Application Type	Original Application
STN	125462/0 Midcycle Memo
CBER Received Date	September 20, 2012
PDUFA Goal Date	March 22, 2013
Division / Office	DH /OBRR
Priority Review	Yes
Reviewer Name(s)	Irwin M. Feuerstein, MD, MS
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Cangene Corporation
Established Name	eBAT NP-018 (Botulism Antitoxin Heptavalent (Equine) Types A-G)
(Proposed) Trade Name	BAT
Pharmacologic Class	Immune Globulin, Antitoxin
Formulation(s), including Adjuvants, etc	<No Formulations>
Dosage Form(s) and Route(s) of Administration	Powder and Solvent for Suspension for Injection, <No Admin Route>, Intravenous, Intravenous, Intravenous, Intravenous, <No Admin Route>
Dosing Regimen	20, 50 ml/vial
Indication(s) and Intended Population(s)	Patients with documented or suspected symptomatic botulism poisoning

Table of Contents

NOTE

All sources are from the BLA application. All section (§) numbers refer to this review memo document.

1. EXECUTIVE SUMMARY

Cangene Corporation has submitted an application for Botulism Antitoxin Heptavalent (Equine) Types A-G, indicated for use in patients with documented or suspected symptomatic botulinum poisoning. The product is manufactured by giving toxin or toxoid to horses which create immune globulin antitoxin. Equine plasma is purified and made into antitoxin for intravenous use. The Sponsor has been working FDA for many years to develop a product for use in sporadic poisoning or national security incidents. Clinical trials of efficacy in the target population have been considered unethical and the Sponsor and FDA have agreed to use the Animal Rule to bring the product to market.

Four human clinical studies are submitted for review.

- BT-001 was a pharmacokinetic and safety study of single and double dose administration in normal volunteers.
- BT-002 stages A and B (two studies) were double-blind, randomized, placebo-controlled, safety and pharmacodynamic trials studying licensed botulism antitoxin types A and B (stage A) and this heptavalent product (stage B) against placebo and each other in a pre-exposure, prophylaxis model against extensor-digitorum-brevis-foot-muscle toxin injection and loss of muscle action potentials.
- IND BB-6750 is an ongoing expanded-access treatment trial in symptomatic subjects with documented or suspected botulism poisoning conducted by CDC, BARDA, and Cangene. IND 6750 was an open-label, uncontrolled trial; no controlled trial has been done for symptomatic treatment.

In BT-002B, there were 15 severe and moderate adverse events in the treatment arm vs. none with the placebo, though only four moderate events are said to be related and most of the other events show no definite pattern. Otherwise, the safety studies have revealed a profile of side effects consistent with those expected with equine immune globulin products, other than an increased incidence of tonsillar hypertrophy in BT-002B. One case of serum sickness occurred in IND 6750 (eventually died) and one in BT-002B. Six subjects died in IND 6750, none is said to be from the product, but this is still awaiting additional information requests. Both single and double dose regimens in BT-001 appear approximately as safe as previously licensed product.

The product is significantly more effective than placebo at preventing local muscle paralysis when administered in standard dose one day prior to injection of botulinum toxin. It is unknown whether this prophylactic model can be generalized to the proposed symptomatic treatment indication. Post-hoc analysis of the CDC data suggests a difference in subject outcomes between those treated before or after two days after presentation. There are no available adequate and well-controlled efficacy studies in humans. Therefore, pivotal animal studies will be used to model efficacy in the target population of symptomatic patients. There are unresolved issues of maximal or repeated dose, and pre-treatment with antihistamines and steroids. The benefit-risk profile from

the available data is positive and favors approval. In accordance with regulation, post-marketing studies will be required.

RECOMMENDATION

This reviewer recommends that the following information requests be sent to the Sponsor. If the responses to the requests are satisfactory and the animal data can establish a reasonable likelihood of efficacy in humans, then the product can be approved for licensure and marketing in accordance with regulation.

LETTER-READY COMMENTS

2012-11-20 Set of comments

1. Please provide an xpt data file for all concomitant medications for IND-6750.
2. The draft label in the highlights and section 2.4 suggest that corticosteroids and anti[-]histamines be considered prior to dosing. However:
    a. The clinical studies do not mention such pretreatment.
        i. Please indicate whether subjects in BT-001, BT-002A/B, or the CDC study IND 6750 received pretreatment.
            1. If yes, please provide any data and discuss the impact on pretreatment on the safety and efficacy of the product.
            2. If no, please explain why pretreatment is recommended on the label when it was not used in any of the trials.
    b. There is some evidence in the literature (see references) that the anticholinergic side effects of some antihistamines might be relatively contraindicated in other diseases of the neuromuscular junction, such as myasthenia gravis. Please discuss the potential impact of antihistamines on safety and efficacy of the product in the setting of symptomatic botulism, particularly the possibility that the antihistamines could make advanced paralytic botulism worse.
3. The administration dilution stated is 1 vial diluted 1:10 in saline for both the 10 to 22 mL fill volumes. Despite the fact that these have nominally the same amount of active ingredient, the end volumes and times for administration will vary by more than two fold. Please justify these instructions and provide data from the clinical trials regarding administration times, clinical acceptability and tolerability relevant to volume and time, provider preference, and other convenience factors.
4. In table 5, the first subject listed who died suffered an adverse reaction and died 52 days after administration. However, the death is listed as unrelated to H-BAT and not caused by botulism itself. Please provide more detailed information about the clinical course, the cause of death, and why the death could not be plausibly related to the study product.

Reference List

Ruhatiya, O. K. (1993). Exacerbation of myasthenia gravis by single dose of Respren (Ethnor) and Astemizole tablets. J Assoc Physicians India, 41, 316.

Kamel, J., Wright, K., & Philip, J. A. (2009). The cautious use of cyclizine in a patient with myasthenia gravis. J Palliat.Med, 12, 879-880. 10.1089/jpm.2009.0028

Cobo, C. A., Alberti Aguilo, M. A., & Casasnovas, P. C. (2011). Myasthenia gravis exacerbation after cetirizine administration. Muscle Nerve., 44, 146-147. 10.1002/mus.22096

2012-12-18 Set of comments

1. Protocol deviation:

   A protocol deviation occurred in BT-002A where the unblinded pharmacy assistant who prepared the infusions also administered both the test drug (Aventis Pasteur botulism antitoxin bivalent (equine) types A and B) and placebo, and adjusted infusion rates for these infusions based on prior experience in administering IV infusions. This was a violation of "To maintain the blinding in this study, only a research pharmacist (or a designate not involved in study drug administration) will know in which arm of the study subjects are enrolled" written on page 25 of the protocol. Even though BT-002A did not study NP-018, it did study the prior licensed product to which NP-018 (Cangene botulism antitoxin heptavalent (equine) types A-G) was compared, "thereby introducing bias into the study" as stated in the report. Please explain how this happened given the prohibition on such an occurrence. Please also analyze the infusion rates chosen by the pharmacy assistant vs. products that the pharmacy assistant administered to quantify the effect of his administration on results in each arm. Finally, please analyze the possible bias that this introduced into the trial, including differential infusion rates, and how this bias impacted on the ultimate outcome. It is important to be sure that the conclusions drawn are not compromised by the bias potentially introduced into the study.

2. Multiple doses:

   The report for IND BB-6750 indicates that five subjects were given multiple doses of NP-018. The protocol allows this per "Repeat dosing may be indicated for patients with recurrent botulism symptoms on an individual basis with consultation with the CDC botulism duty officer by calling the CDC Emergency Operations Center (770-488-7100). If a second dose of NP-018 H-BAT is determined as being clinically appropriate, the patient's treating physician will contact CDC and a second vial of NP-018 H-BAT may be released if necessary." However, the reasons and rationale for multiple dosing were not provided in the report. Please provide a table for the five subjects including 1) the clinical situation and reasons for request of the second dose, 2) the rationale for granting the second dose, 3) detailed ultimate outcome, and 4) discussion of the effectiveness of the second dose. This information could be important in developing the language in the final label.

3. Tonsillar hypertrophy:

In BT-002B which studied NP-018 vs. placebo, both tonsillar hypertrophy and lymphadenopathy occurred in the NP-018 group at a rate higher than occurred in the earlier sequential BT-002A treatment arm (Aventis Pasteur antitoxin types A and B). In part because the rate of lymphadenopathy in BT-002B was similar between treatment (NP-018) and placebo, both the lymphadenopathy and tonsillar hypertrophy were deemed due to intercurrent viral illness. However, though the data support the assertion that the lymphadenopathy could be secondary to viral infection, the four-fold differential rates in tonsillar hypertrophy between the NP-018 and placebo arms are not directly explained by that data. Please parse out tonsillar hypertrophy separately and explain the increased incidence of this adverse incident over placebo and over the licensed product in BT-002A. This explanation is requested because it is possible that tonsillar hypertrophy is an adverse event specific to NP-018.

4. Time course of adverse events in subject 29028
    a. Hematuria was reported in subject 29028 after administration of NP-018 and both before and after transfer to the rehabilitation hospital. However, it is not clear if those events were the same longitudinal event or different adverse events. Please provide complete information about the hematuria in this subject including time course, quality, severity, and diagnostic considerations, and conclusions including discussion of whether the recurring hematuria events were one or several event(s). Please also provide a table of BUN, creatinine, and (if available) creatinine clearance values at all known points. This information is important to help determine the contribution of the serum sickness to the ultimate demise of the subject.
    b. Neuropathic pain was described in subject 29028 after transfer to the rehabilitation hospital. Please describe whether this was present before transfer. Please also describe the known or proposed etiology of this neuropathic pain.

5. Causes of other deaths in IND 6750
    a. On page 222 of the IND 6750 study report for subject BOT IDNUM 10049, it is stated that the "cause of death is unknown" and concluded that the death "was unrelated to HBAT administration." However, it is not clear how that conclusion was reached, since initial tolerance of NP-018 and death 94 days after administration by itself is not sufficient evidence to reach that firm conclusion. Please provide further available information from the course of the subject or other information to justify the conclusion that NP-018 did not contribute to the demise of the subject.
    b. On page 222 of the IND 6750 study report for subject BOT IDNUM 10066, it is stated that the subject died of "Miller Fisher variant of Guillain-Barré syndrome" seven days after administration of NP-018. Though she might have died with that disease, it is not clear exactly how or why she died. Please provide further available information from the course of the subject or other information to explain why she died and

justify a conclusion that NP-018 did not contribute to the demise of the subject.

6. Distribution of moderate and severe adverse events in BT-002B

Table 14 Adverse Event Frequencies by Treatment, Severity and Relationship to eBAT NP-018 in Clinical Trial BT-002 Stage B

		eBAT NP-018 1 Vial	Placebo
		Events (%)	Events (%)
Frequency		50	31
Severity	Mild	35 (70%)	31 (100%)
	Moderate	8 (16%)	0 (0%)
	Severe	7 (14%)	0 (0%)
Relationship	Related	4 (8%)	0 (0%)
	Unrelated	46 (92%)	31 (100%)
Not Serious		50 (100%)	31 (100%)

You conclude in the summary of BT-002B that "no notable differences in the number of AEs […] were reported between the treatment and placebo arms." However, you report a difference in the distribution of moderate and severe adverse events between the treatment and placebo arms (15 vs. 0 in aggregate) in BT-002B. Even though all but four of the events were classified as unrelated and the events are scattered as to their classification, this difference between 15 and zero still represents a highly statistically significant difference ($p < 0.001$ per our statistician) between the two arms. Please offer an explanation as to the difference in distribution of moderate and severe adverse events between treatment and placebo arms in BT-002B.

2. CLINICAL AND REGULATORY BACKGROUND

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2.1 Disease or Health-Related Condition(s) Studied

Botulism is a rare and potentially fatal paralytic illness that occurs when neuromuscular transmission is interrupted by botulinum neurotoxins (BoNT) produced by Clostridium botulinum and related Clostridia species. Serotoxins A through G have different potencies and different time courses. Though some consider the toxin to have irreversible effects, others have presented evidence of reversibility of effect. Patient improvement is theorized to result from regrowth of nerve or resprouting of new axonal branches to heal the synaptic blockade.

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

Treatments for botulism unrelated to antitoxins are typically supportive. Mechanical ventilation and improved nutrition are key. Modern ICU techniques are important to

minimize complications such as pneumonia, aspiration, ileus, need for tracheostomy, other infections, and urinary retention.

2.3 Safety and Efficacy of Pharmacologically Related Products

[5.3.5.2.1, p. 219] There have been other immunoglobulin-based antitoxins for botulism.

1. Licensed botulinum antitoxin ABE
2. Licensed botulinum antitoxin AB

   These were licensed and available in the U.S. for over 40 years. The license for BAT AB expired on March 13, 2010.
3. BabyBIG is used for infant botulism A and B. This is a human product. In general, human products are preferred in this setting in order to avoid lifelong sensitization against equine substances. The drug is approved only for those < 1 year of age.

Data from prior botulinum antitoxin products showed anaphylaxis rates of 1.9% (range 2.9-5.0%) and serum sickness rates of 3.7% (range 1.8-9.5%) [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 223]. Serum sickness is felt to be dose related, with the rate of anaphylaxis less so.

CDC data from 1967 to 1977 reported 9.0% of nonfatal hypersensitivity reactions. Acute and chronic reactions constituted 5.3% and 3.7% of the reactions, respectively. [Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 6]

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

"Previously available antitoxin products, licensed botulinum antitoxin ABE or AB and investigational BAT E, were available for more than 40 years in the United States. With the expiration of BAT AB on March 13, 2010, heptavalent equine-based botulinum antitoxin (H-BAT), manufactured by Cangene Corporation, became the only botulinum antitoxin available in the United States for non-infant botulism (BabyBIG® is used to treat infant botulism; however, H-BAT would be used for infants with botulinum toxin types not covered by BabyBIG®). H-BAT is only available under CDC-sponsored, expanded access Investigational New Drug application (IND 6750)1 through consultation with CDC and state botulism duty officers to determine the need for H-BAT in a suspected botulism patient. The botulism duty officers then process the release of H-BAT, which is pre-positioned nationwide, including 8 quarantine stations and Alaska, within 24 hours of consultation to the hospitals." Further discussion of the CDC IND 6750 experience is expanded upon in §6.4 of this document.

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

Presubmission activities are documented in minutes from previous meetings. These occurred on 2012-06-13, 2011-05-27, 2010-07-13, 2009-12-10, and 2004-08-26. IND investigations were done under 6750 and 12052. FDA granted orphan drug designation

for heptavalent botulism antitoxin on 2011-06-29, as shown in section 1.2 containing a copy of the FDA letter.

Priority review was granted to the Applicant as part of the current approval process.

In November 2012, an information request was sent to the Applicant. On 2012-12-04 CBER received a response to FDA's information request of 2012-11-20. The following points were made. Concomitant medication information in IND 6750 was not captured. The Applicant is open to discussing the premedication issue. The potential for anticholinergic effects had not been previously considered. Tolerability is not linked to the dose volume. Also, the Applicant considers the death of subject 29028 to be unrelated to NP-018. Another information request was generated asking about the course of hematuria and renal function in general. It has not yet been sent.

2.6 Other Relevant Background Information

The exposures to toxin and blood levels achieved vary depend on the particular case, route of exposure, and dose. Routes of exposure include foodborne, inhalational, wound, or intestinal.

For foodborne exposure, the highest recorded serum level in the U.S. is 32 $MIPLD_{50}$/mL. Assuming equilibration between intravascular and extravascular-extracellular compartments, the toxin would be distributed through approximately 15 liters of fluid in the adult. Thus, the 15,000 mL of fluid would contain 480,000 $MIPLD_{50}$ of toxin. Similarly, the highest level ever recorded worldwide was 160 $MIPLD_{50}$, which would correspond to 2,400,000 $MIPLD_{50}$ of toxin in the body. In the instance of the lowest potency antitoxin and the highest ever recorded foodborne dose, this would be a ratio of at least 4:1 antitoxin:toxin molecules in the body using target levels and 2:1 using label levels. The exposure from wound botulism and intestinal colonization is not known. [From *Human Dose Justification,* section 4]

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Data quality and completeness vary between the three controlled and one uncontrolled clinical trials. The methods range from rigorously controlled double-blind, placebo-controlled studies to a "non-research" expanded access program.

BB-IND 6750
The submission describes the nature of the non-research, expanded access IND process. Each case is considered a public health emergency.

"Therefore, information collected under IND 6750 is limited in its scope under a non-research treatment IND protocol (CDC IRB Protocol #4509). Enrolling potential patients under a research program, as defined under 45 CFR 46.102(d), is not feasible because

suspected cases occur unpredictably and antitoxin treatment is most effective if given as soon as possible." [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 219]

Previous experience with investigational BAT E reveals that data collection is difficult. Report #3 details the recurring effort required and implemented by CDC in order to collect the data, beginning with communications to the physician through writing the hospital CEO (n=20) to finally requesting the medical records and extracting the data themselves (n=15) [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 219]. Table 1 shows that only 37% have all documents returned [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 224]. 95% have at least two forms completed. Attempts to contact treating physicians and complete the forms range from 0-24 (mean = 6 attempts).

Furthermore, from page 223, it is stated that there "are limitations in the clinical information received as report forms may be incomplete despite efforts of active follow-up with the hospitals and treating physicians, sending of official letters, and request and review of medical records. CDC's Botulism Treatment Program treats patients in hospital settings, therefore, some of the objective parameters asked for in the report forms are not routinely provided to CDC by treating physicians (e.g., scale used for assessing deep tendon reflexes and musculoskeletal exam). The main objective of assessing adverse events and safety of H-BAT and patient outcomes is able to be accomplished under CDC's program."

3.2 Compliance With Good Clinical Practices And Submission Integrity

No irregularities with good clinical practice and submission integrity were identified separate from the above mentioned matters regarding data collection.

3.3 Financial Disclosures

No financial irregularities were identified.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Awaiting mid-cycle memo

4.2 Assay Validation

Awaiting mid-cycle memo

4.3 Nonclinical Pharmacology/Toxicology

Awaiting mid-cycle memo

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The proposed mechanism of action is specific binding and neutralization of the toxin by the antitoxin antibody fragments. All binding is done in an extracellular location. Once the toxin enters the target cell, the effect of that toxin may be irreversible.

4.4.2 Human Pharmacodynamics (PD)

Awaiting mid-cycle memo

4.4.3 Human Pharmacokinetics (PK)

Awaiting mid-cycle memo

4.5 Statistical

Awaiting mid-cycle memo

4.6 Pharmacovigilance

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

5.1 Review Strategy

To date, the review has consisted of review of the clinical documents submitted with BLA 125462/0.

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

Documents reviewed to date include the clinical summary documents in module 2, most of the clinical reports in module 5, the draft label in module 1, orphan designation letter in module 1, and meeting minutes in module 1. Some of the references were also reviewed.

Documents from IND 6750 and IND 12052 have not yet been reviewed beyond reference to them in BLA 125462.

5.3 Table of Studies/Clinical Trials

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); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/Safety	BT-001	Module 5 Section 5.3.3.1	Primary: evaluate the safety of eBAT NP-018 based upon clinical observations, AEs, and laboratory assessments Secondary: assess the PK of the seven botulism antitoxin serotypes in eBAT NP-018 following IV administration	Phase 1, single center, randomized, double blinded, parallel armed study	Test Product: eBAT NP-018 Dose Regimen: 1 or 2 vials of eBAT NP-018 Route of Administration: Intravenous infusion	N = 40 20 = 1 vial 20 = 2 vials	Healthy	Single administration	Complete
PD/Safety	BT-002 Stage A	Module 5 Section 5.3.4.1	Primary: evaluate the effect of BAT AB (Aventis) in preventing paralysis of the EDB muscle following Botox® or Myobloc® administration Secondary: evaluate the safety of BAT AB (Aventis) in healthy subjects	Phase 1a/2b, single center, randomized, double blinded, parallel armed study	Test Product: BAT AB (Aventis) Placebo: saline Dose Regimen: 1 vial BAT AB Route of Administration: Intravenous infusion	N = 10 5 = Aventis 5 = placebo	Healthy	Single administration	Complete
PD/Safety	BT-002 Stage B	Module 5 Section 5.3.4.1	Primary: evaluate the effect of eBAT NP-018 (Cangene) in preventing paralysis of the EDB muscle following Botox® or Myobloc® administration Secondary:evaluate the safety of eBAT NP-018 (Cangene) in healthy subjects	Phase 1a/2b, single center, randomized, double blinded, parallel armed study	Test Product: eBAT NP-018 (Cangene) Placebo: saline Dose Regimen: 1 vial of eBAT NP-018 Route of Administration: Intravenous infusion	N = 26 16 = 1 vial 10 = placebo	Healthy	Single administration	Complete

AE = adverse events; BAT = Botulism Antitoxin; eBAT NP-018 = Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine); EDB = extensor digitorum brevis; FDA = Food and Drug Administration; IV = intravenous; N/A = not applicable; PD = pharmacodynamic; PK = pharmacokinetic.

[Source: Original BLA 125462/0; tabular-listing.pdf, pp. 9-10]

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

A Blood Products Advisory Committee meeting is tentatively scheduled for February 2013.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed (if applicable)

A collection of 320 articles in pdf format were submitted with the application. In addition, several literature searches produced over 100 articles that appeared clinically

relevant. These Pubmed abstracts were imported into a bibliographic reference manager for continuing consultation.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The studies to be reviewed here are:

1. BT-001
2. BT-002 stage A
3. BT-002 stage B
4. CDC IND 6750

6.1 Trial #1

Pharmacokinetics of a heptavalent equine derived botulinum antitoxin (NP-018)

6.1.1 Objectives (Primary, Secondary, etc)

"The primary objective was to evaluate the safety of NP-018 based upon clinical observations, adverse events (AEs) and laboratory assessments. The secondary objective was to assess the pharmacokinetics (PK) of the seven botulinum antitoxin serotypes contained in NP-018 following intravenous (IV) administration." [Source: Original BLA 125462/0; BT001-study-report-body, p. 2]

6.1.2 Design Overview

"This was a Phase 1, single-centre, randomized, double-blind, parallel arm study. NP-018 was intravenously administered to healthy, male and female volunteers between the ages of 19 and 52 years. Forty subjects were randomized to receive either one or two vials of NP-018, representing a single or double dose of botulinum antitoxin." [Source: Original BLA 125462/0; BT001-study-report-body, p. 2]

6.1.3 Population

The target population for this marketing application is the group of symptomatic patients with proven or suspected botulism. The target population for the application will receive NP-018 after they have already been exposed to toxin and are symptomatic.

The subjects studied in this clinical trial are normal volunteers, none of whom is symptomatic or has been exposed to toxin before administration of test product. It is unproven that they are similar enough to the target population to allow generalization, which has lead to the animal rule decision.

"Screening evaluations occurred within 28 days prior to the baseline visit. The screening process was conducted in 2 visits (Day 1S and Day 2S). As a safety precaution, a horse dander (E3) IgE test on Day 1S and a NP-018 skin sensitivity on Day 2S were performed to exclude subjects who tested positive and could have developed serious reactions, such as anaphylaxis and serum sickness, to the equine-derived NP-018 product." [Source: Original BLA 125462/0; BT001-study-report-body, p. 20]

- Inclusion criteria
  - Male or female
  - Age 18-55 years
  - Body-mass index 20-30, minimum absolute weight of 111 lb (50 kg)
  - Normal, healthy by medical history, physical exam, electrocardiogram, laboratory tests of renal, liver, and hematological functions
  - Adequate contraception for female subjects (two forms or at physician's discretion) or FSH over 40 mIU/mL for postmenopausal women
  - Signed informed consent
- Exclusion criteria
  - Allergies to horses, horse serum, horse products, albumin, latex, rubber, plastic, food (moderate-severe), environmental requiring immunosuppression
  - Plasma donation within 7 days of dosing, blood loss or donation within 56 days
  - Heavy tobacco or alcohol abuse
  - HIV infection or hepatitis
  - Any investigational product within 30 days
  - Asthma
  - Use of nicotine containing product
  - Hemoglobin < 12 grams/dL

6.1.4 Study Treatments or Agents Mandated by the Protocol

"Subjects were randomly assigned to receive either one or two vials of NP-018. Each vial had a nominal potency of serotype A = 7500 U, serotype B = 5500 U, serotype C = 5000 U, serotype D = 1000 U, serotype E = 8500 U, serotype F = 5000 U and serotype G = 1000 U. […] The lot number of the NP-018 used in this study was 2060401Z." [Source: Original BLA 125462/0; BT001-study-report-body, p. 3]

Each vial contains 11.2 mL of product. At a protein concentration of approximately 60 mg/mL, or 6 g/dL, a typical dose is 672 mg per person. For a 67 kg person this is approximately 10 mg/kg.

6.1.5 Directions for Use

"Forty (40) subjects were randomized to receive 1 or 2 vials of NP-018. NP-018 was administered intravenously. Each vial of NP-018 contained a volume of 11.2 mL. The pharmacist (or designate) diluted each vial of NP-018 to 1:10 in 0.9% Sodium Chloride, Injection, USP in intravenous saline bags. To maintain the blind of the study, equivalent volumes were administered to each subject. Each subject received 1 infusion consisting of 2 bags. Subjects randomized to receive 2 vials of NP 018 were administered 2 bags each containing approximately 112 mL of NP-018 in 0.9% saline (total of 224 mL of NP-018 in saline) while subjects receiving 1 vial of NP-018 were administered approximately 112 mL of NP 018 in 0.9% saline followed by 112 mL of 0.9% saline alone. This ensured the blind of the study, as equivalent volumes were administered and the rate of protein

administration was equivalent during the first 112 mL of fluid infused. Upon completion of dosing the intravenous line was flushed with 50 mL of 0.9% saline.

NP 018 was administered at an incremental infusion rate, starting very slowly in the initial period. NP 018 was administered at a rate of 0.5 mL/min for the first 30 minutes, then 1 mL/min for the next 30 minutes and then 2 mL/min for the remainder of the infusion (approximately 80 minutes). The total infusion time was approximately 2 hours 30 minutes." [Source: Original BLA 125462/0; BT001-study-report-body, p. 3, 26]

6.1.6 Sites and Centers

This is a single site study performed at:

Mark J Allison, MD, CCTI
MDS Pharma Services US, Inc.
4747 E Beautiful Lane
Phoenix, AZ,
USA, 85044

The investigator is Dr. Mark J Allison, MD, CCTI.

6.1.7 Surveillance/Monitoring

"This study was conducted in compliance with and monitored according to Good Clinical Practices as outlined in 21 CFR 314.50 (d) (5) ix, xi. […] The clinical site's Institutional Review Board (IRB) reviewed the protocol and the informed consent form (ICF) prior to study initiation. A table of the specific IRB approval dates for the protocol, ICFs and amendments can be found below in Table 5:1. The IRB at MDS Pharma Services (MDS PS) complies with Section 56 of Title 21 of the Code of Federal Regulations (CFR). The protocol, ICFs, amendments, and a list of the IRB composition and contact information are provided […] This study was conducted in accordance with the clinical research guidelines established by the basic principles defined in the US 21 CFR Part 50, 54, 56 and 312 as well as US 45 CFR Part 46. This study was also conducted in compliance with the ethical principles of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practices." [Source: Original BLA 125462/0; BT001-study-report-body, p. 1, 14].

Subjects returned for follow-up visits on Days 1, 3, 7, 14, 21 and 28. The schedule of assessments is given in table 9:1. [Source: Original BLA 125462/0; BT001-study-report-body, p. 3]

"In addition, a Data Safety Monitoring Board was assembled to review the safety data from the study according to the schedule layed out in Section 9.7.1.3 of this report. The purpose of the DSMB committee was to ensure the safety of the study subjects during the study on an ongoing basis. The safety data (clinical observations, AEs and laboratory assessments) from the electronic case report form database were sent to the DSMB committee after each treatment cohort. The DSMB reviewed the safety data from each

cohort and made recommendations concerning continuation and/or stopping of the study." [Source: Original BLA 125462/0; BT001-study-report-body, p. 21]

6.1.8 Endpoints and Criteria for Study Success

"Safety of NP-018 was evaluated based on clinical observations, AEs, laboratory assessments and human anti-equine antibody testing." Pharmacokinetics was evaluated as follows. "Blood samples (50 mL) were collected after NP-018 administration for botulinum toxin neutralizing antibody analysis at the following time points: 0.5, 4 and 8 h; Days 1, 3, 7, 14, 21, 28, and at early withdrawal. The following pharmacokinetic parameters were calculated from the serum drug concentration-time curves for either 1 or 2 vials of NP-018 for all seven botulinum antitoxin serotypes: area under the serum concentration versus time curve (AUC_{0-t}, $AUC_{0-\infty}$, and $AUC_{0-t}/AUC_{0-\infty}$), maximum measured serum concentration (C_{max}), time of the maximum measured serum concentration (T_{max}), terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), clearance (Cl) and volume of distribution (V_d)." [Source: Original BLA 125462/0; BT001-study-report-body, p. 3]

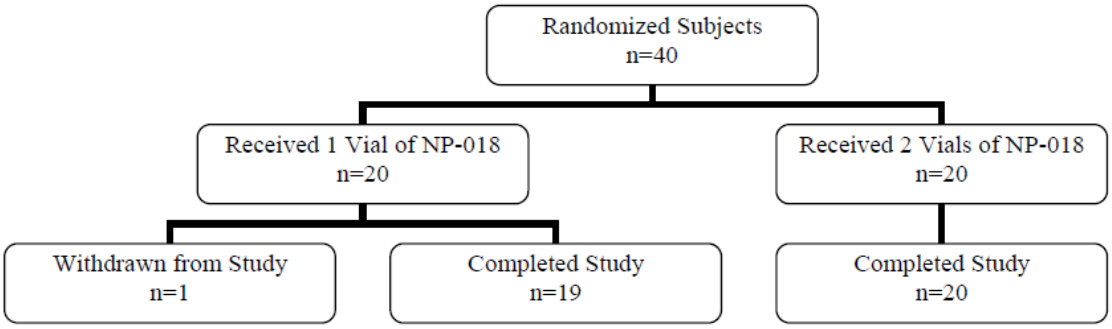
6.1.9 Statistical Considerations & Statistical Analysis Plan

"As this study was to assess the pharmacokinetics and relative safety of NP-018, no formal sample size calculation was performed. Twenty (20) subjects per treatment group were judged to be sufficient to meet the objectives of the study. […] As planned a total of 40 subjects were enrolled in this study. […] Randomization was stratified by gender to ensure an equal number of men and women in each group." [Source: Original BLA 125462/0; BT001-study-report-body, p. 3, 20, 37]

There were no adjustments for covariates or multiplicity. All summary statistics and statistical tests were performed with missing values omitted from the analysis. No imputation was done.

6.1.10 Study Population and Disposition

Figure 10:1 Flow Chart for Disposition of Subjects



[Source: Original BLA 125462/0; BT001-study-report-body.pdf, p. 39]

6.1.10.1 Populations Enrolled/Analyzed

Thirty nine subjects were included in the pharmacokinetic analysis as per the statistical analysis plan (SAP). All 40 subjects were included in the safety assessment. [Source: Original BLA 125462/0; BT001-study-report-body, p. 3]

6.1.10.1.1 Demographics

The study population included 20 men and 20 women. Each dose stratum had equal numbers of men and women (10:10). Mean age and weight were 34 years and 73 kg, respectively. Caucasians constituted 88% of the sample. Out of 40 subjects enrolled, 39 subjects completed the study. One subject withdrew because of adverse events (subject #1). [Source: Original BLA 125462/0; BT001-study-report-body, pp. 40-1]

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects were normal volunteers.

6.1.10.1.3 Subject Disposition

Forty subjects were entered into the study and randomized. Subjects were grouped into cohorts of 5 for dosing purposes. All subjects except one completed the study. The one developed a moderate allergic reaction necessitating discontinuation of the infusion. The subject was followed for the full length of the trial for safety purposes. [Source: Original BLA 125462/0; BT001-study-report-body, p. 38]

6.1.11 Efficacy Analyses

No actual treatment efficacy assessments were done in this trial. Instead, pharmacokinetic measurements were made. “For pharmacokinetics, descriptive statistics such as arithmetic means, median, standard deviation (SD), coefficients of variation (CV%), range (minimum and maximum) were calculated for the pharmacokinetic parameters listed above. Geometric means were calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. Descriptive statistics on the pharmacokinetic parameters were presented by gender.” [Source: Original BLA 125462/0; BT001-study-report-body, p. 4]

Formal analysis of pharmacokinetic data will be done by the clinical pharmacology team.

“Based on the lack of clinically important safety concerns, Cangene Corporation concludes that NP-018 was well tolerated and bioavailable for use in treating patients with botulism.” [Source: Original BLA 125462/0; BT001-study-report-body, p. 5]

6.1.11.1 Analyses of Primary Endpoint(s)

Dose-response, drug-drug, and drug-disease assessments were not made.

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoints were the pharmacokinetic parameter assessments. “The pharmacokinetic parameters varied based upon the antitoxin serotype measured. Although no formal dose proportionality assessment was performed AUC0-t, AUC0-∞ and Cmax values increased in a dose proportional fashion as NP-018 doses increased

from one to two vials. In addition, mean clearance values appeared to be similar between both treatment groups for the seven antitoxin serotypes, suggesting dose linearity of NP-018 over the dose range studied. The half-lives of the different antitoxin serotypes varied with the serotype. Antitoxin serotypes D and E had the shortest mean half-lives whereas antitoxin serotypes B and C had the longest mean half-lives. Overall the half-lives of the various antitoxin serotypes were shorter than expected for an equine derived $F(ab')^2$ hyperimmune product. Comparison of the pharmacokinetic parameters between male and female subjects for antitoxin serotypes A through G showed that there were no gender related differences following a single intravenous administration of either one or two vials of NP-018." [Source: Original BLA 125462/0; BT001-study-report-body, p. 52]

6.1.11.3 Subpopulation Analyses

No differences in pharmacokinetic parameters were found between males and females.

6.1.11.4 Dropouts and/or Discontinuations

One subject (subject -(b)(6)-) discontinued the treatment infusion due to a moderate allergic reaction. The subject was kept in the safety monitoring program to the end of the observation period.

6.1.11.5 Exploratory and Post Hoc Analyses

None.

6.1.12 Safety Analyses

6.1.12.1 Methods

"Safety parameters, including medical history, vital signs, physical examination, electrocardiogram (ECG), laboratory tests, adverse events, concomitant medications, and skin sensitivity testing were summarized and compared by treatment but were not subjected to statistical analysis. In addition, shift tables describing out of normal range shifts were provided for clinical laboratory results. Shift tables were also presented for physical examination results and coagulation parameters." [Source: Original BLA 125462/0; BT001-study-report-body, p. 4]

To reduce the risk of serum sickness and anaphylaxis, only 5 subjects were dosed at a time during the first and second cohorts to allow for observation. Because acute reactions are expected within the first 30 minutes, subjects were spaced at 35 minutes. For indolent reactions like serum sickness which typically manifests in two weeks, cohorts were spaced by 21 days.

Safety assessments and schedules were detailed in table 9:3. Definitions and criteria for safety reporting were given in table 9:4. [Source: Original BLA 125462/0; BT001-study-report-body.pdf, pp. 31-32]

6.1.12.2 Overview of Adverse Events

A total of 53 adverse events were reported in 18 (45%) subjects. These AEs were mild in 47 instances and moderate in seven. There were no severe AE. Seven AE were probably treatment-related and 21 possibly related. No differences were seen between doses of one vs. two vials of NP-018. The most frequent AEs were headaches and somnolence, which are typical and expected.

"There were no substantial safety issues and no serious or severe adverse events occurred during this study. One subject (Subject 1) was withdrawn due to adverse events resulting from a moderate allergic reaction. The most frequently reported adverse events were mild and moderate headache and mild somnolence. The remaining adverse events occurred in less than 10% of subjects. These adverse events were reported as mild or moderate in severity and most were resolved without concomitant therapy. […] Drug-related AEs included headache, dysphagia, flatulence, nausea, throat irritation, feeling cold, pain, pyrexia, swelling, pharyngolaryngeal pain, hyperhydrosis, pruritus, pruritus generalized, skin disorder and urticaria." [Source: Original BLA 125462/0; BT001-study-report-body, pp. 4-5 and summary-clin-safety.pdf, pp. 8-9] Further details for the one withdrawal are given in §6.1.12.7.

The only laboratory change noted by the Data Safety Monitoring Board was a drop in hemoglobin levels of approximately 1 g/dL from screening to the end of the study. The likely reason for this drop was the large volume of blood drawn during the course of the study. There was also a slight elevation in reticulocyte counts at Day 7 post-dosing along with a slight drop in hematocrit at Day 7 and 28 post-dosing. These minor changes were neither statistically significant nor pathological and were most likely associated with the volume of blood drawn during the study." [Source: Original BLA 125462/0; BT001-study-report-body, pp. 4-5]

Table 12:1 Adverse Event Frequency by Treatment, Seriousness, Severity and Relationship to Study Drug

		Severity		Relationship to Study Drug			
Treatment	**Frequency**	**Mild**	**Moderate**	**Probable**	**Possible**	**Unlikely**	**Not Serious**
Treatment A 1 Vial	27	22 (81%)	5 (19%)	7 (26%)	13 (48%)	7 (26%)	27 (100%)
Treatment B 2 Vials	26	25 (96%)	1 (4%)	0 (0%)	8 (31%)	18 (69%)	26 (100%)
Combined	53	47 (89%)	6 (11%)	7 (13%)	21 (36%)	25 (47%)	53 (100%)

[Source: Original BLA 125462/0; BT001-study-report-body.pdf, p. 53]

Table 12:2 Concomitant Medications Due to Adverse Events

Subject	Indication	Medication	Dose	Route	Frequency
1	Itching, posterior scalp	Epinephrine	0.3 mg	SC	Once
		Diphenhydramine	50 mg	IM	Once
	Fever	Ibuprofen	600 mg	PO	Once
	Headache	Ibuprofen	600 mg	PO	Once
	Fever	Ibuprofen	600 mg	PO	Once
9	Full stomach	Metamucil®	1 tbsp	PO	Once
28	Sinus infection	Erythromycin	500 mg	PO	Once
		Guaifensin with codeine cough syrup	2 tsp	PO	At bedtime
		Erythromycin	1000 mg	PO	Twice daily
40	Productive cough	Tylenol® Nighttime	1 tbsp	PO	At bedtime

tbsp = tablespoon; tsp = teaspoon; SC = subcutaneous; IM = intramuscular; PO = oral; NOS = Not otherwise specified

[Source: Original BLA 125462/0; BT001-study-report-body.pdf, p. 54]

Table 12:3 Adverse Events Reported by ≥ 10% of the Total Subjects

Adverse Event Preferred Term	Treatment A 1 Vial	Treatment B 2 Vials	All Subjects
Headache	3 (15%)	2 (10%)	5 (13%)
Somnolence	3 (15%)	1 (5%)	4 (10%)

[Source: Original BLA 125462/0; BT001-study-report-body.pdf, p. 54]

Table 12:4 All Adverse Events in Study

Body System **Preferred term**	**Treatment A** **1 Vial (n=20)**	**Treatment B** **2 Vials (n=20)**	**Overall** **(n=40)**
	n (% of subjects)	**n (% of subjects)**	**n (% of subjects)**
Total	9 (45%)	9 (45%)	18 (45%)
Ear and labyrinth disorders			
Ear pain	0 (0%)	1 (5%)	1 (3%)
Endocrine disorders			
Menstruation irregular	0 (0%)	1 (5%)	1 (3%)
Eye disorders			
Asthenopia	1 (5%)	0 (0%)	1 (3%)
Gastrointestinal disorders			
Abdominal distension	0 (0%)	1 (5%)	1 (3%)
Dysphagia	1 (0%)	0 (0%)	1 (3%)
Flatulence	0 (0%)	1 (5%)	1 (3%)
Glossitis	0 (0%)	1 (5%)	1 (3%)
Nausea	2 (10%)	1 (5%)	3 (8%)
Throat irritation	1 (5%)	0 (0%)	1 (3%)
General disorders and administration site conditions			
Feeling cold	0 (0%)	1 (5%)	1 (3%)
Pain	1 (5%)	0 (0%)	1 (3%)
Puncture site pain	0 (0%)	2 (10%)	2 (5%)
Pyrexia	1 (0%)	0 (0%)	1 (3%)
Swelling	0 (0%)	1 (5%)	1 (3%)
Infections and infestations			
Sinusitis	1 (5%)	0 (0%)	1 (3%)
Injury, poisoning and procedural complications			
Vessel puncture site bruise	0 (0%)	1 (5%)	1 (3%)
Musculoskeletal and connective tissue disorders			
Arthralgia	0 (0%)	1 (5%)	1 (3%)
Joint sprain	0 (0%)	1 (5%)	1 (3%)
Musculoskeletal stiffness	0 (0%)	1 (5%)	1 (3%)

Body System **Preferred term**	**Treatment A** **1 Vial (n=20)**	**Treatment B** **2 Vials (n=20)**	**Overall** **(n=40)**
	n (% of subjects)	**n (% of subjects)**	**n (% of subjects)**
Nervous system disorders			
Headache	3 (15%)	2 (10%)	5 (13%)
Hypoaesthesia	1 (5%)	0 (0%)	1 (3%)
Psychiatic disorders			
Somnolence	3 (15%)	1 (5%)	4 (10%)
Reproductive system and breast disorders			
Menorrhagia	0 (0%)	1 (5%)	1 (3%)
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain	1 (5%)	2 (10%)	3 (8%)
Productive cough	1 (5%)	0 (0%)	1 (3%)
Skin and subcutaneous tissue disorders			
Erythema	0 (0%)	1 (5%)	1 (3%)
Hyperhidrosis	1 (5%)	0 (0%)	1 (3%)
Pruritus	1 (5%)	2 (10%)	3 (8%)
Pruritus generalized	1 (5%)	0 (0%)	1 (3%)
Rash papular	0 (0%)	2 (10%)	2 (5%)
Skin disorder	1 (5%)	0 (0%)	1 (3%)
Urticaria	2 (10%)	0 (0%)	2 (5%)

[Source: Original BLA 125462/0; BT001-study-report-body.pdf, pp. 55-56]

Table 13 Adverse Event Frequencies by Treatment, Severity and Relationship to eBAT NP-018 in Clinical Trial BT-001

		eBAT NP-018 **1 Vial**	**eBAT NP-018** **2 Vials**	**eBAT NP-018** **Combined**
		Events (%)	**Events (%)**	**Events (%)**
Frequency		27	26	53
Severity	Mild	22 (81%)	25 (96%)	47 (89%)
	Moderate	5 (19%)	1 (4%)	6 (11%)
	Severe	0 (0%)	0 (0%)	0 (%)
Relationship	Probable	7 (26%)	0 (0%)	7 (13%)
	Possible	13 (48%)	8 (31%)	21 (40%)
	Unlikely	7 (26%)	18 (69%)	25 (47%)
Not Serious		27 (100%)	26 (100%)	53 (100%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 18]

Seven adverse events were assessed as probably treatment related. No significant increase in adverse events occurred with two vials over one vial, thus no dose effect for the adverse events was seen.

The most common adverse events were headaches and somnolence as given in the following table.

Table 15 Adverse Events Reported by ≥ 10% of the Total Subjects in Clinical Trial BT-001

Adverse Event Preferred Term	eBAT NP-018 1 Vial	eBAT NP-018 2 Vials	eBAT NP-018 Combined
	n (% of subjects)	n (% of subjects)	n (% of subjects)
Headache	3 (15%)	2 (10%)	5 (13%)
Somnolence	3 (15%)	1 (5%)	4 (10%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 19]

The headaches were considered likely related. The somnolence events were considered likely unrelated.

6.1.12.3 Deaths

There were no deaths during this trial or any part of the overall protocol.

6.1.12.4 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events during this part of the trial.

6.1.12.5 Adverse Events of Special Interest (AESI)

Development of immunogenicity against NP-018 is an adverse event of special interest. Subjects were tested prior to dosing and on day 28. The results are given in tables 12:5 and 12:6. Seven subjects converted from negative to positive out of the 26 initially negative subjects (27%). Conversion was not dose dependent. Fourteen others were positive at baseline. There was no clear relationship between development of adverse reactions and serological status. [Source: Original BLA 125462/0; BT001-study-report-body, pp. 60-1]

Table 12:6 Anti-NP-018 Antibody Test Results Shift by Treatment

	Baseline Negative		Baseline Reactive	
	Day 28 Negative	Day 28 Reactive	Day 28 Negative	Day 28 Reactive
Treatment A 1 Vial (n=20)	9 (45%)	4 (20%)	0 (0%)	7 (35%)
Treatment B 2 Vials (n=20)	10 (50%)	3 (15%)	0 (0%)	7 (35%)
Total (n=40)	19 (47.5%)	7 (17.5%)	0 (0%)	14 (35%)

[Source: Original BLA 125462/0; BT001-study-report-body.pdf, p. 60]

The breakdown of immunoglobulin subtypes developed in BT-001 is given in the following table.

Table 19 Immunogenicity Testing Results for Clinical Trial BT-001

Time Point	Screening Assay		Confirmatory Assay				
	Negative	Reactive	Confirmed	IgG	IgM	IgE	IgA
Baseline	26 (65%)	14 (35%)	14 (100%)	14 (35%)	0	0	1 (3%)
Day 28	19 (47%)	21 (53%)	21 (100%)	21 (53%)	0	0	4 (10%)

[Source: Original BLA 125462/0; summary-clin-pharm.pdf, p. 37]

All antibodies formed were IgG or IgA. No IgE antibodies were found. There was no dose-dependence.

There were no other adverse events of special interest (AESI) recorded during this part of the trial. AESI for this class of product would typically include serum sickness, hemolysis, or thrombosis.

6.1.12.6 Clinical Test Results

The only reported laboratory abnormalities in BT-001 were a drop in hemoglobin of ≤ 1 g/dL, decrease in hematocrit, and slight rise in reticulocyte count at day 7, likely caused by the number of blood samples. No significant drops in individual subjects were reported.

Table 23 Clinical Trial BT-001 Hemoglobin Summary by Time Point of Collection and Treatment

Treatment Group	Statistic	Baseline	Day 3	Day 7	Day 14	Day 21	Day 28
One Vial of eBAT NP-018	Mean	14.41	14.15	13.63	13.98	13.56	13.66
	SD	1.08	1.42	1.32	1.43	1.39	1.49
	Minimum	12.70	12.10	12.10	11.60	11.70	11.70
	Median	14.35	14.20	13.25	13.85	13.40	13.50
	Maximum	16.60	16.30	15.90	16.30	15.90	15.90
	N	20	20	20	20	19	20
Two Vials of eBAT NP-018	Mean	14.33	13.73	13.37	13.57	13.49	13.41
	SD	1.34	1.53	1.58	1.60	1.77	1.68
	Minimum	12.30	11.30	10.90	11.40	10.70	10.40
	Median	14.75	14.15	13.80	14.05	13.65	13.95
	Maximum	16.60	16.10	16.20	15.90	16.50	16.20
	N	20	20	20	20	20	20

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 36]

Table 24 Clinical Trial BT-001 Reticulocyte Count Summary by Time Point of Collection and Treatment

Treatment Group	Statistic	Baseline	Day 7	Day 28
One Vial of eBAT NP-018	Mean	1.34	1.70	1.45
	SD	0.50	0.59	0.41
	Minimum	0.60	0.50	0.80
	Median	1.20	1.70	1.45
	Maximum	2.40	2.60	2.30
	N	20	20	20
One Vial of eBAT NP-018	Mean	1.56	1.92	1.52
	SD	0.51	0.71	0.59
	Minimum	0.70	0.90	0.80
	Median	1.45	1.85	1.35
	Maximum	2.80	4.30	2.80
	N	20	20	20

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 37]

Table 25 Clinical Trial BT-001 Hematocrit Summary by Time Point of Collection and Treatment

Treatment Group	Statistic	Baseline	Day 7	Day 28
One Vial of eBAT NP-018	Mean	42.29	39.81	39.95
	SD	3.27	3.72	4.46
	Minimum	37.10	35.10	33.90
	Median	42.70	39.25	39.45
	Maximum	48.00	46.40	46.70
	N	20	20	20
One Vial of eBAT NP-018	Mean	42.11	39.14	39.23
	SD	3.79	4.56	4.84
	Minimum	35.50	31.60	30.60
	Median	43.25	39.70	40.55
	Maximum	48.80	47.20	47.70
	N	20	20	20

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 38]

Thus, no significant areas of concern were identified in the laboratory data.

No substantial abnormalities in vital signs or physical findings were reported.

6.1.12.7 Dropouts and/or Discontinuations

One subject discontinued because of a significant moderate allergic reaction. Urticaria and skin nodularity and swelling occurred 52 minutes into an infusion. Other symptoms included headache, body aches, hot feeling, pyrexia, and pharyngolaryngeal pain. Though he was treated with epinephrine, the reaction was still considered moderate. Some practitioners will treat with epinephrine before a reaction progresses too far. The clinical course in this subject had they been managed without epinephrine and with other measures cannot be known. Skin testing was negative at screening and immunogenicity

testing was negative before and after dosing. [Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 31]

6.2 Trial #2

Botulism Antitoxin effects on paralysis induced by Type A and Type B Botulinum Neurotoxins in the Extensor Digitorum Brevis Muscle

6.2.1 Objectives (Primary, Secondary, etc)

- Primary objectives:
  - To evaluate the efficacy of the licensed botulism antitoxin bivalent (equine) types A and B (Aventis Pasteur) in preventing paralysis of the extensor digitorum brevis (EDB) muscle in the EDB model of paralysis in healthy subjects versus placebo following BOTOX® or MYOBLOC® administration
  - To validate the extensor digitorum brevis muscle model for this purpose in preparation for use in stage B of this development program
- Secondary objective: The secondary objective of this study was to evaluate the safety of Botulism Antitoxin types in healthy subjects.
- Sample size calculations for stage B will be based on Stage A analysis

[Source: adapted from - Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 2-3]

6.2.2 Design Overview

BT-002-A is a phase 1b/2a, single center, randomized, double blind, dual arm, parallel, clinical trial. The design is as an exploratory pharmacodynamic study in a preventive, pre-exposure model. Subject participation length of 28 days was chosen because most adverse reactions to botulinum toxin injected into the EDB muscle occur within a week. Adverse reactions are not related typically to the length of EDB paralysis, which can vary widely.

6.2.3 Population

The target population for this marketing application is the group of symptomatic subjects with proven or suspected botulism. The target population for the application will be getting NP-018 after they have already been exposed to toxin and are symptomatic.

- Inclusion criteria
  - Male or female
  - Age 18-55 years
  - Body-mass index 19-30
  - Normal, healthy by medical history, physical exam, electrocardiogram, nerve conduction studies, laboratory tests of renal, liver, and hematological functions

  - Adequate contraception for female subjects (two forms or at physician's discretion) or FSH over 40 mIU/mL for postmenopausal women
  - Signed informed consent
- Exclusion criteria
  - Previously injected with BOTOX®, BOTOX® COSMETIC, or MYOBLOC®
  - Medical history that might interfere with nerve conduction studies
  - Positive skin test for botulinum antitoxin
  - Conditions associated with other neuromuscular diseases including multiple sclerosis, motor neuron disease, or radiculopathy
  - Abnormal nerve conduction studies at screening
  - Previous botulinum injection
  - Known botulinum infection
  - Allergies to horses, horse serum, horse products, albumin, latex, rubber, plastic, food (moderate-severe), environmental requiring immunosuppression
  - Asthma
  - Current infection or tattoo around the foot area
  - Suspected or known diabetes, coagulopathy, vasculities
  - Heavy tobacco or alcohol abuse
  - HIV infection or hepatitis
  - Any investigational product within 30 days

[Source: adapted from - Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 22-23]

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized 1:1 to active:placebo. The active agent (test article, subject drug) was Botulism antitoxin bivalent (equine) types A and B (Aventis Pasteur) given as a single intravenous infusion one day prior to administration of the challenge toxins. Placebo was 0.9% saline solution similarly given as a single infusion. The challenge toxin agents were FDA approved botulinum toxins: Botulinum toxin type A (Botox, Allergan, Inc.) or Botulinum toxin type B (Myobloc, Elan Pharmaceuticals, Inc.). See the section below for specific directions for use. The toxins were administered one day after administration of test article antitoxin.

A single dose of Botulism antitoxin bivalent (equine) types A and B (Aventis Pasteur) has the following levels: 7500 U anti-A, 5500 U anti-B. Lot number C1810AA was used in the study." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 3]

6.2.5 Directions for Use

The IM injections of botulinum toxins A and B were made into the extensor digitorum brevis muscles of left and right feet, respectively. Based on prior studies of dose-response to botulinum toxins A and B in human foot muscles, doses of 5 U of toxin A and 250 U of toxin B were chosen. Due to investigator miscalculation, 500 U of toxin B were

administered in BT-001 stage A. Dilutions for administration were 1 vial of study product diluted 1:10 in saline and given by slow IV infusion over approximately 82 minutes. [Sources: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, pp. 3-4]

On Day 0 of the study, subjects were IV infused with either Botulism Antitoxin Bivalent (Equine) Types A and B or placebo at an infusion rate of 0.5 mL/min for the first 30 minutes. If no infusion safety concerns were evident, the infusion rate was increased to 1 mL/min for the next 30 min. If the IV infusions continued to be well tolerated after 60 min., the infusion rate was increased to 2.0 mL/min for the remainder of the infusion. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 24]

6.2.6 Sites and Centers

This is a single site study performed at:

R. Richard Sloop, MD
307S 12th Ave. #16
Yakima, WA, USA, 98902

The investigator is Dr. Richard Sloop, MD. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 2]

6.2.7 Surveillance/Monitoring

Subjects were followed for 28 days after the administration of the test articles.

"--------(b)(4)-------- reviewed the protocol, informed consent form (ICF), and supporting study documents prior to the conduct of the clinical trial. The study was initiated only after written approval from -(b)(4)-- was obtained. Further information including IRB address and chair are included". "This study was conducted in accordance with the clinical research guidelines established by the basic principles defined in the US 21 CFR Part 50, 54, 56 and 312, US 45 CFR Part 46, and the principles enunciated in the latest version of The Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH E6)." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 13]

6.2.8 Endpoints and Criteria for Study Success

The primary instrument in this study was determination of the neutralization of injected botulinum toxin as assessed by percent residual muscle function. The muscle function is based on the percent preservation of the extensor digitorum brevis compound muscle action potential (CMAP) M-wave amplitude or area. Amplitude was the primary endpoint, area was the secondary. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 30] Bilateral peroneal motor nerve conduction studies were performed to elicit response. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 3]

Post-treatment percentage of residual muscle function was compared to baseline nerve conduction studies. See statistical measures in §6.2.9 below.

Safety was assessed with review of clinical laboratory results, reported adverse events, vital signs, physical examinations, and electrocardiograms. Adverse events were coded using the MedDRA coding dictionary.

6.2.9 Statistical Considerations & Statistical Analysis Plan

For efficacy, "Summary statistics, including the mean, median, standard deviation, minimum, maximum and coefficient of variation [are] calculated for the percent muscle function using both the M wave amplitude and area." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 5] All summary statistics are presented by treatment arm, botulism toxin type and study visit. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 30-31]

"Treatment effect over time was evaluated using an exploratory repeated-measures analysis of variance (ANOVA) model that fitted to the percent muscle function (CMAP M wave amplitude and area) following exposure to BOTOX® (Botulism toxin Type A) and MYOBLOC® (Botulism toxin Type B) separately. Whereas the treatment and time effects were considered fixed effects, subject effects were considered as a random effects. All the fixed and interaction effects in the ANOVA model were tested separately at an alpha level of 0.05. This analysis was performed separately for each of the percent muscle function endpoints (amplitude and area). An overall graph of the percent muscle function over time was created for each percent muscle function endpoint (amplitude and area) with a separate curve for each treatment group and each toxin type." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 32]

"A longitudinal analysis of variance (ANOVA) model was fitted to the percent muscle function of the EDB muscle. Treatment arm and visit were included in the model. The effect of treatment group, visit and visit by treatment interaction were tested at an alpha level of 0.05. This analysis was performed for both of the percent muscle function endpoints (amplitude and area)." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 5]

For safety, the incidence, intensity, and relationship of events to treatment were evaluated through the use of frequency tables. Summary statistics for laboratory tests and vital signs over time are provided. Count and percentages were provided for categorical variables. For abnormal laboratory values, shift tables and incidence are provided.

"A sample size of 36 subjects (n=10 in Stage A and n=16 in Stage B) was originally selected for this pilot study to provide adequate database for evaluation of the human model of neutralization of Botulinum toxin by antitoxin. The original sample size for this study was not based on formal size and power calculations. Data collected on an initial ten subjects enrolled in Stage A of this study will be used as a proof of concept for Stage B." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 32]

No multiplicity adjustments were made or considered necessary by the investigators. Missing data were considered missing; no imputation methods were used.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 10 subjects were enrolled in this protocol. All ten subjects completed the trial. All subjects were included in the safety and efficacy profile. Since the intent-to-treat population was all the randomized subjects, there is no bias here.

6.2.10.1.1 Demographics

Age range was 18-44 years, mean 33 years, median 35 years. Eight were Caucasian. One was Hispanic. Three female and two males were enrolled in both arms. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 35-36]

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Normal subjects were enrolled for this trial.

6.2.10.1.3 Subject Disposition

Thirteen subjects were screened. Two were excluded because of peroneal nerve conduction abnormalities. One person was saved as a replacement subject. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 33]

All ten subjects completed the trial. All subjects were included in the safety and efficacy profile.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Calculation of the change in muscle function was done with the formula:

$$\%\, MuscleFunction_i = \frac{CMAP_i}{mean(baselineCMAP)} \text{ x } 100$$

"where the subscript i refers to the study visit and CMAP is the arithmetic mean of maximum CMAP M wave amplitudes of three consequent readings for that visit. The mean baseline CMAP is the average of amplitudes from the three baseline assessments (screening, Day 0 prior to Botulism antitoxin administration and Day 1 prior to BOTOX®) (Botulism toxin Type A) or MYOBLOC® (Botulism toxin Type B) administration. […] For the calculation of primary endpoint, CMAPi from one foot will be divided by the mean of baseline CMAP of the same foot." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 30]

"Botulism Antitoxin Bivalent (Equine) Types A and B (Aventis Pasteur) (treatment arm)

protected subjects from a decrease in muscle function following exposure to Botulism toxins A and B (BOTOX® and MYOBLOC®). Subjects receiving placebo demonstrated a loss of greater than 50% muscle function within 3 days of exposure to both Botulism toxins. In the treatment arm, muscle function was stable over time, indicating that the antitoxin is effective in preventing muscle paralysis for up to 28 days following exposure to both Botulism toxins. By longitudinal analysis of variance model, there is a significant decrease of percent muscle function of EDB muscle in the placebo arm as compared to the treatment arm over time (pvalue <0.05) for treatment effect." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, pp. 6]

6.2.11.2 Analyses of Secondary Endpoints

"Stage A results validated the EDB model of muscle paralysis as proof of concept for stage B of this study. […] Based on these results, the EDB model can be used to evaluate the ability of the investigational Botulism Antitoxin Heptavalent (Equine) Types A-G (Cangene Corporation) to neutralise Botulism toxins in Stage B." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, pp. 6, 50]

6.2.11.3 Subpopulation Analyses

Not performed.

6.2.11.4 Dropouts and/or Discontinuations

None.

6.2.11.5 Exploratory and Post Hoc Analyses

None.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety assessments were made per the study assessment schedule given in tables 9.2 and 9.3. Safety was assessed with review of clinical laboratory results, reported adverse events, vital signs, physical examinations, and electrocardiograms. Adverse events were coded using the MedDRA coding dictionary. Definitions of seriousness, severity, and relatedness were given in table 9.4.

6.2.12.2 Overview of Adverse Events

No notable differences in the number of AEs or laboratory abnormalities were reported between the treatment and placebo arms. "The vital signs were consistent within each group and there were no treatment related effects. Physical exam findings were typically unchanged over the course of the study. […] All mean serum chemistry, hematology and urinalysis values were within normal ranges, and mean changes from baseline were unremarkable. […] Some laboratory findings were found to be out-of-range but were judged as not being clinically significant by the investigator. […] All adverse events were resolved by the end of the trial. […] Therefore, it can be concluded that Botulism Antitoxin Bivalent (Equine) Types A and B (Aventis Pasteur) is safe for use in the

prevention of Botulism intoxication in healthy subjects." Glucose levels might have been influenced by meals. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, pp. 6, 28, 49-50]

A total of 11 AEs were reported by seven subjects. For active treatment, three subjects reported six AE. For placebo, four subjects reported four AE. All adverse events were mild or moderate. Only one adverse event was determined to be related to active test product. The most frequent AEs were insomnia and extremity pain. Three of 10 (30%) reported insomnia and one reported pain in two extremities. Two other subjects reported burning or spasm with their feet. The symptoms were presumably from the test procedures. It is not clear why only some reported the adverse events since all underwent the same procedures. Insomnia was more common with placebo. The pain was more common in active treated subjects, though the numbers are very small, typically just one event in the group. [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, p. 46]

6.2.12.3 Deaths

There were no deaths in this trial.

6.2.12.4 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse reactions in this trial.

6.2.12.5 Adverse Events of Special Interest (AESI)

Blood samples were drawn for anti-Botulism Antitoxin reactivity from all ten study subjects on Day 0 (3 hours prior to Botulism Antitoxin administration), as well as on Day 28 (End of Study visit). Anti-Botulism Antitoxin reactivity was measured using an immunogenicity assay developed by Cangene Corporation." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, pp. 17, 49]

The following table shows the results of the testing.

Table 20 Immunogenicity Testing Results for Clinical Trial BT-002 Stage A

Time Point	Screening Assay		Confirmatory Assay				
	Negative	Reactive	Confirmed	IgG	IgM	IgE	IgA
Baseline	9 (90%)	1 (10%)	1 (100%)	1 (10%)	0	0	0
Day 28	6 (60%)	4 (40%)	4 (100%)	4 (40%)	0	0	0

[Source: Original BLA 125462/0; summary-clin-pharm.pdf, p. 38]

One subject in the placebo group was positive at baseline and day 28. All NP-018 subjects were negative at screening but three (60%) turned positive for IgG by day 28. No subjects developed IgM, IgE, or IgA antibodies.

Drug-drug and drug-disease interactions were not assessed.

6.2.12.6 Clinical Test Results

Line item review is still ongoing at the time of this mid-cycle memo. Overall reporting is given as follows. "Post-dose laboratory deviations from normal ranges are noted in the

individual subject data listings. Most out-of range laboratory findings captured were judged as not being clinically significant for this study by the investigator. […] All mean serum chemistry, hematology and urinalysis values were within normal ranges, and mean changes from baseline were unremarkable. […] Few subjects had out of range serum chemistry, hematology and urinalysis values over the duration of the study (Table 14:10 and Table 14:11). Glucose levels measured during the course of the study contributed to most of the out-of range laboratory findings. This can be likely attributed to subjects having a meal prior to study visits. All of the out-of range-values were considered by the investigator to have little clinical significance for this study." [Source: Original BLA 125462/0; bt-002-stage-a-study-report--section-1-15-.pdf, pp. 48-49]

6.2.12.7 Dropouts and/or Discontinuations

None.

6.2.12.8 Protocol Deviations

The unblinded pharmacy assistant aided in selection infusion rates for product and placebo. It is unclear to what extent this has biased the results. An information request was generated.

6.3 Trial #3

BT-002 Stage B: Botulism Antitoxin effects on paralysis induced by Type A and Type B Botulinum toxins in the Extensor Digitorum Brevis Muscle

6.3.1 Objectives (Primary, Secondary, etc)

- Primary objective: To assess the ability of Botulism Antitoxin Heptavalent (Equine) Types A-G (Cangene Corporation) in neutralizing botulinum toxins Types A and B (BOTOX® and MYOBLOC®, respectively) in the extensor digitorum brevis muscle (EDB) muscle model in healthy subjects versus placebo
- Secondary objective: To evaluate the safety of botulism antitoxin subtypes A-G in healthy subjects compared with placebo and with previously available licensed antitoxin A and B (Sanofi-Aventis-Pasteur)
  [Source: adapted from - Original BLA 125462/0; bt-002-stage-b-final-report, p. 2]

6.3.2 Design Overview

BT-002-B is a phase 1b/2a, single center, randomized, double blind, dual arm, parallel, clinical trial. The design is as an exploratory pharmacodynamic study in a preventive, pre-exposure model. Subject participation length of 28 days was chosen because most adverse reactions to botulinum toxin injected into the EDB muscle occur within a week. Adverse reactions are not related typically to the length of EDB paralysis, which can vary widely. Full recovery after MYOBLOC injection was within 11 weeks and after BOTOX injection was over 57 weeks in other studies. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 22]

6.3.3 Population

The target population for this marketing application is the group of symptomatic patients with proven or suspected botulism. The target population for the application will be getting NP-018 after they have already been exposed to toxin and are symptomatic.

The subjects studied in this clinical trial are normal volunteers, none of whom are symptomatic or have been exposed to toxin before administration of NP-018. It is unproven that they are similar enough to the target population to allow generalization, which has lead to the animal rule decision.

- Inclusion criteria
  - Male or female
  - Age 18-55 years
  - Body-mass index 19-30
  - Normal, healthy by medical history, physical exam, electrocardiogram, nerve conduction studies, laboratory tests of renal, liver, and hematological functions
  - Adequate contraception for female subjects (two forms or at physician's discretion) or FSH over 40 mIU/mL for postmenopausal women
  - Signed informed consent
- Exclusion criteria
  - Medical history that might interfere with nerve conduction studies
  - Positive skin test for botulinum antitoxin
  - Any clinically significant abnormality on screening laboratory tests
  - Conditions associated with other neuromuscular diseases including multiple sclerosis, motor neuron disease, or radiculopathy
  - Abnormal nerve conduction studies at screening
  - The presence of identifiable anomalous innervation of EDB muscle (on either side)
  - Previous botulinum injection
  - Known botulinum infection
  - Allergies to horses, horse serum, horse products, albumin, latex, rubber, plastic, food (moderate-severe), environmental requiring immunosuppression
  - Asthma
  - Suspected or known diabetes, coagulopathy, vasculities
  - Heavy tobacco or alcohol abuse
  - HIV infection or hepatitis
  - Any investigational product within 30 days

  [Source: adapted from - Original BLA 125462/0; bt-002-stage-b-final-report, p. 23-25]

6.3.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized 8:5 to active:placebo. The active agent (test article, subject drug) was Botulism antitoxin heptavalent (equine) types A-G (NP-018, Cangene Corporation) given as a single intravenous infusion one day prior to administration of the challenge toxins. Placebo was 0.9% saline solution similarly given as a single infusion. The challenge toxin agents were FDA approved botulinum toxins: Botulinum toxin type A (Botox) or Botulinum toxin type B (Myobloc). See the section below for specific directions for use. The toxins were administered one day after administration of test article.

A single dose of NP-018 has "the following nominal levels: 7500 U anti-A, 5500 U anti-B, 5000 U anti-C, 1000 U anti-D, 8500 U anti-E, 5000 U anti-F and 1000 U anti-G (one 18.51 mL vial of Botulism Antitoxin Heptavalent (Equine) Types A-G diluted 1:10 with saline). Lot number 10805139 was used in the study." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 3]

6.3.5 Directions for Use

The IM injections of botulinum toxins A and B were made into the extensor digitorum brevis muscles of left and right feet, respectively. Based on prior studies of dose-response to botulinum toxins A and B in human foot muscles, doses of 5 U of toxin A and 250 U of toxin B were chosen. Due to investigator miscalculation, 500 U of toxin B were actually administered in BT-001 stage A. Therefore, 500 U of toxin B were given in stage B. Dilutions for administration were 1 vial of study product diluted 1:10 in saline and given by slow IV infusion over approximately 150 minutes. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 3-4]

On Day 0 of the study, subjects were IV infused with either Botulism Antitoxin Heptavalent (Equine) Type A-G (Cangene Corporation) or placebo at an infusion rate of 0.5 mL/min for the first 30 minutes. If no infusion safety concerns were evident, the infusion rate was increased to 1 mL/min for the next 30 min. If the IV infusions continued to be well tolerated after 60 min., the infusion rate was increased to 2.0 mL/min for the remainder of the infusion. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 26]

6.3.6 Sites and Centers

This is a single site study performed at:

Loma Linda University
11370 Anderson Street
Loma Linda, CA 92354, USA

The investigator is Gordon Peterson, MD. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 2]

6.3.7 Surveillance/Monitoring

"The Loma Linda University (LLU) Institutional Review Board (IRB) reviewed the protocol submitted for Stage B of the clinical study BT-002, the informed consent form (ICF), as well as all supporting study documents prior to the conduct of the clinical trial. IRB Contact information, written information for subjects and a copy of the ICF is provided […] This study was conducted and monitored in compliance with and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practices (GCP): Consolidated Guidelines. […] This study was conducted in accordance with the clinical research guidelines established by the basic principles defined in the US 21 CFR Part 50, 54, 56 and 312, US 45 CFR Part 46, and the principles enunciated in the latest version of The Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH E6)." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 13]

Subjects were followed for 28 days after the administration of NP-018.

Monitoring included immunogenicity testing. Blood for anti-botulism antitoxin reactivity from all 26 subjects was drawn on days 0 and 28. Reactivity was measured using a botulism antitoxin (BAT) immunogenicity assay developed by Cangene Corp.

Safety was monitored via examination of AEs, laboratory results, physical examinations, vital signs, and electrocardiograms.

6.3.8 Endpoints and Criteria for Study Success

The primary instrument in this study was determination of the neutralization of injected botulinum toxin as assessed by percent residual muscle function. The muscle function is based on the percent preservation of the extensor digitorum brevis compound muscle action potential (CMAP) M-wave amplitude or area. Bilateral peroneal motor nerve conduction studies were performed to elicit response. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 3]

Post-treatment percentage of residual muscle function was compared to baseline nerve conduction studies. See statistical measures in §6.3.9 below.

Safety was assessed with review of clinical laboratory results, reported adverse events, vital signs, physical examinations, and electrocardiograms. Adverse events were coded using the MedDRA coding dictionary.

6.3.9 Statistical Considerations & Statistical Analysis Plan

For efficacy, "Summary statistics, including the mean, median, standard deviation, minimum, maximum and coefficient of variation [are] calculated for the percent muscle

function using both the M wave amplitude and area." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 5]

"Treatment effect over time was evaluated using an exploratory repeated-measures analysis of variance (ANOVA) model that was fitted to the percent muscle function (preservation of the EDB CMAP M wave amplitude and area, with a reference electrode at either the standard or inactive location) following exposure to BOTOX® (Botulinum toxin Type A) and MYOBLOC® (Botulinum toxin Type B) separately. Whereas the treatment and time effects were considered fixed effects, subject effects were considered as random effects. All the fixed and interaction effects in the ANOVA model were tested separately at an alpha level of 0.05. This analysis was performed separately for each of the percent muscle function endpoints (amplitude and area). An overall graph of the percent muscle function over time was created for each percent muscle function endpoint with a separate curve for each treatment group and each toxin type." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 37]

"A longitudinal analysis of variance (ANOVA) model was fitted to the percent muscle function of the EDB muscle. Treatment arm and visit were included in the model. The effect of treatment group, visit and visit by treatment interaction were tested at an alpha level of 0.05. This analysis was performed for both of the percent muscle function endpoints (amplitude and area)." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 5]

For safety, the incidence, intensity, and relationship of events to treatment were evaluated through the use of frequency tables. Summary statistics for laboratory tests and vital signs over time are provided. For abnormal laboratory values, shift tables and incidence are provided.

"All endpoint calculations and statistical analyses were performed at Cangene Corporation in compliance with SOPs and the Statistical Analysis Plan (SAP) for Stage B of BT-002. […] Reported results were internally peer reviewed and all data tables are audited for accuracy." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 36]

"The original sample size of 26 subjects in Stage B was selected in order to provide an adequate database for the assessment of Cangene's Botulism Antitoxin Heptavalent (Equine) Types A-G to neutralize the Botulinum toxins Type A and B in the human EDB muscle model. […] Percent muscle function of the EDB muscle following exposure to BOTOX® and MYOBLOC® after treatment with Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo serve as co-primary endpoints for Stage B. Stage B is a repeated measure design similar to Stage A, in which each subject is measured 6 times post-baseline for the primary endpoints. In Stage A, the effect size observed following exposure to MYOBLOC® was smaller than the one observed with BOTOX®. To be conservative, the sample size for Stage B is justified based on CMAP M wave amplitudes observed in the Stage A following MYOBLOC® administration. Further sample size calculations for Stage B were based on the assumption that Botulism Antitoxin

Heptavalent (Equine) Types A-G (Cangene Corporation) will be equally effective in neutralizing Botulinum toxin Types A (BOTOX®) and B (MYOBLOC®) as Botulism Antitoxin Bivalent (Equine) Type A and B (data from Stage A). From the data collected in Stage A of this study, the mean and variance-covariance matrix of the EDB CMAP M wave amplitudes following exposure to Botulinum toxins Types A (BOTOX®) and B (MYOBLOC®) over time were calculated. Results are shown in tables 9:5 and 9:6." [Source: Adapted from- Original BLA 125462/0; bt-002-stage-b-final-report, p. 38]

No multiplicity adjustments were made or considered necessary by the investigators. There were no adjustments for covariates made during this study. Missing data were considered missing; no imputation methods were used.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

A total of 26 subjects were enrolled in this protocol. Of the 26, 25 subjects completed the trial. All 26 subjects were included in the safety profile. The remaining 25 subjects were included in the efficacy analysis. All subjects were skin tested for sensitivity to equine product. It is not clear that such testing would be performed in the acute clinically setting, either universally or sporadically. The exclusion of subjects who test positively potentially introduces bias into the sample.

6.3.10.1.1 Demographics

Age range was 19-48 years, mean 28 years, median 25 years. Race was Caucasian in 96%, with 62% non-Hispanic and 39% Hispanic. Thirteen males and thirteen females were randomized, with 8 males and 8 females in the active arm and 5 each in the placebo arm. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 40-44]

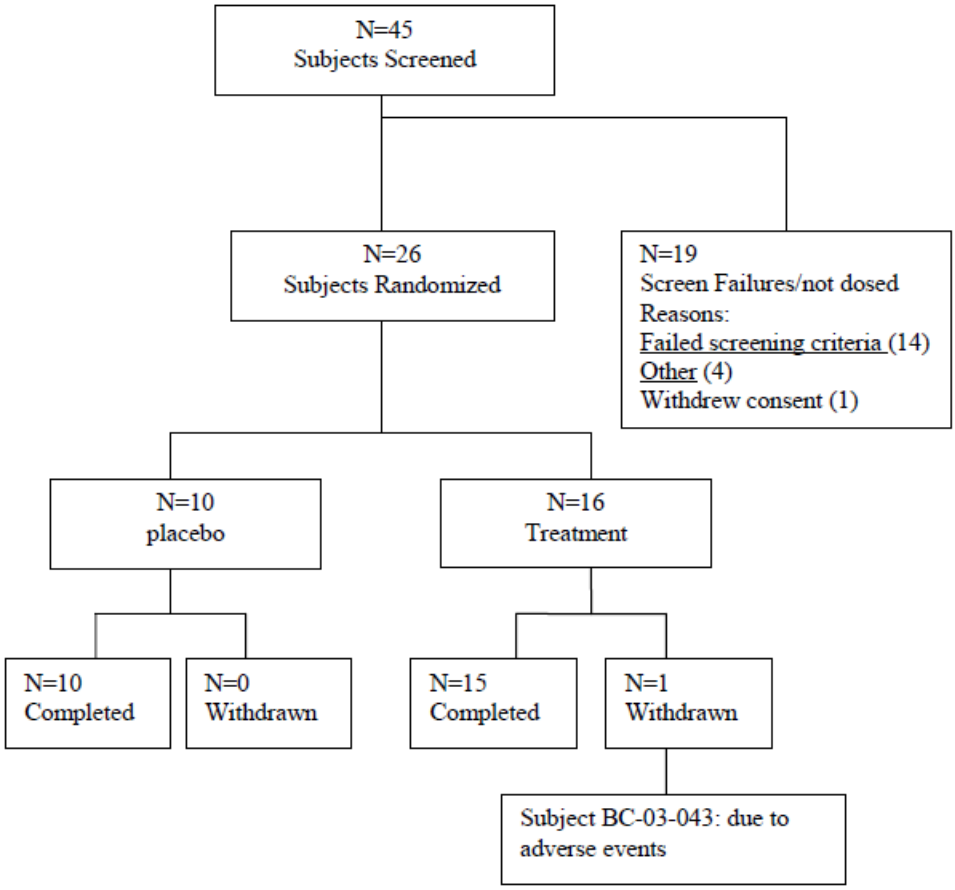
6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Normal subjects were enrolled for this trial.

6.3.10.1.3 Subject Disposition

A total of 45 subjects were screened. From the 45 originally screened, 26 subjects were chosen. Fourteen were not included because they did not meet the criteria including medical history and peroneal nerve conduction abnormalities as shown in report appendix 16.2.5.2. Five were excluded for administrative reasons. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 39-40]

Figure 10:1 Flow Chart of Disposition of Subjects



[Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 41]

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Calculation of the change in muscle function was done with the formula:

$$\%\ MuscleFunction_i = \frac{CMAP_i}{mean(baselineCMAP)} \text{ x } 100$$

where the subscript i refers to the study visit and CMAP is the maximum CMAP M wave amplitude. "The mean baseline CMAP is the average of amplitudes for Baseline NCS #1 which was measured during the Screening visit and Baseline NCS #2 which was measured within 7 days prior to infusion of the study drug on Day 0. […] For the calculation of primary endpoint, CMAPi from each foot will be divided by the mean of baseline CMAP of the same foot." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 34-5] The method as described is slightly different from stage A, but the difference is not considered significant in the context of this evaluation.

"Botulism Antitoxin Heptavalent (Equine) Types A-G (Cangene) (treatment arm) prevented subjects from a decrease in muscle function following exposure to Botulism toxin Types A and B (BOTOX® and MYOBLOC®, respectively). Subjects receiving placebo demonstrated a loss of greater than 50% muscle function within 3 days of exposure to both Botulism toxin types. In the treatment arm, muscle function was stable over time, indicating that the antitoxin is effective in preserving muscle function for up to 28 days following exposure to both Botulism toxin types. By longitudinal analysis of variance model, there is a significant decrease of percent muscle function of EDB muscle in the placebo arm as compared to the treatment arm over time (p-value <0.05). […] In Stage B of the study, subjects given Botulism Antitoxin Heptavalent (Equine) Types A-G prior to exposure to Botulism toxins A and B (BOTOX® and MYOBLOC®, respectively) presented with little to no loss of percent muscle function in the EDB muscles of both feet over the 28 day study period. These results were observed for both pharmacodynamic endpoints: percent muscle function based on the preservation of the EDB muscle CMAP M wave amplitude […] In this study the investigational product Botulism Antitoxin Heptavalent (Equine) Types A-G manufactured by Cangene Corporation demonstrated comparable results in its ability to neutralise Botulinum toxins Types A and B and preserve muscle function (preventing muscle paralysis) as the currently licensed Botulism Antitoxin Bivalent (Equine) from Aventis Pasteur.". [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 5, 55]

6.3.11.2 Analyses of Secondary Endpoints

Secondary endpoints for stage B include:

1. "The percent muscle function following exposure to Botulinum toxins Type A (BOTOX®) and Type B (MYOBLOC®) after administration of either Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo based on the preservation of the CMAP area recorded from EDB with the reference electrode in the 'standard' location.
2. The percent muscle function following exposure to Botulinum toxins Type A (BOTOX®) and Type B (MYOBLOC®) after administration of either Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo based on the preservation of the CMAP amplitude recorded from EDB with the reference electrode in an 'inactive' location.
3. The percent muscle function following exposure to Botulinum toxins Type A (BOTOX®) and Type B (MYOBLOC®) after administration of either Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo based on the preservation of the CMAP area recorded from EDB with the reference electrode in an 'inactive' location."
   [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 35]

The review of these secondary endpoints is ongoing.

6.3.11.3 Subpopulation Analyses

Not performed.

6.3.11.4 Dropouts and/or Discontinuations

One subject discontinued treatment because of an acute urticarial allergic adverse reaction.

6.3.11.5 Exploratory and Post Hoc Analyses

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety assessments were made per the study assessment schedule given in tables 9.3 and 9.4. Safety was assessed with review of clinical laboratory results, reported adverse events, vital signs, physical examinations, and electrocardiograms. Adverse events were coded using the MedDRA coding dictionary.

"All AE information including the onset and resolution dates, seriousness, intensity, relationship to Botulism Antitoxin Heptavalent (Equine) Types A-G, (Cangene Corporation), BOTOX® (Botulinum toxin Type A) and MYOBLOC® (Botulinum toxin Type B), the action taken, outcome and corrective therapy were captured by the investigator in a subjects' source documentation and CRF." [Source: Original BLA 125462/0; bt-002-stage-b-final-report, p. 30]

6.3.12.2 Overview of Adverse Events

No notable differences in the number of AEs or laboratory abnormalities were reported by the Applicant between the treatment and placebo arms. There were increases in some moderate and severe adverse events as discussed below, but these were reported as unrelated to NP-018. Some laboratory findings were found to be out-of-range but were judged as not being clinically significant by the investigator. However, one subject developed AEs from a moderate allergic reaction related to study drug administration including urticaria, elevated body temperature and chest discomfort within 5 min. of the start of the infusion. Elevated fibrinogen levels post-infusion were also detected in this subject. This subject required two rounds of intravenous benedryl and steroids. He later developed lymphadenopathy which likely was mild serum sickness. This was self-limited. This subject tested negative for skin sensitivity prior to the infusion and for immunogenicity on day 28.

A total of 81 AEs were reported by 24 subjects. For treatment with NP-018, 14 subjects reported 50 AEs. For placebo, ten of ten subjects reported 31 AEs. Mild, moderate, or severe events were reported in 66, 8, and 7 events, respectively. No serious adverse events were reported. Four adverse events were determined to be related to active test product. All the four events were in the same subject during the same event and are really one event, discussed in the prior paragraph. Moderate events include urticaria, rash, conjunctivitis, pyrexia, burns, somnolence, panic, and dysmenorrhea. "The most frequently reported AEs were headache (19%), lymphadenopathy (19%), contusions (19%) skin lacerations (19%), and tonsillar hypertrophy (19%). All cases were assessed as being mild in intensity […]. Other reported AEs reported in >10% of the subjects include pain in extremities (12%), somnolence (15%) and upper respiratory tract

infections (12%).” Of the 81 AEs reported, 63 AEs were resolved by study completion. Of the 63 resolved AEs, two were resolved with sequelae. Eighteen AEs were on-going at the time of study completion. For adverse events deemed unrelated, the active arm reported 46 and the placebo arm reported 31. Lymphadenopathy was more common than the comparator, but equal to concurrent placebo so would be interpreted as environmental or seasonal. The number of unrelated events in the study from California could reflect a lifestyle effect. [Source: Original BLA 125462/0; bt-002-stage-b-final-report, pp. 56-61]

“Comparison of AEs reported for Cangene’s Botulism Antitoxin Heptavalent (Equine) Types A-G (Cangene) and those captured for Botulism Antitoxin Bivalent (Equine) Types A and B (Aventis Pasteur) reveals that Cangene’s investigational product is equally well tolerated as the current licensed product (Botulism Antitoxin Bivalent (Equine) Types A and B from Aventis Pasteur.” [Source: Adapted from Original BLA 125462/0; bt-002-stage-b-final-report, pp. 6, 62]

Table 12:1 Adverse Events: Number Observed and Rate with a Subject Incidence of >10% of the total number of subjects enrolled in the study.

System class	Preferred Term	Botulism Antitoxin Heptavalent (Equine) Types A-G (Cangene) (N=16) Number of AEs (% subjects)			placebo (0.9% saline solution) (N=10) Number of AEs (% subjects)		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Blood and Lymphatic System Disorder	Lymphadenopathy	3 (19)	0 (0)	0 (0)	4 (20)	0 (0)	0 (0)
Gastrointestinal disorders	Aphthous Stomatitis	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)
Infections and infestations	Viral Upper Respiratory Tract infection	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)
Injury, Poisoning and Procedural Complications	Contusion	4 (25)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)
	Skin Laceration	1 (6)	0 (0)	3 (13)	1 (10)	0 (0)	0 (0)
Musculoskeletal and Connective Tissue Disorders	Pain in extremity	2 (13)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)
	Rhabdomyolysis	2 (13)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)
Nervous System Disorders	Headache	3 (13)	0 (0)	0 (0)	4 (30)	0 (0)	0 (0)
	Somnolence	1 (6)	1 (6)	0 (0)	2 (20)	0 (0)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	Tonsillar Hypertrophy	4 (25)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)
	Upper Respiratory Tract Infection	0 (0)	0 (0)	1 (6)	2 (20)	0 (0)	0 (0)

[Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 58]

Note in table 12:1 above that tonsillar hypertrophy occurs more often with NP-018 than placebo. Causality remains to be determined. Contusions occurred more often with NP-018 than placebo. Given the lack of an obvious mechanism and biological plausibility, this is more likely considered unrelated. The other adverse events occurred equally commonly between NP-018 and placebo.

Table 12:2 Comparison summary of adverse events observed in subjects receiving Botulism Antitoxin Heptavalent (Equine) Types A-G and those receiving Botulism Antitoxin Bivalent (Equine) Types A and B.

		Stage B		Stage A	
		Botulism Antitoxin Heptavalent (Equine) Types A-G (Cangene) (N=16) Number of AEs (% subjects)		Botulism Antitoxin Bivalent (Equine) Types A and B (Aventis Pasteur) (N=5) Number of AEs (% subjects)	
Body System	**Preferred Term**	**Number of Adverse Events**	**Number of Subjects (% of total)**	**Number of Adverse Events**	**Number of Subjects (% of total)**
Blood and Lymphatic System Disorder	Lymphadenopathy	3	3 (19)	0	0 (0)
Infections and Infestations	Gastroenteritis	0	0 (0)	1	1 (20)
Injury, Poisoning and Procedural Complications	Contusion	4	4 (25)	0	0 (0)
	Skin Laceration	4	3 (19)	0	0 (0)
Musculoskeletal and Connective Tissue Disorders	Muscle Spasms	0	0 (0)	1	1 (20)
	Pain in extremity	2	2 (13)	2	1 (20)
	Rhabdomyolysis	2	2 (13)	0	0 (0)
Nervous System Disorders	Burning Sensation	0	0 (0)	1	1 (20)
	Headache	3	2 (13)	1	1 (20)
	Somnolence	2	2 (13)	0	0 (0)
Reproductive System and Breast disorders	Dysmenorrhoea	2	2 (13)	0	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	Tonsillar Hypertrophy	4	4 (25)	0	0 (0)

[Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 59]

The increase in tonsillar hypertrophy is sustained between NP-018 and comparator BAT AB licensed product, as is the difference between lymphadenopathy, rhabdomyolysis, and contusion. Given that the other event frequencies were equal to placebo, only tonsillar hypertrophy and contusions stand out as possibly related to NP-018.

Table 14 Adverse Event Frequencies by Treatment, Severity and Relationship to eBAT NP-018 in Clinical Trial BT-002 Stage B

		eBAT NP-018 1 Vial	Placebo
		Events (%)	**Events (%)**
Frequency		50	31
Severity	**Mild**	35 (70%)	31 (100%)
	Moderate	8 (16%)	0 (0%)
	Severe	7 (14%)	0 (0%)
Relationship	**Related**	4 (8%)	0 (0%)
	Unrelated	46 (92%)	31 (100%)
Not Serious		50 (100%)	31 (100%)

The most frequent adverse events in this clinical trial are given in the table below.

Table 16 Adverse Events Reported by ≥ 10% of the Subjects Receiving either eBAT NP-018 or Placebo in Clinical Trial BT-002 Stage B

	eBAT NP-018 1 Vial	Placebo
Preferred Term*	**n (%)[1]**	**n (%)**
Acne	0 (0%)	1 (10%)
Aphthous stomatitis	0 (0%)	2 (20%)
Breast mass	0 (0%)	1 (10%)
Contusion	4 (25%)	1 (10%)
Diarrhoea	0 (0%)	1 (10%)
Dysmenorrhoea	2 (13%)	0 (0%)
Excoriation	1 (6%)	1 (10%)
Haematoma	0 (0%)	1 (10%)
Headache	2 (13%)	3 (30%)
Lymphadenopathy	3 (19%)	2 (20%)
Myalgia	1 (6%)	1 (10%)
Nasal congestion	1 (6%)	1 (10%)
Pain in extremity	2 (13%)	1 (10%)
Palpitations	0 (0%)	1 (10%)
Pulmonary granuloma	0 (0%)	1 (10%)
Rhabdomyolysis	2 (13%)	2 (20%)
Skin laceration	3 (19%)	1 (10%)
Somnolence	2 (13%)	2 (20%)
Tonsillar hypertrophy	4 (25%)	1 (10%)
Upper respiratory tract infection	1 (6%)	2 (20%)
Viral upper respiratory tract infection	0 (0%)	2 (20%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 20]

The most common adverse events were contusions, tonsillar hypertrophy, lymphadenopathy, and lacerations, all assessed as being mild in severity. Some of the other events were > 10% in frequency and assessed as moderate or severe. All events were considered unrelated to NP-018 except for the four reported in the same subject who suffered a moderate allergic reaction.

The full list of adverse events in BT-002B is given below.

Table 22 Adverse Event Summary Clinical Trial BT-002 Stage B

Body System Preferred Term	**1 Vial eBAT NP-018 (n=16)**	**Placebo (n=10)**
	n (% of subjects)	**n (% of subjects)**
Total	14 (88%)	10 (100%)
Blood and lymphatic system disorder		
Lymphadenopathy	3 (19%)	2 (20%)
Cardiac disorders		
Palpitations	0 (0%)	1 (10%)
Eye disorders		
Conjunctivitis	1 (6%)	0 (0%)
Gastrointestinal disorders		
Aphthorus stomatitis	0 (0%)	2 (20%)
Diarrhea	0 (0%)	1 (10%)
Dyspepsia	1 (6%)	0 (0%)
Stomatitis	1 (6%)	0 (0%)
General disorders and administration site conditions		
Chest discomfort	1 (6%)	0 (0%)
Feeling cold	1 (6%)	0 (0%)
Injection site pain	1 (6%)	0 (0%)
Pain	1 (6%)	0 (0%)
Pyrexia	1 (6%)	0 (0%)
Infections and infestations		
Cellulitis	1 (6%)	0 (0%)
Viral infection	1 (6%)	0 (0%)
Viral upper respiratory tract infection	0 (0%)	2 (20%)
Injury, poisoning and procedural complications		
Contusion	4 (25%)	1 (10%)
Excoriation	1 (6%)	1 (10%)
Skin laceration	3 (19%)	1 (10%)
Thermal burn	1 (6%)	0 (0%)
Investigations		
Blood fibrinogen increased	1 (6%)	0 (0%)
Body temperature increased	1 (6%)	0 (0%)

Body System **Preferred Term**	**1 Vial eBAT NP-018** **(n=16)**	**Placebo** **(n=10)**
	n (% of subjects)	**n (% of subjects)**
Musculoskeletal and connective tissue disorders		
Musculoskeletal Pain	1 (6%)	0 (0%)
Myalgia	1 (6%)	1 (10%)
Pain in extremity	2 (13%)	1 (10%)
Rhabdomyolysis	2 (13%)	2 (20%)
Nervous system disorders		
Headache	2 (13%)	3 (30%)
Somnolence	2 (13%)	2 (20%)
Psychiatric disorders		
Panic attack	1 (6%)	0 (0%)
Reproductive system and breast disorders		
Breast mass	0 (0%)	1 (10%)
Dysmenorrhea	2 (13%)	0 (0%)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	1 (6%)	0 (0%)
Nasal congestion	1 (6%)	1 (10%)
Pharyngeal erythema	1 (6%)	0 (0%)
Pulmonary granuloma	0 (0%)	1 (10%)
Tonsillar disorder	1 (6%)	0 (0%)
Tonsillar hypertrophy	4 (25%)	1 (10%)
Upper respiratory tract infection	1 (6%)	2 (20%)
Skin and subcutaneous tissue disorders		
Acne	0 (0%)	1 (10%)
Rash	1 (6%)	0 (0%)
Urticaria	1 (6%)	0 (0%)
Vascular disorders		
hematoma	0 (0%)	1 (10%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, pp. 29-30]

Only four adverse events in the treatment group were considered related to NP-018. All of these four related events were from the same episode in the same subject. This subject was treated with benedryl and solumedrol. The subject developed lymphadenopathy after ten days and this may have been a case of mild serum sickness. All other events in the clinical trial were considered unrelated.

6.3.12.3 Deaths

There were no deaths in this trial.

6.3.12.4 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse reactions in this trial.

6.3.12.5 Adverse Events of Special Interest (AESI)

There was one severe urticarial reaction resulting in discontinuation from the trial. It is likely that this subject went on to develop mild serum sickness with lymphadenopathy. This was self-limited without sequelae.
Drug-drug and drug-disease interactions were not assessed.

Immunogenicity is an adverse event of special interest. Table 12:3 shows the following from all 26 study subjects.

Table 12:3 Stage B Summary Results for Anti-Equine Antibody Immunogenicity Testing of Serum Samples.

Timepoint (Visit)	Screening Assay	Screening Assay Result	Confirmatory Assay				
	Negative	Reactive	Confirmed Positive	IgG	IgM	IgE	IgA
Baseline	23 (88.5%)	3 (11.5%)	3 (100%)-	3	0	0	1
Day 28	19 (73.1%)	7 (26.9%)	7 (100%)	7	2	0	0

[Source: Original BLA 125462/0; bt-002-stage-b-final-report.pdf, p. 65]

The three who were reactive at baseline were in the active treatment group, as were all seven at day 28. The discrepancy between treatment and placebo groups at day 0 is unexplained and may be due to chance. Four subjects out of 16 (25%) who received NP-018 converted their serology during the clinical trial. There was no relationship between serology and adverse reactions. Subject 43 who had a moderate allergic reaction was skin testing and serology negative. [Source: Original BLA 125462/0; bt-002-stage-b-final-report.pdf, p. 65]

The following table focuses on the 16 subjects who received NP-018.

Table 21 Immunogenicity Testing Results for Clinical Trial BT-002 Stage B

Time Point	Screening Assay		Confirmatory Assay				
	Negative	Reactive	Confirmed	IgG	IgM	IgE	IgA
Baseline	13 (81%)	3 (19%)	3 (100%)	3 (19%)	0	0	1 (6%)
Day 28	9 (56%)	7 (44%)	7 (100%)	7 (44%)	2 (13%)	0	0

[Source: Original BLA 125462/0; summary-clin-pharm.pdf, p. 38]

Only IgM and IgG antibodies were formed after exposure to NP-018. No IgE or IgA antibodies were formed.

6.3.12.6 Clinical Test Results

No significant trends in the laboratory assessments were identified. Several cases of elevated muscle enzymes were seen in subjects in the active and control arms, before and after treatment, and were ascribed to identified physical overexertion which is apparently common in the geographic region of the study location.

No substantial alterations in vital signs or physical examination findings were reported during this clinical trial.

6.3.12.7 Dropouts and/or Discontinuations

There was one moderate allergic reaction resulting in discontinuation from the trial. All other subjects completed the trial. The one subject who discontinued had four concurrent events including urticaria, chest discomfort, pyrexia, and elevated fibrinogen levels. Infusion was terminated after five minutes. Skin testing was negative at screening and immunogenicity testing was negative before and after dosing. [Source: Original BLA 125462/0; summary-clin-safety.pdf, pp. 31-32]

6.4 Trial #4

BB-IND 6750: Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)- Equine
CDC Expanded Access Program

6.4.1 Objectives (Primary, Secondary, etc)

The purpose of this expanded access protocol was to study the safety and effectiveness of botulism antitoxin heptavalent (equine) in symptomatic subjects suspected of having botulism.

6.4.2 Design Overview

The current version of the protocol is version 8. This is an expanded use program which includes subjects having symptomatic botulism.

The process begins with the physician making the definite or suspected diagnosis of botulism poisoning in a symptomatic patient. The physician then calls CDC and provides information to the CDC botulism officer or designee. The physician and botulism officer consult and make a treatment determination. If accepted, the treatment is done through the CD botulism treatment program.

After the product has been released by CDC for clinical use, the treating physician acts as the site investigator for the protocol. The investigator is responsible for getting informed consent and making the final decision to administer H-BAT. The investigator is also responsible for monitoring adverse events and responsiveness to therapy. It is the responsibility of the investigator to provide documentation on clinical course and outcome of subjects to CDC via case report forms which include signs, symptoms, adverse and positive reactions.

Subject information from CDC was de-identified and provided to FDA, Cangene Corporation, and BARDA (Biomedical Advanced Research and Development Authority). In addition, datasets from case report forms were provided to Cangene for statistical analysis.

6.4.3 Population

The overall population available to this study is the entire cadre of subjects with known or suspected botulism poisoning who require treatment, with the exception of those infants treated with BabyBIG as licensed. Since this expanded access program is the only

authorized pathway to obtain treatment other than BabyBIG, all patients in the United States or other countries requesting treatment for botulism must come through this program. Persons with botulism who are not diagnosed with botulism or do not require treatment with antitoxin would not come into this protocol and not be included in the overall population.

Pediatric subjects were included. Seven pediatric subjects were treated with NP-018.

6.4.4 Study Treatments or Agents Mandated by the Protocol

H-BAT was administered at the single dose level in 143 of 148 (97%) subjects. One ten-day-old child was given two infant doses of study product eight hours apart. One 29-year-old woman was given two adult doses four days apart. One 46-year-old man was given two adult doses one month apart. One 78-year-old woman was given two adult doses eight days apart [Source: Original BLA 125462/0; bb-ind-6750.pdf, pp. 220-221]. An information request has been written for more information on multiple doses.

6.4.5 Directions for Use

The following instructions are provided in protocol version 8.
"NP-018 H-BAT is supplied in either a 20 mL or 50 mL glass vial seated with a butyl rubber stopper and an aluminum seal with a plastic flip-top cap. Irrespective of the vial size and the extractable volume, each single-use intravenous vial is filled to contain the composition specified in Table 2. The product potency is expressed in units (U) based on the amount of toxin-specific neutralizing antibodies to a specific toxin serotype in the mouse neutralization assay. […] NP-018 H-BAT must be diluted 1:10 in 0.9% Sodium Chloride, Injection, USP under aseptic conditions. **DO NOT SHAKE VIAL; AVOID FOAMING.** Visually assess for particulate matter and discoloration. NP-018 H-BAT must not be infused unless it is clear, is not turbid, and contains no particulate matter. The unused IV bag can be stored ----(b)(4)--- for use within approximately -----(b)(4)----. […] Please refer to Section 7.0 for a summary table of administration and required subject monitoring and reporting events. Before administration of NP-018 H-BAT, obtain and record vital signs (pulse, blood pressure, respiratory rate, and temperature), symptoms, and physical exam findings 5 min before start of infusion. During infusion, monitor vital signs (see Section 6.0, "Patient Monitoring, Follow-up and Required Reporting" and Attachment 3, "Patient Monitoring Report"). […] The adult dose of NP-018 H-BAT is one vial diluted 1:10 in 0.9% Sodium Chloride, Injection, USP. Regardless of vial size and extractable volume, which varies by Lot # of NP-018 H-BAT, **one adult dose equals one vial** (see Section 3.1, "Dosage Form and Composition").
For adult patients with suspected history of reaction to equine-derived products and therefore have relative contraindications (see Section 4.0, "Warnings and Precautions"), premedication with corticosteroids and antihistamines is advised.
The initial administration rate of NP-018 H-BAT should begin slowly at 0.5 mL/min for the first 30 min. If no infusion-related safety concerns are evident, the infusion rate can be increased to 1 mL/min for the next 30 min. If no infusion-related safety concerns are evident, the infusion rate can be increased to 2 mL/min for the remainder of the infusion.
Pediatric directions for use are given in section 5.2.2 on page 39.

[Source: Original BLA 125462/0; bb-ind-6750.pdf, pp. 34, 38-39]

6.4.6 Sites and Centers

Individual study sites are determined by the location of subjects presenting with symptoms of botulism. The larger botulinum structure [pg. 219, 5.3.5.2.1] starts with the CDC Botulism Treatment, which is a 24/7 consultation and antitoxin release service. H-BAT is available only through CDC and state botulism officers. The botulism officers release the H-BAT, which is pre-positioned nationwide in positions including 8 quarantine stations and Alaska. H-BAT is intended to be released within 24 hours of consultation by the hospitals.

6.4.7 Surveillance/Monitoring

CDC collected epidemiologic and clinical information on subjects with suspected and confirmed botulism. They characterized subjects' exposures and clinical outcomes. CDC collected subject monitoring reports which include details of H-BAT administration, vital signs, symptoms, physical examination findings, and adverse events/reactions [p. 219].

Six documents are collected as part of the data collection: 1) consent form, 2) case report, 3) patient monitoring reports, 4) outcome report, 5) product report, and 6) form FDA 1572. A minimum collection includes the case and outcome reports. Details are given in section 6 of the protocol [Source: Original BLA 125462/0; bb-ind-6750.pdf, pp. 39-41].

6.4.8 Endpoints and Criteria for Study Success

There were no defined research endpoints or criteria for study success in the protocol. In particular, there were no research efficacy endpoints defined in the protocol. This protocol was designed as an expanded access, treatment protocol.

6.4.9 Statistical Considerations & Statistical Analysis Plan

No statistical considerations were given in the protocol and no statistical analysis plan was proposed. IND 6750 was not primarily designed as a research study but rather as an expanded access treatment protocol.

Post-hoc analysis of subject outcomes was discussed in the cdc-stats-report-v-1.pdf and below herein. Review of this data is ongoing as of this mid-cycle report.

6.4.10 Study Population and Disposition

Between 2008-01-15 and 2011-12-31, 148 subjects received study product. Presumably this number represents the entire population in the United States where treatment with H-BAT was requested/given. Five subjects from Mexico were given treatment [p. 220].

The first subject was treated under IND 13615 as an emergency IND in approx 2008. This was an infant with botulism type F, which is not treated by BabyBIG (types A and B only). IND 13615 was eventually terminated.

For IND 6750, the protocol is an expanded access program to treat those with botulism toxin poisoning as results of natural outbreaks or sporadic incidents.

The overall population is all cases where CDC-released botulism NP-018 antitoxin was used as treatment. The population comes from the CDC reports which are generated periodically, now every six months. Report #4 was released July 2, 2012 and included 184 subjects. Report #3 was released January 30, 2012 and is the basis for this part of the submission. Report #3 covers 148 subjects from January 15, 2008 through December 31, 2011. The interval subjects between reports #3 and #4 are not reported or evaluated.

6.4.10.1 Populations Enrolled/Analyzed

All subjects given drug are enrolled as a matter of protocol. The analysis is proportional to the data provided or obtained, which is further dependent on the compliance of the treating entity. As of 2011-12-31, all six forms were completed in 37.2%. At least two of six forms (minimal completion) were accomplished in 94.6%. Table 1 on page 224 gives a breakdown of the completion rates [Source: Original BLA 125462/0; bb-ind-6750.pdf, pp. 216, 224]. Pediatric and geriatric subjects were included.

6.4.10.1.1 Demographics

Age range was 10 days-88 years (median= 47 years). Seven (5%) of subjects were in the pediatric age range (< 18 years). 104 (70%) were male, 44 (30% female). Races included 41% Caucasian, 7% Alaskan native, 4% Asian, 4% other, and 2% African American. Hispanic/Latinos comprised 37%, non-Hispanic/Latinos 30%, and unknowns 33% [table 2, p. 225]. Further demographics are given in the following table.

Table 11 Demographic Summary of CDC Patients Treated with eBAT NP-018

Parameter		Overall (n = 148)
Age (Years)	Mean ± SD	46 ± 17
	Range	10 days - 88 years
Age Group (n, %)	<18	7 (4.7%)
	18-39	49 (33.1%)
	40-64	72 (48.6%)
	65-75	11 (7.4%)
	>75	9 (6.1%)
Sex (n, %)	Female	43 (29.1%)
	Male	105 (70.9%)
Ethnicity (n, %)	Hispanic/Latino	54 (36.5%)
	Non-Hispanic/Non-Latino	45 (30.4%)
	Unknown	49 (33.1%)
Race (n, %)	African-American/Black	3 (2.0%)
	Alaska Native	8 (5.4%)
	American Indian, Alaska Native	2 (1.4%)
	Asian	6 (4.1%)
	Other	6 (4.1%)
	Unknown	62 (41.9%)
	White	61 (41.2%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 17]

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
[Source: Original BLA 125462/0; bb-ind-6750.pdf, pp. 224-229]

Time from initial symptoms to hospital admission ranged from < 1 day to 37 days (median= 1 day). Time from hospital admission to intensive care unit (ICU) admission ranged from < 1 day to 12 days (median < 1 day). Time from hospital admission to intubation ranged from < 1 day to 6 days (median= 1 day). Time from onset of symptoms to administration of H-BAT ranged from < 1 day to 34 days (median= 3 days).

Clinical symptoms and signs upon presentation were given in table 4 [p. 227/411]. The most common symptoms were weakness (84%), blurred vision (81%), dysphagia (81%), dysarthria (75%), diplopia (70%), and fatigue (70%). The most common signs were ptosis (74%), palatal weakness (56%), impaired gag reflex (54%), AND extraocular palsy (50%).

Suspected transmission categories at the time of H-BAT distribution were wound (47%), foodborne (27%), iatrogenic (1%), infant (1%), other (5%), and indeterminate (20%) [table 5A, p. 228].

Final diagnosis of botulism was made in 97 (66%) of subjects. Of the 97, laboratory confirmation was available for 52 (54% of final diagnosed, 35% of treated). Toxin type A

(67%) was the most common confirmed type, type F in 8%, type B in 6%, type E in 6%, types A and B in 2%, and indeterminate in 12% [table 5C, p. 228].

6.4.10.1.3 Subject Disposition

6.4.11 Efficacy Analyses

Most but not all subjects treated with NP-018 had a final diagnosis of botulism. Out of 148 subjects in IND 6750, 97 (66%) had botulism as a diagnosis. Wound botulism (47%) was the most common source followed by foodborne (27%). [Source: Original BLA 125462/0; summary-clin-safety.pdf, pp. 11-12]

Table 4 Summary of Patient Diagnosis at Discharge

Final Diagnosis*	**Overall (n = 148)**
Botulism	97 (65.5%)
Guillain-Barre Syndrome	14 (9.5%)
Myasthenia gravis	5 (3.4%)
Tick paralysis	1 (0.7%)
Other	21 (14.2%)
Missing	10 (6.8%)

* As reported by the treating physician on the Clinical Outcome Report.

[Source: Original BLA 125462/0; summary-clin-safety.pdf, pp. 11-12]

On page 223/411, study report #3 states that efficacy will be determined "through non-clinical studies and licensure will be based on the Animal Rule (21 CFR 610, subpart H) as human efficacy clinical trials would not be ethical or feasible." The report also states "While conclusions regarding efficacy that could be answered through a placebo-controlled clinical trial or research study cannot be drawn from the clinical information collected on patients treated with H-BAT from CDC's Botulism Treatment Program, disposition of patients (indicated by clinical outcomes summarized in Table 6) suggests that H-BAT might provide therapeutic benefit." [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 223] Post-hoc analysis is discussed in §6.4.11.5 below.

For the 148 subjects treated with H-BAT, duration of hospital admission ranged from 1 to 104 days (median= 15 days) [table 6, p. 229/411]. Duration of ICU stay ranged from 1 to 95 days (median= 12 days). Mechanical ventilation was done in 91 (67%) subjects, ranging from 1 to 83 days (median= 16 days) of ventilatory support. Of the 91 subjects with mechanical ventilation, 55 (60% of ventilated, 37% of treated) underwent tracheostomy.

Six subjects died as part of IND 6750, including five subjects who died in the hospital. Discharge was done to home (n= 58, 41%), rehabilitation facility (n= 39, 27%), nursing home (n=6, 4%), other (n= 25, 18%), or unknown (n= 15). Other includes state prison (n= 7), subacute facility (n= 6), another hospital (n= 5), home with rehabilitation (n= 4), left against medical advice (n= 2), and homeless facility (n= 1).

Disability upon discharge was reported as residual in 82 (57%) treated subjects, residual including proximal extremity weakness in 52, and residual including distal extremity weakness in 40 subjects. No residual disability upon discharge was reported in 29 (20%) subjects. Information regarding disability was unavailable for 32 (22%) treated subjects.

6.4.11.1 Analyses of Primary Endpoint(s)

There were no primary research endpoints in this observational treatment protocol.

6.4.11.2 Analyses of Secondary Endpoints

There were no secondary research endpoints in this observational treatment protocol.

6.4.11.3 Subpopulation Analyses

Seven (5%) of subjects were in the pediatric age range (< 18 years) [p. 220/411]. Age range for pediatric subjects was 10 days-15 years (median= 5 years). Two of the seven subjects had adverse events, including one SAE as described elsewhere. Only one infant less than one year old was included.

Geriatric subjects were more common than pediatric. Twenty subjects older than 65 years were included. One subject reported an adverse reaction after NP-018. The adverse reaction was a rash localized to the right wrist which resolved after 24 hours. Three of the six subjects who died were geriatric.

6.4.11.4 Dropouts and/or Discontinuations

Treatment was discontinued in the one subject described in §6.4.12.4 who suffered a serious adverse reaction of bradycardia and asystole.

6.4.11.5 Exploratory and Post Hoc Analyses

Post-hoc analysis of the human CDC data was done. Initiation of treatment ≤ 2 days after symptom onset was compared to treatment > 2 days after onset. The early treatment group experienced statistically significant shortening in duration of duration of hospitalization, ICU stay, and time on mechanical ventilation.

The logistic regression model shows that “the duration of hospitalization is shorter in subjects who are treated within two days of developing symptoms of botulism, compared to subjects whose treatment is delayed beyond two days”. The same effect was noted for a threshold of three days. [Source: Original BLA 125462/0; cdc-stats-report-v-1.pdf, pp. 17-18]

6.4.12 Safety Analyses

6.4.12.1 Methods

The methods and difficulties in obtaining clinical information via completed forms are described in the study report. At times, multiple attempts and lengthy periods of time were required to obtain the reports. [Source: Original BLA 125462/0; bb-ind-6750.pdf, pp. 219-220]

6.4.12.2 Overview of Adverse Events

Some information regarding adverse events was available in 146 subjects and pending for two remaining individuals. The study product H-BAT was "well-tolerated" in 128 (88%) subjects, including one infant who received two infant doses. Five subjects received multiple doses, discussed in §8.5.1. In 18 subjects, 31 adverse events were reported including fever alone (n= 5), rash (n= 2), fever and chills (n= 2), as well as other less frequent reactions listed in table 7 [p. 229]. There were zero instances of anaphylaxis (0%), and one instance of serum sickness (0.7%) in a subject who ultimately died of undetermined causes. Relatedness and temporal factors could not be determined from the data. Because of the difficulties with data collection and completeness, the effect of underreporting cannot be quantified. The adverse reactions are reported in the tables below.

Table 7: Reported Adverse Events in Patients who Received H-BAT (n=18)

Adverse Events	# Patients
Fever	5
Rash	2
Fever, chills	2
Fever, urinary retention	1
Chills, nausea, vomiting	1
Rash, swelling, nausea, "jittery", chest pressure	1
Hemodynamic instability (characterized by tachycardia, bradycardia and asystole)	1
Tachycardia, bronchospasm, agitation	1
Mild hypertension	1
Slight facial erythema, edema	1
Mild serum sickness, diaphoresis	1
Severe anxiety	1

[Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 29]

Table 18 Adverse Reactions Reported by Patients Treated with eBAT NP-018 Under the CDC Sponsored Expanded Access Program (BB-IND 6750)

		Overall (n = 146)*		
System Organ Class	**Preferred Term**	**# of Events**	**# of Patients**	**% of Patients**
All Body Systems	Overall	31	18	12.3
Cardiac disorders	Tachycardia	1	1	0.7
Gastrointestinal disorders	Nausea	2	2	1.4
	Vomiting	1	1	0.7
General disorders and administration site conditions	Chest discomfort	1	1	0.7
	Chills	3	3	2.1
	Feeling jittery	1	1	0.7
	Oedema	2	2	1.4
	Pyrexia	8	8	5.5
Immune system disorders	Serum Sickness	1	1	0.7
Psychiatric disorders	Agitation	1	1	0.7
	Anxiety	1	1	0.7
Renal and urinary disorders	Urinary retention	1	1	0.7
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1	1	0.7
Skin and subcutaneous tissue disorders	Erythema	1	1	0.7
	Hyperhidrosis	1	1	0.7
	Rash	3	3	2.1
Vascular disorders	Hemodynamic instability	1	1	0.7
	Hypotension	1	1	0.7

Adverse Events are classified according to MedDRA Version 14.0.

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 22]

6.4.12.3 Deaths

This is a high risk population of subjects considered symptomatic from a potentially fatal intoxication. The majority of cases were proven to be botulism. Because this is a potentially fatal disease, death was a clinical efficacy endpoint which will be addressed in §8.4.1.

Table 5, page 25/411, *bb-ind-6750.pdf*, shows six deaths (4% of 134 treated with known outcome) from 2009-07-07 thru 2011-05-18. Age range is from 27-88 year, 4 male: 2 female. Four of the cases were proven botulism, one Guillain-Barré, and one from pneumonia in a subject with final diagnosis of “not botulism”.

The first death is described in table 5 and is further described in detail on pages 350-1/411, *bb-ind-6750.pdf*. Case was BOT IDNUM 29028, a 64 year old man with wound botulism type F treated with lot 20604011. The cause of death is not given but is stated as “unrelated to H-BAT and not directly caused by botulism itself.” He died 52 days later. The subject was first seen on 2009-04-30, placed on ventilator 2009-05-02, treated with one vial of NP-018 on 2009-05-16 (day 19). He had diaphoresis during the infusion and

later developed serum sickness with myalgia, arthralgia, and dark urine, but no rash. The serum sickness was considered mild and did not alter discharge. It is not stated that the serum sickness or signs improved. After discharge to the rehabilitation hospital, course was complicated by bacterial tracheobronchitis, hematuria, neuropathic pain, and tracheostomy plugging. He was given prophylaxis against deep venous thrombosis. It was decided to attempt decannulation of the tracheostomy after discussion and testing including nocturnal oximetry on 2012-07-05. The subject died on 2012-07-07. Though the botulism was likely the initial cause of respiratory difficulties, the immediate cause of death was not definitely determined. The timing suggests more of an issue with the airway than an acute manifestation of the botulism. Also, though there was an early serum sickness and no mention of resolution of the serum sickness, there is neither evidence for chronic sequelae nor persistent adverse effects.

The second death is BOT IDNUM 10038, an 82 year old woman originally diagnosed with foodborne botulism treated with lot 10703696. The factors leading to this diagnosis are not in the table. She tolerated the infusion well. She died of respiratory failure and pneumonia three days after infusion. No evidence was provided that showed any relation of the infusion to her demise.

The third death is BOT IDNUM 10049, a 77 year old man with foodborne botulism type A treated with lot 10703696. It is stated in the table that “Patient died of unknown causes ninety four days after H-BAT administration. Death was unrelated to H-BAT.” He had morbid obesity and sleep apnea. No cause of death is given (p. 222/411).

The fourth death is BOT IDNUM -(b)(6)-, an 88 year old woman originally diagnosed as botulism treated with lot 10703696. Subject was ultimately diagnosed as Guillain-Barré syndrome. She showed no improvement one day after treatment and remained on the ventilator. She “died of Miller Fisher variant of Guillain-Barré syndrome on ---(b)(6)---, 7 days after H-BAT administration. Death was unrelated to H-BAT.” No cause of death was given (p. 222/411).

The fifth death is BOT IDNUM 11025, a 64 year old man with botulism type A treated with lot 10703696. Subject received study product 4 days into the ICU course. He had metastatic prostate cancer and died of cancer and respiratory failure 49 days later. The table states “death was unrelated to H-BAT.”

The sixth death is BOT IDNUM 11037, a 27 year old man with intestinal colonization botulism types A and B treated with lot 10703696. During a tracheostomy tube change 27 hours after H-BAT, the subject suffered a respiratory then cardiac arrest considered secondary to mucous plugging and unrelated to the study product. Supportive care was withdrawn 17 days later. There had been no allergic reaction or other evidence of acute reaction to the study product. Further history [from IND 6750 amendment 71] shows that the subject was admitted to the hospital on 2011-02-10 for a complex course from underlying illness, including many antibiotics. On 2011-04-07 he developed descending paralysis and respiratory insufficiency, and was intubated the next day. Diagnosis of

botulism was made ---(b)(6)--- and study product given the next day. This was reported as amendments 71 to IND 6750. The IND safety reports are included on pages 368-374.

Study report #3 states that none of the deaths were related to H-BAT treatment [p. 222/411]. As above, one of the deaths occurred in a subject with an adverse reaction of serum sickness. The other five deaths occurred in subjects who did not report adverse reaction.

6.4.12.4 Nonfatal Serious Adverse Events

Nonfatal serious adverse events (SAE) are reported in *bb-ind-6750.pdf*, page 24/411. Two SAE are reported.

The first SAE is BOT IDNUM 10996. A ten year old boy with foodborne botulism type indeterminate was treated with lot 20604011. The subject experienced hemodynamic instability during the infusion of study product at 0.1 mL/min. Two episodes of severe bradycardia, including one episode that progressed to asystole, required emergency resuscitation and discontinuation of infusion. Treatment with epinephrine, CPR, and ventilatory support was given. He only received 70% of the intended pediatric dose. He eventually recovered without residual disability. The team reported this as serious, unexpected, and possibly related. The possibility that it could be related to the botulinum toxin could not be ruled out [p. 222/411]. He had no underlying predisposing cardiac or medical condition. This was reported as amendments 61 and 62 to IND 6750. The IND safety reports are included on pages 357-65.

The second SAE is BOT IDNUM 11037, which was a 27 year old man who suffered a respiratory and cardiac arrest 28 hours after NP-018 administration. This was assessed as a procedural complication of a tracheostomy manipulation and unrelated to NP-018. This subject ultimately died seventeen days later. [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 24]

Of the six deaths in the program, page 24/411 states they were due to botulism toxicity and co-morbidity complications. Since only 4/6 cases were due to botulism and the other 2/6 were not botulism, all six cases could not have been due to botulism toxicity. The CDC’s botulism expert determined that all six deaths were unrelated to H-BAT treatment.

6.4.12.5 Adverse Events of Special Interest (AESI)

One subject suffered serum sickness and ultimately died. The case is described in §6.4.12.3. No other cases of serum sickness were reported. There was no mention of thrombosis, hemolysis, transmitted diseases, anaphylaxis, severe classic allergic reactions, or other events of special interest.

Though not specifically an AESI, one subject did experience rebound toxicity from intestinal colonization. She recovered after antibiotic treatment. [Source: Original BLA 125462/0; summary-clin-safety.pdf, pp. 35-36]

6.4.12.6 Clinical Test Results

Clinical test result analysis was not done by the Applicant as part of the IND 6750 report. Included are results of lumbar punctures and other limited clinical data. Review of the define.pdf file that accompanied the raw data does not indicate inclusion of granular, line-item clinical laboratory data to assess safety or efficacy of the product. Still, review of the available raw data will continue into the second half of the review cycle.

6.4.12.7 Dropouts and/or Discontinuations

Only 37% of subjects had complete sets of reports. Six subjects died, as discussed above. Many others were discharged to rehabilitation and their ultimate non-survival outcomes are unknown. One subject suffered a serious adverse reaction with two cardiovascular episodes for which treatment was discontinued.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The first and only indication sought by the Applicant is for symptomatic botulism after known or suspected exposure to botulinum toxin. The indication is being sought for botulism in both the adult and pediatric age groups.

7.1.1 Methods of Integration

The only human studies available to address efficacy of NP-018 are BT-002B and IND 6750. Given the nature of the studies, there is no way to pool the efficacy data in a meaningful way. BT-002B was a double-blind, randomized, preexposure prophylaxis study while IND 6750 was an open-label, non-randomized, non-research, postexposure expanded access treatment protocol. BT-002A employed a different drug and cannot be integrated.

Similarly, BT-002B and IND 6750 were done in completely different subject populations and for different indications. These data cannot be pooled to evaluate efficacy in the proposed target population.

7.1.2 Demographics and Baseline Characteristics

Pediatric and geriatric populations cannot be pooled between BT-002B and IND 6750, since BT-002B included neither geriatric nor pediatric populations. Similarly, baseline characteristics cannot be pooled since BT-002B was conducted in healthy, normal volunteers while IND-6750 was conducted in seriously ill subjects with known or suspected botulinum poisoning.

7.1.3 Subject Disposition

In BT-002B and IND 6750, most subjects who initiated treatment completed their participation without discontinuing treatment or withdrawing from the trial. Thus almost all were included in the final efficacy analyses. One subject in each study discontinued their infusion due to adverse reactions. Six subjects died in IND 6750 while no deaths or SAEs were seen in BT-002B.

7.1.4 Analysis of Primary Endpoint(s)

The time to onset of signs and symptoms depends on the botulinum serotype, route, and level of exposure. Similarly, recovery time varies by toxin serotype, exposure, and time to treatment. The mechanism for action of NP-018 is to bind and neutralize the botulinum toxin, preventing interaction with the target cells. [Source: Original BLA 125462/0; 2.5 Clinical Overview, pp. 28-9/53]

There is evidence that NP-018 was efficacious in both BT-002B and IND 6750. However, primary endpoints cannot be meaningfully integrated since indications, subject populations, and outcome measures were different. The quality and strength of evidence also differed.

7.1.5 Analysis of Secondary Endpoint(s)

Not applicable.

7.1.6 Other Endpoints

Not applicable.

7.1.7 Subpopulations

As mentioned in §7.1.2, age subpopulations cannot be integrated due to lack of overlap. No significant gender or racial differences were noted.

7.1.8 Persistence of Efficacy

The prophylactic effect of NP-018 in BT-002B persisted for the entire 28 day length of the trial. The persistence of efficacy in IND 6750 cannot be determined from the data and post-hoc analyses provided.

7.1.9 Product-Product Interactions

The maltose interaction with certain glucometers will be addressed in labeling. The use of pretreatment with steroids and antihistamines was not evaluated in any trial and will be addressed in labeling.

7.1.10 Additional Efficacy Issues/Analyses

The Applicant acknowledges issues with the non-research, non-controlled, expanded-access nature of IND 6750 as regards data quality and post-hoc analyses of efficacy. BT-002B is in a different population using a different model and endpoints. The Applicant and the Agency have worked on this matter for years, and have agreed to use the Animal Rule in this BLA.

7.1.11 Efficacy Conclusions

There are no adequate and well-controlled human clinical-trial determinations of efficacy for NP-018 in the target population for the proposed indication. Therefore, the pivotal animal studies will be evaluated by other reviewers to provide evidence for efficacy. The human clinical trial data can be used in a supportive role in the determination of efficacy for this product.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The degree of product exposure was agreed upon during formal meetings and considered adequate. Horse serum is a well known product. Products similar to NP-018 have been used and studied in the past. Aside from the issue of pretreatment with antihistamines and steroids, there are no new or unanticipated safety concerns with this product. The frequencies of death, serum sickness, or other adverse reactions were within expected levels.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The most rigorous studies of safety of NP-018 were BT-001 and BT-002B. The safety data from IND 6750 was not as rigorous. The populations were very different, as were the nature of the safety assessments, between the BT studies and IND 6750.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The overall exposure is given in the following table.

Table 7 Overall Extent of Exposure to eBAT NP-018

Study Identifier	Study Population	Number of Subjects Receiving eBAT NP-018	eBAT NP-018 Dose	Route
BT-001	Normal Healthy Subjects	40	20 = one vial 20 = two vials	IV Infusion
BT-002 Stage B	Normal Healthy Subjects	16	16 = one vial	IV Infusion
*CDC BB-IND 6750	Botulism Patients	148	138 = one vial 3 = two vials 5 = one pediatric dose 1 = two pediatric doses 1 = two infant doses	IV Infusion

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 14]

Safety was enhanced by exclusion of subjects with contraindications. It is not clear that this will be possible in the acute exposure situation. [Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 15]

Combined demographics from the BT studies are given in the table below.

Table 10 Demographic Summary of Healthy Subjects Administered with eBAT NP-018

Parameter		BT-001 (n = 40)	BT-002 Stage B (n = 16)	Overall (n = 56)
Age (Years)	Mean ± SD	34 ± 9	28 ± 9	32 ± 9
	Range	(19, 52)	(19, 49)	(19, 52)
Age Groups (n, %)	<18	0	0	0
	18-39	28 (70%)	13 (81%)	41 (73%)
	40-64	12 (30%)	3 (19%)	15 (27%)
	65-75	0	0	0
	>75	0	0	0
Gender (n, %)	Female	20 (50%)	8 (50%)	28 (50%)
	Male	20 (50%)	8 (50%)	28 (50%)
Ethnicity (n, %)	Hispanic or Latino	23 (58%)	5 (31%)	28 (50%)
	Not Hispanic or Latino	17 (43%)	11 (69%)	28 (50%)
Race* (n, %)	American Indian or Alaska Native	1 (3%)	0 (0%)	1 (2%)
	Asian	1 (3%)	0 (0%)	1 (2%)
	Black/American Indian	1 (3%)	0 (0%)	1 (2%)
	Hispanic	1 (3%)	0 (0%)	1 (2%)
	Native Hawaiian or Other Pacific Islander	1 (3%)	0 (0%)	1 (2%)
	White	35 (88%)	*16 (100%)	51 (91%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 16]

No pediatric or geriatric subjects were included in the combined BT controlled trials. In the CDC study, seven pediatric and twenty geriatric subjects were included. [p.16]

8.2.3 Categorization of Adverse Events

The categorization of adverse events is more granular in the BT studies than in IND-6750. Table 7 shows a substantially shorter list of adverse events than seen in the BT studies. [Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 229]

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

There are no substantial issues pooling the data between BT-001 and BT-002B since the studies were both in normal volunteers. Pooling the data between the aforementioned two studies and IND 6750 is more difficult given the differences in capture methods and very different subject populations. The percentages of adverse events in the BT studies and IND-6750 are very different.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in the normal volunteers. Six deaths happened in IND 6750, but none yet has been conclusively related to NP-018. One death after NP-018 was preceded by serum sickness and is still being investigated.

8.4.2 Nonfatal Serious Adverse Events (SAEs)

None of the normal volunteers required hospitalization. Two subjects in the IND 6750 experienced SAEs. One was a case of asystole after NP-018 as mentioned in §6. Another was respiratory arrest during tracheostomy manipulation which was not likely drug related.

8.4.3 Study Dropouts/Discontinuations

In BT-001, one subject discontinued because of a moderate allergic reaction. In BT-002, one subject discontinued because of a moderate allergic reaction. The SAE in IND-6750 is as mentioned above. Tabular information is given below.

Table 8 Subjects Discontinued from eBAT NP-018 Trials

Study Identifier	Subject Characteristics				Reason for Discontinuation
	Study Population	Sex	Age	Race	
BT-001	Normal Healthy Subject	Male	21 years	White	Moderate allergic reaction
BT-002 Stage B	Normal Healthy Subject	Female	26 years	White	Moderate allergic reaction
*CDC BB-IND 6750	Botulism Patients	Male	10 years	Hispanic	**Serious adverse event

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 14]

Table 17 Subjects Discontinued from eBAT NP-018 Clinical Trials BT-001 and BT-002 Stage B

	BT-001 Discontinued Subject	**BT-002 (Stage B) Discontinued Subject**
Horse Dander Test	Negative	ND
Skin Sensitivity Test	Negative	Negative
Immunogenicity Test Study Start Study Finish	 Negative Negative	 Negative Negative
Timing	52 minutes (~ 30% of dose)	5 minutes (~ 1.5% of dose)
Adverse Events	Pruritus (probable) Skin disorder (probable) Headache (probable) Urticaria (probable) Somnolence (unlikely) Headache (possible) Pyrexia (possible) Pharynolaryngeal pain (possible)	Chest discomfort (related) Blood fibrinogen increase (related) Body temperature increase (related) Urticaria (related)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 21]

8.4.4 Common Adverse Events

Overall combined data for BT-001 and BT-002B adverse events are given in the tables below.

Table 12 Number of Adverse Events in eBAT NP-018 Clinical Trials BT-001 and BT-002 Stage B

	BT-001			**BT-002 Stage B**		
	1 Vial n (%)	**2 Vials n (%)**	**Total n (%)**	**1 Vial n (%)**	**Placebo n (%)**	**Total n (%)**
Number of Subjects Dosed	20 (100%)	20 (100%)	40 (100%)	16 (100%)	10 (100%)	26 (100%)
Number of Subjects with Adverse Events	9 (45%)	9 (45%)	18 (45%)	14 (88%)	10 (100%)	24 (92%)
Number of Subjects Without Adverse Events	11 (55%)	11 (55%)	22 (55%)	2 (12%)	0 (0%)	2 (8%)

[Source: Original BLA 125462/0; summary-clin-safety.pdf, p. 18]

Table 7: Reported Adverse Events in Patients who Received H-BAT (n=18)

Adverse Events	# Patients
Fever	5
Rash	2
Fever, chills	2
Fever, urinary retention	1
Chills, nausea, vomiting	1
Rash, swelling, nausea, "jittery", chest pressure	1
Hemodynamic instability (characterized by tachycardia, bradycardia and asystole)	1
Tachycardia, bronchospasm, agitation	1
Mild hypertension	1
Slight facial erythema, edema	1
Mild serum sickness, diaphoresis	1
Severe anxiety	1

[Source: Original BLA 125462/0; bb-ind-6750.pdf, p. 229]

It is not possible to pool data about adverse event rates between the BT studies and the CDC study as shown in the tables above. The side effect rate in the CDC data of eighteen out of 148 treated subjects (12%) is substantially lower than the rates of 45-100% in the BT studies.

8.4.5 Clinical Test Results

Similarly, it is not possible to pool the clinical test results from the CDC study and the BT studies due to differences in collection methods. Differences between BT-001 and BT-002A/B were discussed in §6 and include differences in the distribution of severe and moderate adverse events. Differences in tonsillar hypertrophy were also mentioned in those sections.

8.4.6 Systemic Adverse Events

One subject each from clinical trials BT-001 and BT-002B developed moderate allergic reactions. One may have developed serum sickness with lymphadenopathy. Both were negative for antibodies against NP-018 before and after treatment. Development of immune reactions against the equine product is discussed in §8.4.8 below.

8.4.7 Local Reactogenicity

No significant contribution.

8.4.8 Adverse Events of Special Interest

Immunogenicity is addressed in §8.5.8. No evidence for thrombosis or hemolysis was discovered in any subject in any trial.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

The large majority of subjects received treatment with one dose of study product. Five subjects received multiple doses. Four subjects did not have adverse events reported. A four-year-old boy was febrile (99.4 degrees) prior to administration of study product. His temperature was as high as 101.8 degrees during both doses of product. He was treated with acetaminophen and eventually the fever lysed. It is not clear if or how much the fever was from the study product, given the fever before administration.

8.5.2 Time Dependency for Adverse Events

Evaluation of the line data regarding time dependence is still ongoing at the time of the midcycle and may continue into the second half of the review cycle.

8.5.3 Product-Demographic Interactions

No evidence of gender or racial interactions have been provided or discovered at midcycle.

8.5.4 Product-Disease Interactions

No product-disease interactions other than efficacy were sought or discovered. The trials were not designed to evaluate this parameter. As mentioned previously, a possible interaction between antihistamine pretreatment and anticholinergic synaptic blockade has been raised and will probably be addressed in labeling.

8.5.5 Product-Product Interactions

Maltose in NP-018 can interfere with some blood monitoring systems. This is dealt with in the labeling. Maltose can be mistaken as glucose by some methods, and in subjects receiving NP-018 glucose should be measured with a glucose specific method. It is not clear for how long after administration this interaction persists.

Interference with live attenuated viral vaccines is a known issue with human immunoglobulin administration. The impact of equine antibody fragments is unknown. Labeling includes a deferral of vaccination after NP-018 for three months, as a precautionary measure.

8.5.6 Human Carcinogenicity

Not evaluated.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no drug abuse potential, withdrawal, or rebound effects to the medication. Rebound of the botulism has been reported but is not what is meant here. Overdosage in

humans has not been studied. Clinical pharmacology may discuss upper limits of dosage though even a double dose of NP-018 is not a large amount of protein.

8.5.8 Immunogenicity (Safety)

Immunogenicity is an adverse reaction of special interest. Data from BT-001 and BT-002B were pooled. Of the 56 healthy subjects, 30% (n=17) had antibodies against NP-018 at baseline. After exposure to study drug, 50% (n=28) had antibodies against NP-018. Therefore 20% (n=11) developed antibody against NP-018 during the trials. [Source: Original BLA 125462/0; 2.5 Clinical Overview, p. 27/53, summary-clin-pharm.pdf, p. 36]

Two subjects, one each in stages A and B, experienced moderate allergic reactions. Neither of these subjects tested positive for anti-NP-018 antibodies before or after the trials. [Source: Original BLA 125462/0; summary-clin-pharm.pdf, p. 36]

In study BT-002A with the comparator BAT AB, 60% (n=3) of subjects were positive for antibody against BAT AB on day 28 after dosing. Table 11 shows that all were negative before dosing. Therefore, NP-018 is not more immunogenic than licensed product. [Source: Original BLA 125462/0; 2.5 Clinical Overview, pp. 27-28/53]

8.5.9 Person-to-Person Transmission, Shedding
This is no applicable to this application.

8.6 Safety Conclusions

NP-018 in the well-controlled BT-001 and BT-002 studies showed safety profiles that are largely expected for an equine and/or immune globulin product. Matters of continuing inquiry are the distribution of moderate and severe adverse events in the treatment group of BT-002 and the rate of tonsillar hypertrophy. Review of line item data will continue into the second half of the cycle. Information requests are also pending for some of the deaths in IND 6750. Large differences in the frequency of adverse events between the controlled studies and IND 6750 suggests underreporting of adverse events in IND 6750.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

NP-018 has not been studied in pregnant women. Animal reproductive studies have not been done with NP-018.

9.1.2 Use During Lactation

9.1.3 Pediatric Use and PREA Considerations

NP-018 has orphan drug designation and is not controlled by PREA.

Pediatric subjects were included in IND 6750 but not the other clinical trials. Seven (5%) of subjects in IND 6750 were in the pediatric age range [p. 220/411]. Age range for pediatric subjects was 10 days-15 years (median= 5 years). Two of the seven subjects had adverse events, including one SAE as described elsewhere.

Only one infant was treated in the CDC trial, and that was serotype F. It is assumed that the other infants received BabyBIG outside of the protocol. There is insufficient data to determine safety or efficacy for infants in this study.

9.1.4 Immunocompromised Patients

This was not evaluated.

9.1.5 Geriatric Use

Geriatric subjects were included in IND 6750 but not the other clinical trials. Geriatric subjects were more common than pediatric subjects. Twenty subjects older than 65 years were included. One subject reported an adverse reaction after NP-018. The adverse reaction was a rash localized to the right wrist which resolved after 24 hours. Three of the six subjects who died in IND 6750 were > 65 years of age. Information requests are pending for two of these deaths.

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

10. CONCLUSIONS

A safety assessment is ongoing, but the midcycle assessment is that the product is acceptably safe, approximately as safe as prior licensed product, and at least as safe as prior equine antitoxins. Consideration of these factors will continue into the second half of the cycle.

Assessment of efficacy for the requested indication has been a subject of discussion between the Applicant and FDA for almost a decade. It has been decided in previous sessions that the Animal Rule should be used to evaluate efficacy since adequate and well controlled studies cannot be done ethically in humans. BT-002B is well controlled and shows convincingly that NP-018 works in a preexposure, prophylaxis model of localized foot injection of toxin. However, it is not generalizable and does not prove that NP-018 would be effective in a postexposure, treatment model of botulinum poisoning. IND 6750 is not well-controlled but could play a modest supportive role for the pivotal animal data if that route is ultimately chosen.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Botulism is a serious, life-threatening disease for which there is no available licensed medication in adults and for which only supportive care is available. Mortality has been reduced by modern ventilatory and other intensive unit care but has not been eliminated. Morbidity from the condition is substantial and the outcomes often far less than optimal even if death is averted.

NP-018 has demonstrated a reasonable safety profile although review will continue into the second half of the review cycle. Many of the risks are manageable. Pretreatment may play a role in managing that risk and will be addressed in the labeling.

11.2 Risk-Benefit Summary and Assessment

Assuming that use of the Animal Rule can provide persuasive evidence for efficacy in humans and supported by the human efficacy data above, the benefits of NP-018 in symptomatic botulism would exceed the risk in adults and older children.

11.3 Discussion of Regulatory Options

Regulatory options will be discussed in the second half of the cycle and be included in the final review memo.

11.4 Recommendations on Regulatory Actions

As of this midcycle memo, the recommendation would be approval for marketing for adults. The recommendation for pediatrics remains to be determined.

11.5 Labeling Review and Recommendations

Pending.

11.6 Recommendations on Postmarketing Actions

Pending.