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Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

BLA Supplement Number: STN 125462/0

Product Name: Botulism Antitoxin (Equine), Heptavalent (NP-18),
------(b)(4)-----

Indication(s): Treatment of Symptomatic Botulism Following
Documented or Suspected Exposure to Botulinum
Neurotoxin Serotype A, B, C, D, E, F, G

Applicant: Cangene Corporation

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1. EXECUTIVE SUMMARY

1.1 Conclusion and Recommendations

The sponsor submitted a biologic licensure application for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-(Equine) for the indication of treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotype A, B, C, D, E, F, G.

Clinical trials in a population exposed to botulinum neurotoxin (BoNT) are not feasible due to the small number of naturally occurring cases and the fact that it is unethical to deliberately expose healthy individuals to serious life-threatening pathogen, the pivotal efficacy of NP-018 is assessed in two animal models (guinea pig and non human primate Rhesus macaques) in accordance with the Animal Rule. The pivotal safety of NP-018 is assessed with two clinical trial studies that provided information on the pharmacokinetics (PK), pharmacodynamics (PD). A limited amount of efficacy and safety information was also gathered from patients treated with NP-018 under a Centers for Disease Control and Prevention (CDC) sponsored expanded access program (BB-IND 6705).

For the efficacy evaluation, the primary endpoint for both studies is the survival rate. The overall results of the efficacy endpoint of both studies show that the survival rates were statistically significantly higher for the NP-018 group than the placebo group at the 0.05 significance level. The secondary endpoints of both studies also support the outcomes of the primary efficacy endpoint. For safety evaluation, no formal statistical analysis was performed on the collected data. There were no notable differences in the number of adverse events or laboratory abnormalities between the NP-018 and placebo treated groups. Clinical reviewer should provide more in-depth review from a clinical perspective.

1.2 Brief Overview of Animal and Clinical Studies

Both guinea pig and Rhesus macaque were selected for use as a primary model for NP-018 efficacy evaluation. Six efficacy studies were performed on guinea pig and four efficacy studies were performed on Rhesus macaques investigating the ability of NP-018 to improve survival of intoxicated animals when administered either at a range of dose levels in a post-exposure prophylactic study to asymptomatic animals, or at a scaled intended human dose as a therapeutic to symptomatic animals. Study BBRC 1180-G005630 and study LBERI FY10-066 were submitted as the pivotal therapeutic efficacy studies supporting licensure. Both studies are randomized, blinded and control studies. Study G005630 contained 34 animals per group for each of the seven test serotypes groups and study FY10-666 contained 60 animals with 30 animals per treatment group. Clinical trials BT-001 and BT-002 Stage B were submitted as pivotal safety studies to support the licensure. Both studies were single center, double blinded, randomized and parallel arm studies. BT-001 contained 40 patients and BT-002 Stage B contained 26 patients.

1.3 Major Statistical Issues and Findings

There is no major statistical issue with the analysis of the pivotal efficacy endpoints. The analysis results of both animal models show that the survival rates were statistically significantly higher for the NP-018 group than the placebo group at the 0.05 significance level. The secondary endpoints of both studies also support the outcomes of the primary efficacy endpoint. For safety evaluation, no formal statistical analysis was performed on the collected data. There were no notable differences in the number of adverse events or laboratory abnormalities between the NP-018 and placebo treated groups.

2. INTRODUCTION

2.1 Overview

Cangene Corporation is using the “Animal Rule” (Title 21 Code of Federal Regulations (CFR) 601 Subpart H) to seek licensure for its NP-018. The “Animal Rule” applies to new products that intend to reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic biological substances. Under this rule the Food and Drug Administration (FDA) may grant marketing approval based on adequate and well-controlled animal studies showing that the biological product is reasonably likely to produce clinical benefits in humans. Cangene Corporation originally submitted their intention to seek licensure under this pathway in 2004 (BB-IND 12052). FDA agreed that the efficacy demonstrated in two animal models (guinea pig and Rhesus macaque) would be adequate for consideration of licensure (FDA Pre-IND Meeting Minutes of August 26, 2004) under the “Animal Rule”. Additionally, the clinical data collected by the CDC under their expanded access program (BB-IND 6750) is clinically relevant and supportive in nature to animal efficacy data for licensure under the “Animal Rule”. The indication being sought for NP-018 is for the treatment of symptomatic botulism following documented or suspected exposure to BoNT serotypes A, B, C, D, E, F or G. This indication is supported by the data from two pivotal nonclinical studies; Pivotal Therapeutic Efficacy Study in the Guinea Pig (BBRC 1180-G005630) and Pivotal Therapeutic efficacy Study in the Rhesus Macaques (LBERI FY10-066) where NP-018 was administered intravenously to symptomatic animals thereby mimicking the intervention when administered to human patients with botulism. To demonstrate the product’s safety in humans, two clinical trials (BT-001 and BT-002 Stage B) were also conducted in normal healthy human subjects.

The rest of this review is organized as below: (a) brief description of the studies that provide the efficacy and safety information to support the licensure of NP-018 (section 2.1.1 and 2.1.2), (b) the efficacy (3.1) and safety (3.2) in details, and (c) summary of the current review assessment.

2.1.1. Efficacy

2.1.1.1 Guinea Pig

The guinea pig was selected for use as a primary model for NP-018 efficacy evaluation against all seven serotypes of BoNTs known to cause botulism in humans. Six efficacy studies were performed investigating the ability of NP-018 to improve survival of intoxicated animals when administered either at a range of dose levels in a post-exposure

prophylactic study to asymptomatic animals, or at a scaled intended human dose as a therapeutic to symptomatic animals. Although each of the studies was designed to assess the efficacy of NP-018, study BBRC 1180-G005630 was the pivotal therapeutic efficacy study against all seven serotypes supporting licensure. Therefore this review memo focuses on results of study G005630.

2.1.1.2 Rhesus Macaque

Rhesus macaque was identified as the secondary model to demonstrate the product efficacy against BoNT serotype A only. Four efficacy studies were performed in Rhesus macaques, investigating the ability of NP-018 to improve survival of intoxicated animals when administered either as a post-exposure prophylactic to asymptomatic animals, or as a therapeutic to symptomatic animals. Although each of the four studies was designed to assess the efficacy of NP-018, only study LBERI FY10-066 provided the pivotal therapeutic efficacy data against serotype A supporting licensure. Therefore, this review memo focuses on results of study FY10-066.

2.1.1.3 Human

Since 2008, NP-018 has been available through a CDC sponsored expanded access program (BB IND 6750). This expanded access program was put in place to enable the use of NP-018 for the treatment of individuals with botulism as a result of naturally occurring outbreaks or in cases of isolated, unintentional incidents. The number of patients treated with NP-018 has increased since March of 2010 when NP-018 became the only botulism antitoxin product available in the United States. This was a result of the expiration of the previously licensed Botulism Antitoxin Bivalent (Equine) Types A and B product and an investigational Botulism Antitoxin Monovalent (Equine) Type E product. Between January 15, 2008 and December 31, 2011, NP-018 was administered to 148 patients. Subsequently, the CDC provided Cangene Corporation with datasets developed from the case report forms from these patients. Using these case report datasets Cangene Corporation has generated a statistical analysis report which summarizes the data and provides results of an exploratory efficacy analysis. The datasets represent the most up to date information at the time of data transfer; however data collection and data cleaning activities are ongoing by the CDC. The sponsor anticipated that the complete database will be available after NP-018 licensure and that a final statistical analysis report will be generated. The results of this post-hoc analysis have been reviewed.

2.1.2 Safety

The pivotal clinical safety of NP-018 was obtained from two clinical trials (BT-001 and BT-002 Stage B), which included a total of 66 healthy subjects administered either one or two vials of NP-018. Clinical trial BT-001 was a safety and pharmacokinetic study in which a total of 40 healthy subjects were administered either a single adult dose (one vial; n = 20) or a double adult dose (two vials; n = 20) of NP-018. Clinical trial BT-002 Stage B was a safety and PD study in which 26 subjects were administered either placebo (n = 10) or a single adult dose of NP-018 (n = 16). In addition to the two clinical trials described above, NP-018 was administered to 148 patients with suspected or confirmed botulism under a CDC expanded access program (BB-IND 6750). A limited amount of

safety information was gathered from patients under the CDC sponsored expanded access program.

2.2 Data Sources

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Room (EDR).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 BBRC 1180-G005630

3.1.1.1 Study Design

Study Objectives:

The objective of the study was to evaluate the therapeutic efficacy of NP-018 when administered intravenous (IV) to guinea pigs at the onset of clinical signs (i.e., to symptomatic animals) following exposure to BoNT serotypes A to G. The study was conducted as a randomized, blinded and controlled GLP (Good Laboratory Practice) study. Secondary objectives included comparisons of (a) time to death, (b) incidence of clinical signs, (c) time to onset of clinical signs, and (d) resolution of clinical signs between treatment and placebo control groups.

Endpoints:

The primary study endpoint is the survival rate, which is defined as the proportion of animals in each group that survived to 21 days post-intoxication. The survival rate for each treatment group was calculated as

$$P = \frac{n}{N}$$

Where

n = the number of animals in the analysis set that survived to the scheduled phase termination on Day 21 post-intoxication for a given group.

N = the total number of animals in the analysis set for a given group.

In this study, death refers to all pre-terminal deaths, whether the animals were found dead or euthanized. Any animals meeting one of the following criterion were pre-terminally euthanized: (a) any animal has a 25.0% or greater weight loss (when compared to last preintoxication body weight) in conjunction with any concurrent severe sign of intoxication; (b) any animal has two consecutive observations of total paralysis; and (c) any animal that did not meet either of the first two criteria but was judged to be moribund. Only the study director (or, if study director was not available, the Battelle staff veterinarian in consultation with a lead technician as study director's designee) determined if an animal was moribund.

The secondary endpoints include: (a) time to death (number of hours from the time the challenge dose was administered until the time of death of animals in the analysis set), (b) incidence of clinical signs, (c) time to onset of clinical signs and (d) resolution of clinical signs between treatment and placebo control groups.

All endpoints were calculated separately for each serotype.

Sample Size:

The sample size was calculated based on the assumption that the placebo group has a survival rate of less than or equal to 65% and an expected survival rate in the NP-018 treated group of equal to or greater than 95%. A sample size of 34 in each group (17 males and 17 females) is needed to achieve greater than 80% power to detect the difference between the two treatment groups at the 0.05 significance level. The study actually contained 34 animals per group for each of the seven test groups.

Randomization Scheme:

1. Serotypes A, B, C, E, F and G

Each animal shipment of 44/sex (except for Serotype D) per serotype was randomized on Study Day -1 into two test groups of 17/sex/group and one spare group of 3/sex. For randomization, groups were filled with randomly selected animals that met the weight range on Day -1. If fewer than 37/sex met the weight range on Day -1, animals outside the weight range (selected from the remaining 7 animals in each shipment) were randomized to study groups until a total of 37/sex were assigned. The random intoxication order for the 68 treatment and control animals were determined. The six spares were also assigned a random intoxication order, following the 68 treatment and control animals. A random replacement order was assigned to the extras.

On Study Day 0, animals that had Day -1 body weights <410.0 g or >490.0 g were reweighed. Starting with the study groups, any animals that did not meet the 400.0 to 500.0 g weight criteria were removed in the order they would have been intoxicated and replaced with the first available extra of the same sex that met the weight requirement. Each replacement animal assumed the random intoxication order previously assigned to the animal that was replaced. If there were insufficient extras available, spares were used to ensure that the treatment groups achieved 17/sex within the weight range whenever possible.

For serotype C, insufficient female extras or spares were available, and consequently 7 males were assigned as replacements in order to ensure that 34 treated/control and 6 spare animals within the weight range were available for intoxication. Animals with a last pre-intoxication weight outside 400.0 to 500.0 g on Day 0 were removed from the study.

2. Serotype D

Serotype D animals were randomized and replaced pre-intoxication by weight in a different manner than other serotypes. It is documented in the amendment that for Serotype D, the randomization on Study Day -1 was performed in steps:

- (1) Animals that were within the 400.0 to 500.0 g weight range were randomized by gender and Study Day -1 weights to study groups;
- (2) Animals under the weight range (weighing 350.0 to 400.0 g) were assigned to study groups in order of absolute deviation from the weight range until a total of 34/sex were assigned. All remaining animals were assigned as extras. The random intoxication order for the 68 treatment and control animals were determined. On Study Day 0, Serotype D animals with body weights <410.0 g or >490.0 g on Study Day -1 were reweighed.

Animals assigned to study groups that did not meet the 400.0 to 500.0 g weight criteria were replaced with an extra, using the following order of preference: (a) an extra of the same sex in the weight range, if any were available; (b) an extra of the opposite sex in the weight range, if any were available; and (c) an extra of either sex under the weight range (350.0 to 400.0 g) in order of absolute deviation from the weight range. If no suitable replacement (based on the replacement preference order 1-3) was available, the original animal was used. Each replacement animal assumed the random intoxication order previously assigned to the animal that was replaced. Following all Study Day 0 pre-intoxication replacements, any extra or replaced animals within 350.0 to 525.0 g became spares and were intoxicated in cage order following all group-assigned animals. Animals with a last pre-intoxication weight below 350.0 g or above 525.0 g were not used in the study.

Blinding:

All study personnel involved in the observations or treatments were blinded to the study groups and treatment materials.

Population Proposed and Analyzed in the Protocols and BLA:

All animals that were intoxicated with BoNT and who survived to receive the NP-018 or control treatment material were included in the Intent-to-Treat (ITT) analysis set, in the treatment group to which they were assigned. The ITT analysis set was used to assess all study endpoints.

Animals that were intoxicated with BoNT, successfully received the assigned treatment and had scheduled clinical observations were included in the Per-Protocol (PP) analysis set, with the exception of animals that died or were removed from study due to reasons completely unrelated to toxin challenge or treatment related toxicity (based on pathologist and/or Study Director's decision). The PP analysis set was used to assess survival endpoints (survival rate and time-to-death) to evaluate the robustness of the conclusions based on the ITT population. Only Serotype C had a different PP analysis set vs. ITT analysis set, due to exclusion of animal ID #3711 from the PP analysis set.

Protocol Amendment and Deviation:

There are 12 amendments and 79 deviations listed in the final study report. This review only focuses on the ones that related to the study design and statistical analysis.

1. Amendment 10 expanded the animal weight range to 400 to 500 g for serotype D analysis. The impact of the amendment on the study is slight. In addition, the additional statistical analysis included in the animal randomization report and supporting document for serotype D showed that there was no effect of weight on groups within each gender.
2. Deviation 11401, animal #286 and #294 were only weighted on Day -1, but were not weighted on Day 0. This deviation was acceptable since both of these animals were assigned to Extras on the Day -1 randomization and neither animal was used on the study.
3. Deviation 11388, animal #208 and #284's observation period on 8/10/2011 was incorrectly recorded and the errors were not caught by the verifier. Since both animals died 8/30/2011 and neither of these time points from animal #208 or #284 was included in the data package for statistical analysis, the impact of this deviation is minor.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

Seven separate 44/sex animal shipments were randomized pre-study to 14 groups, each group targeted to contain 17 animals /sex. Due to replacements, Serotype C and E had 18 males/16 females for the NP-018 treatment group; serotype D and F had 16 males/18 females for the NP-018 treatment group; and serotype C had 20 males/14 females for the placebo control group.

3.1.1.3 Statistical Methods

For the efficacy analysis of the primary endpoint, the null hypothesis was that there would be no improvement in survival between the NP-018 treated group and the placebo control group for each serotype. Survival rate at 21 days was calculated for each treatment and control group, along with an exact 95% confidence interval using Clopper-Pearson method. Two-tailed Fisher's exact tests were used to determine if there was a statistically significant difference between the survival rates for the NP-018 treatment group and the placebo control group for each serotype. This analysis was performed on both ITT and PP analysis sets.

For the secondary endpoint, Kaplan-Meier curves along with log-rank tests were used to compare the time to death between the NP-018 treatment group and the placebo group for each serotype. The median time to death was determined along with a two-sided 95% confidence interval for each group using the product limit method. This analysis was performed on both ITT and PP analysis sets.

For the additional secondary endpoint, incidence of clinical signs in intoxicated guinea pigs, the statistical analysis method is the same as the method used for the primary endpoint (survival rate). The statistical analysis method for time to onset of clinical signs and time to solution of clinical signs was identical to the analysis method for time to death. This review only focuses on the analysis of the primary endpoint: survival rate and the first secondary endpoint: time to death.

3.1.1.4 Results and Conclusions

Survival in the control-treated groups ranged from 0% to 15% except in the serotype G control group, which had 17/34 (50%) survival. NP-018 treatment provided significant protection against all botulinum neurotoxin serotypes (A, B, C, D, E, F and G). Two sided Fisher's exact tests showed that the survival rates were statistically significantly higher for the NP-018 group than the placebo control group for all 7 serotypes at the 0.05 significance level. Table 1 presents the survival rates, 95 percent Clopper-Pearson confidence intervals and two-sided Fisher's exact test comparison between the NP-018 treated group and the control group for each serotype for the ITT analysis set.

Table 1. Survival Rates (95% Confidence Interval) and Two-Sided Fisher’s Exact Test Comparisons between Treated and Control Groups, for the ITT Analysis Set (Source: Sponsor’s submission-Module 5, Section 5.3.5.1.1,1180-G005630 Study Report Table 8, page 23)

Serotype	Group	Number Survived/Total Animals (Percent Survived) (95 Percent Confidence Interval) ^a	Two-Sided Fisher’s Exact Test Comparison (P- Value)
A	A1 (Treated)	34/34 (100%) (90%, 100%)	<0.0001*
	A2 (Control)	0/34 (0%) (0%, 10%)	
B	B1 (Treated)	34/34 (100%) (90%, 100%)	<0.0001*
	B2 (Control)	1/34 (3%) (0%, 15%)	
C	C1 (Treated)	33/34 (97%) (85%, 100%)	<0.0001*
	C2 (Control)	4/34 (12%) (3%, 27%)	
D	D1 (Treated)	33/34 (97%) (85%, 100%)	<0.0001*
	D2 (Control)	5/34 (15%) (5%, 31%)	
E	E1 (Treated)	34/34 (100%) (90%, 100%)	<0.0001*
	E2 (Control)	0/34 (0%) (0%, 10%)	
F	F1 (Treated)	34/34 (100%) (90%, 100%)	<0.0001*
	F2 (Control)	4/34 (12%) (3%, 27%)	
G	G1 (Treated)	34/34 (100%) (90%, 100%)	<0.0001*
	G2 (Control)	17/34 (50%) (32%, 68%)	

* Comparison significant at the 0.05 level of significance.

^a Clopper-Pearson confidence interval

Time-to-death was censored at the end of the study for all surviving animals. The NP-018 treated groups had statistically significantly different (P<0.0001) time-to-death than the control groups for all seven serotypes. Table 2 presents the Kaplan-Meier median time-to-death and its 95 percent confidence interval, the p-values from log-rank test comparisons of the survival data between NP-018 treated and control animals for each serotype, for the ITT analysis set.

Table 2. Kaplan-Meier Median Time-to-Death, 95% Confidence Interval, and Log-Rank Test Comparisons between Treated and Control Groups, for the ITT Analysis Set (Source: Sponsor’s submission-Module 5, Section 5.3.5.1.1, 1180-G005630 Study Report, Table 9, page 26)

Serotype	Group	Survival Time (hours)	Log-Rank Test Time-to-Death Comparison (P-Value)
		Kaplan-Meier Median (95% Confidence Interval)	
A	A1 (Treated)	--(--)	<0.0001*
	A2 (Control)	99 (87, 113)	
B	B1 (Treated)	--(--)	<0.0001*
	B2 (Control)	94 (94, 112)	
C	C1 (Treated)	--(--)	<0.0001*
	C2 (Control)	114 (111, 141)	
D	D1 (Treated)	--(--)	<0.0001*
	D2 (Control)	156 (141, 180)	
E	E1 (Treated)	--(--)	<0.0001*
	E2 (Control)	29 (27, 30)	
F	F1 (Treated)	--(--)	<0.0001*
	F2 (Control)	58 (45, 68)	
G	G1 (Treated)	--(--)	<0.0001*
	G2 (Control)	168 (143, --) ^a	

-- The Kaplan-Meier median time-to-death could not be estimated since animal death was not observed for Serotypes A, B, E, F, and G and only one death was observed for Serotypes C and D.

* Comparison significant at the 0.05 level of significance.

^a The upper bound of the 95 percent confidence interval could not be estimated due to the high incidence (50 percent) of censoring in the data.

Serotype C was the only serotype with different Intent-to-Treat (ITT) vs. PP analysis sets, because animal ID #3711 was euthanized for humane purposes following an injury (not related to BoNT intoxication), and therefore it was excluded from the PP analysis set. For serotype C, the analysis result of the primary endpoint for the PP population is consistent with the analysis result for the ITT population.

Study G005630 successfully demonstrated the efficacy of Heptavalent Botulism Antitoxin (Equine) ABCDEFG (NP-018) when administered therapeutically to guinea pigs intoxicated with 1.5x GPIMLD₅₀ of a single serotype (A, B, C, D, E, F or G) of Botulinu Neurotoxin Complex (BoNT). Treatment with NP-018 resulted in a statistically significant (p<0.0001) improvement in survival when compared to control animals for all serotypes.

3.1.2 LBERI FY10-066

3.1.2.1 Study Design

Study Objectives:

The objective of this study was to demonstrate the therapeutic efficacy of a single IV dose of Botulinum Antitoxin Heptavalent NP-018, when administered following the

onset of clinical signs in reducing mortality among Rhesus macaques (*Macaca mulatta*) intoxicated with Botulinum Neurotoxin Serotype A Complex, with minimal supportive care provided.

Endpoints:

The primary endpoint is the survival rate at 21 days post-toxin exposure. The proportion of animals in each group survive to 21 days post-toxin exposure was calculated as

$$P = \frac{n}{N}$$

Where

n = the number of animals in the efficacy analysis set that survived to 21 post-intoxication for a given group.

N = the total number of animals in the efficacy analysis set for a given group.

Secondary endpoints include: (a) time to death, (b) time to onset of clinical signs, (c) duration of a clinical sign, (d) time from onset of clinical signs to recovery, (e) the proportion of animals recovering after the onset of clinical signs, (f) clinical severity scores, and (g) time to onset of the treatment.

Sample Size:

Sample size was determined based on the assumption that the placebo group has a survival rate of less than or equal to 10% and the NP-018 treatment group has an expected survival rate equal or greater than 45%. A total of 29 animals per group are needed to achieve 80% power to detect the assumed difference in the survival rates between treatment group and placebo group using the two-sided Fisher's exact test at the 5% significance level. In order to achieve gender balancing in each group, a total of 30 animals per group are proposed in the protocol. The study actually consisted of 60 animals with 14 males and 16 females in treatment group and 15 males and 15 females in placebo group.

Randomization Scheme:

Nonhuman primates were allocated to study groups (and then to cohorts) by use of a stratified (body weight) randomization procedure, using a computerized data acquisition system (------(b)(4)-----).

The original randomization procedure generated by --(b)(4)-- has been changed due to various reasons (See page 306, 308 & 309 of Appendix I of final report). This reviewer defers to the primary reviewer to decide whether the randomization procedure is acceptable or not.

Blinding:

To control bias, randomization and loading of syringes with test and control article were performed by technicians not involved in dosing or post-dosing observations of nonhuman primates so that those observing animals were unaware of treatment group allocations.

Population Proposed and Analyzed in the Protocols and BLA:

The efficacy analysis set is defined to include all animals that have been successfully intoxicated with Botulinum Neurotoxin Serotype A Complex and survive to receive the assigned treatment. Both survival data and observational data based on clinical signs were evaluated on all 60 animals challenged with the toxin.

Protocol Amendment and Deviation:

There are several amendments and 45 deviations included in the final study report. This review focuses on the ones that related to the study design and statistical analysis.

1. Deviation 5. On the date specified, animal 08R0115 was euthanized. However, a necropsy was not performed due to technical error. This resulted in the loss of data from a single animal. None of the remaining 29 animals in the group showed significant lesions or obvious signs of toxicity. This deviation is not going to affect the analysis of the primary endpoint.
2. Deviation 6. The toxin was flushed with 1-mL of 0.9% sterile saline (instead of 0.2% Gelatin Phosphate Buffer stated in the protocol) for animals 08R0120, 08R0143, 08R0147 and 08R0196. For those animals, the entire dose of toxin was delivered and no adverse events were noted other than expected toxin administration. All these animals are in the NP-018 treatment group and none of them survive to Day 21. Therefore, even if this deviation did not happen and all these animals survived to Day 21, it is only going to increase the survival rate of the NP-018 treatment group, which will not change the result that there is a significant difference in the survival rate for the two treatment groups.
3. Deviation 22, each treatment group was planned to consist of 30 animals (15/sex) in the protocol. However there is a gender imbalance due to incidents. The study was completed with 60 animals, 30 animals per group (treatment group included 14 males and 16 females; placebo group 2 included 15 males and 15 females). A separate paragraph was added to the protocol to address the deviation from the planned sample size with respect to gender balance. An assessment of the impact to the study was also provided. The impact of this deviation is minor.
4. Deviation 28. After the animals were randomized as specified in the protocol, two pairs of animals: animal 06R018 and 08R0108, animal 08R0094 and 06R0094 were switched into the opposite treatment groups due to the similarity in identification. Since the swapped animals were all females and the study technicians were blinded to the treatment groups, the impact of this deviation is minor.

3.1.2.2 Patient Disposition, Demographic and Baseline Characteristics

Sixty nonhuman primates (30 animals/group) completed the study. Treatment group consisted of 14 males and 16 females and placebo group 2 consisted of 15 males and 15 females.

3.1.2.3 Statistical Methods

Primary Analysis

The proportion of animals in the efficacy analysis set for each group that survived to 21 days post-toxin exposure was calculated along with two-sided 95% confidence intervals, using the exact binomial distribution. The proportion of animals that survived to 21 days

post-toxin exposure in each group was compared using Fisher’s exact test, with the probability of type I error set at a 0.05 significance level.

To conclude that the survival rate in NP-018-treated animals with minimal (nutritional) supportive care is greater than the survival rate in placebo-treated animals, the p-value of the two-sided Fisher’s exact test must be less than 0.05 and the observed treatment difference must lie in the appropriate direction.

Secondary Analysis

This review focuses on the first two secondary endpoints: time to death and time-to-onset of clinical signs. The median time to death was calculated along with corresponding two-sided 95% confidence intervals for each treatment group, using the product-limit method. Kaplan-Meier plots are also provided. The survival curves were compared between the treatment and placebo groups using the log-rank test.

3.1.2.4 Results and Conclusions

None of the animals challenged with botulinum neurotoxin serotype A complex and treated with placebo survived to the end of the study; 14 of 30 (46.7%) animals treated with NP-018 survived to the end of the study. The two-sided Fisher’s Exact test ($p < 0.0001$) shows that there is a statistically significant difference in the survival rate (0% vs. 46.7%). Table 3 lists the analysis results.

Table 3. Analysis of Survival Rates at 21 Days Post Challenge (Source: Sponsor’s submission-Module 5, Section 5.3.5.1.1, FY10-066 Study Report, Table 14:1, page 43 of 1581)

Group	Survival Rate (No. of Survivors/No. in Group)	95% Confidence	p-value
NP-018	0.47 (14/30)	(0.28, 0.66)	< 0.0001 *
Placebo	0.00 (0/30)	(0.00, 0.12)	

*A statistically significant ($\alpha = 0.05$) difference was detected using Fisher’s Exact test.

The Kaplan-Meier median time to death and corresponding 95% confidence interval were calculated for each group (Table 4). The log-rank test ($p < 0.0001$) shows a statistically significant difference in the survival distribution for the two groups,

Table 4. Analysis of Survival Time in hours(Source: Sponsor’s submission-Module 5, Section 5.3.5.1.1, FY10-066 Study Report, Table 14: 2, page 43 of 1581)

Group	Median Survival Time	95% Confidence Interval	p-value
NP-018	189.5	(102, -) ^a	< 0.0001 ^b
Placebo	74.5	(63, 81)	

^a The upper bound of the confidence interval could not be estimated due to the limited number of events (i.e., 14 animals survived until study termination).

^b A statistically significant ($\alpha = 0.05$) difference was detected using the log-rank test.

The Kaplan-Meier median times to onset of each clinical sign along with the corresponding 95% confidence intervals were calculated for each treatment group (Table 5). The time to onset of each clinical sign is defined as the first time-point where its score is greater than zero. The log-rank test was performed to compare the survival distributions between the two treatment groups for each clinical sign. There was no significant difference in the time to onset of all clinical signs except for nasal discharge.

Table 5. Analysis of Time-to-onset (hours) of Clinical Signs(Source: Sponsor’s submission-Module 5, Section 5.3.5.1.1, FY10-066 Study Report, Table 14:3, page 44 of 1581)

Clinical sign	NP-018 Median (95% CI)	Placebo Median (95% CI)	p-value
Ptosis	62 (55, 66)	64 (55, 67)	0.2939
Muscular weakness	60.5 (53, 63)	59 (52, 63)	0.1294
Respiratory distress	59.5 (55, 63)	58 (53, 63)	0.3466
Oral discharge	61.5 (58, 65)	56 (53, 60)	0.0718
Nasal discharge	107 (90, -) ^a	84 (67, 110)	0.0481 ^b
Food intake	24 (23, 28)	23.5 (23, 30)	0.4791

^a The upper bound of the confidence interval (CI) could not be estimated due to the limited number of events.

^b A statistically significant ($\alpha = 0.05$) difference was detected using the log-rank test.

3.1.3 BB-IND 6750

3.1.3.1 Study Design

Study Objectives:

The objective of this statistical analysis is to determine if the data collected through the CDC expanded access program demonstrate the effectiveness of Cangene Corporation’s NP-018 product in treating patients with suspected or confirmed botulism.

Endpoints:

The primary efficacy endpoint is the duration of hospitalization.

Randomization Scheme and Blinding:

N/A

Datasets and Population Analyzed in the BLA:

In total, data from 148 patients treated with NP-018 was submitted to Cangene Corporation by the CDC. All 148 patients who received at least one dose of NP-018 are included in the safety analysis population, regardless of whether the final diagnosis was botulism, Guillain-Barré syndrome, myasthenia gravis, tick paralysis or other. The efficacy analysis population includes patients with a discharge diagnosis of suspected or confirmed botulism, or where the final diagnosis was unknown. The inclusion of patients for which the discharge diagnosis is unknown is based on the principle of intent-to-treat. A total of 109 patients are included in the efficacy analysis population including 97 patients with a final diagnosis of botulism per the treating physician or based on confirmation from the CDC; 10 patients with the final diagnosis unknown; and 2 patients with a diagnosis of suspected botulism captured under “other”.

A subset of the efficacy analysis population includes only those patients with a CDC confirmed diagnosis of botulism and/or serotype identification.

Missing data were treated as missing and no imputation methods were used.

3.1.3.2 Patient Disposition, Demographic and Baseline Characteristics

As of December 31, 2011, 148 patients with suspected or confirmed botulism have received NP-018 under the CDC’s expanded access program (BB-IND 6750 [1 patient was treated under emergency IND: BB-IND 13615]). These patients consisted of 105 males (70.9%) and 43 females (29.1%) ranging in age from 10 days to 88 years at the time of NP-018 treatment. The majority of patients were Caucasian (41.2%) or of unknown race (41.9%). A summary of patient demographics is provided in Table 6.

Table 6. Summary of Patient Demographics for BB-IND 6750(Source: Sponsor’s submission-Module 5, Section 5.3.5.2.1, CDC Stats Report V10, Table 14:3, page 1 of 305)

Parameter		
Age (Years)	Mean	46.1
	SD	17.63
	Median	46.5
	Range	10 days - 88 years
Age Group	<18	7 (4.7%)
	18-39	49 (33.1%)
	40-64	72 (48.6%)
	65-75	11 (7.4%)
	>75	9 (6.1%)
Sex	Female	43 (29.1%)
	Male	105 (70.9%)
Ethnicity	Hispanic/Latino	54 (36.5%)
	Non-Hispanic/Non-Latino	45 (30.4%)
	Unknown	49 (33.1%)
Race	African-American/Black	3 (2.0%)
	Alaska Native	8 (5.4%)
	American Indian, Alaska Native	2 (1.4%)
	Asian	6 (4.1%)
	White	61 (41.2%)
	Other	6 (4.1%)
	Unknown	62 (41.9%)

3.1.3.3 Statistical Methods

A log linear model was fitted to the data. The sponsor called the analysis a logistic regression model in the report. Since the primary endpoint was the duration of hospitalization in days and log transformation was applied to the analysis, the model should be called a log linear model. Only patients who were confirmed to have foodborne or wound forms of botulism were included in the log linear model analysis since the sample sizes in the rest of the other categories is small. Botulinum neurotoxin serotype was not included in the model as a factor due to small sample sizes for all serotypes other than A. After a backward selection procedure with an alpha level of 0.10, three factors were included in the model: (a) botulism route of exposure (food-borne or wound), (b) intubation (1 = required or 2 = not required) and (c) time from onset of symptoms to treatment with NP-018.

In order to evaluate the effectiveness of NP-018 in the treatment of botulism, patients were stratified on the basis of the time from onset of symptoms to the first administration

of NP-018. It is anticipated that delayed treatment with NP-018 will have limited efficacy based on the mechanism of action, thus patients in the delayed treatment group will act as a comparator group for the evaluation of efficacy. A stratification cutoff of 2 days from the onset of symptoms to first administration of NP-018 was selected because circulating toxins are anticipated to still be present 2 days from the onset of symptoms. Two days is also a sufficient period of time to allow a diagnosis of suspected botulism to be made by the attending physician and for NP-018 to be shipped by the CDC. In order to evaluate the impact of defining early administration as being within 2 days from the onset of symptoms, the model was also fitted using 3 days from symptom onset as the definition of early administration.

Two separate log linear models were fitted to the data, one for each of the two efficacy analysis populations (n = 40 for confirmed cases and n= 72 for all suspected cases). The statistical modeling was performed using the generalized linear model (GLM) procedure in SAS version 9.2.

In addition to the log linear modeling performed on the duration of hospitalization data, a simple two sample t-test was performed on the log-transformed duration of hospitalization for patients treated early (0 – 2.0 days) or late (>2.0 days) from the time of onset of symptoms. Patients who were confirmed to have iatrogenic, infant or other forms of botulism were also included in the analysis. Subset analysis on patients with confirmed case was also conducted.

Summary statistics were generated to describe the patient population treated with NP-018. Statistics include the mean, median, standard deviation (SD), minimum and maximum for all continuous variables, and include the count and percentage for all categorical variables.

3.1.3.4 Results and Conclusions

For analyses on the population with confirmed botulism and population with suspected botulism, the duration of hospitalization of patients was statistically significant different between the early treatment group and the late treatment group at 0.10 significance level (P=0.0611). Route of exposure and intubation were also statistically significant in the model (P=0.0705 and P<0.001 respectively). The result of the two sample t-test was consistent with the log linear model analysis result (P=0.0640).

For the subgroup analysis of population with confirmed botulism, similar results were obtained. Intubation and early/late treatment were both statistically significant at 0.10 significance level (p<0.001 and p=0.0158 respectively). However, route of exposure was not significant any more in the model (p=0.5713). The two sample t-test also showed significant difference between the early treatment group and the late treatment group (p=0.0208) at 0.10 significance level.

The choice of statistical methods and the cutoff point for the time from onset of symptoms to first treatment with NP-018 were examined to determine if there was any impact on the overall efficacy results. The positive relationship between time to treatment

and duration of hospitalization was also demonstrated when the cutoff point was 3 days instead of 2 days for the time from onset of symptoms to first treatment. The results were consistent with the results from the analysis with the 2 days cutoff point.

The sponsor considered the results reported in study BB-IND 6750 as preliminary and are intended to be verified using additional data collected through the CDC expanded access program which is currently ongoing. The sponsor anticipated that the complete database will be available after NP-018 licensure and that a final statistical analysis report will be generated.

It is noted that the efficacy analysis of study 6750 was performed *post-hoc*. There was no pre-specified or FDA agreed statistical analysis plan for the efficacy analyses. In most circumstances, the statistical significance for clinical trial results is considered to be 0.05. Since study 6750 is not submitted as the pivotal efficacy and the analysis is post-hoc, a 0.10 significance level is acceptable to this reviewer.

3.2 Evaluation of Safety

3.2.1. Study BT-001: Pharmacokinetics of a heptavalent equine-derived botulinum antitoxin (NP-018)

3.2.1.1 Study Design

Study Objective:

Study BT-001 was a Phase 1, single center, double blind, randomized, parallel arm study to assess the safety and PK of NP-018 following IV administration of either a single dose (one vial; n = 20) or double dose (two vials; n = 20) of NP-018 to normal healthy subjects. The primary objective of the study was to evaluate the safety of NP-018 based upon clinical observations, adverse events (AE) and laboratory assessments. The subjects were followed for twenty eight days. The secondary objective was to assess the PK of the seven botulism antitoxin serotypes contained in NP-018 following IV administration.

Sample Size and Population Analyzed:

As planned a total of 40 subjects were enrolled in this study. All randomized subjects were included in the safety population for safety analysis.

Randomization Scheme:

The subjects were randomized to receive a single administration of either 1 or 2 vials of NP-018 intravenously. 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. Each dose was administered by slow intravenous infusion. The infusion rate was incremental, starting slowly and increasing if no safety related events were evident.

The randomization scheme was generated by a separate group (----- (b)(4) -----) at the contract research organization (CRO). Subjects were randomized into two groups to receive either 1 or 2 vials of NP-018. The randomization scheme was stratified by gender to ensure an equal number of male and female subjects in each group.

Blinding:

The principal investigator, all the study personnel, and all the sponsor personnel remained blinded during the study with the exception of the research pharmacist and pharmacy staff.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

The study population consisted of 20 males and 20 females of primarily white descent, with a mean age of 34 years and mean weight of 72.8 kg. A summary of the overall demographic characteristics is presented below in Table 7. Overall the demographic characteristics were similar between the two treatment groups with no obvious imbalances

Table 7. Summary of Patients Demographics for Study BT-001 (Source: Sponsor’s submission-Module 5, Section 5.3.3.1.3, BT-001 Study-Report-Body, Table 11:1, page 40 of 244)

Characteristic	Variable	Treatment A 1 Vial (n=20)	Treatment B 2 Vials (n=20)	All Subjects (n=40)
Gender	Male	10 (50%)	10 (50%)	20 (50%)
	Female	10 (50%)	10 (50%)	20 (50%)
Race	American Indian of Alaska Native	1 (5%)	0 (0%)	1 (3%)
	Asian	0 (0%)	1 (5%)	1 (3%)
	Black/American Indian	0 (0%)	1 (5%)	1 (3%)
	Hispanic	1 (5%)	0 (0%)	1 (3%)
	Native Hawaiian or Other Pacific Islander	0 (0%)	1 (5%)	1 (3%)
	White	18 (90%)	17 (85%)	35 (88%)
Age (years)	Mean (SD)	33 (9)	35 (9)	34 (9)
	Range	21.0 - 52.0	19.0 - 50.0	19.0 - 52.0
Weight (kg)	Mean (SD)	73.5 (12.7)	72.2 (10.7)	72.8 (11.6)
	Range	54.7 - 102.3	56.2 - 94.6	54.7 - 102.3
Height (cm)	Mean (SD)	166.5 (12.4)	167.1 (9.9)	166.8 (11.0)
	Range	144.0 - 191.0	152.0 - 189.0	144.0 - 191.0
Body Mass Index*	Mean (SD)	26.4 (2.3)	25.8 (2.6)	26.1 (2.5)
	Range	21.7 - 29.9	21.2 - 29.8	21.2 - 29.9
Body Mass Index**	Mean (SD)	26.4 (2.3)	25.8 (2.5)	26.1 (2.5)
	Range	21.6 - 29.9	21.2 - 29.9	21.2 - 29.9

*Body mass index was derived in ----(b)(4)---- from the collected height (in) and weight (lbs) and was used for enrolment.

**Calculated body mass index was derived from the reported height (cm) and weight (kg) on the CRF.

3.2.1.3 Statistical 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.

3.2.1.4 Results and Conclusions

Of the 40 subjects enrolled, 39 subjects completed the study as per the protocol. One subject (Subject 1) did not complete NP-018 dosing due to adverse events judged to be possibly or probably related to study treatment. Thirty nine subjects were included in the pharmacokinetic analysis as per the statistical analysis plan. All 40 subjects were included in the safety assessment.

The most frequently reported adverse events in this study were mild and moderate headache, and mild somnolence. The remaining adverse events occurred in less than 10% of subjects. Drug-related AEs occurring in less than 10% of subjects included dysphagia, flatulence, nausea, throat irritation, feeling cold, pain, pyrexia, swelling, pharyngolaryngeal pain, hyperhidrosis, pruritus, pruritus generalized, skin disorder and urticaria. These adverse events were mild or moderate in severity and most were resolved without concomitant therapy. There was no difference in the number or severity of AEs in subjects receiving either one or two vials of NP-018.

3.2.2 Study BT-002 Stage B: Botulism antitoxin effects on paralysis induced by type A and type B botulinum toxins in the extensor digitorum brevis muscle

3.2.2.1 Study Design

Study Objective:

Study BT-002 Stage B was a single center, randomized, double-blind study with two parallel arms. The study was designed as an exploratory PD study to evaluate the ability of Botulism Antitoxin Heptavalent (Equine) Types A-G in neutralizing Botulism toxins Types A and B (BOTOX® and MYOBLOC®, respectively) in a validated muscle model in healthy subjects. The primary objective of this study is to assess the ability of Botulism Antitoxin to neutralize Botulinum toxin in the Extensor Digitorum Brevis (EDB) model of muscle paralysis. Since the principle effect of exposure to botulism in humans is muscle paralysis, inhibition of muscle paralysis induced by BoNT serotype A (Botox) or BoNT serotype B (Myobloc), was used as a surrogate endpoint to demonstrate the effectiveness of NP-018 in humans. The secondary objective of this study is to evaluate the safety of Botulism Antitoxin types in healthy subjects. Subjects received injections of Botulinum toxins Types A (BOTOX®) and B (MYOBLOC®) into the EDB muscle of the left and right foot (respectively), 24 hrs following a single IV infusion (1 vial diluted 1:10 in saline) of either the antitoxin or placebo. The subjects were followed for a total of twenty eight days. Table 8 summarizes the overall study design for Stage B.

Table 8. Summary of study Design for BT-002 Stage B (Source: Sponsor’s submission-Module 5, Section 5.3.4.1.3, BT-002 Stage B Final Report, Table 9:1, page 19 of 208)

STAGE B		
Group (n=number of subjects)	Day 0	Day 1
Group 1 (n = 10)	placebo (0.9% saline solution)	BOTOX® in the left EDB muscle MYOBLOC® in the right EDB muscle
Group 2 (n = 16)	Botulism Antitoxin Heptavalent (Cangene Corporation)	BOTOX® in the left EDB muscle MYOBLOC® in the right EDB muscle

Sample Size and Population Analyzed:

Twenty-six healthy adult subjects were enrolled for Stage B study. The safety population includes all randomized subjects who were administered either placebo or Heptavalent Botulism Antitoxin.

Randomization Scheme:

Each screened subject was assigned a unique screening number for subject identification purpose. Each subject who completed the study screening assessments, met all eligibility criteria, and was accepted for Stage B of the study, was assigned a unique randomization number and received the corresponding product according to a randomization scheme generated by ----(b)(4)---- (CRO). Subjects were randomized on Day 0 to receive either Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo (0.9% saline solution) in an 8:5 ratio. The randomization scheme was sent to the investigational drug pharmacist at the investigational site in Loma Linda, California, USA.

Blinding:

Stage B of the study was designed as a double-blind study. The principle investigator and all other investigational site staff, laboratory personnel, and the sponsor personnel remained blinded as to which subjects received Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo (0.9% saline solution). To maintain the study blind, only the investigational drug pharmacist was provided and had access to the randomization scheme generated by MedSource.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

The demographic characteristics are similar between treatment and placebo groups, and there is no imbalance in the characteristic across the groups. Table 9 lists a summary of the study population demographics.

Table 9. Summary of Study Population Demographics for Study BT-002 Stage B (Source: Sponsor’s submission-Module 5, Section 5.3.4.1.3, BT-002 Stage B Final Report, Table 11:1, page 43 of 208)

Characteristic		Treatment N=16	placebo N=10	Overall 26
Age (years)	Mean SD	27.6	29.7	28.4
	Minimum	9.2	7.0	8.3
	Median	19	23	19
	Maximum	24.0	27.3	24.9
	N	49	44	49
		16	10	26
Characteristic		Treatment N=16	placebo N=10	Overall 26
Gender (N, %)	Female	8 (50%)	5(50%)	13 (50%)
	Male	8 (50%)	5 (50%)	13 (50%)
Race (N, %)	White	16 (100%)	9 (90%)	25 (96.2%)
	Black or African American	0 (0%)	1 (10%)	1 (3.8%)
Ethnicity (N, %)	Hispanic or Latino	5 (31.3%)	5 (50%)	10 (38.5%)
	Not Hispanic or Latino	11 (68.8%)	5 (50%)	16 (61.5%)

3.2.2.3 Statistical Methods

Safety evaluations included monitoring AEs, laboratory results, physical examinations, vital signs and electrocardiograms (ECG). No formal statistical analysis but only summary statistics was provided for the safety assessments conducted during clinical trial BT-002 Stage B.

Twenty four healthy subjects (92%) experienced adverse events with most being mild in severity (70% for NP-018 group and 100% for the placebo group). There were 81 AEs reported in clinical trial BT-002 Stage B, and the majority (95%) classified as being unrelated to NP-018 treatment. Only 4 AEs were determined by the Principal Investigator (PI) to be related to NP-018 administration. All 4 AEs were in the same subject and included urticaria, chest discomfort, elevated body temperature and elevated fibrinogen levels.

3.2.2.4 Results and Conclusions

Overall, no apparent difference in the number or severity of AEs reported in each of the treatment arms was observed. However, one subject developed AEs relating to study drug administration. Some laboratory findings were found to be out-of-range but were judged as not being clinically significant for this study by the investigator.

3.2.3 BB-IND 6750: Use of NP-018 heptavalent equine-based botulinum antitoxin (HBAT) after exposure to *Clostridium botulinum* toxin or other closely-related botulinum toxin-producing *Clostridia* species due to a naturally-occurring outbreak or isolated, unintentional incident.

Refer to section 3.1.3 for details in study design of BB-IND 6750. No formal statistical analysis was conducted for safety evaluation, but only summary statistics was provided. Adverse event information from patients treated with NP-018 under the CDC's expanded access program was not collected however; adverse reaction information was collected on 146 of 148 patients treated for botulism with NP-018. It was well tolerated by 128 patients (87.7% of the patients), with 18 patients (12%) experiencing adverse reactions related to NP-018 administration. No patients experienced anaphylaxis however; one patient did experience mild serum sickness. A second patient experienced hemodynamic instability including two episodes of severe bradycardia with one episode progressing to cardiac arrest. A third patient experienced rebound toxicity. Six deaths (4.1%) were also reported to the CDC. Based on information provided by the treating physician/hospital, all the death cases were determined to be unrelated to NP-018 treatment by the CDC's botulism subject matter expert (SME).

4. SUMMARY AND CONCLUSIONS

There are three efficacy and three safety studies reviewed in the memo. From a statistical point of view, this review did not find any major discrepancy or any major problems regarding the efficacy and safety analysis of the studies currently.

The overall results of the efficacy endpoint of both pivotal studies show that the survival rates were statistically significantly higher for the NP-018 group than the placebo group at the 0.05 significance level. The secondary endpoints of both studies also support the outcomes of the primary efficacy endpoint. For safety evaluation, no formal statistical analysis was performed on the collected data. There were no notable differences in the number of adverse events or laboratory abnormalities related to NP-018 between the NP-018 and placebo treated groups. The clinical reviewer should provide more in-depth review of the safety data from a clinical perspective.

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