FDA Briefing Document

Bezlotoxumab Injection

Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

June 9, 2016

The committee will discuss biologic license application (BLA) 761046 bezlotoxumab injection, submitted by Merck Sharpe & Dohme Corp., for the proposed indication of prevention of Clostridium difficile infection (CDI) recurrence.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought bezlotoxumab injection to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Introduction

This briefing document describes the review of safety and efficacy data for bezlotoxumab, prepared by the FDA for the panel members of the Advisory Committee. We would like the committee to discuss whether the data are adequate to support safety and efficacy of bezlotoxumab for the prevention of *Clostridium difficile* infection (CDI) recurrence.

2 Bezlotoxumab Product Information

Bezlotoxumab is a fully human monoclonal IgG1/kappa antibody that binds to *C. difficile* toxin B. It is hypothesized that bezlotoxumab prevents binding of toxin B to colonic cells, thus averting colonic cell inflammation.

Bezlotoxumab drug product is a sterile, aqueous, preservative-free solution filled into a 50 mL vial. Each vial contains 1000 mg bezlotoxumab. Bezlotoxumab is diluted with either 0.9% sodium chloride or 5% dextrose prior to administration. The recommended dose of bezlotoxumab is 10 mg/kg administered as an intravenous (IV) infusion over 60 minutes as a single dose.

3 Bezlotoxumab Clinical Development and Regulatory History

The proposed indication for bezlotoxumab is prevention of CDI recurrence in patients 18 years or older receiving antibacterial therapy for CDI. No drugs are currently approved for the prevention of CDI recurrence.

The investigational new drug application (IND) was submitted on November 25, 2005. Early in product development, the applicant hypothesized that an anti-toxin A antibody (actoxumab) or the combination of anti-toxin A and B antibodies would be the most effective in prevention of CDI recurrence.

The first Phase 2 trial (Study P018) evaluated the efficacy and safety of a single infusion of an anti-toxin A antibody versus placebo. The trial was conducted in 2005-2006 and was terminated early after 46 subjects received study drug (29 actoxumab and 17 placebo) because emerging nonclinical data suggested that the combination of antibodies against toxin A and B would be more effective for the prevention of CDI recurrence.

A Phase 2 trial (Study P017) comparing a combination of *C. difficile* toxin A and B antibodies with placebo in patients receiving antibacterial therapy for CDI was conducted from 2006-2008. The trial enrolled 101 patients in the combination antibody arm and 99 patients in the placebo arm. The recurrence rate was lower among patients treated with the combination of antibodies compared to those treated with placebo (7% vs. 25%; $p < 0.001$). No Phase 2 trials evaluated bezlotoxumab (anti-toxin B) alone.

Per 21 CFR 300.50(a), (Fixed-combination prescription drugs for humans), the FDA recommended that the applicant conduct a four arm study that compared the combination of monoclonal antibodies to *C. difficile* toxins A and B, to antibody to *C. difficile* toxin A alone, antibody to *C. difficile* toxin B alone, and placebo, all given in conjunction with standard of care antimicrobial therapy for CDI.

In December 2010, a Special Protocol Assessment (SPA) agreement was reached on the design of Study P001, a Phase 3, randomized, double-blind, placebo-controlled, adaptive-design trial of the efficacy in the prevention of CDI recurrence of a single infusion of human monoclonal antibody to *C. difficile* toxin A, human monoclonal antibody to *C. difficile* toxin B, and the combination of human monoclonal antibodies to *C. difficile* toxin A and toxin B in patients receiving antibacterial therapy for CDI. The primary endpoint in the protocol was CDI recurrence following clinical cure of the baseline CDI episode. The proportion was calculated as the number of subjects with CDI recurrence divided by the total number of subjects in the analysis population regardless of whether or not they had a successful resolution of the initial episode of CDI. Study P001 was initiated in November 2011.

The protocol for Study P002, the second Phase 3 trial was not submitted for an SPA. Upon review of the protocol, FDA recommended changing the primary endpoint from CDI recurrence to global cure. The reason for this recommendation was the concern that in the calculation of the CDI recurrence rate, subjects who failed treatment of the initial CDI episode would be counted as not having a recurrence.

For the binary endpoint of CDI recurrence, a successful outcome would group those who were initially cured and did not have a recurrence with those who failed initial treatment. This is not a logical grouping of outcomes. Additionally, a greater number of subjects who failed initial treatment within a treatment group would result in a smaller number of subjects who could potentially develop recurrence. Therefore, an imbalance between treatment groups in the number of subjects who failed treatment of the initial CDI episode could confound the assessment of recurrence rates. This would be most concerning if the monoclonal antibody arm had a lower initial cure rate than placebo. The endpoint of global cure avoids this problem by defining treatment success as clinical cure of the initial CDI episode and the absence of CDI recurrence.

In August 2012, FDA conveyed their recommendation to the applicant for changing the primary endpoint in Study P002 from CDI recurrence to global cure. The FDA noted that while the recurrence rate based on the Full Analysis Set (FAS) population maintains randomization and is not based only on the subset of subjects with treatment success of the initial CDI episode, it essentially treats subjects who failed treatment of the initial CDI episode as "successes" (not a recurrence) since they are included in the denominator of the recurrence rate. This approach is particularly concerning if there is an imbalance between treatment groups in the number of subjects who failed treatment of the initial CDI episode.

In November 2012, the applicant responded that they would like to preserve CDI recurrence as the primary efficacy endpoint. The applicant indicated that they did not expect that antibodies to *C. difficile* toxins would have an impact on the clinical cure rate and noted that it is important to have replicate trials with similar design.

In February 2013, FDA noted concerns regarding the efficacy evaluation in Study P002 and reiterated that the primary efficacy analysis should be based on rate of global cure. Although in the Phase 2 trial, the rates of initial cure were slightly in favor of the monoclonal antibody arm compared to the placebo arm, the results were not completely reliable due to the relatively small sample size. If the monoclonal antibody arm were to have a favorable effect on the initial cure rate then there would be fewer failures of initial treatment in the monoclonal antibody arm compared to the control arm. So, in the analysis of recurrence rate where the failures of initial treatment are brought forward as no recurrence, the results may look less favorable for the monoclonal antibody arm due to more control failures being carried forward as no recurrence. A similar problem might occur if the monoclonal antibody arm had a negative effect on the initial cure, with more failures making the results more favorable to the monoclonal antibody arm in this instance.

In February 2013, FDA also stated that it was not necessary that the two trials be designed identically, and cited the guidance titled "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" that specifically indicates that precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design.[1]

[1] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM

The applicant disagreed with changing the primary endpoint in Study P002. In July 2013, the applicant acknowledged the FDA's recommendation regarding the global cure endpoint and noted that global cure would remain a key secondary endpoint in both trials. The applicant also proposed to evaluate global cure by analyzing pooled data from the two Phase 3 trials rather than conducting separate analyses for global cure in each Phase 3 trial.

In August 2013, FDA acknowledged the applicant's intent to preserve the use of CDI recurrence as the primary efficacy endpoint but noted that interpretation of the results of these trials would depend on the number of subjects with clinical cure of the initial infection and that if the monoclonal antibody arm has a lower initial cure rate than placebo, interpretation of the CDI recurrence endpoint may be difficult. FDA also indicated that they did not agree with the proposed pooled analysis for assessing the global cure endpoint, noting that they would want confirmatory evidence from separate trials and therefore would base their assessment of the global cure endpoint on the analyses from the two individual trials.

In November 2015, the applicant submitted a BLA with the results of two Phase 3 trials to support approval of bezlotoxumab for the prevention of CDI recurrence. The results of these trials are the main subject of this briefing document.

4 Clinical Pharmacology

The pharmacokinetics (PK), safety, and immunogenicity of bezlotoxumab were characterized in Phase 1 trials. The dose of bezlotoxumab evaluated in Phase 3 trials (i.e., single IV administration of 10 mg/kg) was determined based on the safety and tolerability results from a Phase 1 dose escalating study (Study P020). No dose-ranging study was conducted to evaluate bezlotoxumab efficacy in CDI patients. Population PK (PopPK) and exposure-response analyses were conducted using pooled data from three Phase 1 trials (Studies P004, P005, and P006) and two Phase 3 trials (Studies P001 and P002).

Following single IV administration of bezlotoxumab 10 mg/kg in CDI patients, the mean clearance (CL) of bezlotoxumab was 0.317 L/day, with a volume of distribution (Vd) of 7.33 L, and an elimination half-life (t½) of approximately 19 days. These findings are consistent with PK characteristics of typical human monoclonal antibodies, which have low clearance, small volume of distribution, and long half-life. Bezlotoxumab has moderate PK variability (40% and 21% CV for $AUC_{0\text{-inf}}$ and Cmax, respectively) in CDI patients.

As a monoclonal antibody, bezlotoxumab is degraded into small peptides and individual amino acids through protein catabolism. Thus, bezlotoxumab is not expected to be metabolized by the liver or excreted by the kidney. Bezlotoxumab is not a substrate of hepatic metabolic enzymes or transporters. The target of bezlotoxumab is an exogenous toxin but not a cytokine modulator. Therefore, bezlotoxumab is not expected to inhibit or induce metabolic enzymes or transporters.

There were no clinically meaningful relationships between bezlotoxumab systemic exposure and clinical responses, including efficacy and safety.

Effect of intrinsic/extrinsic factors

The PopPK analysis of serum bezlotoxumab concentrations from the Phase 1 and Phase 3 trials demonstrated no clinically relevant effects of renal impairment and hepatic impairment on bezlotoxumab PK. In addition, the PopPK analysis showed that other intrinsic or extrinsic factors (e.g., albumin, gender, age, race/ethnicity, clinical comorbidities, CDI severity and concomitant use of non-standard care of antibacterial drugs) would not affect the exposure of bezlotoxumab to a clinically meaningful extent. Hence, no dose adjustments are required for intrinsic or extrinsic factors beyond the weight-based dose.

Effect on QT prolongation

There is no evidence from nonclinical or clinical data to suggest that bezlotoxumab has the potential to prolong ventricular repolarization. Most therapeutic monoclonal antibodies have low likelihood of direct ion channel interactions and are typically not associated with clinically meaningful effects on QTc interval. No clinically significant effect on QTc interval was observed after administration of bezlotoxumab alone or actoxumab plus bezlotoxumab in the Phase 3 trials. No dedicated QTc trial was conducted for bezlotoxumab.

Immunogenicity

In healthy subjects and CDI patients, no bezlotoxumab treatment-emergent anti-drug antibody against bezlotoxumab was observed following a single 10 mg/kg bezlotoxumab administration, indicating that there may be very limited immunogenicity due to bezlotoxumab.

5 Microbiology

The two exotoxins produced by *C. difficile*, toxin A (TcdA) and toxin B (TcdB) glucosylate members of the Rho-family of GTPases leading to physiological events in the cell that contribute to disease.

Mechanism of Action

Bezlotoxumab is a monoclonal antibody that binds toxin B with an affinity equilibrium dissociation constant (K_d) of $<1 \times 10^{-9}$ M. Bezlotoxumab inhibits the binding of toxin B to mammalian cells, preventing the intracellular entry of toxin B, including the enzymatic components responsible for the pathogenic effects of toxin B. Toxins A and B contribute to the persistence of tissue damage and immune system effects that underlie the symptoms of CDI. Bezlotoxumab does not bind to toxin A.

Activity *in vitro*

Bezlotoxumab binds in vitro to toxin B from the *C. difficile* VPI10463 strain (reference strain). Bezlotoxumab binds to an epitope on toxin B that is conserved across reported strains of *C. difficile*, although amino acid sequence variation within the epitope does occur.

In vitro studies in cell-based assays using Vero cells or Caco-2 cells, suggest that bezlotoxumab neutralizes the toxic effects of toxin B. Higher concentrations of bezlotoxumab were needed to neutralize purified toxin B of ribotypes 027 and 078 (hypervirulent ribotypes) compared to other ribotypes. Similarly, bezlotoxumab binds to purified toxin B of ribotypes 027 and 078 with lower affinity than other ribotypes. Sequence differences in the epitope of toxin B in different ribotypes can impact the binding affinity of bezlotoxumab and the resulting neutralization activity. It is of note that similar observations were made using actoxumab and toxin A.

Activity *in vivo*

The hamster model is considered to be a relevant model for *C. difficile* disease, although the infection occurs primarily in the cecum of hamsters in contrast to the infection in humans which occurs primarily in the colon. The mouse model is reportedly less severe, and has a lower rate of mortality than the hamster model. *C. difficile* causes enteritis in piglets, and CDI in pigs is similar to that seen in humans. In a gnotobiotic piglet model, anti-toxin B antibody alone protected 100% of piglets from development of systemic CDI and minimized lesions.

Animal models of mouse and hamster CDI were also used to characterize the activity of bezlotoxumab on CDI and recurrence; however, many of these studies were done in the presence of actoxumab. Infection in these models was initiated using toxins or spores and mortality, and damage and inflammation of the gut wall were evaluated. In these studies, the combination of actoxumab and bezlotoxumab was required for protection from morbidity and mortality, therefore making it difficult to discern the contribution of bezlotoxumab alone.

6 Nonclinical Toxicology

No safety pharmacology studies were conducted and no safety pharmacology endpoints were directly assessed in toxicology studies conducted with bezlotoxumab in mice. Pharmacokinetic properties of bezlotoxumab appear relatively consistent between mice and humans, particularly after a single dose administration. In mice, bezlotoxumab has a half-life in plasma of 16.8 days after a single dose, similar to 19 days observed in patients.

Single and repeat intermittent-dose toxicology studies in mice with IV bezlotoxumab administered for 14 days (5 doses/3 day interval) and 21 days (2 doses/14 day interval), failed to demonstrate any clinical signs or evidence of toxicity, at doses up to 50 and 125 mg/kg respectively, and at approximately 2.5 and 7 times greater exposure than observed in humans after a single 10 mg/kg dose. All histopathological evaluations of tissues from bezlotoxumab treated animals were similar to controls.

No targets of bezlotoxumab toxicity were identified in any of the animal toxicology studies. Bezlotoxumab does not appear to be immunogenic; however there is potential interference noted in the anti-drug antibody (ADA) assay in the presence of high serum antibody levels. Bezlotoxumab injection sites appeared free of irritation and inflammation. Tissue cross-reactivity studies conducted in vitro in at least 38 mouse and human tissues with bezlotoxumab showed no reactivity (positive staining) of tissue samples. No genotoxicity, reproductive/developmental toxicity, or carcinogenicity studies were conducted with bezlotoxumab.

7 Sources of Clinical Data

7.1 Overview of Bezlotoxumab Clinical Program

The bezlotoxumab development program included five Phase 1 studies, two Phase 2 trials, and two Phase 3 trials, **Table 1**.

Table 1: Clinical Trials in Bezlotoxumab Clinical Program [a]

Trials	Anti-toxin B (Bezlotoxumab)	Anti-toxin A and B	Anti-toxin A (Actoxumab)	Placebo
Phase 1 (n=5)	30	96	36	12
Phase 2 (n=2)	-	101	-	99
	-	-	39[b]	17
Phase 3 (n=2)				
P001	390	387	235	400
P002	396	390	-	381

[a] Number of subjects exposed to any dose of study drug
[b] The Phase 2 study evaluating anti-toxin A antibody was terminated early because additional animal data indicated that combination antibody treatment was more likely to be clinically effective. The study was not terminated due to safety concerns.

Phase 2 and 3 clinical trials were randomized, double-blind, placebo-controlled trials in patients 18 years of age or older who were receiving antibacterial treatment for a primary or recurrent episode of CDI. The trials were designed to demonstrate that a single IV infusion of monoclonal antibody(ies) at a dose of 10 mg/kg, when given in addition to antibacterial CDI therapy, decreases the proportion of subjects with CDI recurrence. Antibacterial CDI therapy included oral metronidazole, vancomycin, or fidaxomicin. Patients receiving vancomycin or fidaxomicin could also receive IV metronidazole. Subjects were followed for the evaluation of recurrence for 85 days.

A Phase 2 trial (Study 017) comparing actoxumab plus bezlotoxumab to placebo randomized 101 subjects to the combination and 99 subjects to the placebo arm. Overall, the trial population was similar to that in the Phase 3 trials and included primarily female (66%) and white (87.5%) patients with a mean age of 63.8 years. In comparison to Phase 3 trials, 70-80% of subjects received metronidazole for their CDI therapy; whereas in the Phase 3 trials, subjects were split evenly between metronidazole and vancomycin. Approximately 25% of subjects were infected with the 027 strain as compared to 9-17% in the Phase 3 trials. The number of unformed stools on the day of infusion averaged 6-8 episodes over 24 hours in subjects in the Phase 2 trial as compared to 1-3 episodes for subjects in the Phase 3 trials.

In this trial, efficacy analyses were conducted in the Intent-To-Treat population. Treatment failure was defined as recurrence of diarrhea while on SOC treatment during the first 14 days, or change in SOC treatment, or diarrhea episode lasting ≥ 14 days. Treatment failure rates were 24% in the placebo and 20.8% in the actoxumab plus bezlotoxumab arms. Recurrence rates were lower in the actoxumab plus bezlotoxumab arm (7%) compared to the placebo arm (25%).

The Phase 3 trials are described in subsequent sections of this briefing document.

7.2 Phase 3 Trials

7.2.1 Study Design

Two Phase 3 trials, P001 and P002, were conducted to support the proposed indication. Study P001 was designed as an adaptive, 4-arm, factorial trial to evaluate the efficacy, safety, and PK of actoxumab (anti-toxin A antibody), bezlotoxumab (anti-toxin B antibody), or actoxumab + bezlotoxumab versus placebo (0.9% sodium chloride) in the prevention of CDI recurrence in subjects who were receiving antibacterial treatment for CDI. The factorial design was used to provide an assessment of each antibody's contribution to the overall treatment effect. The study design also included an interim analysis which allowed for the halting of further enrollment into one or both of the

individual monoclonal antibody treatment groups if there was sufficient evidence of superiority of the combination over the individual monoclonal antibody arms. Based on the results of the interim analysis, enrollment in the actoxumab arm was stopped following the recommendation of an independent Data Monitoring Committee (DMC). Enrollment in this arm was stopped because of safety concerns of actoxumab relative to the placebo arm and low efficacy relative to the combination arm. Enrollment in the remaining three treatment groups continued until trial completion.

Study P002 was identical in design to Study P001 with the following exceptions: (1) the actoxumab alone arm was not included, (2) there was no planned interim analysis, and (3) the study had an extended follow-up period through Month 12 in a subset of patients to assess for CDI recurrence and colonization with toxigenic *C. difficile* (CDI recurrence and colonization through month 12 will not be presented in this briefing document).

Both trials were randomized, multicenter, double-blind, placebo-controlled trials. Eligible subjects were male or female aged ≥ 18 years with a confirmed diagnosis of CDI as defined by diarrhea (passage of 3 or more loose stools in 24 or fewer hours) and a positive stool test for toxigenic *C. difficile* from a stool sample collected not more than 7 days before the study drug infusion. Diarrhea was not required to be present on the day of the infusion. Subjects also needed to be receiving or planning to receive a 10 to 14 day course of SOC therapy for CDI. The SOC was oral metronidazole, vancomycin, or fidaxomicin. Subjects receiving vancomycin or fidaxomicin could also receive IV metronidazole. A subject in whom SOC was to be initiated on the same day as the study drug infusion was eligible as long as the SOC was administered prior to or within a few hours following the infusion. Subjects were monitored through phone calls and in-person visits over the 12-week study period. Subjects kept a daily log of loose stools, and this was queried by study personnel using both phone calls and site visits in order to determine if a recurrence had occurred.

In Study P001, eligible subjects were randomized 1:1:1:1 to receive a single IV infusion of actoxumab, bezlotoxumab, actoxumab plus bezlotoxumab, or placebo. In Study P002, subjects were randomized 1:1:1 into three treatment groups: bezlotoxumab, actoxumab plus bezlotoxumab, or placebo. The intended sample size was 400 subjects in each treatment group; thus, approximately 1600 subjects were to be enrolled in Study P001 and approximately 1200 subjects were to be enrolled in Study P002. Subjects were stratified by oral SOC therapy (metronidazole, vancomycin, fidaxomicin) and the subject's hospitalization status (inpatient or outpatient) at the time of randomization.

The primary efficacy objective of both trials was to determine if treatment with a single infusion of actoxumab plus bezlotoxumab or the individual monoclonal antibodies (actoxumab and/or bezlotoxumab) given in addition to SOC therapy decreased the

proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo with SOC therapy. An additional objective (primary in Study P001 and secondary in Study P002) was to determine if treatment with a single infusion of actoxumab plus bezlotoxumab with SOC therapy decreased the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of individual monoclonal antibody (actoxumab or bezlotoxumab) with SOC therapy.

A secondary objective was to determine the proportion of subjects who achieved global cure in each treatment arm as compared to placebo. An exploratory objective was to evaluate the proportion of subjects in each arm who achieved clinical cure as compared to placebo.

The primary efficacy endpoint was the proportion of subjects in the Full Analysis Set (FAS) population with CDI recurrence during the 12-week (Day 85 ± 5 days) follow-up period after a clinical cure of the baseline CDI episode. The FAS population was a subset of all randomized subjects, excluding those who did not receive an infusion of study medication, or did not have a positive stool test for toxigenic *C. difficile* at study entry, or did not receive a protocol-defined SOC therapy within a 1 day window of the infusion. Additionally in Study P001, subjects from a single investigative site that was found by the Applicant to have serious Good Clinical Practice (GCP) non-compliance issues were excluded from the FAS.

CDI recurrence was defined as the development of a new episode of diarrhea (3 watery stools in 24 hours) associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline episode. Clinical cure of the baseline episode required the subject to receive a SOC regimen of ≤ 14 days (up to 16 calendar days) and not have diarrhea on the two days immediately following the last day of SOC treatment. Global cure was a secondary endpoint and was defined as a subject who had clinical cure of the baseline CDI episode and no CDI recurrence.

The primary analysis of the efficacy endpoints was a comparison of treatment groups in the proportion of subjects with CDI recurrence, global cure, or clinical cure using the FAS population. Adjusted differences in the rate (monoclonal antibody – placebo) and corresponding 95% confidence intervals (CI) stratified by SOC therapy and hospitalization status were also calculated. To control type I error due to multiple treatment comparisons, a sequential testing approach was used. In addition, in Study P001 the alpha level was adjusted to control for the interim analysis as well as the second primary objective to compare the actoxumab + bezlotoxumab arm to each component. In both studies, the order of testing was the combined monoclonal antibody vs. placebo followed by the bezlotoxumab vs. placebo comparison.

Efficacy results presented in this briefing package are by individual trial and not pooled since the evidence from two independent trials is of interest. Furthermore, pooled analyses may mask treatment differences when discordant results are observed.

7.2.2 Demographics

In both Phase 3 trials, the demographic characteristics in the treatment arms were well matched (See **Table 2**). All arms had a slight preponderance of females and about 50% of subjects were ≥ 65 years old and ~25% were ≥ 75 years old. The majority of subjects were white, ~ 90% and 80% in Study P001 and P002, respectively. Around 50% of subjects in Study P001 and about 40% of subjects in Study P002 were enrolled in North America. Around 45% of subjects in Study P001 and 35% of subjects in Study P002 came from U.S. sites.

In terms of severity of baseline disease, around 15-20% of subjects in each trial had a Zar score ≥ 2. The score assigns one point for age > 60 years, temperature > 38.3°C, albumin level < 2.5 mg/dL, or peripheral WBC count > 15,000 cells/mm^3 within 48 hours of enrollment. Two points are given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit[2]. About 20% of subjects in each trial were immunocompromised (defined as having an active hematological malignancy, using an antineoplastic or immunomodulating agent, using corticosteroids, having received a prior solid organ transplant, being asplenic, being neutropenic/pancytopenic, or having AIDS/immunodeficient condition). About 25% of subjects in each arm in both trials had been on SOC for > 4 days by the time they received their study drug infusion. On the day of study drug infusion, over 70% of subjects in each study had ≤ two loose stools that day.

In Study P002, more hypervirulent strains of *C. difficile* defined as ribotypes 027, 078, or 244 were noted in the placebo arm relative to the other two arms (19% in the placebo arm vs. 13 and 12% in the other two arms). No difference between study arms in the rate of infection with hypervirulent strains was observed in Study P001. Around 30% of subjects in each arm in both trials had an episode of CDI in the 6 months prior to enrollment. Around 50% of subjects in each arm in both trials were stratified to metronidazole or oral vancomycin.

[2] Zar FA, Bakkanagari SR ae al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007 Aug 1; 45(3):302-7.

There were some differences of note between the FAS populations between the two trials. In Study P002 subjects were slightly older relative to those in Study P001, had a higher proportion of Asian subjects, and had a higher proportion of ex-U.S. subjects. In Study P002, more subjects in each arm had received > 4 days of SOC at the time of study drug infusion. In Study P002, fewer placebo subjects were immunocompromised relative to Study P001, but a higher proportion of subjects had hypervirulent strains. Also in Study P002, more subjects in the bezlotoxumab arm had ≤ 2 loose stools on the day of study drug infusion relative to Study P001.

Table 2: Key Demographic Characteristics in Studies P001 and P002 (FAS Population)

	Study P001		**Study P002**	
	Placebo (N=395) n (%)	**Bezlotoxumab (N=386) n (%)**	**Placebo (N=378) n (%)**	**Bezlotoxumab (N=395) n (%)**
Female	223 (56.5%)	229 (59.3%)	226 (59.8%)	213 (53.9%)
Age				
Mean years (SD)	62	60	64	62
≥ 65 years	199 (50.4%)	185 (47.9%)	206 (54.5%)	205 (51.9%)
Race				
White	366 (92.7%)	338 (87.6%)	309 (81.7%)	311 (78.7%)
Black or African American	18 (4.6%)	28 (7.2%)	10 (2.6%)	17 (4.3%)
Asian	1 (0.2%)	4 (1%)	57 (15.1%)	63 (15.9%)
Other	10 (2.5%)	16 (4.1%)	2 (0.5%)	4 (1%)
Region				
U.S.	186 (47.1%)	171 (44.3%)	131 (34.7%)	136 (34.4%)
Ex U.S.	209 (52.9%)	215 (55.7%)	247 (65.3%)	259 (65.6%)
History of CDI in prior 6 months	109 (27.6%)	103 (26.7%)	110 (29.1%)	113 (28.6%)
Immunocompromised	92 (23.3%)	87 (22.5%)	53 (14%)	82 (20.8%)
≤ 2 loose stools on Day 1	272 (68.9%)	264 (68.4%)	277 (73.3%)	316 (80.0%)
Hypervirulent strains	44 (11.1%)	51(13.2%)	71 (18.8%)	51 (12.9%)
Prior SOC ≤ 4 days	292 (75.6%)	287 (74.4%)	269 (71.1%)	270 (68.4%)

SOC – standard of care

8 Evaluation of Efficacy

In Study P001, 1452 subjects were randomized into the trial. The FAS population consisted of 1396 subjects: 383 in the actoxumab plus bezlotoxumab, 232 in actoxumab, 386 in bezlotoxumab, and 395 in placebo arms, respectively.

A significantly lower proportion of subjects had CDI recurrence in the actoxumab plus bezlotoxumab group (15.9%) and the bezlotoxumab group (17.4%) as compared to placebo (27.6%). The actoxumab plus bezlotoxumab arm is referred to as acto plus bezlo in the tables provided in this briefing document. The adjusted differences in CDI recurrence and 95% CI were -11.6% (-17.3%, -5.9%) between actoxumab plus bezlotoxumab and placebo, and -10.1% (-15.9%, -4.3%) between bezlotoxumab and placebo, **Table 3**. A slightly lower proportion of subjects had CDI recurrence in the actoxumab plus bezlotoxumab group as compared to bezlotoxumab but the difference was not statistically significant (2-sided p-value= 0.5944).

Clinical cure of the initial CDI episode was lower for both actoxumab plus bezlotoxumab (74.7%, significantly 2-sided p=0.0057) and bezlotoxumab (77.5%, numerically 2-sided p=0.0622) as compared to placebo (82.8%). Due to this negative imbalance in initial clinical cure, the interpretation of the CDI recurrence endpoint becomes difficult. Thus, global cure is the more appropriate endpoint to consider. Although the proportion of subjects with global cure was numerically in favor of actoxumab plus bezlotoxumab (58.7%) and bezlotoxumab (60.1%) in comparison to placebo (55.2%), the differences were not statistically significant. The adjusted differences in global cure and 95% CI were 3.5% (-3.4%, 10.4%) between actoxumab plus bezlotoxumab and placebo, and 4.8% (-2.1%, 11.7%) between bezlotoxumab and placebo.

Table 3 : Results of Clinical Cure, CDI Recurrence and Global Cure (FAS) in Study P001

	Acto plus Bezlo n=383	**Actoxumab** n=232	**Bezlotoxumab** n=386	**Placebo** n=395
Clinical Cure	286 (74.7) -8.2 (-13.9, -2.4) **p=0.0057**	169 (72.8) -10.0 (-16.8, -3.2) p=0.0031	299 (77.5) -5.3 (-10.9, 0.3) p=0.0622	327 (82.8)
CDI Recurrence	61 (15.9) -11.6 (-17.3, -5.9) **p<0.0001**	60 (25.9) -1.7 (-8.8, 5.4) p=0.6368	67 (17.4) -10.1 (-15.9, -4.3) **p=0.0006**	109 (27.6)
Global Cure	225 (58.7) 3.5 (-3.4, 10.4) p=0.3165	109 (47.0) -8.3 (-16.4, -0.3) p=0.0470	232 (60.1) 4.8 (-2.1, 11.7) p=0.1647	218 (55.2)

Difference (95% CI) for monoclonal antibody - placebo
Two-sided p-values based on chi-square test for comparison of monoclonal antibody arm vs placebo, **bold** indicates significant at a cutoff value ≤ 0.025, hierarchical ordering of tests: actoxumab plus bezlotoxumab vs placebo followed by bezlotoxumab vs. placebo. Two-sided rather than one-sided p-values are presented for ease in interpretation due to situations where the placebo arm was better than the monoclonal antibody arm.

In Study P002, 1203 subjects were randomized into the trial. The FAS population consisted of 1163 subjects: 390 in the actoxumab plus bezlotoxumab, 395 in bezlotoxumab, and 378 in placebo arms, respectively.

A significantly lower proportion of subjects had CDI recurrence in the actoxumab plus bezlotoxumab group (14.9%) and the bezlotoxumab group (15.7%) as compared to placebo (25.7%). The adjusted differences in CDI recurrence and 95% CI were -10.7% (-16.3%, -5.1%) between actoxumab plus bezlotoxumab and placebo, and -9.9% (-15.5%, -4.2%) between bezlotoxumab and placebo, **Table 4**. A slightly lower proportion of subjects had CDI recurrence in the actoxumab plus bezlotoxumab group as compared to bezlotoxumab but the difference was not statistically significant (2-sided p-value= 0.7483).

Clinical cure of the initial CDI episode was numerically lower for actoxumab plus bezlotoxumab (72.3%) compared to placebo (77.8%). However, clinical cure was numerically higher for bezlotoxumab (82.5%) as compared to placebo. Neither of these comparisons was statistically significant (two-sided p=0.0801 and p=0.0973, respectively).

Although the proportion of subjects with global cure was numerically in favor of actoxumab plus bezlotoxumab (57.4%) compared to placebo (52.1%), the adjusted difference 5.2%, 95% confidence interval (-1.7%, 12.2%), was not statistically significant (two-sided p=0.1386). The proportion of subjects with global cure in the bezlotoxumab group (66.8%) was significantly higher (two-sided p<0.001) than placebo with an adjusted difference of 14.6% and 95% confidence interval (7.8%, 21.4%). The significance of this difference should be interpreted with caution given the pre-defined testing strategy in which the actoxumab plus bezlotoxumab vs. placebo comparison was to be tested first.

Table 4: Results of Clinical Cure, CDI Recurrence and Global Cure (FAS) in Study P002

	Acto plus Bezlo (n=390)	**Bezlotoxumab** (n=395)	**Placebo** (n=378)
Clinical Cure	282 (72.3) -5.5 (-11.6, 0.6) p=0.0801	326 (82.5) 4.8 (-0.9, 10.4) p=0.0973	294 (77.8)
CDI Recurrence	58 (14.9) -10.7 (-16.3, -5.1) **p=0.0002**	62 (15.7) -9.9 (-15.5, -4.2) **p=0.0006**	97 (25.7)
Global Cure	224 (57.4) 5.2 (-1.7, 12.2) p=0.1386	264 (66.8) 14.6 (7.8, 21.4) **p<0.0001**	197 (52.1)

Difference (95% CI) for monoclonal antibody – placebo

Two-sided p-values chi-square test for comparison of monoclonal antibody arm vs placebo, **bold** indicates significant at a cutoff value ≤ 0.05, hierarchical ordering of tests: actoxumab plus bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

Two sensitivity analyses were performed on the CDI recurrence and global cure endpoints. In the primary analysis, the assessment of CDI recurrence was based on the last available information for a subject. Therefore, subjects with incomplete stool information (subject had a new episode of diarrhea but stool sample not collected for toxin testing, died prior to Week 12, or whose last stool information collected was prior to Day 80) were treated as not having a CDI recurrence. Treating incomplete information in this way could lead to an underestimate of the CDI recurrence rate. Therefore, a sensitivity analysis (Sensitivity 1) was conducted that imputed those subjects who had incomplete data to assess recurrence through Week 12 as recurrence/failure. Additionally, it was noted that some subjects received a concomitant medication or procedure potentially useful in the treatment of CDI during the follow-up period which could confound the assessment of recurrence. Thus, a second sensitivity analysis (Sensitivity 2) that imputed these subjects as a recurrence/failure in addition to the criteria for imputation in the first sensitivity analysis was conducted.

In Study P001, a similar proportion of subjects in the actoxumab plus bezlotoxumab, bezlotoxumab, and placebo groups were imputed as having a CDI recurrence due to not having a stool sample of a new episode of diarrhea collected for toxin testing, having died before week 12, or not having stool information past Day 80. Therefore the results of Sensitivity 1 are consistent with those of the primary analysis.

A slightly higher proportion of placebo subjects received an active concomitant medication or procedure potentially useful in the treatment of CDI during follow-up as compared to actoxumab plus bezlotoxumab or bezlotoxumab subjects. Thus, a slightly higher proportion of placebo patients were imputed as CDI recurrence in Sensitivity 2. This resulted in slightly larger treatment differences for CDI recurrence and for global cure than were observed in the primary analysis. However, the overall conclusions are the same, **Table 5**.

Table 5: Sensitivity Analyses of CDI Recurrence and Global Cure (FAS) in Trial P001

	Acto plus Bezlo n=383	**Actoxumab** n=232	**Bezlotoxumab** n=386	**Placebo** n=395
Sensitivity 1*				
CDI Recurrence	112 (29.2)	89 (38.4)	118 (30.6)	160 (40.5)
	-11.2 (-17.8, -4.6)	-2.2 (-10.1, 5.6)	-9.9 (-16.5, -3.3)	
	p=0.001	p=0.5963	**p=0.0037**	
Global Cure	174 (45.4)	80 (34.5)	181 (46.9)	167 (42.3)
	3.1 (-3.8, 10.0)	-7.8 (-15.6, 0.02)	4.6 (-2.3, 11.5)	
	p=0.3757	p=0.0538	p=0.1947	
Imputed Recurrence/Failure***	51 (13.3)	29 (12.5)	51 (13.2)	51 (12.9)
NED not tested	25 (6.5)	12 (5.2)	21 (5.4)	20 (5.1)
Death before Week 12	10 (2.6)	16 (6.9)	14 (3.6)	13 (3.3)
Alive but last stool info before Day 80	19 (5.0)	2 (0.9)	18 (4.7)	21 (5.3)
Sensitivity 2**				
CDI Recurrence	128 (33.4)	99 (42.7)	133 (34.5)	185 (46.8)
	-13.4 (-20.1, -6.7)	-4.4 (-12.3, 3.6)	-12.3 (-19.1, -5.6)	
	p=0.0001	p=0.3120	**p=0.0004**	
Global Cure	158 (41.3)	70 (30.2)	166 (43.0)	142 (35.9)
	5.2 (-1.5, 12.0)	-5.7 (-13.2, 1.9)	7.1 (0.3, 13.8)	
	p=0.1286	p=0.1399	p=0.0437	
Imputed Recurrence/Failure***	67 (17.5)	39 (16.8)	66 (17.1)	76 (19.2)
NED not tested	25 (6.5)	12 (5.2)	21 (5.4)	20 (5.1)
Death before Week 12	10 (2.6)	16 (6.9)	14 (3.6)	13 (3.3)
Alive but last stool info before Day 80	19 (5.0)	2 (0.9)	18 (4.7)	21 (5.3)
Received CDI treatment	19 (5.0)	19 (8.2)	23 (6.0)	37 (9.4)

*Imputes subjects with new episode of diarrhea (NED) but no stool sample collected for toxin testing, subjects who died prior to Week 12, or had their last stool data collected prior to Day 80 as recurrence/failure

** Imputes subjects with new episode of diarrhea but no stool sample collected for toxin testing, subjects who died prior to Week 12, had their last stool data collected prior to Day 80, or received an active concomitant medication or procedure for CDI during follow-up as recurrence/failure

***Some subjects may have met more than one criterion for imputation as a failure

Difference (95% CI) for monoclonal antibody - placebo

Two-sided p-values chi-square test for comparison of monoclonal antibody arm vs placebo, **bold** indicates significant at a cutoff value ≤ 0.025, hierarchical ordering of tests: actoxumab plus bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

In Study P002, a larger proportion of actoxumab plus bezlotoxumab and bezlotoxumab subjects were imputed as having a CDI recurrence than placebo subjects. This is primarily due to the imbalance between the monoclonal antibody groups and placebo in the number of subjects who did not have a stool sample of a new episode of diarrhea collected for toxin testing. There was also a slightly larger proportion of bezlotoxumab subjects who received an active concomitant medication or procedure for CDI during follow-up.

The overall imbalance impacts the conclusions drawn for the CDI recurrence endpoint in which the bezlotoxumab vs. placebo comparison is no longer significant. Although the difference in global cure is statistically significant for the bezlotoxumab vs. placebo comparison, the difference is less than that observed for the primary analysis and driven as much by the observed difference in clinical cure of the initial CDI episode as the

difference in CDI recurrence. As observed in the primary analysis, the actoxumab plus bezlotoxumab vs placebo comparison for global cure is not significant, **Table 6**.

Table 6: Sensitivity Analyses of CDI Recurrence and Global Cure (FAS) in Trial P002

	Acto plus Bezlo n=390	**Bezlotoxumab** n=395	**Placebo** n=378
Sensitivity 1*			
CDI Recurrence	113 (29.0)	119 (30.1)	135 (35.7)
	-6.7 (-13.3, -0.1)	-5.5 (-12.1, 1.1)	
	p=0.0458	p=0.0983	
Global Cure	169 (43.3)	207 (52.4)	159 (42.1)
	1.2 (-5.7, 8.2)	10.2 (3.3, 17.2)	
	p=0.7221	**p=0.004**	
Imputed Recurrence/Failure***	55 (14.1)	57 (14.4)	38 (10.1)
NED not tested	22 (5.6)	22 (5.6)	6 (1.6)
Death before Week 12	11 (2.8)	14 (3.5)	13 (3.4)
Alive but last stool info before Day 80	26 (6.7)	24 (6.1)	21 (5.6)
Sensitivity 2**			
CDI Recurrence	127 (32.6)	141(35.7)	150 (39.7)
	-7.1 (-13.9, -0.4)	-4.0 (-10.7, 2.8)	
	p=0.0400	p=0 2528	
Global Cure	155 (39.7)	185 (46.8)	144 (38.1)
	1.6 (-5.2, 8.5)	8.7 (1.8, 15.6)	
	p=0.6395	**p=0.0140**	
Imputed Recurrence/Failure***	69 (17.7)	79 (20.0)	53 (14.0)
NED not tested	22 (5.6)	22 (5.6)	6 (1.6)
Death before Week 12	11 (2.8)	14 (3.5)	13 (3.4)
Alive but last stool info before Day 80	26 (6.7)	24 (6.1)	21 (5.6)
Received CDI treatment	23 (5 9)	30 (7.6)	21 (5.6)

*Imputes subjects with new episode of diarrhea but no stool sample collected for toxin testing, subjects who died prior to Week 12, or had their last stool data collected prior to Day 80 as recurrence/failure

** Imputes subjects with new episode of diarrhea but no stool sample collected for toxin testing, subjects who died prior to Week 12, had their last stool data collected prior to Day 80, or received an active concomitant medication or procedure for CDI during follow-up as recurrence/failure

***Some subjects may have met more than one criterion for imputation as a failure

Difference (95% CI) for monoclonal antibody - placebo

Two-sided p-values chi-square test for comparison of monoclonal antibody arm vs placebo, **bold** indicates significant at a cutoff value ≤ 0.05, hierarchical ordering of tests: actoxumab plus bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

Numerous subgroup analyses were also conducted and in general the results of most subgroups were consistent and treatment differences trended in the same direction as the overall population of each study.

Efficacy Summary and Conclusions

The intended role of the monoclonal antibody is for preventing CDI recurrence. CDI recurrence was defined as the development of a new episode of diarrhea associated with a positive stool test for *C. difficile* toxin following clinical cure of the initial CDI episode. The design of the trials allowed for treatment with the monoclonal antibody to occur at any time during the SOC treatment for the enrolling episode of CDI rather than until treatment with SOC was complete and the subject was considered to be successfully treated. The protocol-specified primary endpoint chosen for assessing the efficacy of the

monoclonal antibody was the proportion of subjects in the FAS population with CDI recurrence through Week 12. Although the definition of CDI recurrence requires clinical cure of the initial CDI episode, the proportion was based on the FAS population. There are some concerns with use of the FAS population for this analysis. In this analysis, subjects who were not initial clinical cures (i.e. clinical failures) are included in the denominator of the calculation of the recurrence rate and thus treated as not having a recurrence. This intuitively does not seem appropriate, as subjects with sustained response are grouped with those who were clinical failures of the initial CDI episode. Additionally, subjects who were clinical failures of the initial CDI episode cannot be evaluated for recurrence since one has to be cured first in order to develop recurrence. This endpoint is therefore difficult to interpret.

However, the use of this endpoint is of most concern if there is an imbalance in the proportion of subjects with initial clinical cure between the treatment groups, particularly if the monoclonal antibody group has a lower initial clinical cure rate than the placebo group, because this will result in a smaller number of subjects in the antibody group that can potentially develop recurrence and, more importantly, a larger proportion of subjects in the antibody group who are essentially imputed as non-recurrences. Given these concerns, the more relevant endpoint for assessing the efficacy of the monoclonal antibody would be the protocol-specified secondary endpoint of global cure which is defined as clinical cure of the initial CDI episode and no CDI recurrence through Week 12. With this endpoint, those who are not clinical cures are more appropriately considered failures in the analysis.

While there appears to be a decrease in CDI recurrence with the use of bezlotoxumab, there is concern as to whether the efficacy of bezlotoxumab for the prevention of CDI recurrence has been adequately demonstrated. It was anticipated that the monoclonal antibody would have no impact on clinical cure of the initial CDI episode. However there were numerical differences observed in clinical cure between bezlotoxumab and placebo in both trials. In Study P001, the difference was in favor of placebo whereas the difference was in favor of bezlotoxumab in Study P002.

It should be noted that there was also a difference in clinical cure between bezlotoxumab plus actoxumab and placebo arms. In both trials, the difference was in favor of placebo and significantly better for placebo in Study P001. Thus, a negative effect of bezlotoxumab on clinical cure of the initial CDI episode cannot be ruled out. As such, the efficacy of bezlotoxumab is better assessed by global cure.

The results for global cure are only statistically significant for one of the two trials. However, this statistical significance in one trial should be interpreted with caution for two reasons. The first reason is the non-significant result observed for the test of global

cure between the bezlotoxumab plus actoxumab and placebo arms which was to occur first in the hierarchical ordering of the prespecified testing strategy. Initially, the focus of the clinical development program was the combined monoclonal antibody (bezlotoxumab plus actoxumab). The Phase 3 trials were designed with the inclusion of the individual monoclonal antibodies so that the contribution of the components in the combination product could be assessed. As such, in order to preserve overall type I error, the pre-defined testing strategy included a hierarchical approach in which testing of the combined monoclonal antibody compared to placebo was to be conducted prior to the conduct of the individual monoclonal antibody vs. placebo comparison. If the combined monoclonal antibody vs. placebo comparison was not found to be significant, then further testing was to be halted. Therefore in this situation, any "significant" finding for the individual monoclonal antibody vs. placebo comparison should be interpreted with caution.

The second reason for cautious interpretation of these results, and possibly more clinically relevant, is the discordant results observed in clinical cure for bezlotoxumab between the two trials. In Study P001, the clinical cure rate in both study arms that included bezlotoxumab, either alone or in combination with anti-toxin A is lower than in the placebo arm. In contrast, in Study P002, the clinical cure rate in the monoclonal antibody arms as compared to placebo is lower in one arm (actoxumab plus bezlotoxumab), which is consistent with the results observed in Study P001, but higher in the bezlotoxumab only arm. Therefore, one might tend to put more strength in the results observed for Study P001 without further evidence suggesting otherwise. Overall, these results suggest that bezlotoxumab may negatively affect cure rate of the initial CDI episode.

9 Evaluation of Safety

9.1 Summary

Bezlotoxumab, given as a single IV infusion, had an overall favorable safety profile with the rates of treatment-emergent adverse events (TEAE), serious adverse events (SAE) and deaths similar to placebo. No increase in adverse events (AEs) related to potential immune-mediated reactions was observed in bezlotoxumab-treated subjects as compared to placebo-treated subjects. A safety finding identified during the review of data from the two Phase 3 trials is the numerically higher numbers of SAEs and deaths in bezlotoxumab-treated subjects with baseline congestive heart failure as compared to placebo.

9.2 Methods

The safety analysis focuses on the results of the two Phase 3 trials, P001 and P002. The safety population includes subjects that received partial or full infusion of bezlotoxumab alone or in combination with actoxumab. The subjects that received the same study treatment in the two Phase 3 trials, i.e. actoxumab plus bezlotoxumab, bezlotoxumab, or placebo, are pooled. For the safety analysis, subjects were grouped into the treatment arm they received (as treated), as opposed to the group to which they were randomized. A total of 7 subjects received treatments different from their randomized arm.

9.3 Overall Exposure to Bezlotoxumab

A total of 1790 subjects were exposed to bezlotoxumab either alone or in combination with actoxumab. Among 126 healthy subjects in Phase 1 studies, 30 subjects received bezlotoxumab alone and 96 received bezlotoxumab in combination with actoxumab. In Phase 2 and 3 trials, 786 subjects received bezlotoxumab and 878 received actoxumab plus bezlotoxumab. Of these, 1741 subjects were exposed to bezlotoxumab dosed at 10 mg/kg, while 30 and 19 were exposed to doses of < 10 mg/kg dose and 20 mg/kg, respectively. With the exception of 30 subjects in one Phase 1 study who received two doses of actoxumab plus bezlotoxumab, all subjects were exposed to a single dose of bezlotoxumab or actoxumab plus bezlotoxumab.

The safety population in the two Phase 3 trials included 786 bezlotoxumab, 777 actoxumab plus bezlotoxumab, and 781 placebo-treated subjects. Out of 786 bezlotoxumab-treated subjects, 97.1% (n=763) received the intended bezlotoxumab dose defined as ≥ 9.5 to < 10.5 mg/kg. Only 1.8% (n=9) subjects received less than the intended dose and 1.1% (n=9) received more than the intended dose. Among the 777 subjects that received actoxumab plus bezlotoxumab, 96.7% (n=751) received the intended dose of 10 mg/kg, and 2.3% (n=18) and 1% (n=8) received less than and more than the intended dose, respectively. The doses of bezlotoxumab ranged from about 300 to 2000 mg with the median dose of 700 mg.

9.4 Study Discontinuation

Study drug was given as one-time infusion. Disposition of subjects in Phase 3 studies in terms of study completion is presented in **Table 7**.

Table 7: Disposition of Subjects in Phase 3 Trials (All Randomized Subjects)

	Acto plus Bezlo N=800	Bezlotoxumab N=810	Placebo N=803
Completed the study	665 (83.1%)	677 (83.6%)	651 (81.1%)
Discontinued the study [a]	135 (16.9%)	133 (16.4%)	152 (18.9%)
Deaths [b]	54 (6.8%)	64 (8%)	62 (7.7%)
Adverse Event	1 (0.1%)	2 (0.2%)	2 (0.2%)
Lost to follow-up	26 (3.3%)	21 (2.6%)	22 (2.7%)

[a] Selected reasons for study discontinuation are provided; [b] Two randomized subjects who died but did not receive study treatment are not included. There were also 28 deaths in the actoxumab arm in study P001.

Overall, the proportions of subjects who discontinued the study, including those who discontinued due to AEs, death, or loss to follow-up were similar between study arms. About 83% of subjects in each arm completed the trials.

There were 47 study drug infusion interruptions, with 9, 34 and 4 interruptions in the bezlotoxumab, actoxumab plus bezlotoxumab and actoxumab arms, respectively. The majority of these were due to technical difficulties. The higher frequency of technical difficulties in the actoxumab plus bezlotoxumab arm was reportedly due to the propensity of actoxumab to form visible particles at low concentrations.

There was one infusion interruption in the bezlotoxumab arm that led to permanent discontinuation and was considered to be related to study drug. This occurred in a 32- year-old white male with history of AIDS, *Pneumocystis* pneumonia, electrolyte abnormalities (hyponatremia and hypokalemia), and with no history of arrhythmias or baseline ECG abnormalities. Concomitant medications included pentamidine, potassium pantoprazole, and prednisone. He developed ventricular arrhythmia with heart rate of 200 beats per minute, chills, and dizziness approximately 36 minutes after the start of bezlotoxumab infusion. The infusion was discontinued, and the subject was treated with steroids and histamine blockers intravenously. The chills and ventricular tachyarrhythmia resolved within 5 minutes, and dizziness resolved within 90 minutes. An ECG performed 30 minutes after discontinuing the infusion showed atrial and ventricular rates of 99 and signs of pre-excitation syndrome. The event was considered infusion-related.

9.5 Deaths

There were 212 deaths in the Phase 3 trials. Of these, 166 deaths (77 in study P001 and 89 in study P002) occurred in the 12-week post-infusion follow-up period. The remaining 46 deaths occurred in the following groups: deaths excluded by applicant for not meeting reporting criteria (n=9); death during the extension phase of study P002 (n=9), deaths among subjects that received actoxumab alone (n=28).

Table 8 summarizes the deaths that occurred in the Phase 3 trials. The rates of deaths were comparable among the three pooled study arms. In terms of the causes of death, the highest proportion of deaths in all study arms was due to sepsis and septic shock. Deaths due to sepsis and septic shock were observed at a higher rate in the placebo arm, 14/59 (23.7%) as compared to bezlotoxumab, 7/56 (12.5%), and actoxumab plus bezlotoxumab, 7/51 (13.7%) arm. Notably, in the discontinued actoxumab arm in Study P001, the proportion of deaths due to sepsis and septic shock was 9/27 (33%).

There was a numerical imbalance between study arms in deaths due to cardiovascular diseases with 8 (14.3%), 6 (11.8%), and 4 (6.8%) deaths in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arms, respectively. Otherwise, no appreciable differences between study arms in terms of cause of deaths were observed.

Table 8: Mortality Rate in Phase 3 Trials (Safety Population)

Study	Bezlotoxumab	Acto plus Bezlo	Placebo	Any Bezlotoxumab exposure	Actoxumab [a] N=236
Over 12 week study period					
P001	31/390(8%)	20/387(5.2%)	26/400(6.5%)	51/777(6.6%)	27/235(11.5%)
P002	25/396(6.3%)	31/390(8%)	33/381(8.7%)	56/786(7.1%)	1/1(100%) [b]
Total	56/786 (7.1%)	51/777(6.6%)	59/781(7.5%)	107/1563(6.8%)	28/236 (11.9%)
During Extension phase					
P002	5/100(5%)	2/112(1.8%)	2/83(2.4%)	3/212(3.3%)	

[a] Actoxumab arm is not included in the safety population and data for this arm is presented for comparison
[b] This subject in study P002 inadvertently received actoxumab only

Compared to the overall safety population, those who died were older (median age 77 years vs. 63 years), had severe CDI disease (more than 40% in those who died vs. 15-17% in overall population), and had high Charlson co-morbidity score (70-80% for those who died vs. 40-43% in overall population).

Of note, in terms of baseline characteristics, the actoxumab plus bezlotoxumab arm had higher number of subjects with severe CDI at baseline (51% compared to 40% in placebo and bezlotoxumab arm) and higher percentage of immunocompromised subjects at baseline (35% vs. 28% and 20% in bezlotoxumab and placebo arm, respectively). Otherwise, the baseline characteristics were comparable among those who died in each of the three arms.

9.6 Serious Adverse Events

Table 9 summarizes selected SAEs that occurred during 12 weeks following infusion.

Table 9: Selected SAEs in Phase 3 Trials That Occurred Within 12 Weeks Following Infusion (Safety Population)

MedDRA Preferred Term	**Bezlotoxumab N=786 n (%)**	**Acto plus Bezlo N=777 n (%)**	**Placebo N=781 n (%)**
Subjects with ≥1 SAE	231 (29.4%)	212 (27.3%)	255 (32.7%)
Cardiac failure*	17 (2.2%)	17 (2.2%)	7 (1%)
Diarrhea	16 (2%)	10 (1.3%)	12 (1.5%)
Abdominal pain	7 (0.9)	4 (0.5%)	4 (0.5%)
Respiratory failure	5 (0.6%)	5 (0.6%)	6 (0.8%)
Acute kidney injury	6 (08%)	4 (0.5%)	10 (1.3%)

*Cardiac failure terms "cardiac failure", "cardiac failure acute", "cardiac failure congestive" and "cardiac failure chronic" were combined.

Overall, there was no major imbalance in the frequency of SAEs among the three arms: 29.4%, 27.3%, and 32.7% of subjects in the bezlotoxumab, actoxumab plus bezlotoxumab and placebo arm, respectively, experienced at least one SAE in the 12-week study period. In all three arms, adverse events in the infection and infestation and gastrointestinal MedDRA System Organ Classes accounted for the majority of the SAEs. Of the SAEs, cardiac failure occurred more frequently in the bezlotoxumab arm as compared to the placebo arm. Similarly, there were more subjects with cardiac failure in the actoxumab plus bezlotoxumab arm (n=17, 2.2%) as compared to placebo. Please refer to section 9.8 for detailed analysis of subjects by presence or absence of congestive heart failure (CHF) at baseline.

9.7 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) are defined as any AE that was reported during or after infusion of the study drug. Data on all TEAEs that occurred in the first 4-week of the study were collected; after that, only SAEs were reported. Hence, the data for the 12-week period includes all the TEAEs reported in the 4-week period. In general, no significant imbalance was seen in the frequency of AEs in the bezlotoxumab and actoxumab plus bezlotoxumab arms compared to the placebo arm.

Table 10 summarizes incidence of TEAEs in the 4-week and 12-week study periods. Overall, the percentage of subjects that experienced TEAE is comparable across the three arms in the safety population.

Table 10: Treatment-Emergent Adverse Events (TEAE) That Occurred Over 4-weeks and 12-weeks Following Infusion (Safety Population)

	4-week period	12-week period
Number of individuals with AE	1418	1622
Actoxumab* (n, %)	159 (67.4)	184(78)
Acto plus Bezlo (n, %)	455 (58.6)	529 (68)
Bezlotoxumab (n, %)	485 (61.7)	548 (69.7)
Placebo (n, %)	478 (61.2)	545 (69.8)

*Actoxumab arm is not included in the safety population; denominators for percentage calculations are total number of subjects in each arm: n=236 for actoxumab, n=777 for actoxumab plus bezlotoxumab), n=786 for bezlotoxumab and n=781 for placebo.

Table 11 summarizes the common TEAEs that occurred in >2% of subjects within 4 weeks following infusion and were more frequent in the bezlotoxumab arm. There was no noticeable imbalance in common TEAEs between treatment arms.

Table 11: Selected Common TEAEs That Occurred in >2% of Subjects During 4 weeks Following Infusion

MedDRA Preferred Term	Bezlotoxumab N=786 n (%)	Acto plus Bezlo N=777 n (%)	Placebo N=781 n (%)
Subjects with ≥ 1 TEAE	485 (61.7%)	455 (58.6%)	478 (61.2%)
Nausea	52 (6.6%)	47 (6.0)	39 (5.0%)
Diarrhea	47 (6.0%)	46 (5.9)	45 (5.8%)
Pyrexia	36 (4.6%)	31 (4.0)	27 (3.5%)
Headache	35 (4.4%)	33 (4.2)	24 (3.1%)
Vomiting	31 (3.9%)	24 (3.1%)	21(2.7%)
Peripheral edema	19 (2.4%)	15 (1.9%)	14 (1.8%)
Fatigue	18 (2.3%)	21 (2.7%)	12(1.5%)
Cough	17 (2.2%)	7 (0.9%)	8 (1.0%)
Dyspnea	17 (2.2%)	6 (0.8%)	13(1.7%)

In regard to laboratory findings, there were no significant differences in changes from baseline in liver tests (ALT, AST, total bilirubin), renal function tests (creatinine, blood urea nitrogen) and hematologic parameters (hemoglobin, platelet and neutrophil counts) between study arms. There were also no significant differences between study arms in TEAE, SAEs, and deaths when comparing subjects by sex, race, and age.

9.8 Adverse Reactions of Special Interest and Submission Specific Safety Issues

Infusion-related Reactions

Infusion-related adverse reactions were of particular interest since bezlotoxumab is administered intravenously. Adverse reactions that could potentially be related to study

drug were assessed within 24 hours following the infusion and included cutaneous, respiratory, cardiovascular, gastrointestinal, musculoskeletal, nervous system reactions, as well as pyrexia, fatigue, and asthenia.

Four subjects in the bezlotoxumab arm had adverse reactions that could potentially be attributed to infusion. The first subject, whose case narrative was provided above when describing study discontinuations, was a 32 year-old white male who developed ventricular arrhythmia after the start of after the start of bezlotoxumab infusion. Two bezlotoxumab-treated subjects developed hypotension during the infusion. In neither of these two subjects systolic blood pressure (SBP) decreased below 90 mm Hg or by 30% or more from baseline. One subject in the bezlotoxumab arm was found to have a drop in SBP by 30% from baseline 30 minutes after start of infusion and at the end of infusion.

Safety Analysis by Body Weight

Since bezlotoxumab is dosed by body weight, potential effects of higher body weight, and overall higher dose, was assessed. There was no increase in TEAEs, SAEs or death by body weight when comparing the active arms to the placebo arm. There were numerically higher number of SAEs and deaths in subjects weighing $\leq$ 70 kg as compared to subjects weighing > 70kg in all study arms. The weight range for the safety population was large (29.8 kg-200 kg).

Safety Analysis by Baseline Congestive Heart Failure

Numerically more subjects in the bezlotoxumab arm were reported to have CHF as an SAE. To further explore this difference, an analysis of subjects with baseline CHF for each study arm was performed (See Table 12 and Table 13). The analyses show that while subjects with baseline CHF had more AEs, SAEs and death in general, there was a numerical difference in the occurrence of AEs, SAEs, and death among the bezlotoxumab-treated subjects with baseline CHF as compared to the actoxumab plus bezlotoxumab and placebo-treated subjects.

Table 12: Adverse Events in Subjects with and without Baseline CHF

	Baseline CHF N=325 n (%)	No baseline CHF N=2019 n (%)
TEAE	250 (66.9%)	1372 (68%)
Bezlotoxumab	99 (30.5%)	449 (22.2%)
Acto plus Bezlo	78 (24%)	451 (22.3%)
Placebo	73 (22.5%)	472 (23.4%)
SAE	159 (48.9%)	539 (26.7%)
Bezlotoxumab	63 (19.4%)	168 (8.3%)
Acto plus Bezlo	46 (14.2%)	166 (8.2%)
Placebo	50 (15.4%)	205 (10.2%)
Death	54 (16.6%)	112 (5.5%)
Bezlotoxumab	23 (7.1%)	33 (1.6%)
Acto plus Bezlo	18 (5.5%)	33 (1.6%)
Placebo	13 (4%)	46 (2.3%)

TEAE: Treatment emergent adverse event; SAE: serious adverse event

Table 13: Adverse Events among Subjects with Baseline CHF by Treatment Arm.

	Bezlotoxumab N=118 n (%)	Acto plus Bezlo N=103 n (%)	Placebo N=104 n (%)
TEAE	99 (83.9%)	78 (75.7%)	73 (70.2%)
SAE	63 (53.4%)	46 (44.7%)	50 (48%)
Death	23 (19.5%)	18 (17.5%)	13(12.5%)

TEAE: All subjects with at least one TEAE during the 12-week study period;
SAE: All subjects with at least one serious AE during the 12-week study period
Death: All subjects who died due to an AE that occurred during the 12-week study period

10 Points for Advisory Committee Discussion

1. Has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence?

    - If yes, please provide any recommendations concerning labeling.
    - If no, what additional studies/analyses are needed?