were randomized and treated with either a single intravenous infusion of 15 U/kg of NP-015 or an equivalent volume of IGIV (50 rabbits per treatment group) at the onset of toxemia (PA detection). The remaining 10 animals served as process controls. All rabbits except for 2 control animals were later confirmed to be bacteremic prior to treatment. The average time to treatment was 32.4 hours post-challenge. There were no serious deviations during the conduct of the study.

Results:

Of the NP-015 treated animals 26% survived as compared to 2% in the IGIV controls, with an average time to death of 148.5 hours post-challenge for non-survivors in the NP-015 treatment group as compared to 75.8 hours for the IGIV controls. Both the increase in survival and time to death for the NP-015 treatment group were statistically significant ($P=0.0009$, Fisher's Exact Test).

All animals that died on study had gross and/or microscopic evidence of anthrax, including the presence of rod-shaped bacteria consistent with *B. anthracis* in one or more organs. There were no *B. anthracis*-related findings in study survivors. No microscopic findings were found in organs (including brain) from study survivors examined, with the exception of two female animals treated with NP-015 which were recorded as having focal dermal necrosis. The lesions were negative for *B. anthracis* and this finding was considered incidental with no relation to the *B. anthracis* challenge or treatment.

There was no significant differences in the median time from challenge until toxemia (first instance of PA detected in the serum post-challenge; 24.1 hours for IGIV group and 24.3 hours for NP-015 group) or from challenge until bacteremia (24.3 hours for IGIV group and 24.7 hours for NP-015 group) between the treatment groups. There was also no significant differences in the PA levels just prior to treatment (23.02 ng/mL for IGIV group and 26.29 for NP-015 group; geometric means). However after treatment, the proportion of rabbits toxemic or bacteremic and the levels of circulating PA were significantly decreased in the NP-015 group. The time to toxemia or bacteremia resolution was also significantly shorter in rabbits that received NP-015.

FINAL REPORT on Determination of Dose and Time Range Efficacy of Anthrax Immune Globulin, NP-015 in Rabbits Exposed to Inhalation Anthrax:

GLP Study Conducted under [REDACTED] Study No. 677-G005681

September 2008

Study Design:

The objective of this study was to assess the effectiveness of treatment with NP-015 in New Zealand White (NZW) rabbits exposed to *Bacillus anthracis* (Ames strain) spores by aerosol route. The study design contained 2 fixed treatment times of 20 hours and 30 hours post-challenge with 3 different treatment doses of 7.5, 15, and 30 U/kg. One hundred and twenty-two (122) NZW rabbits randomized into 8 dose groups and 1 untreated control group were challenged with an average dose of 265 ± 37 LD₅₀ equivalents of *B. anthracis* (Ames strain) spores. Following challenge, each rabbit was monitored for clinical manifestations of disease including abnormal body temperature, outward clinical signs, hematological abnormalities, positive bacteremia cultures, and circulating levels of PA (determined by (b) (4)). Group 1 rabbits (10 total) served as untreated controls, whereas Group 2 and 3 rabbits (14 animals per group) were treated with Normal Human IGIV (IGIV) at 20 hours or 30 hours post-challenge, respectively. Group 4 and 5 rabbits received a target dose of 7.5 U/kg of NP-015 at 20 hours or 30 hours post-challenge, respectively. A target dose of 15 U/kg of NP-015 at 20 hours or 30 hours post-challenge was provided to Groups 6 and 7, respectively. At 20 hours or 30 hours post-challenge Groups 8 and 9 received an average dose of 30 U/kg, respectively. All doses given were within 15% of the target dose and within ± 1 hour of the assigned treatment time. There were no serious deviations during the conduct of the study.

Results:

All 10 untreated control animals died with a median time-to-death of 94.73 hr. IGIV provided no survival benefit to Group 2 or 3 rabbits, as none of the IGIV-treated animals survived (0/28). The median time-to-death for Group 2 was 70.86 hr, and the median time-to-death for Group 3 was 61.53 hr. NP-015 provided a significantly higher survival when compared to IGIV when administered at the 20 hours post-challenge time point - 57% (Group 4, 7.5 U/kg), 79% (Group 6, 15 U/kg), and 93% (Group 8, 30 U/kg). However, since none of the animals were positive for the presence of PA or bacteremia this data can only be used as post-exposure prophylaxis data and is not relevant to the treatment indication that is being sought for this product. The raw data also suggested NP-015 provided a significant increase in survival when compared to IGIV when administered at the 30 hours post-challenge time point particularly with increasing doses of NP-015 (29% (Group 5, 7.5 U/kg), 43% (Group 7, 15 U/kg), and 36% (Group 9, 30 U/kg)). However, only a percentage of the animals were bacteremic and PA positive animals at the time of treatment. If only these animals are taken into consideration the 7.5 U/kg treatment group had 2 out of 10 survive (20%), the 15 U/kg treatment group had 2 out of 8 (25% survival), and the 30 U/kg group had 4 out of 12 (30% survival). No animals in the IGIV control groups or no treatment group survived so the survival numbers comparing NP-015 treatment groups to the IGIV groups are statistically significant but the numbers between the 30 hour NP-015 groups are not.

FINAL REPORT on Efficacy Evaluation of NP-015 (AIGIV) in Combination with Levofloxacin when administered at 96 hour Post exposure in the Rabbit Model of Inhalational Anthrax:

GLP Study Conducted under (b) (4) Study No. 1182-100011472

June 2014

Study Design:

The primary objective of this study was to assess the therapeutic efficacy of the combination treatment of NP-015 (15 U/kg) and levofloxacin over that of IGIV and levofloxacin when either treatment was initiated 96 hours after aerosol exposure to a lethal dose of *B. anthracis* spores, in New Zealand White rabbits. Because treatment with antibiotics at earlier time points leads to very high numbers of surviving animals the relatively late fixed treatment time was chosen. However, large numbers of rabbits were required because the delay in treatment result in many animals dying before treatment was completed.

Three hundred and thirty-six (336) rabbits (gender balanced) were challenged with an average of 238 x LD₅₀ equivalents of *B. anthracis* spores via the inhalational route of exposure. Rabbits surviving to 96 hours post-exposure were treated with a combination of either NP-015 and levofloxacin or IGIV and levofloxacin. Levofloxacin was administered via oral gavage at a concentration of 50mg/kg once daily for three days. NP-015 or Control IGIV was administered via slow IV infusion at 4.7 mL/kg over a single 2.5 hour infusion. Blood specimens (whole blood and serum) were analyzed for the presence of bacteria, protective antigen (PA), and changes in hematology parameters at various collection time points prior to and following treatment. Animals succumbing to disease following treatment were subjected to gross necropsy and histopathology. All technical staff were blinded to treatment status (Test or Control).

Eighty-four (84) animals survived long enough to receive at least a single dose of levofloxacin. In total sixty-four (64) animals were successfully treated (completed the 2.5 hour infusion required by the protocol) with either NP-015 (n=31) or IVIG (n=33) and all were positive for toxemia and bacteremia prior to treatment. There were no serious deviations during the conduct of the study.

Results:

For animals which successfully completed treatment those infused with IGIV exhibited a 39% (13/33) survival rate compared to the animals infused with NP-015 that exhibited a 58% (18/31) survival rate. This increase in survival following treatment with NP-015 was not statistically significant. In addition to overall survival, treatment with NP-015 resulted in an almost immediate clearance of free PA from circulation. All 31 rabbits (100%) treated with NP-015 exhibited positive PA in circulation prior to treatment. One hour following treatment with NP-015, only 8 animals (26%) were positive for PA in the circulation. In comparison, animals infused with IGIV exhibited toxemia for an additional 24 hours following treatment. Treatment with IGIV or NP-015 in combination with levofloxacin resolved bacteremia in all animals within 24 hours of treatment. Minimal inhibitory concentrations determined from bacterial cultures analyzed prior to and following treatment with levofloxacin suggest no resistance was gained during the short course of levofloxacin treatment.

Conclusions:

Analysis of this data supports that the treatment with AIG reduces circulating PA levels and the results in significant delays in time to death, when compared with the IGIV treated control group. These results also confirm a statistically significant improvement in the survival of AIG-treated animals compared to placebo treated animals. While the levels of protection were not high (~25% survival) AIG is not intended as a stand-alone treatment but is expected to be used in combination with approved antibiotics. The studies conducted were appropriately designed and executed. As such they support approval of this BLA under the Animal Rule.