CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Electronic stamp
From	Dmitri Iarikov, MD, PhD
Subject	Cross-Discipline Team Leader Review
BLA #	761046
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	November 22, 2015
Date of Major Amendment	June 30, 2016
Original PDUFA Goal Date	July 23, 2016
Extended PDUFA Goal Date	October 23, 2016
Proprietary Name / Non-Proprietary Name	Zinplava / Bezlotoxumab
Dosage form / Strength	1,000 mg/40 mL (25 mg/mL) solution in a single-dose vial.
Applicant Proposed Indication/Population	Prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	To reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years or older who are receiving antibacterial therapy for CDI and are at a high risk of CDI recurrence.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bezlotoxumab is a fully human monoclonal antibody directed against *C. difficile* toxin B. The drug is proposed for the prevention of *C. difficile* infection (CDI) recurrence in patients receiving antibacterial therapy for CDI and is administered as a single infusion (b) (4) during (b) (4) for CDI. No drugs are currently approved for the prevention of CDI recurrence.

The efficacy and safety of bezlotoxumab is supported by two Phase 3 clinical trials where bezlotoxumab was compared to a placebo infusion. The trials showed that the proportion of subjects with sustained clinical response defined as the cure of the initial CDI episode and no CDI recurrence through 12 weeks after study drug infusion was higher in bezlotoxumab-treated subjects. In one trial the clinical cure rate of the baseline CDI episode was lower for bezlotoxumab as compared to placebo whereas in the other trial the cure rate of the initial CDI episode was lower for placebo. Additional analyses, however, showed that differences in the clinical cure rate of the baseline CDI episode were balanced between treatment arms by 3 weeks post study drug infusion.

Bezlotoxumab had a satisfactory safety profile with the rates of adverse events and deaths similar to placebo. A safety finding identified during the review is a higher rate of serious adverse events of heart failure in bezlotoxumab-treated subjects (2.2%) as compared to placebo (0.9%). The reason for this observation is uncertain and it will be presented as a warning in the bezlotoxumab package insert.

In summary, I conclude that bezlotoxumab demonstrated a favorable-risk benefit profile and recommend its approval for the reduction of recurrence of CDI in patients 18 years or older who are receiving antibacterial therapy for CDI and are at a high risk of CDI recurrence.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Clostridium difficile* infection (CDI) is caused by a bacterium called *Clostridium difficile* that is transmitted by spores through the fecal-oral route. CDI can vary in severity from mild diarrhea to severe colitis that may result in intestinal perforation and death. The symptoms of CDI are mediated by two endotoxins produced by the bacterium, toxin A and B. • The main risk factor for CDI is the use of antimicrobial drugs altering normal colonic flora and making the person susceptible to CDI. A total of 453,000 cases of	CDI is a serious, life-threatening and frequently recurrent condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	CDI resulting in 29,000 deaths were estimated to occur annually in the United States[1]. • One of the distinctive features of CDI is its high recurrence rate which is associated with significant morbidity and high medical cost. Approximately 20% of subjects develop a recurrence after the resolution of the first episode of CDI. Once a recurrence occurs, the risk of subsequent recurrences become even higher.	
Current Treatment Options	• No drugs are approved for the prevention of CDI recurrence. While fecal transplantation has been tried for the prevention of CDI recurrence, its efficacy and safety have not been fully characterized.	There is a lack of approved safe and effective drugs for the prevention of CDI recurrences.
Benefit	• Efficacy and safety of bezlotoxumab in the prevention of CDI recurrence was supported by two Phase 3 trials where bezlotoxumab was compared to placebo, Studies P001 and P002. The trials also evaluated bezlotoxumab in combination with actoxumab (a monoclonal antibody to *C. difficile t*oxin A) and actoxumab alone, but these treatments were found to be less efficacious as compared to bezlotoxumab and were not submitted for approval. Bezlotoxumab was administered as a single 10 mg/kg infusion at any time during CDI antibacterial therapy, which was 10-14 days in duration. • The trials showed that the proportion of subjects who were cured of the initial CDI episode and did not have CDI recurrence through 12 weeks after study drug infusion (sustained clinical response) was higher in bezlotoxumab-treated subjects. In Study P001 the percentage of subjects with sustained clinical response was 60.1% in the bezlotoxumab and 55.2% in the placebo arm, respectively, 95%CI (-2.1; 11.7). In Trial P002 the percentage of subjects with Sustained clinical response was 66.8% in the bezlotoxumab and 55.1% in the placebo arm, respectively, 95%CI (7.8; 21.4). • Trial results raised a concern that bezlotoxumab may negatively affect cure of the initial CDI episode. In Study P001 CDI cure rate was 77.5% in the bezlotoxumab and 82.8% in the placebo arm. In Study P002, however, cure rate of the initial CDI episode was 82.5% in the bezlotoxumab and 77.8% in placebo arm. Additional analyses showed that by week 3 post infusion cure rates in all study arms in both trials were similar. Overall, protocol defined clinical failures were associated with	Bezlotoxumab development program demonstrated that the drug provided clinically meaningful reduction in CDI recurrence over 12 weeks post-infusion. The recurrence of CDI represents a significant burden on a patient's well-being and quality of life. In subjects enrolled in the bezlotoxumab trials a first CDI recurrence resulted in hospitalization in greater than 30% of cases. There is a concern that bezlotoxumab may potentially prolong the resolution of the initial CDI episode. This concern is mitigated by the fact that by week 3 post infusion cure rates in all study arms became similar.

[1] Lessa FC et al. Burden of Clostridium difficile Infection in the United States. N Engl J Med. 2015 Feb 26; 372 (9): 825-34.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the extension of CDI treatment by 3-4 days or with 3 to 4 days of diarrhea after completion of therapy.	
Risk	• The rates of adverse events and deaths in bezlotoxumab-treated subjects were similar to placebo. However, a higher number of serious adverse events related to heart failure were noted in bezlotoxumab (2.2%) as compared to placebo-treated subjects (0.9%). These events were mainly observed in subjects with baseline congestive heart failure (CHF). There were also more deaths in subjects with baseline CHF in the bezlotoxumab arm, 19.5% (23/118), as compared to placebo, 12.5 % (13/104). The reason for these findings is uncertain.	Bezlotoxumab had an overall favorable safety profile. However, a higher number of adverse events related to heart failure and a higher number of deaths in subjects with baseline CHF were noted in bezlotoxumab-treated patients in comparison to placebo.
Risk Management	• A risk of heart failure associated with bezlotoxumab use in subjects with a history heart failure and the recommendation to reserve the use of bezlotoxumab in such subjects to situations when the benefit clearly outweighs the risk will be described in a warning in the bezlotoxumab label. Otherwise, no additional risk-mitigation measures except for routine post-marketing pharmacovigilance are deemed necessary at this point.	A warning is deemed sufficient to address a potential risk of heart failure associated with bezlotoxumab use in subjects with baseline CHF.

2. Background

Bezlotoxumab is a fully human monoclonal IgG1 antibody directed against *C. difficile* toxin B. The proposed indication is for prevention of CDI recurrence in subjects 18 years or older receiving (b) (4) therapy for CDI. It is hypothesized that bezlotoxumab prevents binding of toxin B to colonic cells, thus averting colonic cell inflammation and preventing the development of CDI. Bezlotoxumab is administered as a single 10 mg/kg infusion (b) (4) during CDI antibacterial therapy, (b) (4). No drugs are currently approved for the prevention of CDI recurrence.

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. When anti-toxin B compared more favorably to anti-toxin A alone and to the combination in phase 3 trials, bezlotoxumab was selected for BLA submission.

There were two Phase 2 trials evaluating the efficacy and safety of antibodies against *C. difficile* toxins for the prevention of CDI recurrence. The first Phase 2 trial evaluated a single infusion of an anti-toxin A antibody (actoxumab) versus placebo. The trial was terminated early after 46 subjects received study drug (29 actoxumab and 17 placebo) because emerging non-clinical data suggested that the combination of antibodies against toxin B and A would be more effective for the prevention of CDI recurrence. The second Phase 2 trial compared a combination of *C. difficile* toxin A and B antibodies with placebo. The trial enrolled 101 subjects in the antibodies and 99 subjects in the comparator arm. The recurrence rate was lower among subjects treated with monoclonal antibodies (7% vs. 25%; $p < 0.001$). No Phase 2 trials evaluated bezlotoxumab alone.

For Phase 3 trials, pursuant to 21 CFR 300.50(a), (Fixed-combination prescription drugs for humans), the FDA recommended that the Applicant conduct a four arm study comparing 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 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 the prevention of CDI recurrence in subjects receiving antibacterial therapy for CDI. The trial primary endpoint was CDI recurrence following clinical cure of the baseline CDI episode. The proportion of subjects with CDI recurrence was calculated as the number of subjects with CDI recurrence divided by the total number of subjects in the analysis population regardless of whether they had a successful resolution of the initial episode of CDI.

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 rate 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, i.e., as "successes". Consequently, a greater number of subjects who failed initial treatment within a treatment arm would result in a smaller number of subjects who could potentially develop recurrence. This would be especially concerning if the monoclonal antibody negatively affects initial cure rate.

The FDA recommended the endpoint of global cure where success is defined as clinical cure of the initial CDI episode and the absence of CDI recurrence. The Applicant, however, decided to preserve CDI recurrence as the primary efficacy endpoint in both trials and indicated that they did not expect that antibodies to *C. difficile* toxins would have an impact on the clinical cure rate. Global cure was included as one of the secondary endpoints.

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. In one of the two Phase 3 trials, Study P001, cure rates of the baseline CDI episode were lower in all antibody arms as compared to placebo. In contrast, in Study P002 the clinical cure rate was higher in the bezlotoxumab arm as compared to placebo.

To address concerns regarding the differences in clinical cure, the Applicant proposed a post hoc efficacy analysis using an expanded definition of clinical cure. The Applicant believed that the original definition may not be fully clinically relevant because most clinical failures subsequently completed SOC and resolved diarrhea. In June 2016 to further assess the risk-benefit profile of bezlotoxumab, the Division requested additional analyses and subject level data from the Applicant. The aim of these analyses was to better characterize clinical consequences of failures of initial cure and clinical significance of observed CDI recurrences.

The response to this request constituted a major amendment to the BLA necessitating the extension of the review clock. On June 30, 2016 the major amendment was received and the review goal date was extended by 3 months. The results of the analyses of Phase 3 trials are the main subject of this review.

3. Product Quality

The product quality reviewer for this application is William Hallett, PhD. The manufacturing facility reviewer is Thuy Nguyen, MPH. The microbiology assessment reviewer is Natalia Pripuzova, PhD.

The Office of Pharmaceutical Quality recommends approval of bezlotoxumab. The reviewers conclude that the data submitted in this application demonstrate that the drug product and drug substance manufacturing processes of bezlotoxumab are well controlled and capable of producing a product that is pure, potent and of consistent quality.

Bezlotoxumab drug substance is manufactured at [redacted]. The data provided in the BLA support a shelf of [redacted] months for bezlotoxumab drug substance when stored at [redacted]°C.

Bezlotoxumab drug product is manufactured at Merck, Sharp, and Dohme in Carlow, Ireland. [redacted] bezlotoxumab is placed in a single-dose, 50 mL glass vial. Each vial contains 25 mg/mL bezlotoxumab for a total of 1000 mg/ 40 mL per vial. Each mL of the drug product contains bezlotoxumab (1,000 mg), sodium chloride (351 mg), sodium citrate dihydrate (190 mg), citric acid monohydrate (32 mg), polysorbate 80 (10 mg), diethylenetriaminepentaacetic acid (0.31 mg), and Water for Injection, USP. Additionally, the vial may contain NaOH to adjust the pH to 6.0. The stability data in the BLA support a shelf life of 24 months for the drug product when stored at 2 - 8°C.

The following post-marketing commitments to address some minor product quality issues which do not preclude approval of the BLA are recommended:

Product Quality

1. Re-evaluate drug substance and drug product lot release and stability specifications after a minimum of 30 drug substance lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods.
2. Perform additional testing to support the clonality of the bezlotoxumab master cell bank.
3. Conduct a study to support the worst case cumulative hold times in the bezlotoxumab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of bezlotoxumab drug substance.

Product Quality Microbiology

1. Perform additional viability studies and a subsequent microbial retention study for the validation [redacted].
2. Develop a valid in vitro endotoxin assay for drug product release testing.
3. Perform Low Endotoxin Recovery studies [redacted]

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Terry Miller, PhD.

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 subjects.

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.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this BLA is Yang He, PhD. The reviewer concludes that clinical pharmacology results support approval of bezlotoxumab and recommends approval of the BLA. The summary of the review is presented below and the reader is referred to Dr. He's review for more detail.

The clinical dose of 10 mg/kg bezlotoxumab was selected because in healthy subjects this dose resulted in median serum levels that were approximately equivalent to the levels that provided protection from acute CDI in a hamster model. Population PK and exposure-response analyses were conducted using pooled data from three Phase 1 trials and two Phase 3 trials (Studies P001 and P002).

- General clinical pharmacology considerations

Following the infusion the mean clearance (CL) of bezlotoxumab is 0.317 L/day with a volume of distribution (Vd) of 7.33 L and an elimination half-life ($t_{½}$) of approximately 19 days. Bezlotoxumab has moderate PK variability [40% and 21% coefficient of variation (CV) for $AUC_{0\text{-inf}}$ and C_{max}, respectively] in CDI subjects.

- Distribution, metabolism and excretion

The estimated inter-individual variability in bezlotoxumab central volume of distribution (Vc) was approximately 10.6%. The drug is not expected to bind to serum proteins. Bezlotoxumab is degraded into small peptides and individual amino acids through protein catabolism. Bezlotoxumab was detected in stools in ≤16% of CDI subjects who gave stool samples after the bezlotoxumab administration. The effect of renal or hepatic impairment on bezlotoxumab is not clinically meaningful and no dose adjustment is warranted.

- Effect of intrinsic/extrinsic factors

No dose adjustments are required for intrinsic or extrinsic factors beyond the weight-based dose. The population PK analysis of serum bezlotoxumab concentrations from the Phase 1 and

Phase 3 showed that intrinsic or extrinsic factors (e.g., albumin, gender, age, race/ethnicity, clinical comorbidities, CDI severity and concomitant use of non-standard care of antibiotics) would not affect the exposure of bezlotoxumab to a clinically meaningful extent.

- Exposure-response relationships for efficacy and safety

There was no apparent relationship between serum exposure to bezlotoxumab and clinical efficacy endpoints. The exposure-response for safety, including adverse events (AEs) and serious adverse events (SAEs), indicated that patient covariates (i.e. albumin, concomitant use of non-standard of care systemic antibacterial drugs or PPIs, hospitalization, Charlson Comorbidity Index ≥ 3, and age), rather than exposure, are the primary factors influencing the incidence of AEs and SAEs.

- Effect on QT prolongation

No dedicated QTc trial was conducted for bezlotoxumab. In the two Phase 3 trials and in the three Phase 1 trials no clinically significant effect on QTc interval was observed after administration of bezlotoxumab alone or actoxumab plus bezlotoxumab. There is also no evidence from nonclinical data to suggest that bezlotoxumab has the potential to delay ventricular repolarization.

- Immunogenicity

In healthy subjects and CDI patients, no bezlotoxumab treatment-emergent anti-drug antibody against bezlotoxumab has been observed following a single 10 mg/kg bezlotoxumab administration.

6. Clinical Microbiology

The clinical microbiology reviewer for this BLA is Kerian Grande, PhD.

Activity *in vitro*

Bezlotoxumab binds toxin B with an affinity equilibrium dissociation constant (Kd) of <1×10-9M. 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. Bezlotoxumab does not bind to toxin A.

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*

In a gnotobiotic piglet model, anti-toxin B antibody alone protected 100% of piglets from development of systemic CDI and minimized lesions. In animal models of mouse and hamster

the combination of actoxumab and bezlotoxumab was associated with the best protection from morbidity and mortality as compared to bezlotoxumab alone.

7. Clinical/Statistical- Efficacy

The clinical review was conducted by Shrimant Mishra, MD, MPH, and the statistical review was conducted by Cheryl Dixon, PhD. The reviewers conclude that the Applicant provided sufficient evidence of efficacy of bezlotoxumab in reducing CDI recurrences but indicate that bezlotoxumab may potentially negatively affect cure of the initial CDI episode.

The clinical reviewer concludes that the analysis of both the severity/frequency of recurrences as well as the clinical variables associated with clinical failures indicates that potential negative effects on initial clinical cure are overall minor and the benefit of reducing the frequency/severity of recurrences outweigh possible negative effects on initial clinical cure. The clinical reviewer recommends approval of bezlotoxumab.

The statistical reviewer defers to the clinical reviewers to determine if the possibility of a negative effect of bezlotoxumab on the initial cure is of less concern given that clinical cure rates becomes fairly balanced across treatment arms by week 3 post study drug infusion. The statistical reviewer also points out that a favorable risk benefit assessment of bezlotoxumab is supported by somewhat lesser severity of CDI recurrences in subjects treated with bezlotoxumab as compared to placebo.

The efficacy of bezlotoxumab is supported by two randomized, double-blind, placebo-controlled Phase 3 trials. The first trial, Study P001, compared the efficacy of actoxumab, bezlotoxumab, actoxumab plus bezlotoxumab, and placebo. The second trial, Study P002, compared the efficacy of bezlotoxumab, actoxumab plus bezlotoxumab, and placebo. The actoxumab (antitoxin A) arm was discontinued from the first trial and was not included in the second trial after an interim analysis demonstrated increase in mortality in this arm relative to the placebo, 11.9% and 6.5%, respectively, and low efficacy relative to the combination. The reasons for these findings remain uncertain.

Eligible subjects for Phase 3 trials were male or female aged ≥ 18 years with a confirmed diagnosis of CDI defined as diarrhea (≥ 3 loose stools in ≤ 24 hours) and a positive stool test for toxigenic *C. difficile*. Diarrhea was not required to be present on the day of study drug infusion. Subjects needed to receive standard of care (SOC) therapy (metronidazole, vancomycin, or fidaxomicin) for CDI at the time of the infusion and SOC was to last for 10 to 14 days.

The protocol-specified primary endpoint in both trials was the proportion of subjects with CDI recurrence through Week 12. Recurrence was defined as the development of a new episode of diarrhea (≥ 3 loose stools in ≤ 24 hours) and a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode. Clinical cure required the subject to receive a SOC treatment for ≤ 14 days (up to 16 calendar days) and not have diarrhea on the two days immediately following the last day of treatment.

As discussed above, the concern with this endpoint is that subjects who failed treatment of the initial CDI episode are counted as not having a recurrence, i.e., these subjects are counted as success. Subsequently, a treatment arm with a greater number of subjects who failed CDI treatment will have a smaller number of subjects who could potentially develop recurrence. As a result, negative effect of the monoclonal antibody on initial cure could confound the assessment of recurrence rates.

The FDA considered that the endpoint of global cure, or sustained clinical responses, where success is defined as clinical cure of the initial CDI episode and the absence of CDI recurrence as more appropriate to assess the efficacy of bezlotoxumab in the prevention of recurrences.

The efficacy was evaluated in the full analysis set (FAS) population defined as 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. In Study P001 the FAS population included 386 bezlotoxumab and 395 placebo subjects. In Study P002 the FAS population included 395 bezlotoxumab and 378 placebo subjects.

In both Phase 3 trials, 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. In Study P002 in comparison to Study P001 there was a higher proportion of Asian subjects, ~ 15% vs. ~ 5% respectively, and a higher proportion of ex-U.S. subjects, ~ 65% vs. ~54%, respectively. A similar proportion of patients were receiving oral metronidazole (48%) or oral vancomycin (48%) as their SOC antibacterial and 4% of the patients received oral fidaxomicin.

There were some differences in population characteristics between the two trials. The number of subjects with resolved diarrhea (≤ 2 loose stools a day) on the day of study drug infusion was greater in Study P002 in comparison to Study P001, 80% vs. 68% in the bezlotoxumab and 73% vs. 69% in the placebo arm, respectively. The number of subjects who had been on SOC for > 4 days by the time of study drug infusion was also greater in Study P002 in comparison to Study P001, 32% vs. 26% in the bezlotoxumab, and 29% vs. 24% in the placebo arm, respectively. More infections with hypervirulent strains of *C. difficile* defined as ribotypes 027, 078, or 244 were noted in the placebo arm of Study P002 relative to other two arms, 19% vs. ~12.5%, respectively. The proportion of subjects with hypervirulent strains in study P001 was comparable across treatment arms.

In Study P001, clinical cure of the baseline CDI episode was lower for actoxumab plus bezlotoxumab (74.7%) and bezlotoxumab (77.5%) as compared to placebo (82.8%), **Table 1**. At the same time, a significantly lower proportion of subjects had CDI recurrence in the actoxumab plus bezlotoxumab (15.9%) and the bezlotoxumab arm (17.4%) as compared to placebo (27.6%).

Table 1: Results of Clinical Cure, CDI Recurrence and Global Cure (FAS) in Study P001

	Actoxumab plus Bezlotoxumab n=383	**Actoxumab (anti-toxin A)** n=232	**Bezlotoxumab (anti-toxin B)** 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.
Source: Table 8, FDA Statistical Review

As to global cure (sustained clinical response), although the proportion of subjects was numerically in favor of bezlotoxumab (60.1%) in comparison to placebo (55.2%), the difference was not statistically significant. The adjusted differences in global cure and 95% CI were 4.8% (-2.1%, 11.7%) between bezlotoxumab and placebo.

In contrast, in the second trial, the clinical cure rate was higher in the bezlotoxumab arm (82.5%) as compared to placebo (77.8%), **Table 2**. Neither of these comparisons was statistically significant.

Table 2: Results of Clinical Cure, CDI Recurrence and Global Cure (FAS) in Study P002

	Actoxumab plus Bezlotoxumab (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.
Source: Table 17, FDA Statistical Review

A significantly lower proportion of subjects had CDI recurrence in the actoxumab plus bezlotoxumab (14.9%) and bezlotoxumab arm (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. The proportion of subjects with global cure in the bezlotoxumab arm (66.8%) was significantly higher (two-sided $p<0.001$) than placebo with an adjusted difference of 14.6% and 95% CI (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.

Overall, the review of preplanned efficacy analyses showed that while the use of bezlotoxumab resulted in decrease in CDI recurrence there is concern that differences in clinical cure between bezlotoxumab and placebo may have affected the assessment of the recurrence rate.

To address concerns regarding the differences in clinical cure, the Applicant proposed post hoc analyses using an expanded definition of clinical cure. The Applicant indicated that the original definition may be too strict and not fully clinically relevant because most clinical failures subsequently completed SOC and resolved diarrhea.

According to the original definition to be a clinical cure a patient should receive ≤14 days of SOC therapy (up to 16 calendar days) and have no diarrhea (≤2 loose stools per 24 hours) for two consecutive days immediately following completion of SOC therapy. The expanded cure definition allows longer durations of SOC and longer time for resolution of diarrhea. It defines clinical cure as resolution of diarrhea on any two consecutive days after completion of any duration of SOC therapy and is assessed at various time points relative to the time of infusion (2, 3, 4, 6, 8 and 12 weeks). Thus, a subject who completed SOC for the baseline CDI episode and resolved diarrhea (had ≤2 loose stools per 24 hours for two consecutive days at any point after completing SOC) by week 3 post-infusion would be considered cured at week 3 evaluation.

When the expanded definition was used, the majority of subjects achieved clinical cure by week 3 post infusion with no apparent differences in cure rates between bezlotoxumab and placebo arms. **Table 3** presents the number and percent of subjects with clinical cure based on the original definition and the expanded definitions.

Table 3: Clinical Cure Based on Original and Expanded Definition (FAS)

	P001		**P002**	
	Bezlotoxumab N=386	**Placebo** N=395	**Bezlotoxumab** N=395	**Placebo** N=378
Original Definition	299 (77.5)	327 (82.8)	326 (82.5)	294 (77.8)
Expanded Definition				
2 weeks	297 (76.9)	313 (79.2)	308 (78.0)	296 (78.3)
3 weeks	353 (91.5)	361 (91.4)	367 (92.9)	340 (89.9)
6 weeks	370 (95.9)	375 (94.9)	376 (95.2)	353 (93.4)
12 weeks	373 (96.6)	379 (95.9)	377 (95.4)	356 (94.2)

Source: Adapted from Table 1 and 2, FDA Statistical Review Addendum

The rates of recurrence and global cure calculated based on the expanded definition demonstrate that by week 3 post-infusion bezlotoxumab-treated subjects consistently had approximately 10% lower recurrence and approximately 10% higher global cure rate as compared to placebo, **Table 4** and **Table 5**.

Table 4: Recurrence Rate and Global Cure Based on Original and Expanded Definition (FAS) in Study P001

	Recurrence Rate		Global Cure	
	Bezlotoxumab N=386	**Placebo** N=395	**Bezlotoxumab** N=386	**Placebo** N=395
Original Definition	67 (17.4) -10.1 (-15.9, -4.3) p=0.0006	109 (27.6)	232 (60.1) 4.8 (-2.1, 11.7) p=0.1647	218 (55.2)
Expanded Definition				
2 weeks	66 (17.1) -8.9 (-14.7, -3.2) p=0.0026	103 (26.1)	231 (59.8) 6.6 (-0.3, 13.5) p=0.0596	210 (53.2)
3 weeks	78 (20.2) -10.6 (-16.6, -4.5) p=0.0006	122 (30.9)	275 (71.2) 10.6 (4.1, 17.2) p=0.0015	239 (60.5)
6 weeks	81 (21.0) -10.0 (-16.1, -3.9) p=0.0014	123 (31.1)	289 (74.9) 11.0 (4.6, 17.3) p=0.0008	252 (63.8)
12 weeks	82 (21.2) -10.0 (-16.1, -3.9) p=0.0014	124 (31.4)	291 (75.4) 10.7 (4.4, 17.1) p=0.0009	255 (64.6)

Adjusted difference (95% CI) for monoclonal antibody – placebo stratified by SOC therapy and hospitalization status. Two-sided p-values chi-square test for comparison of monoclonal antibody arm vs placebo.
Source: Adapted from Table 3 and 5, FDA Statistical Review Addendum

Table 5: Recurrence Rate and Global Cure Based on Original and Expanded Definition (FAS) in Study P002

	Recurrence Rate		Global Cure	
	Bezlotoxumab N=395	**Placebo** N=378	**Bezlotoxumab** N=386	**Placebo** N=395
Original Definition	62 (15.7) -9.9 (-15.5, -4.2) p=0.0006	97 (25.7)	264 (66.8) 14.6 (7.8, 21.4) p<0.0001	197 (52.1)
Expanded Definition				
2 weeks	60 (15.2) -11.2 (-16.8, -5.5) p=0.0002	100 (26.5)	248 (62.8) 10.7 (3.8, 17.6) p=0.0021	196 (51.9)
3 weeks	80 (20.3) -10.0 (-16.1, -4.5) p=0.0006	115 (30.4)	287 (72.7) 13.0 (6.4, 19.5) p=0.0001	225 (59.5)

6 weeks	82 (20.8) -10.3 (-16.3, -4.2) p=0.001	118 (31.2)	294 (74.4) 12.1 (5.6, 18.5) p=0.0002	235 (62.2)
12 weeks	82 (20.8) -10.3 (-16.3, -4.2) p=0.001	118 (31.2)	295 (74.7) 11.6 (5.1, 18.0) p=0.0004	238 (63.0)

Adjusted difference (95% CI) for monoclonal antibody – placebo stratified by SOC therapy and hospitalization status. Two-sided p-values chi-square test for comparison of monoclonal antibody arm vs placebo.
Source: Adapted from Table 4 and 6, FDA Statistical Review Addendum

To better understand whether the use of an expanded definition of clinical cure is clinically acceptable, clinical characteristics of subjects reclassified as cures were analyzed, **Table 6**.

Table 6: Clinical Characteristics of Initial CDI Episode Reclassified from Clinical Failure to Clinical Cure Using Expanded Definition of Clinical Cure (FAS)

	P001		**P002**	
	Bezlotoxumab	**Placebo**	**Bezlotoxumab**	**Placebo**
Subjects Reclassified (n)	74	52	51	62
Median Duration of SOC, Days (25%-75%)	16 (10.5-19)	16 (12-22)	17 (15-21)	16 (14-20)
Median Duration from End of SOC to Resolution of Diarrhea, Days (25%-75%)	3 (2-5)	3 (2-8)	3 (2-5)	3.5 (2-6)

Number of reclassified subjects provided for a 12-week evaluation; SOC – standard of care therapy of the initial CDI episode
Source: Adapted from Table 28, FDA Clinical Efficacy Review

The analysis of the clinical characteristics of the reclassified cures indicates that they were not overall worrisome. The median duration of SOC therapy of the initial CDI episode was 16 days with the majority of subjects completing the treatment within 21 days. Thus, even if the assumption that bezlotoxumab may negatively affect initial cure rate is correct, it appears that the clinical impact of this negative effect is not major.

To further assess a risk-benefit profile of bezlotoxumab and to weigh the benefit of reducing recurrences of CDI against a potential harm of prolonging the resolution of the baseline *C. difficile* episode, clinical consequences of CDI recurrences were analyzed, **Table 7**.

Table 7: Severity of 1st CDI Recurrence in Subjects Meeting Expanded Definition of Clinical Cure (FAS)

	P001		**P002**	
	Bezlotoxumab	**Placebo**	**Bezlotoxumab**	**Placebo**
Subjects with Recurrences	N=82	N=124	N=82	N=118
No of loose stools at onset				
Median	3	4	4	4
Min-Max	3-10	3-18	3-22	3-20
Time to Resolution (days)				
≤ 2	50 (61%)	58 (46.8%)	42 (51.2%)	58 (49.2%)
3-7	23 (28%)	53 (42.7%)	33 (40.2%)	49 (41.5%)

Table 7: Severity of 1st CDI Recurrence in Subjects Meeting Expanded Definition of Clinical Cure (FAS)

	P001		P002	
	Bezlotoxumab	**Placebo**	**Bezlotoxumab**	**Placebo**
Subjects with Recurrences	N=82	N=124	N=82	N=118
8-10	2 (2.4%)	9 (7.3%)	3 (3.7%)	1 (0.8%)
≥ 10	7 (8.5%)	4 (3.2%)	4 (4.9%)	10 (8.5%)
WBC ≥ 15,000 cell/mm^2	1 (1.2%)	7 (5.6%)	1 (1.2%)	12 (10.2%)
Temperature > 38.3°C	1 (1.2%)	3 (2.4%)	1 (1.2%)	3 (2.5%)
Treated in a healthcare facility	28 (34.1%)	40 (32.3%)	30 (36.6%)	41 (34.7%)
ICU admission	4 (4.9%)	3 (2.4%)	4 (4.9%)	3 (2.5%)
CDI antibacterial treatment*	46 (56.1%)	76 (61.3%)	45 (54.9%)	77 (65.3%)
Duration of treatment				
≤ 14	21 (25.6%)	29 (23.4%)	16 (19.5)	32 (27.1%)
15-21	10 (12.2%)	15 (12.1%)	12 (14.6%)	26 (22%)
≥ 22	12 (14.6%)	21 (16.9%)	11 (13.4%)	16 (13.6%)
Unknown**	3 (3.7%)	11 (8.9%)	6 (7.3%)	3 (2.5%)
Fecal transplantation	3 (3.7%)	6 (4.8%)	2 (2.4%)	16 (13.6%)

*Vancomycin, metronidazole or fidaxomicin
** Duration of treatment was unknown if subject was on treatment at time of study completion or discontinuation.
Source: Adapted from Table 2 and 3, Sponsor response to FDA information request received July 18, 2016

Overall, clinical implications of CDI recurrences were not trivial. More than a half of the patients required a repeat course of SOC, about a third of the subjects required hospitalization and 2.5-5% of subjects required ICU admission. Notably, the recurrences in the bezlotoxumab-treated subjects may be less severe as indicated by a smaller proportion of recurrences in the bezlotoxumab arm requiring antibacterial treatment as compared to placebo.

In summary, I conclude that the Applicant provided substantial evidence of effectiveness to support approval of bezlotoxumab. In the two Phase 3 trials the recurrence rates of CDI were significantly lower in bezlotoxumab treated patients. While there was concern that imbalances in cure rates of the baseline CDI episode may have confounded the assessment of recurrence rates, subsequent analyses showing that CDI cure rates become balanced between treatment arms by 3 weeks post study drug infusion make the assessment of recurrence rates in the trials informative. The analyses also showed that potential negative effects on initial CDI cure are overall minor and are outweighed by the benefit of reducing the frequency of recurrences.

8. Safety

The safety review was conducted by Hiwot Hiruy, MD, PhD. Dr. Hiruy concluded that the safety profile of a single intravenous infusion of bezlotoxumab at 10 mg/kg in the prevention of CDI recurrence was overall favorable. In the Phase 3 trials the rates of deaths, serious adverse events (SAEs), and treatment-emergent adverse events (TEAEs) were similar to those of placebo. No increase in adverse events (AEs) related to potential immune-mediated reactions was observed in bezlotoxumab- as compared to placebo-treated subjects.

However, the review identified a greater number of SAEs related to heart failure in bezlotoxumab, 2.2% (17/786), as compared to placebo arm, 0.9% (7/781). In subjects with baseline CHF there were more deaths in the bezlotoxumab as compared to placebo arm, 19.5% (23/118) versus 12.5 % (13/104), respectively.

Bezlotoxumab clinical program included 1790 subjects who received bezlotoxumab either alone or in combination with actoxumab. In Phase 1 trials, 30 subjects received bezlotoxumab and 96 received actoxumab plus bezlotoxumab. In Phase 2 trials, 101 subjects received actoxumab plus bezlotoxumab. In Phase 3 trials, 786 subjects received bezlotoxumab and 777 received actoxumab and bezlotoxumab.

The safety analyses focused on the results of the two Phase 3 trials, Studies P001 and P002. The subjects that received the same study treatment in the trials are pooled. All TEAEs defined as any AE that occurred during or after infusion of study drug were reported for the first 4 weeks after the infusion. Serious AEs such as those resulting in deaths, significant disability or prolonged hospitalization were reported throughout 12 weeks. The actoxumab arm in Study P001 was not included in the pooled analysis. Enrollment in the arm was discontinued after an interim analysis revealed an increase in the number of deaths relative to placebo and low efficacy relative to the actoxumab plus bezlotoxumab arm among 235 subjects who received actoxumab.

The intended dose of bezlotoxumab in the Phase 3 trials was 10 mg/kg ($\geq$ 9.5 to < 10.5 mg/kg). In the actoxumab plus bezlotoxumab arm subjects received each antibody at 10 mg/kg. Overall, 97.1% (763/786) of bezlotoxumab- and 96.7% (751/777) of actoxumab plus bezlotoxumab-treated subjects received the intended bezlotoxumab dose.

Among all randomized subjects 16.4%, 16.9%, and 18.9% of subjects discontinued the study in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively. The proportions of subjects who discontinued the study and the reasons for discontinuation were balanced between study arms.

The main reason for study discontinuation was death. The mortality rate in the safety population was overall balanced between the treatment arms and was 7.1% (56/786), 6.6% (51/777), and 7.5% (59/781) in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively. Notably, 11.9% (28/235) of subjects died in the discontinued actoxumab arm in Study P001.

The incidence of serious adverse events was comparable between the treatment arms with the exception of SAEs related to heart failure. These SAEs reported with the terms of cardiac failure, cardiac failure acute, cardiac failure congestive, and cardiac failure chronic were more commonly observed in subjects treated with monoclonal antibodies and reported in 17 (2.2%), 17 (2.2%), and 7 (1%) subjects in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively.

To further explore potential impact of bezlotoxumab on heart function, safety analyses in subjects with baseline CHF were conducted. There were 118/786 (15%), 103/777 (13.3%), and 104/781 (13.3%) subjects with CHF in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively. The mortality rate in subjects with CHF was higher in the bezlotoxumab arm, 19.5% (23/118), and actoxumab plus bezlotoxumab arm, 17.5% (18/103), as compared to the placebo arm, 12.5% (13/104). The incidence of SAEs in subjects with CHF was also somewhat higher in the bezlotoxumab arm, 53.5% (63/118) as compared to actoxumab plus bezlotoxumab, 44.7% (46/103), and placebo arm, 48.1% (50/104). Heart failure was the most common SAE in subjects with baseline CHF in the bezlotoxumab arm, 23.8% (15/63) whereas in the placebo arm the incidence of cardiac failure in such subjects was 10% (5/50).

The incidence of infusion-related reactions within 24 hours after study drug infusion was evaluated by the reviewer. The reactions were defined as muco-cutaneous (e.g., hives, urticaria), respiratory (e.g., dyspnea, stridor), cardiac (e.g., syncope, tachycardia), gastrointestinal (e.g., crampy abdominal pain, vomiting), or general (e.g., pyrexia, asthenia) symptoms with at least one symptom from any two of the symptom groups to be present, or as a decrease in blood pressure, i.e., systolic blood pressure (SBP) < 90mmHg or a > 30% decrease in SBP from baseline. The incidence of at least one infusion related AEs within 24 hours post infusion was 13.5% (106/786), 9.9% (77/777), and 10% (78/781) subjects in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively.

With regard to infusion-related reactions during the infusion, there were 4 subjects in the bezlotoxumab arm, 4 subjects in the placebo arm and 1 subject in the actoxumab plus bezlotoxumab arm who developed such reactions including the only subject in the Phase 3 trials who discontinued study drug infusion. This bezlotoxumab-treated subject with HIV, *Pneumocystis* pneumonia treated with intravenous pentamidine, hypokalemia, and normal baseline ECG developed ventricular tachyarrhythmia 36 minutes after the start of infusion. The arrhythmia resolved within 5 minutes after the infusion was stopped. In addition one subject had a decrease in SBP by 30% during the infusion and 2 subjects had a decrease in SBP but to a lesser degree than the pre-defined hypotension criteria of SBP <90mmHg or a >30% SBP decrease from baseline.

The overall incidence of TEAEs was balanced between the treatment arms with 61.7% (485/786), 58.6% (455/777), and 61.2% (478/781) of subjects in the bezlotoxumab, actoxumab plus bezlotoxumab and placebo, respectively, experiencing one or more TEAE. The most common TEAEs included nausea reported in 6.6% (52/786), 6% (47/777) and 5% (39/781), and diarrhea reported in 6% (47/786), 5.9% (46/777) and 5.8% (45/781) of subjects in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively. Safety analyses by age (<65 vs ≥65 years), sex, race, and body weight (≤ 70 kg vs > 70 kg) have not revealed significant differences in death, SAEs, and TEAEs.

The development of anti-drug antibodies and neutralizing anti-drug antibodies were also assessed in the Phase 3 trials following dosing with bezlotoxumab alone or in combination with actoxumab. A total of 1414 subjects were evaluable for the immunogenicity analysis

including 710 subjects dosed with bezlotoxumab alone. No treatment-emergent or neutralizing anti-drug antibodies were detected.

I agree with Dr. Hiruy conclusions that the results of Studies P001 and P002 demonstrate an acceptable safety profile of a single 10 mg/kg infusion of bezlotoxumab for the reduction of recurrence of CDI in patients who are at a high risk of CDI recurrence. I also agree with her conclusions that the findings of an imbalance in the incidence of SAE of CHF as well as a greater number of deaths and SAEs in subjects with baseline CHF among bezlotoxumab- as compared to placebo-treated subjects are concerning. A warning informing about these findings and instructing that in patients with a history of heart failure bezlotoxumab should be reserved for use in situations when the benefit clearly outweighs the risk will be included in the product label.

9. Advisory Committee Meeting

The advisory committee for this BLA took place on June 9, 2016. The committee was asked whether the Applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence. There were10 yes votes, 5 no and 1 abstention.

The committee members who voted no indicated that they felt that the bezlotoxumab development program did not provide consistent evidence of the efficacy of bezlotoxumab in the prevention of CDI recurrence. Several committee members considered potential negative impact of bezlotoxumab on the cure of the initial CDI episode as well as the lack of clear understanding of its mechanism of action in the prevention of CDI as a reason to vote no. Some committee members indicated that they factored in their risk-benefit assessment of bezlotoxumab an increase in adverse events related to heart failure in the antibody arms as compared to placebo.

The committee members who voted no recommended conducting additional Phase 3 clinical trial(s) of bezlotoxumab. It was suggested that in these trials bezlotoxumab be administered upon successful cure of the initial CDI episode to avoid potential interference of bezlotoxumab with CDI cure.

The ten committee members who voted yes stated that the provided evidence of the efficacy and safety of bezlotoxumab in the prevention of *C. difficile* infection recurrence is substantial although the mechanism of action of bezlotoxumab and its effect on initial cure of CDI may not be fully understood. They also underscored that there is unmet medical need for therapies to prevent CDI recurrence and that bezlotoxumab is the first drug proposed for this indication.

10. Pediatrics

The Applicant requested deferral of pediatric studies because adult trials were completed and the product is ready for approval. The Applicant proposed PK and safety studies of pediatric patients from birth to 18 years. It should be noted, however, that while extrapolation of efficacy of bezlotoxumab from adults to the pediatric population is appropriate due to similar

pathogenesis of CDI, the extrapolation of efficacy may not be applicable to the youngest pediatric age groups. High rates of asymptomatic colonization with *C. difficile* in children < 6 months suggest that CDI may not exist in this age group. For a recently approved product for the treatment of CDI, pediatric studies were waived for children < 6 months and the same approach should be applicable for products developed to reduce CDI recurrence.

The application was discussed with the Pediatric Review Committee (PeRC) on June 22, 2016. The Division indicated that they consider waiving the studies in the youngest pediatric age groups (between 6-12 months of age). The PeRC agreed with this recommendation. Postmarketing requirements for pediatric PK and safety studies have been proposed.

11. Other Relevant Regulatory Issues

A clinical inspection summary (CIS) report was completed by John Lee, MD on May 11, 2016. Four clinical investigator sites that enrolled in the Phase 3 trials as well as the sponsor site were inspected. Clinical investigator (CI) included one site for Study P001, one site for Study P002, and two sites that enrolled in both trials. Sites with high numbers of subjects enrolled, deaths, serious adverse events (SAEs), and/or protocol deviations were selected.

No significant issues that could affect the trials conclusions were identified. At all inspected sites study conduct appeared compliant with good clinical practice, including study oversight by the sponsor and by the institutional review board. All audited NDA data were adequately verifiable against source records and case report forms.

12. Labeling

The major proposed labeling changes include a clarification of the indication to specify that bezlotoxumab is indicated to reduce recurrence of CDI in patients who are at a high risk for recurrence and an inclusion of a warning on a higher incidence of heart failure associated with bezlotoxumab use in subjects with baseline CHF.

The statement that bezlotoxumab should be used in patients who are at a higher risk for CDI was prompted by concerns that bezlotoxumab may prolong the resolution of the baseline CDI episode and may increase a risk of heart failure in patient with baseline CHF. The risk factors for CDI recurrences are known to health care providers and also discussed in the Clinical Studies section of the label. The risks factors include but may not be limited to advanced age, receipt of systemic antibacterial drugs, history of prior episodes of CDI, immunocompromised state, and presentation with clinically severe CDI.

The clarification that bezlotoxumab is indicated to reduce, rather than prevent CDI recurrence was made to emphasize that bezlotoxumab does not fully prevent CDI recurrence but reduce its rate.

The warning on the heart failure informs that in Phase 3 trials heart failure was reported more commonly in patients with a history of CHF treated with bezlotoxumab as compared to placebo. The warning also informs that in patients with baseline CHF there were more deaths

in bezlotoxumab - than in placebo-treated patients. The warning states that in patients with a history of heart failure, bezlotoxumab should be reserved for use in when the benefit clearly outweighs the risk.

Other labeling revisions include the addition of the Limitation of Use section. The section states that bezlotoxumab is not indicated for the treatment of CDI and should only be used only in conjunction with antibacterial drug treatment of CDI.

The Clinical Studies section was revised to present the efficacy results separately for each Phase 3 trial, to include the rates of sustained clinical response and to describe additional analyses of cure rates of the baseline CDI episode. In addition several clarifying revisions were made throughout the label.

The proprietary name review was conducted by Sevan Kolejian, Pharm. D., Division of Medication Error Prevention and Analysis (DMEPA). The proposed proprietary name, Zinplava, was considered acceptable. The Office of Prescription Drug Promotion (OPDP) labeling review was conducted by Adam George, Pharm.D. The DMEPA review of the proposed container label, carton labeling, and Full Prescribing (FPI) was conducted by Sevan Kolejian, Pharm. D. The recommendations from these reviews were incorporated in the labeling recommendations to the Applicant. Of note, the content of the labeling continues to be discussed at the time this review was written.

13. Postmarketing Recommendations

No risk evaluation and mitigation strategy (REMS) was considered necessary for bezlotoxumab. The review by the Division of Risk Management (DRISK) conducted by Mona Patel, Pharm.D., concurred that REMS is not needed.

The recommended postmarketing requirements include one pediatric study to evaluate safety, efficacy, and pharmacokinetics of bezlotoxumab in pediatric patients from 1 to less than 18 years of age. Pediatric assessments in pediatric patients less than 1 year of age will be waived. The postmarketing requirements and commitments and the proposed timelines for reporting are provided below:

REQUIRED PEDIATRIC ASSESSMENTS

- Conduct a randomized, double-blind, placebo-controlled trial of safety, efficacy, and pharmacokinetics of Zinplava (bezlotoxumab) in pediatric patients from 1 to less than 18 years of age receiving antibacterial therapy for *C. difficile* Infection.

  Final protocol submission: April 30, 2017
  Trial completion: May 31, 2022
  Final report submission: November 30, 2022

The reader is referred to the Product Quality section of this review listing postmarketing commitments recommended by the product quality reviewers. The timelines for these commitments will be provided in the approval letter.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DMITRI IARIKOV
10/14/2016