CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Summary Review
BLA #	761046
Applicant	Merck Sharpe and Dohme
Date of Submission	November 22, 2015
PDUFA Goal Date	October 21, 2016
Proprietary Name	Zinplava
Dosage Form(s) / Strength	Intravenous 1000 mg/40 mL vial
Applicant Proposed Indication	Prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI
Recommended Action for NME	Approval
Recommended Indication/Population(s)	To reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Shrimant Mishra MD MPH Hiwot Hiruy MD PhD
Statistical Review	Cheryl Dixon PhD
Pharmacology Toxicology Review	Terry Miller PhD
OPQ Review	Rashmi Rawat PhD
Microbiology Review	Kerian Grande Roche
Clinical Pharmacology Review	Yang He PhD

OPDP	Adam George PharmD
OSI	John Lee MD
CDTL Review	Dmitri Iarikov MD PhD
OSE/DMEPA	Sevan Kolejian PharmD
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OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In my assessment, the Applicant has provided substantial evidence to support the effectiveness of bezlotoxumab in reducing recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

As noted in this review, there were a number of significant challenges in interpreting the data from the two Phase 3 trials conducted to demonstrate the safety and efficacy of bezlotoxumab. The pre-specified primary endpoint in both trials was the proportion of subjects with CDI recurrence during the 12-week (Day 85 ± 5 days) follow-up period after infusion of study drug. The Agency had raised concerns about the CDI recurrence endpoint prior to the commencement of the second trial while the first trial was still ongoing. The concern with the CDI recurrence endpoint is that it ignores the potential impact of the investigational drug on initial clinical cure and counts patients who do not have initial clinical cure of their presenting CDI episode as successes (i.e. not having a recurrence). The Agency had noted that if an imbalance in the initial cure rates is seen, the effect of the study drug on recurrence can be very difficult to interpret. The Agency recommended that the Applicant use a primary endpoint of global cure (sustained clinical response) defined as clinical cure of the initial CDI episode and absence of CDI recurrence.

In both Phase 3 trials, recurrence rates in the 12-week follow up period were lower in patients who received bezlotoxumab compared to those who received placebo in addition to standard of care (SOC) antibacterial drugs for treatment of CDI. However, the imbalance in initial cure rates, especially the lower cure rates seen in the bezlotoxumab arm in Study P001, make it difficult to interpret the efficacy of bezlotoxumab using recurrence rate as the primary endpoint. Global cure or sustained clinical response is a valid measure of the efficacy of bezlotoxumab and is the more interpretable endpoint because it considers both initial cure of the CDI episode and absence of recurrence. To be a success, a patient needs to achieve clinical cure of the CDI episode and not have a recurrence. While in both trials, there was favorable treatment effect with bezlotoxumab for the pre-specified primary endpoint of reducing recurrences, in both trials there was an imbalance in the initial cure rate (one in favor of bezlotoxumab, the other against bezlotoxumab). While sustained clinical response was not the Applicant's pre-specified primary endpoint, in the setting of an imbalance in the initial cure rate, the recurrence endpoint is difficult to interpret making it reasonable to evaluate the trials using sustained clinical response as the primary endpoint.

Additional post hoc analyses were performed to allow for a better assessment of the negative impact of bezlotoxumab, if any, on initial clinical cure, seen in Study P001. It does appear that the impact on clinical cure might be a reflection of the protocol-specified definition of clinical cure that stipulated the duration of SOC to no more than 14 days and required resolution of diarrhea in the two days immediately following the bezlotoxumab infusion. While a negative impact on clinical cure cannot be definitively ruled out based on the information available (e.g., a delay in achieving cure), it does not appear to cause a significant worsening of the baseline CDI episode. The difference in clinical cure between the treatment arms does resolve with extending the allowed duration of SOC to 3 weeks post infusion nd the finding of reduction in recurrence rates remains significant. As there is no longer a difference in clinical cure rates using this expanded definition, the effect on global cure/sustained clinical response is also significant.

Based on the effect on sustained clinical response, the additional analyses that allow for an extended duration of SOC to 3 weeks post infusion, and the trials meeting their pre-specified primary endpoint (with the shortcomings described above), the evidence supports the efficacy of bezlotoxumab for the reduction of recurrence of CDI.

There are no currently approved therapies for reducing the risk of recurrences in patients with CDI. Recurrent CDI is a significant cause of morbidity and there is an unmet medical need for this condition. Approximately 20% of patients develop a recurrence after the resolution of the first episode of CDI and with a recurrent episode, the risk of subsequent recurrences is greater than that after the first episode.

Although the overall safety profile of bezlotoxumab was acceptable, it is important to note that the adverse reaction of heart failure was more common in patients who received bezlotoxumab, especially in those with congestive heart failure.

Given the uncertainties in assessing any potential negative impact on clinical cure of CDI and the safety signal for cardiac failure, it is prudent that bezlotoxumab only be indicated in patients at high risk for CDI recurrence. The Indications and Usage section of labeling will specify that bezlotoxumab is only approved for patients at high risk of recurrence of CDI and the Warnings and Precautions and the Adverse Reactions sections will include information regarding the risk of cardiac failure.

The following table has been adapted from the table in the CDTL review.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	*Clostridium difficile* infection (CDI) is a toxin mediated disease caused by the bacterium *C. difficile*. The clinical manifestations of the disease can vary from mild diarrhea to severe colitis that could result in intestinal perforation and death. A total of 453,000 cases of CDI resulting in 29,000 deaths are estimated to occur annually in the United States. About 20% of patients with CDI develop recurrence following resolution of the first episode and the risk of recurrence increases once the disease recurs.	CDI is a serious disease that can be associated with mortality and significant morbidity. In addition to the initial episode of CDI, recurrent CDI is a cause of significant morbidity.
Current Treatment Options	Currently, there are no approved therapies to reduce or prevent CDI recurrence.	There is an unmet medical need for this clinical condition.
Benefit	Efficacy of bezlotoxumab in reducing CDI recurrence was supported by two Phase 3 trials in which bezlotoxumab was compared to placebo in addition to SOC in both arms (Studies P001 and P002). Bezlotoxumab was administered as a single 10 mg/kg infusion at any time during CDI SOC therapy. In both trials the proportion of patients who did not have CDI recurrence through 12 weeks after study drug infusion was higher in the bezlotoxumab arm in the full analysis set (FAS) population. However, interpretation of this endpoint was challenging as it was based on the FAS population and as such classified all clinical failures of the initial CDI episode as successes as they could not develop recurrences. In both trials, there was an imbalance in the initial cure rates of the baseline CDI. In Study P001, the cure rate was 77.5% in the bezlotoxumab and 82.8% in the placebo arm. In Study P002, 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 the cure rates in all study arms in both trials were similar and that the negative impact, if any on initial cure did not result in clinically significant worsening of the baseline CDI.	There are some uncertainties if bezlotoxumab can have a negative impact on clinical cure of the baseline CDI episode. However, data available so far do not suggest a significant clinical worsening of the baseline CDI episode and the finding may be related to the specific definitions used in the protocol. Both trials showed a benefit in reducing recurrence of CDI in patients who had received bezlotoxumab in addition to SOC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	The overall rates of adverse events and deaths in patients who received bezlotoxumab were similar to that seen in placebo recipients. A higher number of serious adverse events (SAEs) related to heart failure were seen in the bezlotoxumab arm (2.2%) compared the placebo arm (0.9%). These SAEs were mainly observed in patients with baseline congestive heart failure (CHF). There were also more deaths in patients with baseline CHF in the bezlotoxumab arm, 19.5% (23/118), compared to the placebo arm, 12.5 % (13/104). The reason for this finding is unclear. Bezlotoxumab is a fully human monoclonal antibody and tissue cross-reactivity studies did not suggest any potential for cardiac toxicity. The finding also does not appear to be temporally related to bezlotoxumab administration or to volume overload.	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, especially in patients with underlying CHF cannot be ruled out based on the available data.	Labeling will include a warning about the risk of heart failure, especially in those with baseline CHF and a recommendation to reserve the use of bezlotoxumab in patients with CHF to situations when the benefit clearly outweighs the risk. No additional risk mitigation measures except for routine postmarketing pharmacovigilance are considered necessary at this point.

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) for CDI. 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 at any time during CDI antibacterial therapy.

Early in product development, the Applicant had hypothesized that an anti-toxin A antibody (actoxumab) would be effective. As nonclinical data suggested that the combination of antibodies would be more effective, the clinical development program was designed to evaluate the efficacy of actoxumab and bezlotoxumab in combination. Upon completion of the Phase 3 trials, when clinical outcomes were more favorable with bezlotoxumab, the Applicant chose to seek approval of bezlotoxumab alone.

Two Phase 2 trials were conducted. The first 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) as it was thought that the combination would be more effective. The second Phase 2 trial compared a combination of antitoxin A and B with placebo. The trial enrolled 101 subjects in the antibody arm 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.

Consistent with 21 CFR 300.50(a) (Fixed-combination prescription drugs for humans), the Division 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 toxin A alone, antibody to toxin B alone, and placebo to demonstrate the contribution of the components. The Division's advice proved essential as the hypotheses that were pursued, first that anti-toxin A was the essential therapy, and second that a combination of anti-toxin A and B would be needed, were not borne out by the results from clinical trials. The clinical trials supported the role of anti-toxin B (bezlotoxumab) as the therapeutic with a positive effect. The findings from the clinical trials demonstrated the limits of our understanding of mechanisms of disease and the pathophysiology of 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 primary endpoint was CDI recurrence and was calculated as the number of subjects with CDI recurrence divided by the total number of subjects 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, the Division 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.

Global cure was 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.

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 and the review clock was extended by three months.

3. Product Quality

The application technical lead and team leader for this BLA is Rashmi Rawat, PhD. Bezlotoxumab is produced from a (b) (4) (b) (4) using standard cell culture techniques. Testing for the identity, safety and genetic stability of the cell bank was performed. However, as the cell cloning procedure did not provide a high assurance of clonality of the master cell bank. The cell line genetic stability and product quality data submitted to the BLA provide assurance that the current manufacturing process is not impacted by the clonality of the cell bank; however it did not address the impact of different manufacturing conditions throughout the product life cycle. To address this issue the Applicant agreed to perform additional testing of the master cell bank to support clonality as a postmarketing commitment.

Bezlotoxumab drug substance is manufactured at (b) (4). (b) (4)

[redacted] The manufacturing process of bezlotoxumab is well controlled. Validation of the drug substance manufacturing process included viral clearance validation, commercial scale process validation, and process intermediates hold time validation. An adequate microbial control strategy is in place for the drug substance manufacturing process.

[redacted]

The container closure system (CCS) for bezlotoxumab drug substance is a [redacted] A proprietary extractable study has been conducted on the DS container closure system to demonstrate that the [redacted] system for bezlotoxumab is safe and acceptable for storage of the drug substance at the recommended storage conditions. The data provided in the BLA support a shelf-life of [redacted] months for bezlotoxumab drug substance when stored at [redacted] °C.

The bezlotoxumab drug product (Zinplava) is a preservative free, clear to moderately opalescent, colorless to pale yellow solution and is provided in sterile, [redacted] vial [redacted] Each mL of Zinplava contains bezlotoxumab, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 80, diethylenetriaminepentaacetic acid, and Water for Injection, USP. Additionally, the vial may contain NaOH to adjust the pH to 6.0.

Bezlotoxumab drug product is manufactured by Merck, Sharp, and Dohme in Carlow, Ireland. The manufacturing process of the drug product includes [redacted]

The stability data in the BLA support a shelf life of 24 months for the drug product when stored at 2 - 8°C.

The product quality review team recommends approval of the BLA. I agree with their assessment.

4. Nonclinical Pharmacology/Toxicology

The pharmacology-toxicology reviewer for this BLA is Terry Miller, PhD. In the BLA, the Applicant has submitted results of in vitro and in vivo pharmacology studies with bezlotoxumab in several animal models of CDI. Single and repeat dose toxicity studies were conducted in mice administered bezlotoxumab IV. Two tissue cross-reactivity studies were conducted with bezlotoxumab against a panel of mouse and human tissues. No safety pharmacology studies were conducted and no safety pharmacology endpoints were directly assessed in toxicology studies conducted with bezlotoxumab in mice. In single and repeat-dose studies in mice with IV bezlotoxumab administered for 14 days (5 doses/3 day interval) and 21 days (2 doses/14 day interval), no clinical signs or evidence of toxicity were seen at doses up to 50 and 125 mg/kg respectively, and at approximately 2.5 and 7 times greater exposure than that seen in humans after a single 10 mg/kg dose. 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.

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.

The 14-day repeat dose toxicology study in mice and the tissue cross-reactivity studies with bezlotoxumab were previously reviewed by Dr. Wendelyn Schmidt.

The pharmacokinetic properties of bezlotoxumab are consistent between mice and humans, particularly after a single dose administration. Bezlotoxumab has a half-life in plasma of 16.8 days after a single dose in mice.

Dr. Miller recommends approval of the BLA and I agree with this recommendation.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this BLA is Yang He, PhD. The pharmacokinetics (PK), safety, and immunogenicity of bezlotoxumab were evaluated in four Phase 1 trials (Studies P020, P004, P005, and P006), two Phase 2 and two Phase 3 trials. The dose of bezlotoxumab evaluated in these studies was 10 mg/kg administered intravenously. No dose ranging study was conducted. Population PK 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), since the bioanalytical methods used in the initial Phase 1 and 2 studies were not specific enough to measure bezlotoxumab concentration in serum.

Geometric mean clearance (CL) of bezlotoxumab is 0.317 L/day, geometric mean volume of distribution (Vd) is 7.33 L, and elimination half-life (t½) is approximately 19 days in CDI patients. The %CV for geometric mean of AUC0-inf and Cmax was 40% and 21%, respectively. The estimated inter-individual variability in CL and central volume of distribution (Vc) was approximately 28.7% and 10.6%, respectively. Bezlotoxumab is degraded into small peptides and individual amino acids through protein catabolism. Bezlotoxumab can be detected in stools from a limited number of CDI patients after IV administration. No exposure-response relationship for efficacy or safety was seen. No dose adjustment is needed with renal or hepatic impairment or based on gender/age when using the proposed weight-based dosing.

Dr. He recommends approval of the BLA and I agree with his assessment.

6. Clinical Microbiology

The clinical microbiology reviewer for this BLA is Kerian Grande Roche, PhD. Bezlotoxumab binds to toxin B produced by *C. difficile*. 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. 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.

Animal models of mouse and hamster CDI were used to characterize the efficacy 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 full protection from morbidity and mortality, therefore making it difficult to discern the contribution of bezlotoxumab alone. In a gnotobiotic piglet model, anti-toxin B antibody alone protected 100% of piglets from development of systemic CDI and minimized lesions.

In the Phase 3 trials, presence of toxigenic *C. difficile* was detected using different methods including ELISA, cell cytotoxicity, cell culture, and PCR-based tests. The most common ribotype isolated was 027. Among patients with recurrences in Study P001, ribotypes at recurrence were the same as baseline in 51% of subjects in the bezlotoxumab arm and 42% in

the placebo arm. In Study P002, ribotypes at recurrence were the same as baseline in 44% of subjects in the bezlotoxumab arm and 45% of subjects in the placebo arm.

Dr. Grande Roche recommends approval of the BLA and I agree with her assessment.

7. Clinical/Statistical-Efficacy

The clinical reviewer for this BLA is Shrimant Mishra, MD MPH and the statistics reviewer is Cheryl Dixon, PhD.

The Applicant submitted data from two Phase 3 trials to support the proposed indication. Both trials were randomized, multicenter, double-blind, placebo-controlled trials conducted in patients aged 18 years of age or older who were receiving SOC antibacterial drugs (oral metronidazole, vancomycin, or fidaxomicin) for an episode of CDI. Patients receiving vancomycin or fidaxomicin could also receive IV metronidazole. In Study P001, patients were randomized 1:1:1:1 to receive a single IV infusion of actoxumab, bezlotoxumab, actoxumab + bezlotoxumab, or placebo. In Study P002, there were three treatment arms, bezlotoxumab, actoxumab + bezlotoxumab, or placebo. Subjects were stratified by oral SOC therapy and hospitalization status (inpatient or outpatient) at the time of randomization. Study P001 allowed for halting of further enrollment into one or both of the individual monoclonal antibody treatment groups based on the results of an interim analysis if there was sufficient evidence of superiority of the combination over the individual monoclonal antibody(ies). Following the interim analysis, the actoxumab arm was dropped due to low efficacy and higher number of deaths and serious adverse events in the actoxumab arm compared to placebo.

The primary objective in both trials was to determine if treatment with a single infusion of the combination and the individual monoclonal antibodies decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to placebo. An additional objective (primary in Study P001 and secondary in Study P002) was to determine if treatment with a single infusion of actoxumab + bezlotoxumab decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to a single infusion of individual monoclonal antibodies. An important secondary objective was to determine the proportion of subjects who achieve global cure in the treatment group receiving a monoclonal antibody compared to the treatment group receiving 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 infusion of study drug. The FAS population was a subset of all randomized patients excluding those who did not receive study medication or did not have a positive stool test for toxigenic *C. difficile* at study entry or did not receive protocol defined SOC within a one-day window of

the infusion. Additionally in Study P001, subjects from one site that was found by the Applicant to have serious good clinical practice (GCP) non-compliance issues were excluded from the FAS population.

CDI recurrence was defined as a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline episode. Clinical cure of the baseline episode required patients to have received a SOC regimen of ≤ 14 days (16 calendar days) and not have diarrhea on the two days immediately following the last day of SOC. Global cure was defined as clinical cure of the baseline CDI episode and no CDI recurrence.

To control the type I error due to multiple treatment comparisons, a sequential testing approach was used. 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 plus bezlotoxumab arm to each of the individual monoclonal antibody arms. In both trials, the order of testing was actoxumab plus bezlotoxumab vs. placebo followed by the bezlotoxumab vs. placebo comparison.

As the proportion of patients with CDI recurrence is based on the FAS population, patients who were not initial clinical cures will be considered as not having a recurrence. Hence, any imbalance in the clinical cure rates between treatment arms will complicate the ability to fully interpret the CDI recurrence endpoint, especially if a larger proportion of patients in the monoclonal antibody arms do not achieve clinical cure. Global cure endpoint overcomes this issue as those who are not initial clinical cures will be considered failures.

In both Phase 3 trials, ~50% of patients were ≥ 65 years of age and ~25% were ≥ 75 years of age; ~50% of patients in Study P001 and ~ 40% in Study P002 were enrolled at North American sites. In Study P002, there was a higher proportion of Asian and non-US patients. A similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%) as SOC.

The population characteristics were fairly similar between the two trials, with some exceptions. The number of subjects with resolved diarrhea (≤ 2 loose stools/day) on the day of study drug infusion was greater in Study P002, 80% vs. 68% in the bezlotoxumab and 73% vs. 69% in the placebo arms, respectively. The number of subjects who had been on SOC for > 4 days at the time of study drug infusion was also greater in Study P002 compared to Study P001, 32% vs. 26% in the bezlotoxumab, and 29% vs. 24% in the placebo arms, 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 compared to the other two arms, 19% vs. ~12%, respectively. The proportion of subjects with hypervirulent strains in Study P001 was comparable across treatment arms.

In the BLA, the Applicant is seeking approval of only bezlotoxumab and so most of the efficacy results in this review will focus on the comparison between bezlotoxumab and placebo. In Study P001, 1452 subjects were randomized and 1396 were included in the FAS population: 383 actoxumab +bezlotoxumab, 232 actoxumab, 386 bezlotoxumab, and 395 placebo. Recurrence rates were significantly lower in the bezlotoxumab arm (17.4%) compared to the placebo arm (27.6%). The adjusted differences in CDI recurrence and 95% confidence intervals (CI) between bezlotoxumab and placebo arms were -10.1% (-15.9%, -4.3%). Clinical cure of the initial CDI episode was lower in the bezlotoxumab arm (77.5%) compared to placebo (82.8%), making interpretation of the CDI recurrence endpoint difficult. Global cure rates were numerically in favor of bezlotoxumab (60.1%) compared to placebo (55.2%) but did not achieve statistical significance. (Table 1)

Table 1: Clinical Cure, CDI Recurrence and Global Cure FAS Population Study P001

	Actoxumab + Bezlotoxumab n=383	**Bezlotoxumab n=386**	**Placebo n=395**
Clinical Cure	286 (74.7) -8.2 (-13.9, -2.4)	299 (77.5) -5.3 (-10.9, 0.3)	327 (82.8)
	p=**0.0057**	p=0.0622	
CDI Recurrence	61 (15.9) -11.6 (-17.3, -5.9)	67 (17.4) -10.1 (-15.9, -4.3)	109 (27.6)
	p<0.0001	**p=0.0006**	
Global Cure	225 (58.7) 3.5 (-3.4, 10.4)	232 (60.1) 4.8 (-2.1, 11.7)	218 (55.2)
	p=0.3165	p=0.1647	

Adjusted difference (95% CI) for monoclonal antibody- placebo stratified by SOC therapy and hospitalization status
Two-sided p-values based on chi-square test for comparison of monoclonal antibody arm vs placebo, bold indicates significant at a cut-off value ≤ 0.025, hierarchical ordering of tests: Acto plus bezlo vs. placebo followed by bezlotoxumab vs. placebo
Modified from Statistics review, Table 8

In Study P002, 1203 subjects were randomized and 1163 were included in the FAS population: 390 actoxumab +bezlotoxumab, 395 bezlotoxumab, and 378 placebo. Recurrence rates were significantly lower in the bezlotoxumab arm (15.7%) compared to the placebo arm (25.7%). The adjusted differences in CDI recurrence between bezlotoxumab and placebo arms were -9.9%, (95% CI -15.5, -4.2%). Clinical cure of the initial CDI episode was higher in the bezlotoxumab arm (82.5%) compared to placebo (77.8%). Global cure rates were significantly higher in the bezlotoxumab arm (66.8%) compared to placebo (52.1%). (Table 2)

Table 2: Clinical Cure, CDI Recurrence and Global Cure FAS Population Study P002

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

Adjusted difference (95% CI) for monoclonal antibody- placebo stratified by SOC therapy and hospitalization status
Two-sided p-values based on chi-square test for comparison of monoclonal antibody arm vs placebo, bold indicates significant at a cut-off value ≤ 0.025, hierarchical ordering of tests: Actoxumab plus bezlotoxumab vs. placebo followed by bezlotoxumab vs. placebo
Modified from Statistics review, Table 17

Sensitivity analyses were conducted which imputed subjects with incomplete stool information (i.e. due to toxin test not conducted, death, or incomplete follow-up) as well as those who received a concomitant medication or procedure potentially useful in the treatment of CDI during the follow-up period as a recurrence/failure. The results for global cure were robust to the sensitivity analyses in both trials. For CDI recurrence, the results remain significantly different in Study P001. In Study P002, the bezlotoxumab vs. placebo comparison of CDI recurrence is no longer statistically significant with either of the sensitivity analyses.

The Applicant performed additional post hoc analyses to assess the impact on clinical cure and to determine if this finding was mainly driven by the protocol specified definition or if in fact there was a worsening of the clinical condition. The Applicant used an expanded definition of clinical cure that allowed for patients who received SOC longer than the 14 days as specified in the protocol and those who had resolution of diarrhea (≤ 2 loose stools per 24 hours) for any two consecutive days at any time after completion of SOC to be considered as clinical cures. Based on these additional analyses, the Applicant concluded that the effect on clinical cure was mainly due to the protocol-specified definition, as most patients completed a course of SOC and subsequently had resolution of their diarrhea. The following table summarizes the clinical cure rates using the expanded definition at various timepoints.

Table 3: Clinical Cure Rates Using Expanded Definition of Clinical Cure

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

Modified from Tables 1 and 2, statistics review addendum

CDI recurrences remain significant using the expanded definition of clinical cure. As by 3 weeks post infusion, the majority of patients had achieved clinical cure and there was no imbalance between treatment arms, the recurrence endpoint is more interpretable and will be consistent with the global cure/sustained clinical response endpoint.

Table 4: CDI Recurrence based on Original and Expanded Definition of Clinical Cure (FAS population)

	Bezlotoxumab	**Placebo**	**Treatment difference (95% CI)**
Study P001			
	N=386	N=395	
Original Definition	67 (17.4)	109 (27.6)	-10.1 (-15.9, -4.3), p=0.0006
Expanded definition 3 weeks	78 (20.2)	122 (30.9)	-10.6 (-16.6, -4.5), p=0.0006
Study P002			
	N=395	N=378	
Original Definition	62 (15.7)	97 (25.7)	-9.9 (-15.5, -4.2), p =0.0006
Expanded definition 3 weeks	80 (20.3)	115 (30.4)	-10.0 (-16.1, -4.0), p=0.0006

Adjusted difference (95% CI) for monoclonal antibody- placebo stratified by SOC therapy and hospitalization status; two-sided p-values based on chi-square test for comparison of monoclonal antibody arm vs placebo
Modified from addendum to statistics review, Tables 3 and 4

In Study P001, the global cure rates using the 3 week expanded definition of clinical cure was 71.2% in the bezlotoxumab arm compared to 60.5% in the placebo arm, treatment difference 10.6 (95% CI, 4.1, 17.2, p=0.0015). In Study P002, the global cure rates using the 3 week expanded definition of clinical cure was 72.7% in the bezlotoxumab arm compared to 59.5% in the placebo arm, treatment difference 13.0 (95% CI, 6.4, 19.5, p=0.0001).

To further evaluate the post hoc analyses, severity of recurrences, and clinical variables associated with clinical failure, particularly in patients reclassified from initial clinical failure to initial clinical cure, the review clock was extended as submission of this additional information was considered to be a major amendment.

To better understand the reasons for failure of initial clinical cure and to assess if expanding the definition of clinical cure had any negative clinical impact, key characteristics of patients who were classified as failures using the protocol-specified definition and cures using the expanded definition were analyzed and are summarized in Table 5.

Table 5: Clinical Characteristics in Reclassified Patients

	Study P001		**Study P002**	
	Bezlotoxumab N=74	**Placebo N=52**	**Bezlotoxumab N=51**	**Placebo N=62**
Median Duration in days of SOC (25%-75%)	16 (10.5-19)	16 (12.25-21.75)	17 (15-21)	16 (13.75-20)
Median Duration in days from End of SOC to Resolution of Diarrhea (25%-75%)	3 (2-5.25)	3 (2-7.75)	3 (2-5)	3.5 (2-6)
Number of patients with Recurrences	15	15	20	21

Modified from Table 28, clinical review

Based on the information above, it appears that the clinical course of patients who were reclassified is not suggestive of clinically significant worsening of the baseline CDI.
Dr. Mishra reviewed the case report forms (CRFs) of a subset of patients in Study P001 who were reclassified and concluded that in the majority of cases it was difficult to identify a direct relationship between receipt of bezlotoxumab and clinical failure and that any potential negative effect on clinical cure was only a modest prolongation of the duration of the initial illness. It is however, difficult to exclude any potential negative impact on clinical cure and it does appear that the negative impact if any does not appear to cause significant worsening of the CDI. Given these uncertainties, it is important that prescribers be informed of the potential for bezlotoxumab to impact clinical cure and this information will be included in product labeling.

Dr. Mishra evaluated the recurrences in terms of severity based on criteria including the need for/type of treatment, hospitalization, ICU stay and clinical characteristics. Overall, it appeared that in both trials there was a trend towards less severe illness in the bezlotoxumab arm with regard to need for treatment.

Dr. Mishra's assessment is that bezlotoxumab appeared to have an effect on reducing

recurrences, irrespective of the specific definition of recurrence used. With regard to clinical cure, Dr. Mishra concludes that the effect on initial clinical cure is unclear. Based on the expanded definition of clinical cure and review of CRFs, the potential negative effect of bezlotoxumab on clinical cure, appears to be clinically minor and such risk may be acceptable. Overall, in Dr. Mishra's assessment, there appears to be a positive risk benefit and he recommends that bezlotoxumab should be used in patients with significant risk factors for CDI recurrence.

In a review dated May 10, 2016, Dr. Dixon notes that while there appears to be a decrease in CDI recurrence with the use of bezlotoxumab, there is concern regarding its impact on initial clinical cure. Numerical differences were observed in initial clinical cure between bezlotoxumab and placebo favoring placebo in Study P001 and bezlotoxumab in Study P002. Also, in both trials, the difference in clinical cure was in favor of placebo compared to actoxumab plus bezlotoxumab arm. So, a negative effect of bezlotoxumab on clinical cure of the initial CDI cannot be ruled out. On the global cure endpoint, results were only statistically significant in Study P002. This finding should be interpreted with caution as global cure rates in the actoxumab plus bezlotoxumab vs. placebo were not significant. This was to be demonstrated first in the hierarchical ordering of the prespecified testing strategy. Dr. Dixon suggested that an additional trial may help resolve this issue and deferred a decision on the clinical relevance of the results to the review Division.

In an addendum dated September 16, 2016, Dr. Dixon notes that the analyses based on the post hoc expanded definition of clinical cure may allow for a more interpretable assessment of the CDI recurrence endpoint as there are no longer imbalances in the initial clinical cure rates. The finding of reduction in CDI recurrence is maintained with the new definition. Additionally, the results for global cure may now be considered significant in both trials using the expanded definition of clinical cure. However, Dr. Dixon defers to the review Division to determine if the possibility of a negative effect on the initial cure of treatment with bezlotoxumab observed with the protocol-specified definition of clinical cure is less concerning given that with the expanded definition, the time to initial clinical cure does not seem to extend much beyond 3 weeks post infusion in the majority of patients and becomes fairly balanced across treatment groups.

Dr. Dmitri Iarikov, the CDTL is of the opinion that the Applicant has provided substantial evidence of effectiveness to support approval of bezlotoxumab for reducing recurrences in patients with CDI. In the two Phase 3 trials, the proportion of subjects who did not have CDI recurrence was higher in bezlotoxumab compared to placebo-treated patients. While there is a concern that bezlotoxumab may prolong the resolution of the initial CDI episode, subsequent analyses showed that potential negative effects on initial clinical cure are overall minor, clinical cure rates become balanced between treatment arms by 3 weeks post study drug

infusion, and the benefit of reducing the frequency of recurrences outweigh possible negative effects on initial clinical cure.

8. Safety

The safety reviewer for the BLA is Hiwot Hiruy, MD, PhD.

A total of 1790 subjects received bezlotoxumab either alone or in combination with actoxumab of whom 1741 were exposed to a bezlotoxumab dose of 10 mg/kg. In Phase 1 trials, 30 subjects received bezlotoxumab and 96 received actoxumab plus bezlotoxumab, and in Phase 2 and 3 trials, 786 received bezlotoxumab alone and 878 received actoxumab plus bezlotoxumab. Treatment emergent adverse events (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 were reported through 12 weeks.

The focus of the safety review was the two Phase 3 trials, Studies P001 and P002. As in both trials, bezlotoxumab was administered as a single 10 mg/kg IV dose, pooled safety analyses are presented. Data on patients who received the same study treatment in the two trials are pooled. The actoxumab arm in Study P001 was not included in the pooled analysis. Enrollment in the actoxumab 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. In the pooled trials, 97.1% (763/786) of bezlotoxumab and 96.7% (751/777) of actoxumab plus bezlotoxumab-treated subjects received the 10 mg/kg dose.

Among all randomized subjects the proportions of subjects who discontinued the study and the reasons for discontinuation were balanced between study arms.

The mortality rate was similar between the treatment arms and placebo; 7.1% (56/786), 6.6% (51/777), and 7.5% (59/781) in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arms, respectively. Dr. Hiruy performed a review of all the death narratives and concluded that the majority of deaths appear to be related to the underlying co-morbidities.

The incidence of Serious Adverse Events (SAEs) was similar between the treatment arms with the exception of SAEs related to cardiac failure (includes the terms cardiac failure, cardiac failure acute, cardiac failure congestive, and cardiac failure chronic) and were reported in 17/786 (2.2%), patients in the bezlotoxumab arm and 7/781 (0.9%) in the placebo arm.

Additional analyses were performed on the subgroup of patients with CHF. Approximately 14% of patients had CHF across the three arms; 118/786 (15%), 103/777 (13.3%), and 104/781 (13.3%) in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arms, respectively. In patients with CHF, mortality rate was higher in the bezlotoxumab arm, 23/118

(19.5%), and actoxumab plus bezlotoxumab arm, 18/103 (17.5%), compared to the placebo arm, 13/104 (12.5%). The incidence of SAEs in subjects with CHF was also higher in the bezlotoxumab arm, 63/118 (53.5%) compared to actoxumab plus bezlotoxumab, 46/103 (44.7%), and placebo arm, 50/104 (48%).

At least one infusion related AEs within 24 hours post infusion was reported in 106/786 (13.5%), 77/777 (9.9%), and 78/781 (10%) subjects in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arm, respectively. Four patients each in the bezlotoxumab and placebo arms and one in the actoxumab plus bezlotoxumab arm developed infusion-related reactions. One bezlotoxumab-treated patient with HIV and 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. 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 <90 mmHg 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 arms, respectively, experiencing one or more TEAE. The most common TEAEs (>4%) were nausea, pyrexia and headache.

The development of anti-drug antibodies and neutralizing anti-drug antibodies were assessed in the 1414 subjects in the Phase 3 trials including 710 subjects who received bezlotoxumab alone. No treatment-emergent or neutralizing anti-drug antibodies were detected.

In Dr. Hiruy's assessment, the safety of bezlotoxumab has been fairly well characterized and the finding of higher rates of cardiac failure in patients who received bezlotoxumab will need to be communicated in labeling. I concur with her assessment.

9. Advisory Committee Meeting

This BLA was discussed at a meeting of the Antimicrobial Drugs Advisory Committee on June 9, 2016. The committee was asked to vote on the following question:

Has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence in patients aged 18 years and older?

There were 10 Yes votes, 5 No votes, and 1 abstention.

Many committee members were of the opinion that benefit with regard to recurrence had been demonstrated and some members expressed concerns regarding the potential negative impact

on clinical cure. Some committee members noted that the trials were well conducted and that there was an unmet need for products that can reduce recurrence rates. Several committee members recommended that the product be labeled for use only in high-risk patients and that labeling should include a warning related to use in patients with underlying CHF. Among committee members who voted no, there was concern that the efficacy finding was not convincing and that there was a safety signal. Some committee members recommended that an additional trial should be conducted to better delineate the treatment effect.

10. Pediatrics

The Applicant requested deferral of pediatric studies because adult trials were completed and the product is ready for approval. The Applicant has proposed a PK and safety study in pediatric patients from ≥1 year to <18 years of age. A waiver will be granted in pediatric patients younger than a year of age as CDI is not common in pediatric patients less than a year of age making studies in this age group not feasible.

The pediatric study plan was discussed with the Pediatric Review Committee (PeRC) and found to be acceptable.

11. Other Relevant Regulatory Issues

- *Office of Scientific Investigations (OSI) Audits*

  John Lee, MD is the OSI reviewer for this BLA. Five inspections were conducted, one at the Applicant site and four at clinical investigator (CI) sites with high numbers of subjects enrolled, deaths, serious adverse events (SAEs), and/or protocol deviations. A Form FDA 483 was issued at the Applicant site and at two CI sites for minor or limited deficiencies. In Dr. Lee's assessment, at all four CI sites, the overall study conduct appeared GCP-compliant, including study oversight by the Applicant and by the IRB. Dr. Lee notes that data from the four CI sites appear reliable as reported in the BLA.

12. Labeling

Sevan Kolejian, PharmD, from the Division of Medication Error and Prevention and Analysis and Jibril Abdus-Samad, PharmD, from the Office of Biotechnology Products found the revised carton and container label to be adequate. Recommendations provided by Adam George, Pharm D, from OPDP have been incorporated in labeling.

The major sections of the package insert that were revised include the following:

- INDICATIONS AND USAGE:
    - The Applicant's proposed indication was broad and not limited to any specific patient population. Given some of the uncertainties in the efficacy results of the two Phase 3 trials and the safety finding of cardiac failure, the indication was limited to patients at high risk of CDI recurrence. In addition, bezlotoxumab will be indicated for reducing recurrences and not preventing recurrences.
    - A limitation of use statement is included to inform the prescriber that bezlotoxumab is not indicated for the treatment of CDI and should only be used in conjunction with antibacterial drug treatment of CDI.

- WARNINGS AND PRECAUTIONS: A warning has been added regarding the risk of cardiac failure to describe the higher incidence of heart failure reported in the two Phase 3 trials in patients who received bezlotoxumab compared to those who received placebo, especially in patients with congestive heart failure. The warning also includes a statement that in patients with a history of CHF, bezlotoxumab should be reserved for use when the benefit clearly outweighs the risk.

- CLINICAL STUDIES: Information presented in this section were streamlined to summarize the key aspects of the clinical trials that would be useful to the prescriber, such as demographic characteristics of patients in the clinical trials that are associated with higher risk of CDI recurrence and a description of the finding of potential impact on initial clinical cure with bezlotoxumab. Efficacy results (sustained clinical response rates) and reasons for not achieving sustained clinical response are presented in a tabular format. A statement has also been included regarding efficacy results in patients at high risk for CDI recurrence being consistent with that seen in the overall trial population.

13. Postmarketing

- Postmarketing Requirements and Commitments

The Applicant has agreed to the following postmarketing commitments related to product quality. There are no postmarketing requirements.

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 (b) (4).
2. Develop a valid in vitro endotoxin assay for drug product release testing.
3. Perform Low Endotoxin Recovery studies (b) (4) (b) (4).

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/s/

SUMATHI NAMBIAR
10/21/2016