Application Type	Original Application
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CBER Received Date	September 20, 2012
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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	
Dosage Form(s) and Route(s) of Administration	Powder and Solvent for Suspension Intravenous
Dosing Regimen	20, 50 ml/vial
Indication(s) and Intended Population(s)	Patients with documented or suspected symptomatic botulism poisoning

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1. EXECUTIVE SUMMARY

Cangene Corporation has submitted an application for Botulism Antitoxin Heptavalent Types A-G, (Equine), indicated for use in symptomatic patients with documented or suspected botulinum poisoning. The product is manufactured by giving toxin or toxoid to horses which create antitoxin antibodies. The antibodies are cleaved to despeciate the immunoglobulins by removal of the Fc segments. The equine plasma is purified and made into antitoxin for intravenous use. Clinical trials of efficacy in the target population have been considered unethical and the Applicant and FDA have agreed to use the Animal Rule to support licensure of the product.

A total of 287 total subjects were exposed to BAT in three clinical studies. Study BT-001 was a single-center, double-blind, parallel, pharmacokinetic and safety study of single- and double-dose administration of BAT in 40 normal volunteers. Study BT-002 stage B was a single-center, double-blind, randomized, placebo-controlled study of safety and pharmacodynamics with administration of BAT to 16 normal volunteers. IND BB-6750 is an ongoing expanded-access treatment protocol for symptomatic subjects with documented or suspected botulism poisoning conducted by CDC. As of December 2012, 231 subjects had been treated under this program.

Safety assessment in BT-001 found no dose effect on the frequency of adverse events. The most frequent AEs (≥10%) were headache and somnolence. Less frequent drug-related AEs were pruritis (8%), nausea (8%), throat pain (8%), urticaria (5%), and pyrexia (3%). All events were mild or moderate. There were no deaths, serious adverse events, or cases of anaphylaxis or serum sickness. One moderate acute allergic reaction required termination of infusion; the subject was treated and recovered. Development of anti-equine antibodies occurred in 27% of BAT recipients who were negative at baseline.

Safety assessment in BT-002B found that the most common adverse events in the treatment arm which exceeded placebo were tonsillar hypertrophy (25%), contusions (25%), and skin lacerations (19%). These events were considered unrelated to BAT because of lack of biological plausibility. There were no deaths, serious adverse events, or case of anaphylaxis. One moderate acute allergic reaction required termination of infusion; the subject was treated and recovered. This subject also developed a mild, self-limited case of serum sickness. Development of anti-equine antibodies occurred in 31% BAT recipients who were negative at baseline.

The combined exposure in BT-001 and BT-002B was 56 subjects. The most common adverse reactions in the 56 subjects were headache (9%), pruritis (5%), nausea (5%), and urticaria (5%). All other adverse reactions were reported in less than 4% of subjects and included pyrexia and throat discomfort. All reported adverse reactions were mild or moderate. No severe or serious adverse reactions were reported.

Safety assessment in the expanded access program included 231 subjects enrolled until December 2012. There were 11 deaths in the 231 subjects. None of these deaths were considered to be directly related to administration of BAT. One serious adverse reaction in a 10-year-old boy manifested with bradycardia/asystole followed by bradycardia upon rechallenge. The subject was treated and recovered. There was one case of serum sickness in a man who ultimately died of unrelated causes. Adverse reactions or combinations of adverse reactions were reported in 22 of 228 subjects (10%). The most common reactions were fever (n=9), rash (n=4), chills (n=3), nausea (n=2), and edema (n=2). Two adverse reactions occurred in 15 pediatric subjects (13%), including the SAR described above and one child whose fever worsened.

There are no adequate or well-controlled human efficacy studies available for BAT for the proposed indication. Efficacy of BAT was determined from the animal data as per the Animal Rule regulations. Supportive post hoc analysis of the human expanded access protocol suggested a beneficial impact on length of hospitalization from earlier treatment, although the uncontrolled study could not compare results for treated versus untreated subjects. Analysis of the animal data has provided a reasonable likelihood that BAT will be efficacious in humans. The clinical pharmacology team finds the dose acceptable. The life-threatening nature of the disease and the available safety data supports licensure of the product. The expected ARs of serum sickness and allergic reactions, and unexpected AR of bradycardia/asystole is addressed in the Warnings and Precautions sections of the label.

The benefit-risk profile from the available data is positive and favors approval.

RECOMMENDATION
This reviewer recommends approval of BAT.

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. The disease has typically been the result of sporadic infection or intoxication, but botulism toxin has been considered a potent bioterrorism agent. The majority of cases of botulism are wound, foodborne, infant, or iatrogenic.

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 proper nutrition are important for improved survival. Modern ICU techniques are important to minimize complications such as pneumonia, aspiration, ileus,

need for tracheostomy, other infections, and urinary retention. Botulism immune globulin intravenous (human) (BIG-IV) is available for infants < 1 year of age with intestinal botulism.

2.3 Safety and Efficacy of Pharmacologically Related Products

There have been other licensed immunoglobulin-based antitoxins for botulism that are no longer available.

1. Licensed equine botulinum antitoxin ABE
2. Licensed equine botulinum antitoxin AB
   These were licensed and available in the U.S. for over 40 years. The license for BAT AB expired March 2010.
3. Botulism immune globulin intravenous (human) (BIG-IV) is used for infant botulism A and B. The drug is approved only for infants with intestinal botulism < 1 year of age. The product has lower potency than BAT.

CDC data actively monitored 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.

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

This product has been available only through the CDC and for the clinical studies described herein. There has been no other human exposure.

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 June 2012, May 2011, July 2010, December 2009, and August 2004. IND investigations were conducted under 6750 and 12052. FDA granted orphan drug designation for BAT July 2011. Priority review was granted as part of the current approval process. The Blood Product Advisory Committee was convened 12-February-2013 and voted to recommend approval of BAT with postmarket studies.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission includes data from three trials: (a) a randomized, single-center, dual-dose, uncontrolled pharmacokinetic and study; (b) a randomized, single-center, placebo-controlled pharmacodynamic and safety study; and (c) an expanded access protocol.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The review of the submission from the Bioresearch Monitoring Inspections reviewer concluded that there were no problems that impacted the data integrity..

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

The CMC review recommends approval with a postmarketing commitment to develop a qualified ----(b)(4)---- test for canine hepacivirus and GBV-like viruses in equine plasma. They state that in the event of a mass exposure, ------(b)(4)------ could be released through the usual lot release procedures or under an existing emergency use authorization.

4.2 Assay Validation

The CMC reviewer recommends developing an assay to detect and quantify canine hepacivirus and GBV-like viruses.

4.3 Nonclinical Pharmacology/Toxicology

Non-clinical toxicology studies were not done, since this class of products is well understood and the product well characterized.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

There are no unresolved issues.

4.4.2 Human Pharmacodynamics (PD)

There are no unresolved issues. As a product being approved under the "Animal Rule," efficacy will be determined by the pivotal trials in the two non-human species studied.

4.4.3 Human Pharmacokinetics (PK)

There are no pharmacokinetic data for pediatric subjects. Postmarket studies will address this issue.

The review by the clinical pharmacology team found the studies acceptable. The animal asimulation and modeling data suggest that the single-vial dose is efficacious in humans.

4.5 Statistical

There are no outstanding issues.

4.6 Pharmacovigilance

The OBE review memo states that the Applicant proposes to carry out passive postmarketing surveillance including monitoring of adverse event reports. All serious and unexpected events including death would be submitted as 15-day reports. FDA did not agree with the Applicant's proposal. FDA negotiated an enhanced active surveillance for sporadic cases. This would be accomplished in the form of 15-day reports for all serious adverse events expected and unexpected and nonserious events related to bradycardia, allergic reactions, serum sickness, febrile reactions, or tonsillar hypertrophy.

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

5.1 Review Strategy

The review has consisted of review of the clinical documents submitted with BLA 125462/0, with reference to INDs 6750 and 12052 when needed.

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

Documents reviewed included the clinical summary submitted in Module 2, clinical reports in Module 5, draft labeling, orphan designation letter in Module 1, and meeting minutes in Module 1. Literature references were also reviewed. IND safety reports were reviewed from IND 6750. Nine amendments came in during the review and the clinical data from those reports was reviewed.

5.3 Table of Studies/Clinical Trials

Type	Name	Design	Product	# Subjects	Diagnosis
PK/Safety	BT-001	Single-center, randomized, double-blind, parallel	BAT	40 total 20 = 1 vial 20= 2 vials	Normal volunteers
PD/Safety	BT-002A	Single-center, randomized, double-blind, placebo-controlled, parallel	BAT AB	10 total 5 BAT AB 5 placebo	Normal volunteers
PD/Safety	BT-002B	Single-center, randomized, double-blind, placebo-controlled, parallel	BAT	26 total 16 BAT 10 placebo	Normal volunteers
Expanded	Expanded	Uncontrolled,	BAT	231	Known or

Type	Name	Design	Product	# Subjects	Diagnosis
Access	access program	open-label			suspected botulism at presentation

5.4 Consultations

5.4.1 Advisory Committee Meeting

Blood Products Advisory Committee meeting was convened February 2013. The committee voted to recommend approval with postmarket studies.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed

Several literature searches produced over 100 articles. 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 study

6.1.1 Objectives (Primary, Secondary, etc)

The objectives of this study were to establish safety and pharmacokinetics of BAT in normal volunteers. Dose effect on adverse events was also evaluated. The primary endpoint was safety and pharmacokinetics was the secondary endpoint.

6.1.2 Design Overview

BT-001 was a single-centre, randomized, double-blind, parallel arm study in adult normal volunteers. Subjects were randomized to a single (1 vial) or double dose (2 vials) of BAT and followed for 28 days.

6.1.3 Population

Normal volunteers were screened for risk factors or sensitivity to horses or horse products. Exclusion criteria included allergies to horses, horse serum, or horse products;

severe food or seasonal allergies; asthma; and positive horse allergy testing prior to dosing.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects (n=40) were randomized equally to a dose of one or two vials. The vials have nominal potencies 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.

6.1.5 Directions for Use

Study drug was administrated in equal volumes of fluid to maintain blinding. The infusion rate started at 0.5 mL /min for 30 minutes, then 1 mL/min for 30 minutes, then 2 mL/min for the remainder. Infusion time for the highest rate was about 80 minutes, and total infusion time was about 2.5 hours.

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

Subjects returned for follow-up visits on Days 1, 3, 7, 14, 21 and 28. A data monitoring board was utilized for safety evaluation. The schedule of assessments can be found in table 9:1 of the study report document.

6.1.8 Endpoints and Criteria for Study Success

Pharmacokinetic endpoints are evaluated by the clinical pharmacology reviewer. There were no predefined endpoints for safety. Clinical observations and descriptive statistics were done and compared between the single- and double-dose arms.

6.1.9 Statistical Considerations & Statistical Analysis Plan

No specific statistical considerations or statistical analysis were needed in the descriptive statistical comparisons between the two dose arms.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In total, 40 normal volunteers were enrolled. All subjects were analyzed for safety. One subject discontinued the infusion because of an allergic reaction and was not analyzed for pharmacokinetics, but did stay in the study for safety assessment.

6.1.10.1.1 Demographics
The study population included 20 men and 20 women. Mean age and weight were 34 years and 73 kg, respectively.

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. All subjects except one completed infusion. This one subject developed a moderate allergic reaction necessitating discontinuation of the infusion. This subject was treated and recovered. The subject was followed for the full length of the study for safety assessment.

6.1.11 Efficacy Analyses

No clinical efficacy assessments were done in this trial. The pharmacokinetics will be reported by the clinical pharmacology team.

6.1.11.1 Analyses of Primary Endpoint(s)

Analysis of the primary endpoint of safety was conducted using clinical observations and descriptive statistics. These are provided in section 6.1.12 below.

6.1.11.2 Analyses of Secondary Endpoints

Analysis of secondary endpoint of pharmacokinetics will be reported by the clinical pharmacology team.

6.1.11.3 Subpopulation Analyses

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

6.1.11.4 Dropouts and/or Discontinuations

One subject 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

The schedules of visits and clinical assessments can be found in tables 9:1 and 9:3 in the study report. These were found to be acceptable.

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 dose effect on frequency of adverse events was found between the two dose arms. The most frequent AEs (≥10%) were headache and somnolence. Headache was considered related to drug administration but somnolence was not. Less frequent drug-related AEs were pruritis (8%), nausea (8%), throat pain (8%), urticaria (5%), and pyrexia (3%). The only laboratory changes noted were minor drops in hemoglobin and hematocrit levels and increase in reticulocyte, likely associated with the volume of blood drawn.

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 BAT was an adverse event of special interest. Subjects were tested prior to dosing and on day 28. Fourteen were found to be positive at baseline for anti-equine antibodies. Seven of the 26 subjects (27%) who were negative at baseline become positive by day 28. Development of antibodies was not dose dependent. There was no clear relationship between development of adverse reactions and serological status. All antibodies were IgG or IgA. There were no IgE antibodies detected on any assay at screening or at the end of the study.

There were no reports of anaphylaxis, 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 clinically significant abnormalities in vital signs or physical findings were reported.

6.1.12.7 Dropouts and/or Discontinuations

One subject discontinued because of a moderate allergic reaction characterized by urticaria, skin nodularity, and swelling during the infusion. Other symptoms included headache, body aches, hot feeling, pyrexia, and pharyngolaryngeal pain. Skin testing was negative at screening and immunogenicity testing was negative before and after dosing.

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)

The primary objective of this study was to evaluate the pharmacodynamics of 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. The secondary objective was to evaluate the safety of licensed botulism antitoxin bivalent (equine) types A and B (Aventis Pasteur) for use as comparison with BAT. Other objectives were to validate the electrophysiological tests as a pharmacodynamic marker and obtain data for sample size calculation.

6.2.2 Design Overview

BT-002-A is a phase 1b/2a, single center, randomized, double-blind, dual-arm, parallel, clinical study. The design was an exploratory pharmacodynamic and safety study in a preventive, pre-exposure model.

6.2.3 Population

Adult normal volunteers were screened for risk factors or sensitivity to horses or horse products. Exclusion criteria included allergies to horses, horse serum, or horse products; severe food or seasonal allergies; asthma; positive horse allergy testing prior to dosing; previous treatments with commercial botulism neurotoxins, and abnormalities of nerve conduction.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects (n=10) were randomized equally to licensed antitoxin or placebo. One vial (9 mL) of licensed antitoxin contains 7500 IU of anti-A and 5500 IU of anti-B. Challenge agents were botulinum toxin type A (Botox, Allergan, Inc.) or botulinum toxin type B (Myobloc, Elan Pharmaceuticals, Inc.).

6.2.5 Directions for Use

On day 0 of the study, subjects were infused intravenously with either licensed botulism antitoxin bivalent types A and B (equine) or placebo at an infusion rate of 0.5 mL/min for the first 30 minutes. The rate was then increased to 1 mL/min for 30 minutes, then 2 mL/min for the remainder. The total infusion time was about 82 minutes.

Twenty-four hours after administration of antitoxin, botulinum toxin was injected. The intramuscular 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.

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.

6.2.7 Surveillance/Monitoring

Subjects returned for study or protocol visits on Days 1, 3, 4, 7, 14, 21 and 28. A data safety monitoring board was utilized. The schedule of assessments can be found in table 9:2 of the study report document.

6.2.8 Endpoints and Criteria for Study Success

Part of this study was to validate the pharmacodynamic effect of the product. The primary endpoint chosen was neutralization of injected botulinum toxin as assessed by percent residual muscle function. Muscle function was 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.

There were no predefined endpoints for safety. Clinical observations and descriptive statistics were to be done and compared between previously licensed antitoxin and placebo. Safety was assessed with review of clinical laboratory results, reported adverse events, vital signs, physical examinations, and electrocardiograms.

6.2.9 Statistical Considerations & Statistical Analysis Plan

For pharmacodynamics, summary statistics were calculated for the percent muscle function using both the M wave amplitude and area. Further discussion of the statistics is provided in the statistical review memo.

For safety, the incidence, intensity, and relationship of events to treatment were evaluated. Summary statistics for laboratory tests and vital signs were generated.

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 subjects were normal volunteers. Ten subjects (100%) completed the trial. All subjects were included in the analysis set.

6.2.10.1.1 Demographics
Age range was 18-44 years, mean 33 years, median 35 years. Three females and two males were enrolled in each arm.

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
Ten study subjects completed the trial. All subjects were included in the analysis set.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

Analysis of the pharmacodynamics revealed a statistically significant difference between the treatment and placebo arms ($p< 0.05$). Subjects who received placebo experienced a loss of muscle function greater than 50% within three days of toxin injection. Subjects who received licensed botulism antitoxin demonstrated preservation of muscle function for the 28 day study period.

6.2.11.2 Subpopulation Analyses

None.

6.2.11.3 Dropouts and/or Discontinuations

None.

6.2.11.4 Exploratory and Post Hoc Analyses

None.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety assessments included review of clinical laboratory results, reported adverse events, vital signs, and physical examinations.

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. 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, extremity pain, was determined to be related to licensed antitoxin. 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 in their feet, likely from toxin injections. Insomnia was more common in the placebo arm.

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)

Development of immunogenicity against BAT was an adverse event of special interest. Subjects were tested prior to dosing and on day 28. Three of out the five subjects (60%) in the treatment arm who received licensed antitoxin and who were negative at baseline for anti-equine antibodies become positive by day 28. All antibodies were IgG. There were no IgE antibodies detected on any assay at screening or at the end of the study.

6.2.12.6 Clinical Test Results

No clinically significant laboratory abnormalities were found.

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. There is no evidence that this compromised the final conclusions of the review.

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)

The primary objective of this study was to evaluate the pharmacodynamics of BAT 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. The secondary objective was to evaluate the safety of BAT.

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 an exploratory pharmacodynamic study in a preventive, pre-exposure model.

6.3.3 Population

Normal volunteers were screened for confounding risk factors or sensitivity to horses or horse products. Exclusion criteria included allergies to horses, horse serum, or horse products; severe food or seasonal allergies; asthma; positive horse allergy testing prior to dosing; previous treatments with commercial botulism neurotoxins, and abnormalities of nerve conduction.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized 8:5 to BAT or placebo. A single adult dose of BAT (1 vial) has the following nominal levels: 7500 IU anti-A, 5500 IU anti-B, 5000 IU anti-C, 1000 IU anti-D, 8500 IU anti-E, 5000 IU anti-F and 1000 IU anti-G.

6.3.5 Directions for Use

On day 0 of the study, subjects were infused intravenously with either BAT or placebo at an infusion rate of 0.5 mL/min for the first 30 minutes. The rate was then increased to 1

mL/min for 30 minutes, then 2 mL/min for the remainder. The total infusion time was about 150 minutes.

Twenty-four hours after administration of antitoxin, toxin was injected. The intramuscular 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 500 U of toxin B were chosen.

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.

6.3.7 Surveillance/Monitoring

Subjects returned for study or protocol visits on Days 1, 3, 4, 7, 14, 21 and 28. A data safety monitoring board was utilized. The schedule of assessments can be found in table 9:2 of the study report document. These were considered acceptable.

6.3.8 Endpoints and Criteria for Study Success

The primary endpoint was neutralization of injected botulinum toxin as assessed by percent residual muscle function. Muscle function was 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.

There were no predefined endpoints for safety. Clinical observations and descriptive statistics were to be done and compared between BAT and placebo. Safety was assessed with review of clinical laboratory results, reported adverse events, vital signs, physical examinations, and electrocardiograms.

6.3.9 Statistical Considerations & Statistical Analysis Plan

For pharmacodynamics, summary statistics were calculated for the percent muscle function using both the M wave amplitude and area. Further discussion of the statistics is provided in the statistical review.

For safety, the incidence, intensity, and relationship of events to treatment were evaluated. Summary statistics for laboratory tests and vital signs were generated.

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.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

A total of 26 subjects were enrolled in this protocol. All subjects were normal volunteers. Of the 26, 25 subjects completed the treatment. One subject discontinued because of an acute allergic reaction. All 26 subjects were included in the safety profile. The remaining 25 subjects were included in the pharmacodynamic analysis.

6.3.10.1.1 Demographics

Study population included 13 men and 13 women. Age range was 19-48 years, mean 28 years, median 25 years. There were 8 males and 8 females in the active arm and 5 each in the placebo arm.

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

Twenty-six subjects were enrolled into the study and randomized. All subjects except one completed infusion. This one subject developed a moderate allergic reaction necessitating discontinuation of the infusion. Subject was treated and recovered. The subject was followed for the full length of the study for safety assessment.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Analysis of the pharmacodynamics revealed a statistically significant difference between the treatment and placebo arms ($p< 0.05$). Subjects who received placebo experienced a loss of muscle function greater than 50% within three days of toxin injection. Subjects who received licensed botulism antitoxin demonstrated preservation of muscle function for the 28 day study period.

6.3.11.2 Subpopulation Analyses

None.

6.3.11.4 Dropouts and/or Discontinuations

One subject 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.

6.3.11.5 Exploratory and Post Hoc Analyses

None.

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety assessments included review of clinical laboratory results, reported adverse events, vital signs, and physical examinations.

6.3.12.2 Overview of Adverse Events

A total of 81 AEs were reported by 24 subjects in both groups. For treatment with BAT, 14 subjects reported 50 AEs. For placebo, all ten subjects reported 31 AEs. From the two arms combined, adverse events were categorized as mild, moderate, or severe in 66, 8, and 7 events, respectively. Four adverse events were related to the moderate allergic reaction in the same person. The most common adverse events in the treatment arm that exceeded placebo were tonsillar hypertrophy (25%), contusions (25%), and skin lacerations (19%). Given the lack of biological plausibility, these events were considered unrelated to BAT. Other adverse events similar in frequency to placebo included lymphadenopathy (19%), extremity pain (13%), and headache (13%).

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 moderate allergic reaction resulting in discontinuation from the trial. This subject later developed a mild self-limited lymphadenopathy which was considered to be mild serum sickness.

Immunogenicity is an adverse event of special interest. Subjects were tested prior to dosing and on day 28. Of the 13 subjects in the BAT treatment arm who were negative at baseline for anti-equine antibodies, 4 (31%) became positive by day 28. Antibodies were either IgG or IgM. No IgE antibodies were detected on any assay at screening or at the end of the study.

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 identifiable physical overexertion which is apparently common in the geographic region of the study location.

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

6.3.12.7 Dropouts and/or Discontinuations

One subject had a moderate allergic reaction during the infusion. The infusion was discontinued, and the subject was treated and recovered. This subject tested negative for skin sensitivity prior to the infusion and for immunogenicity on day 28.

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 BAT in symptomatic subjects suspected of having botulism.

6.4.2 Design Overview

This is an expanded access program which includes subjects having symptoms compatible with a botulism syndrome. The process began with the physician making the definite or suspected diagnosis of botulism poisoning in a symptomatic patient. The physician then called CDC and provided information to the CDC botulism officer or designee. The physician and botulism officer consult and made a treatment determination.

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

6.4.3 Population

The overall population available to this study was all subjects with known or suspected botulism poisoning who required treatment, with the exception of those infants treated with licensed BabyBIG. Fifteen pediatric subjects were treated with BAT.

6.4.4 Study Treatments or Agents Mandated by the Protocol

BAT was administered as a single dose in 226 of 231 (97%) subjects. Five subjects received two doses. One adult subject received a CDC-approved second dose for recurrent botulism. Another adult subject received a CDC-approved second dose for a second, separate episode of botulism. Two pediatric subjects were given two planned doses, as was the protocol at the time. One was a 10-day-old infant who received two full infant doses 8 hours apart, and the other was a 3-year-old boy who received two infant doses 7 hours apart. The fifth subject was an adult who received two doses; this was not CDC approved and was a protocol violation. The 3-year-old did experience an adverse event of fever which is discussed in section 6.4.12.2. No other adverse events were reported in the remaining four subjects who received more than one dose.

6.4.5 Directions for Use

BAT is supplied in 20 or 50 mL vials with butyl rubber stopper, containing 11-22 mL of liquid. Vial is for single use only. Contents of the vial should be completely drawn out

and diluted 1:10 in 0.9% Sodium Chloride, Injection, USP. Solution should not be shaken. Once diluted, the unused IV bag can be stored ----(b)(4)--- for use within approximately -----(b)(4)-----. For any formulation, one adult dose is one vial.

Initial rate for adults was 0.5 mL/min for 30 minutes, followed by 1 mL/min for 30 minutes, then 2 mL/min as tolerated for the remainder. For pediatric subjects, initial rate was 0.1-0.5 mL/min for 30 minutes, followed by 0.2-1 ml/min for the remainder. For infants, initial rate was 0.1 mL/min for 30 minutes, followed by 0.2 mL/min for the remainder.

6.4.6 Sites and Centers

Individual study sites are determined by the location of subjects presenting with symptoms of botulism. BAT is pre-positioned nationwide in 8 ----(b)(4)---- stations and Alaska.

6.4.7 Surveillance/Monitoring

CDC collected epidemiologic and clinical information on subjects with suspected and confirmed botulism. 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.

6.4.8 Endpoints and Criteria for Study Success

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

6.4.9 Statistical Considerations & Statistical Analysis Plan

No statistical considerations were given in the protocol and no statistical analysis plan was proposed.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

CDC study report #5 describes subjects who received BAT between January 2008 and December 2012. As of December 2012, 231 subjects received BAT. All enrolled subjects were analyzed.

6.4.10.1.1 Demographics

Age range was 10 days-88 years (median= 46 years). Study included 15 pediatric recipients (6.5% of 231) ages 10 days-17 years (median= 5 years). Of the 231 subjects, 73% (n= 169) were male, 27% female (n=62).

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Time from initial symptoms to hospital admission ranged from < 1 day to 22 days (n=210, median= 1 day). Time from hospital admission to intensive care unit (ICU)

admission ranged from < 1 day to 12 days (n=164, median < 1 day). Time from hospital admission to intubation ranged from < 1 day to 7 days (n=128, median= 1 day). Time from onset of symptoms to administration of H-BAT ranged from < 1 day to 34 days (n=210, median= 3 days). The numbers reported above are the number with available information, not necessarily those treated.

Clinical symptoms and signs upon presentation were dysphagia (87%), weakness (85%), blurred vision (77%), dysarthria (76%), fatigue (71%), and diplopia (67%). The most common signs were ptosis (76%), impaired gag reflex (62%), palatal weakness (61%), and extraocular palsy (54%).

Suspected transmission categories at the time of BAT distribution were wound (39%), foodborne (32%), iatrogenic (<1%), infant (<1%), other (4%), and indeterminate (24%). Final clinical diagnosis of botulism was made in 150 subjects (65%). Of the 150, laboratory confirmation was available for 90 (60% of final diagnosed, 39% of treated). Toxin type A (79%) was the most common confirmed type; types B, E, and F in 4% each; and indeterminate in 8%.

6.4.10.1.3 Subject Disposition

No surviving patient discontinued from the expanded access protocol. One subject with a serious adverse event of bradycardia/asystole had the infusion stopped at approximately 70% of a pediatric dose. Most subjects were discharged to home (49%) or a rehabilitation facility (29%). Eleven subjects died during the program.

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

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

6.4.11.2 Analyses of Secondary Endpoints

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

6.4.11.3 Subpopulation Analyses

Fifteen (6.5%) of subjects were in the pediatric age range. Age range for pediatric subjects was 10 days-17 years (median= 5 years). Two of the fifteen subjects had adverse events, including one SAR described elsewhere. Only one infant less than one year old was included.

6.4.11.4 Dropouts and/or Discontinuations

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

6.4.11.5 Exploratory and Post Hoc Analyses

Amendment #7 contained Summary Report #5 which included data from January 2008 – December 2012. Duration in hospital ranged from 1-182 days (median=16 days). Duration in ICU ranged from 1-182 days (median=13 days). Approximately two-thirds (65%) received mechanical ventilation for 1-182 days (median=16 days). Of those on a ventilator, approximately two-thirds (67%) received a tracheostomy. Approximately two-thirds (n=148, 67%) had residual disability upon discharge.

No predetermined efficacy endpoints were defined. Post-hoc analysis of this data was performed. For subjects with laboratory-confirmed botulism who survived (n=84), median hospital stays for those treated ≤ 2 days vs. > 2 days after onset of symptoms were 15 vs. 17.5 days, respectively ($p \leq 0.05$). Median ICU stays for those treated ≤ 6 days vs. > 6 days after onset of symptoms were 14 vs. 22.5 days, respectively ($p \leq 0.05$). Median duration of intubation for those treated ≤ 6 days vs. > 6 days after onset of symptoms were 16.5 vs. 24.5 days, respectively (p= n.s.).

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.

6.4.12.2 Overview of Adverse Events

Information regarding adverse reactions was available in 228 subjects and pending for three remaining individuals. No adverse reaction was reported in 206 (90%) subjects. Adverse reactions were categorized into 14 different types, more than half of which were composed of several different reactions, as shown in the following table.

Table 9: Reported H-BAT-Related Adverse Events, January 15, 2008 – December 31, 2012*

Adverse Events	# Patients		
	All patients	**Adults**	**Pediatrics***
No adverse event	206/228 (90%)	193/213 (91%)	13/15 (87%)
Adverse Event	22/228 (10%)	20/213 (9%)	2/15 (13%)
Fever	6	5	1
Rash	3	3	
Fever, chills	2	2	
Fever, urinary retention	1	1	
Chills, nausea, vomiting	1	1	
Rash, edema, nausea, "jittery", chest pressure	1	1	
Hemodynamic instability (characterized by tachycardia, bradycardia and asystole)	1		1
Tachycardia, bronchospasm, agitation	1	1	
Mild hypotension	1	1	
Slight facial erythema, edema	1	1	
Mild serum sickness, diaphoresis	1	1	
Severe anxiety and abdominal pain	1	1	
Increased blood pressure	1	1	
Increased white blood cell count	1	1	
Pending follow-up	*3*	*3*	

*One infant was treated with H-BAT during the period of January 15, 2008 – December 31, 2012; patient did not experience any adverse events related to H-BAT administration.

The following table separates the combined reactions into single reactions.

Adverse reaction	Number of reactions
Fever	9
Rash	4
Chills	3
Nausea	2
Edema, swelling	2
Vomiting	1
Urinary retention	1
Jittery	1
Chest pressure	1
Hemodynamic instability	1
Tachycardia	1
Bronchospasm	1
Agitation	1
Hypotension	1
Erythema	1
Serum sickness	1
Diaphoresis	1
Anxiety	1
Abdominal pain	1
Hypertension	1
Increased WBC count	1
Total	36

These totaled 36 separate reactions in 22 subjects including 20 adult (9% of 231) and 2 pediatric (13% of 15) subjects. There was no case of anaphylaxis and one case of serum sickness (0.4%) 12 days after BAT administration.

Two pediatric subjects reported adverse reactions. There was one case of hemodynamic instability and one case of increased temperature during and after an infusion. The case of hemodynamic instability was a 10-year-old boy with a sequence of bradycardia/asystole followed by resuscitation followed by another episode of bradycardia. This was considered serious, unexpected, and a positive rechallenge. In the other child with worsened fever, he was already febrile at entry. However, the fever did increase during and after the infusion and was considered related.

There was a cohort of eight subjects from a state prison who developed foodborne botulism after consumption of a homemade alcoholic beverage called pruno. This complicated outbreak reported adverse events in 7 of 8 BAT recipients including thrombophlebitis, pancreatitis, elevated lipase, decubitus ulcers, and cholecystitis. These events are not likely related to BAT administration but rather due to pruno ingestion and intercurrent illnesses.

6.4.12.3 Deaths

Eleven deaths (4.8% of 231) were reported up until December 2012. Narratives were reviewed for all cases, as well as responses to additional information requests.

A 64 year old man with history of recent antibiotic-treated sinusitis and wound botulism type F died at day 52 after BAT administration. The cause of death is not known but may be related to trying to wean off a tracheostomy. Adverse reaction of diaphoresis occurred during infusion but resolved after a few hours. The subject developed mild serum sickness 12 days after BAT administration, characterized with myalgia, arthralgia, and dark urine. Recurrent hematuria and neuropathic pain complicated chronic rehabilitation. Requests for further information were made, but the records could not be released. There is no evidence that BAT contributed directly to this death.

An 82 year old woman with dementia and foodborne botulism died at day 3 after BAT administration. The cause of death was pneumonia and respiratory failure. No adverse events were reported during infusion. There is no evidence that BAT contributed to the death.

A 77-year-old man with morbid obesity and botulism type A died at day 94 after BAT administration. The cause of death was unknown. No adverse events were reported during infusion. There is no evidence that BAT contributed to the death.

An 88-year-old woman with myelodysplastic syndrome died 7 days after BAT administration. The cause of death was reported as Miller-Fisher variant of Guillain-Barré syndrome. No adverse events were reported during infusion. Request for more information was made but information was unavailable. There is no evidence available that BAT contributed to the death.

A 64-year-old man with botulism type A with metastatic prostate cancer and botulism type A died 45 days after BAT administration. The cause of death was metastatic prostate cancer with respiratory failure. No adverse events were reported during infusion. There is no evidence available that BAT contributed to the death.

A 27-year-old man with intestinal colonization botulism types A and B and a complex prior medical history died 17 days after BAT administration. The cause of death was anoxia from cardiorespiratory arrest secondary to tracheostomy manipulation and mucus plugging. No adverse events were reported during infusion. There is no evidence available that BAT contributed to the death.

An 85-year-old man with previous stroke died 5 days after BAT administration. The cause of death was sepsis. No adverse events were reported during infusion. There is no evidence available that BAT contributed to the death.

A 49-year-old man with history of intravenous drug injection died 10 days after BAT administration. The cause of death was septic shock and respiratory failure secondary to

methicillin-resistant staphylococcus aureus. No adverse events were reported during infusion. There is no evidence available that BAT contributed to the death.

A 61-year-old man with history of coronary artery disease died 2 days after BAT administration. The cause of death was acute myocardial infarction. No adverse events were reported during the infusion. There is no evidence available that BAT contributed to the death.

A 57-year-old man with botulism type A and no contributory past medical history died 45 days after BAT administration. The cause of death was never determined although myocardial infarction was considered. No adverse events were reported during the infusion. There is no evidence available that BAT contributed to the death.

A 43-year-old man with recent gastric band manipulation and botulism type A died 175 days after BAT administration. The cause of death was acute respiratory distress syndrome and cardiopulmonary arrest. There is no evidence available that BAT contributed to the death.

6.4.12.4 Nonfatal Serious Adverse Events

There were two non-fatal serious adverse events. The first is the 10-year-old boy with bradycardia/asystole described in section 6.4.12.2. This was detailed extensively in amendments 61 and 62 to IND 6750. The second is listed as death #6 above. The serious adverse event was a non-fatal hypoxic cardiopulmonary arrest complicating a tracheostomy manipulation. The death 17 days later was a sequela of the cardiopulmonary arrest but not of the BAT administration.

6.4.12.5 Adverse Events of Special Interest (AESI)

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

Subject 12064 is listed as having a mass or stroke, but there is no suggestion that this is related to treatment.

Subject 12075 was said to have a stroke or mass lesion, but there is no suggestion that this is related to treatment.

Subject 12033 suffered an acute myocardial infarction 2 days after BAT administration; he had known coronary artery disease.

Subject 12035 died 45 days after BAT administration. Pulmonary embolism and myocardial infarction were considered but never definitively diagnosed.

6.4.12.6 Clinical Test Results

Routine clinical laboratory tests were not collected as part of the expanded access program.

In mid-2012, the IND was modified to include testing for circulating botulinum toxin 24 hours after BAT administration. To date, 11 subjects have been tested and all were negative for circulating toxin.

6.4.12.7 Dropouts and/or Discontinuations

See section 6.4.11.4.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

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

7.1.1 Methods of Integration

No adequate and well-controlled human efficacy data are available for the proposed indication. The efficacy of BAT will be determined in animals as per the Animal Rule.

Supportive efficacy data was provided from the expanded access protocol as described in section 6.4.11. This was an open-label, uncontrolled treatment program.

7.1.2 Demographics and Baseline Characteristics

No adequate and well-controlled human efficacy data are available for the proposed indication. The efficacy of BAT will be determined in animals as per the Animal Rule.

The supportive efficacy data in the expanded access program were collected from subjects treated for known or suspected symptomatic botulism. The median age was 46 years, with range of 10 days to 88 years. There were 169 males and 62 females. Fifteen pediatric subjects were included.

7.1.3 Subject Disposition

Not applicable to primary or secondary endpoints. In the expanded access program, 49% of subjects who survived were discharged to home and 29% were sent to rehabilitation or subacute care facility.

7.1.4 Analysis of Primary Endpoint(s)

Not applicable.

7.1.5 Analysis of Secondary Endpoint(s)

Not applicable.

7.1.6 Other Endpoints

Post hoc analysis of the uncontrolled expanded access program suggested a possible shortening of duration of hospital stay between those treated 2 days before versus 2 days after onset of symptoms. A similar difference was noted for difference in duration of ICU stay for treatment before and after 6 days after onset of symptoms. Because the study was not controlled, there were no data comparing subjects treated and not treated.

7.1.7 Subpopulations

None.

7.1.8 Persistence of Efficacy

No adequate and well-controlled human efficacy data are available for the proposed indication. The efficacy of BAT will be determined in animals as per the Animal Rule.

7.1.9 Product-Product Interactions

The maltose interaction with certain glucometers will be addressed in labeling.

7.1.10 Additional Efficacy Issues/Analyses

As per the Animal Rule, postmarket studies should be conducted when it becomes ethical and feasible to evaluate efficacy in humans for the proposed indication. These are addressed in the pharmacovigilance section.

7.1.11 Efficacy Conclusions

No adequate and well-controlled human efficacy data are available for the proposed indication. The data from the expanded access program was supportive, though neither adequate nor well-controlled. The efficacy of BAT will be determined in animals as per the Animal Rule.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Products similar to BAT have been used and studied in the past. BAT has only been available through the CDC expanded access program and for the studies included here. Safety was assessed in normal volunteers and in ill patients thought to have botulism.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Three clinical studies were used to demonstrate safety of BAT. BT-001 was an uncontrolled, randomized, single- and double-dose, safety and pharmacokinetic study in 40 normal volunteers. BT-002B was a randomized, placebo-controlled, safety and pharmacodynamic study in 26 normal volunteers, 16 who received BAT. IND-6750 is an ongoing CDC expanded access program which as treated 231 subjects as of December 2012.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The overall exposure is 287 subjects. There were 40 exposures in BT-001, 16 exposures in BT-002B, and 231 exposures under IND 6750. Two doses were given in 20 subjects in BT-001 and five from IND 6750.

Demographics combined from the BT studies include mean age of 32 years, age range of 19-52 years, and equal (1:1) gender distributions. No pediatric or geriatric subjects were included in the combined BT controlled trials. In the CDC study, 15 pediatric subjects were included.

The data from the BT studies and the expanded access study were not pooled due to differences in design and population.

8.2.3 Categorization of Adverse Events

Events in the BT studies were categorized into serious, severe, moderate, and mild as per definitions in the protocols. These categories comport with standard ICH definitions methods and were acceptable. Relatedness was similarly determined using ICH and CFR definitions are were acceptable. For the expanded access protocol, clinicians had forms provided to them for recording of adverse events. When received by CDC, they were reviewed and reported to FDA and CDC institutional review board as required, including requirements per 21 CFR 312.32.

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

The safety data from studies BT-001 and BT-002B were pooled as they both were conducted in normal volunteers. Pooling the data between the aforementioned two studies and IND 6750 was not done because of very different study designs and populations.

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in the normal volunteers. Eleven deaths happened in IND 6750, but none yet has been conclusively related to BAT.

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 bradycardia/asystole in a pediatric subject discussed above. Another was respiratory arrest during tracheostomy manipulation which was not likely drug related. Because of the nature of the bradycardia/asystole SAE with a pediatric patient and positive rechallenge, pharmacovigilance for this event will be evaluated in the postmarket setting.

8.4.3 Study Dropouts/Discontinuations

In BT-001, one subject discontinued infusion because of a moderate allergic reaction but did not drop out. In BT-002, one subject discontinued infusion because of a moderate allergic reaction but did not drop out. The pediatric subject with the SAE in IND-6750 discontinued infusion but did not drop out.

8.4.4 Common Adverse Events

The combined exposure in BT-001 and BT-002B was 56 subjects. The most common adverse reactions in the 56 subjects were headache (9%), pruritis (5%), nausea (5%), and urticaria (5%). All other adverse reactions were reported in less than 4% of subjects and included pyrexia and throat discomfort. All reported adverse reactions were mild or moderate. No severe or serious adverse reactions were reported. In BT-001 and BT-002B combined, two moderate acute allergic reactions required termination of infusion; the subjects were both treated and recovered. In the BT-002B study events of tonsillar hypertrophy and injuries were reported more often than with placebo, and further evaluation in the postmarket setting will be conducted.

8.4.5 Clinical Test Results

There were no standard laboratory tests that raised concern.

8.4.6 Systemic Adverse Events

Anaphylaxis was not reported though two moderate allergic reactions were reported. These were not unexpected. The event of bradycardia/asystole was discussed in 8.4.2. No relationship was detected between circulating anti-equine antibodies and adverse reactions. Two cases of serum sickness were reported. One was a case of mild, self-limited lymphadenopathy. Another occurred in one out of 231 expanded access patients and was considered mild. The subject ultimately died but this was not related to the BAT administration.

8.4.7 Local Reactogenicity

No significant contribution.

8.4.8 Adverse Events of Special Interest

Immunogenicity is addressed in section 8.5.8. No evidence for 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 or the dose, given the fever before administration.

In study BT-001, there was no dose effect on adverse events demonstrated. Immunogenicity was not affected by dose.

8.5.2 Time Dependency for Adverse Events

Acute hypersensitivity reactions occurred during or soon after the infusion. The two cases of serum sickness occurred 10 and 12 days after infusion.

8.5.3 Product-Demographic Interactions

The bradycardia/asystole event occurred in a child. The significance of this single association is unknown but should be studied in the postmarket setting.

8.5.4 Product-Disease Interactions

None.

8.5.5 Product-Product Interactions

Maltose in BAT 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 BAT glucose should be measured with a glucose specific method.

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.

8.5.8 Immunogenicity (Safety)

Immunogenicity is an adverse reaction of special interest. Data from BT-001 and BT-002B were pooled. Eleven out of 39 (28%) subjects who were negative at baseline for anti-equine antibodies developed antibody against BAT. These were mostly IgG with a few IgM, but none were IgE. In BT-002A with BAT AB, 60% of subjects who were negative at baseline developed antibody.

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.

8.5.9 Person-to-Person Transmission, Shedding
This is not applicable to this application.

8.6 Safety Conclusions

The safety profile of BAT is acceptable. Some adverse events including a single case of bradycardia/asystole, tonsillar hypertrophy, and injuries need further postmarketing evaluation.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

BAT has not been studied in pregnant women. Animal reproductive studies have not been done with BAT.

9.1.2 Use During Lactation

Not studied.

9.1.3 Pediatric Use and PREA Considerations

BAT has orphan drug designation and does not trigger PREA.

Pediatric subjects were included in IND 6750 but not the other clinical trials. Fifteen subjects in IND 6750 were in the pediatric age range. Age range for pediatric subjects was 10 days-17 years (median= 5 years). Two of the 15 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. Six of the 11 deaths in the expanded access program were in subjects ≥ 64 years old.

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

10. CONCLUSIONS

The safety profile for BAT appears acceptable.

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 or children over one year old, and for which only supportive care is currently 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.

There were two cases of mild serum sickness. Two moderate allergic reactions occurred. An isolated case of bradycardia/asystole occurred in a pediatric subject with positive rechallenge. No anaphylaxis or hemolysis has been reported. No deaths have been attributed to BAT.

11.2 Risk-Benefit Summary and Assessment

Analysis of the animal data has provided a reasonable likelihood that BAT will be efficacious in humans. The data from the expanded access program were supportive. The clinical pharmacology team finds the dose acceptable. The life-threatening nature of the disease and the spectrum of adverse events lead to the conclusion that BAT should be licensed for marketing in the United States. Serum sickness, allergic reactions, and bradycardia/asystole are addressed in the Warnings and Precautions sections of the label.

11.3 Discussion of Regulatory Options

BAT should be licensed in the United States based upon the totality of the evidence. Further regulatory decisions involve the postmarketing studies that are required under the Animal Rule, result from the bradycardia/asystole reaction, and would provide further pharmacokinetic and safety data in pediatric subjects. These are addressed in section 11.6.

11.4 Recommendations on Regulatory Actions

BAT is approvable under the Animal Rule with the postmarketing studies as described in section 11.6.

11.5 Labeling Review and Recommendations

The labeling is still under review at the time of this writing.

11.6 Recommendations on Postmarketing Actions

Because safety data are limited, it is likely that some common adverse events may have not been detected in the three clinical studies assessed for safety. Therefore, collection of additional postmarketing safety data is warranted. The two likely scenarios for postmarket data collections are in sporadic cases and in a mass exposure.

Section 4.6 discusses postmarket pharmacovigilance.

A registry would be created as part of a required postmarket safety study (PMR) under section 901 of FDAAA 2007 Title IX, to identify an unexpected serious risk when available data suggests the potential for a serious risk and to assess a known serious risk related to the use of the drug involved. This will be modeled after the existing expanded access program, will be in place no later than six months after licensure, and would run for a minimum of 3 years. Additional data compared with the original EAP would include concomitant medications including premedications.

In the event of a mass exposure, the Animal Rule requires postmarketing studies to monitor safety and efficacy of products approved under the Rule when such studies become ethical and feasible. To address this requirement, the Agency proposed that Cangene reactivate the previously established registry and expand data collection to all confirmed and suspected botulism patients. This would allow Cangene to capture safety and efficacy data in any mass exposure scenario. Data collection would include analysis of botulism subjects treated and not treated with BAT. Efficacy endpoints would include death and length of hospitalization and other forms of care. Safety endpoints would capture all adverse events occurring within 30 days of the last infusion.