BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	BLA 761046/S-012
Priority or Standard	Priority
Submit Date(s)	November 28, 2022
Received Date(s)	November 28, 2022
PDUFA Goal Date	May 26, 2023
Division/Office	DAI/OID
Review Completion Date	May 24, 2023
Established/Proper Name	Bezlotoxumab
(Proposed) Trade Name	ZINPLAVA
Pharmacologic Class	Monoclonal Antibody
Code name	MK-6072
Applicant	Merck Sharp and Dohme, Corp., a subsidiary of Merck & Co., Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	Single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes
Applicant Proposed Indication(s)/ Population(s)	ZINPLAVA is indicated to reduce recurrence of *Clostridioides difficile* infection (CDI) in adults and pediatric patients 1 year of age and older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	789685005 | Recurrent infection caused by *Clostridioides difficile* (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/ Population(s) (if applicable)	ZINPLAVA is indicated to reduce recurrence of CDI in adults and pediatric patients 1 year of age and older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	789685005 | Recurrent infection caused by *Clostridioides difficile* (disorder)
Recommended Dosing Regimen	Single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes

Abbreviations: CDI, *Clostridioides difficile* infection; DAI, Division of Anti-Infectives; OID, Office of Infectious Diseases; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Abbreviations: ADL, Associate Director for Labeling; DAI, Division of Anti-Infectives; DPTID, Division of Pharmacology and Toxicology for Infectious Diseases; OCP, Office of Clinical Pharmacology

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Glossary

ADA	antidrug antibody
AE	adverse event
ALL	acute lymphocytic leukemia
AML	acute myeloid leukemia
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BP	blood pressure
CDI	*Clostridioides difficile* infection
CHF	congestive heart failure
C_{max}	maximum serum concentration
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
DMC	data monitoring committee
ECI	Events of Clinical Interest
ER	exposure-response
FMT	fecal microbiota transplant
FDA	Food and Drug Administration
GMR	geometric mean ratio
GoF	goodness-of-fit
IDSA	Infectious Disease Society of America
IV	intravenous
mAb	monoclonal antibody
mITT	modified intent to treat
MRSA	methicillin-resistant *Staphylococcus*
NAb	neutralization antibody
NCA	noncompartmental analyses
OBP	Office of Biological Products
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OFV	objective function value
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance

PDUFA	Prescription Drug User Fee Act
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PWR	Pediatric Written Request
SAE	serious adverse event
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VOD	veno-occlusive disease
VPC	visual predictive check

1 Executive Summary

1.1 Product Introduction

Bezlotoxumab (ZINPLAVA) is a human monoclonal antibody (mAb) to *Clostridioides difficile* toxin B. ZINPLAVA was initially approved in 2016 to reduce the recurrence of *C. difficile* infection (CDI) in patients 18 years or older who are receiving antibacterial drug treatment for CDI and are at a high risk of recurrence (Merck 2016). At the time of approval, FDA issued a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR 3118-1) to conduct a study of the safety, efficacy, pharmacokinetics (PK) of ZINPLAVA in the pediatric population 1 to less than 18 years of age. Pediatric study requirements for patients <1 year of age were waived because the disease does not commonly occur in this age group.

In 2020, FDA issued a Pediatric Written Request (PWR) for a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, PK, and efficacy of a single infusion of bezlotoxumab compared to placebo in pediatric patients from 1 to less than 18 years old receiving antibacterial drug treatment for CDI. The PWR was accepted by the Applicant without amendment in 2020. An amendment to the PWR was subsequently issued in 2022 in response to the Applicant's request to decrease the overall size of the study to enable completion of the study by the PREA PMR due date, citing declining enrollment rates impacted by the COVID-19 pandemic. PWR Amendment 1 was issued in April 2022.

This efficacy supplement (BLA 761046, S-012) proposes to add a new population, pediatric patients aged 1 to less than 18 years who are receiving antibacterial (b) (4) for CDI and are at high risk for CDI recurrence. The submission is based on data from a single randomized, placebo-controlled, double-blind, multicenter pediatric study (MODIFY III) to evaluate the PK, safety, tolerability, and efficacy of a single 10 mg/kg infusion of ZINPLAVA in patients aged 1 to less than 18 years old receiving antibacterial treatment for CDI. The proposed pediatric dosing of a single 10 mg/kg intravenous (IV) infusion is the same as the approved dose in adults for this indication.

Supplement S-012 was submitted to fulfil PMR 3118-1 and the requirements of PWR Amendment 1. The Applicant requested pediatric exclusivity determination. The Applicant met the dates for study completion (May 2022) and study report submission (November 2022) for the PMR and Amendment 1 of the PWR. The completed study met the requirements for granting pediatric exclusivity and on May 15, 2023, the Applicant was informed that pediatric exclusivity had been granted for studies conducted on bezlotoxumab under section 505A of the Federal, Food, Drug, and Cosmetic Act (21 U.S.C. 355a) effective May 12, 2023.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness to support the approval of ZINPLAVA for reduction in recurrence of CDI in pediatric patients aged 1 to less than 18 years who are receiving antibacterial drug treatment for CDI and are at high risk for CDI recurrence was extrapolated from the adult CDI prevention trials MODIFY I and MODIFY II. Extrapolation is appropriate for this indication since the mAb targets a bacterial exotoxin and the pathophysiology of recurrent CDI is similar in adults and pediatric patients greater than 1 year of age. The extrapolation of effectiveness from adult patients to pediatric patients is based on the comparison of bezlotoxumab exposures observed in pediatric patients enrolled in the MODIFY III trial that evaluated the proposed bezlotoxumab dosage to the exposures reported in adults enrolled in the MODIFY I and MODIFY II trials that evaluated the currently approved bezlotoxumab dosage (see Section 6.2.2).

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

ZINPLAVA (bezlotoxumab) is approved to reduce the recurrence of *Clostridioides difficile* infection (CDI) in patients 18 years or older who are receiving treatment for CDI and are at a high risk of recurrence. This pediatric efficacy supplement proposes to add pediatric patients 1 to <18 years of age to the indication. The dosing regimen for pediatric patients remains the same as for adults, a one-time intravenous (IV) infusion of ZINPLAVA dosed at 10 mg/kg.

Data from one randomized (3:1 ZINPLAVA: placebo), placebo-controlled, parallel group, multisite, double blinded study (MODIFY III) of pediatric patients aged 1 to <18 years were submitted to support the use of ZINPLAVA in the proposed pediatric population. The study included a total of 143 patients who received study treatment (107 ZINPLAVA, 36 placebo) with the primary objectives of evaluating the safety, tolerability, and pharmacokinetics (PK) of ZINPLAVA in this group. Efficacy was evaluated as a key secondary endpoint, but the study was not powered for formal statistical testing and efficacy endpoints were descriptively analyzed. The efficacy of ZINPLAVA was extrapolated from the efficacy data from two adequate and well-controlled trials supporting approval of ZINPLAVA for this indication in the adult population (MODIFY I and MODIFY II). Extrapolation is appropriate for this indication because ZINPLAVA targets a specific bacterial toxin produced by the *C. difficile* organism, and the pathophysiology of CDI is similar between adult and pediatric patients aged 1 year and older. The extrapolation of effectiveness at the proposed pediatric dosing regimen is supported by the comparison of bezlotoxumab exposures (e.g., $AUC_{0\text{-}inf}$, $AUC_{Days\ 0\text{-}84}$) in adult and pediatric CDI patients.

The safety profile of ZINPLAVA observed in the pediatric study was similar to the safety profile in adults with CDI. Treatment emergent adverse events (TEAEs) occurred at a similar rate in subjects who received ZINPLAVA (95/107, 88.8%) and subjects who received placebo (34/36, 94.4%). There were 6 deaths [5 of 107 patients (4.9%) in the ZINPLAVA-treated arm and 1 of 36 patients (2.8%) in the placebo arm] during the 12-week study period, and one death that occurred after 12 weeks in the ZINPLAVA-treated arm. ZINPLAVA was not causally associated with any of the deaths. No patients discontinued the study drug due to adverse events. The most common adverse reactions occurring in greater than 10% of patients treated with ZINPLAVA were pyrexia (19 patients, 18%), and headache (15 patients, 14%). Heart failure was observed more frequently in adult patients with CDI receiving ZINPLAVA versus those that received placebo in clinical trials and is included as a warning in the current labeling, but heart failure was not observed in the pediatric study.

Overall, ZINPLAVA has a favorable safety profile for the indication of reduction in the recurrence of CDI in pediatric patients ages 1 to <18 years of age. The risks associated with ZINPLAVA use in the pediatric population can be adequately addressed through the product labeling and routine postmarketing surveillance. Substantial evidence of effectiveness is extrapolated from adequate and well-controlled trials in adult patients with CDI (MODIFY I and MODIFY II).

Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CDI is a common healthcare-associated infection that can cause a wide range of clinical manifestations including severe complications such as toxic megacolon and shock. • The risk of developing CDI is increased by frequent antibacterial drug exposure. Patients who experience CDI are at increased risk of developing recurrent disease, which can be difficult to treat. • In adults, risk factors for recurrent CDI include age >65 years, concomitant antibacterial drug use during CDI treatment, and severe underlying medical disease. • In children, risk factors for recurrent CDI are less well established, but include malignancy, recent surgery, and exposure to multiple courses of antibacterial drugs.	CDI can lead to increased morbidity and mortality, as well as recurrent disease which can result in multiple hospitalizations, prolonged antibacterial drug use, and contribute to increased medical costs.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Current Treatment Options</td><td>Recurrent CDI is treated primarily with antibacterial drugs.
For pediatric patients, current treatment guidelines recommend oral vancomycin or metronidazole for the first CDI recurrence, with oral vancomycin preferred for severe disease.
In adult patients, the current guidelines recommend fidaxomicin as the preferred agent for treatment of the first CDI recurrence, given its higher rate of sustained clinical response in clinical trials.
The guidelines for pediatric recurrent CDI treatment have not been updated since fidaxomicin was approved for treatment of CDI in pediatric patients ages 6 months and older in 2020.
There are no FDA approved treatments to reduce the incidence of recurrent CDI in pediatric patients.
Fecal microbiota transplant (FMT) has been used under investigative new drug applications to reduce CDI recurrence. FMT is occasionally used for children with recurrent CDI in specific circumstances but there are limited data evaluating its safety and efficacy.
Since the submission of this sBLA, two fecal microbiota products (REBYOTA for fecal administration and VOWST for oral administration) have been approved by FDA to prevent recurrence of CDI in patients 18 years of age or older. Neither was approved for use in pediatric patients.
ZINPLAVA is approved to reduce recurrence of CDI in patients 18 years or older who are receiving antibacterial drug treatment for CDI and are at high risk for CDI recurrence.</td><td>There is a need for new medications to reduce the recurrence of CDI in pediatric patients.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of ZINPLAVA to reduce the recurrence of CDI was established based on data from two adequate and well-controlled trials in adult patients with CDI (MODIFY I and MODIFY II). • A single randomized, double-blind, placebo-controlled trial (MODIFY III) was conducted in pediatric patients aged 1 to <18 years. The study enrolled 143 patients randomized 3:1 (107 ZINPLAVA-treated, 36 placebo-treated) • The primary objectives were to characterize the PK of ZINPLAVA in pediatric participants to support dose selection, and to evaluate the safety and tolerability of a single infusion of ZINPLAVA as compared to placebo through 12 weeks postinfusion. • Descriptive efficacy analyses were performed on the modified intention to treat (mITT) population consisting of patients who received study treatment, had a positive *C. difficile* toxin assay, and were taking protocol-defined antibacterial drugs for CDI treatment (n=139). Sustained clinical response was observed in 83.7% (87/104) of ZINPLAVA-treated patients and 82.9% (29/35) of placebo-treated patients. CDI recurrence was observed in 11.2% (11/98) of ZINPLAVA-treated patients and 14.7% (5/34) of placebo-treated patients. However, the study was not powered for formal statistical testing of efficacy endpoints. • The extrapolation of effectiveness at the proposed pediatric dosing regimen is supported by the comparison of bezlotoxumab exposures (e.g., $AUC_{0\text{-inf}}$, $AUC_{\text{Days 0-84}}$) in adult and pediatric CDI patients.	Efficacy of ZINPLAVA has been established in adult patients with CDI and can be extrapolated to pediatric patients 1 to less than 18 years of age. The basis for extrapolation includes that the monoclonal antibody (mAb) has the same target (*C. difficile* toxin B), the pathophysiology of CDI is similar in adult and pediatric patients, and the mAb exposure is comparable in adult and pediatric patients with CDI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In MODIFY III, pyrexia and headache were the most common adverse reactions (ARs) in pediatric patients treated with ZINPLAVA. In MODIFY I and MODIFY II, the most common ARs observed in adults were nausea, pyrexia, and headache. • The most common serious adverse events were categorized as "infections and infestations" and "blood and lymphatic system disorders" in children. This is consistent with the expected complications of the underlying illnesses of these patients. • There were 6 deaths reported during the study, 5 of 107 patients (4.9%) in the ZINPLAVA arm and 1 of 36 patients (2.8%) in the placebo arm and one additional death in the ZINPLAVA arm after the 12 weeks had concluded. ZINPLAVA was not causally associated with any of these deaths. • Heart failure was observed more frequently in adult CDI patients treated with ZINPLAVA versus placebo in MODIFY I and MODIFY II and is included as a warning in the current labeling. Heart failure was not observed in pediatric patients treated with ZINPLAVA in MODIFY III.	The safety profile observed with ZINPLAVA use in pediatric patients was similar to that observed in adults. The risks associated with ZINPLAVA use in the pediatric population can be adequately addressed through product labeling and routine postmarketing pharmacovigilance. No safety issues would require a Risk Evaluation and Mitigation Strategy at this time

Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from 0 to infinity; $AUC_{Days0\text{-}84}$, area under the curve from day 0 to 84; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplant; mAb, monoclonal antibody; mITT, modified intent to treat; PK, pharmacokinetics

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		x☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1 Analysis of Condition

CDI is a toxin-mediated disease caused by *Clostridioides difficile,* an anaerobic, spore-forming gram-positive bacterium that produces two pathogenic enterotoxins, Toxin A and Toxin B. CDI presents both a clinical and economic challenge to patients and health care settings alike. CDI is a cause of antibiotic-associated diarrhea and it is a common healthcare-associated infection (Lessa et al. 2015). While the clinical manifestations of CDI can be as mild as asymptomatic colonization, infection can also lead to severe complications such as ileus, toxic megacolon, and shock. CDI is less common in children than adults, but the incidence of pediatric cases is increasing (Campbell et al. 2019).

In pediatric patients, the severity of CDI appears to increase with age. Neonates and children under 12 months of age are commonly found to be colonized with *C. difficile* but do not develop clinically significant symptoms (Rousseau et al. 2012). Colonization rates decrease with increasing age, and by 2 to 3 years of age, the number of children who are asymptomatic carriers is similar to that observed in healthy adults (Tougas et al. 2021). Symptomatic CDI in children typically begins during or following antibacterial drug treatment with acute-onset of watery, profuse, and foul-smelling diarrhea. Other symptoms include fever, abdominal pain, and vomiting. The disease can become severe and cause elevated white blood cell counts, increased creatinine levels, and pseudomembranous colitis. Fulminant disease can include toxic megacolon and bowel perforation.

Recurrent CDI can occur in up to 30% of children who are diagnosed with CDI between the ages of 1 to 18 years (Nicholson et al. 2017) and some children have multiple recurrences. Recurrent CDI is defined as the return of symptoms with a positive *C. difficile* toxin assay result that occurs after a period of symptom resolution and within 8 weeks of the initial episode. The mechanism of recurrent disease is not well understood, but recurrent disease can be poorly responsive to treatment, require prolonged courses of therapy, cause hospital admission, and result in increased medical costs (Nicholson et al. 2015). A statistically significant increase in CDI risk has been noted in pediatric patients with malignancy, recent surgery, and multiple antibacterial drug exposures; recent hospitalization, acid blocker use and immunosuppressant therapy have also been identified as possible risk factors for recurrent CDI.

2.2 Analysis of Current Treatment Options

Antibacterial drug therapy for an initial episode of CDI is currently based on the severity of the disease (Johnson et al. 2021). In adult patients with non-fulminant disease, oral fidaxomicin or vancomycin are first-line treatments, with fidaxomicin being favored in the current Infectious Disease Society of America (IDSA) treatment guidelines as it has been shown be noninferior to vancomycin for initial cure of CDI and a lower rate of recurrence (Louie et al. 2011).

Metronidazole is an alternative option but is less effective than vancomycin or fidaxomicin, as it has been associated with higher rates of treatment failure (Musher et al. 2005).

Recurrent CDI treatment focuses on treating the acute infection with antibacterial drug therapy as well as reducing the risk of another recurrence. In the 2021 IDSA Focused Update Guidelines on the Management of CDI in Adults (Johnson et al. 2021), fidaxomicin is preferred over vancomycin for patients with first CDI recurrence given its higher rate of sustained clinical response (cure of initial infection without recurrence). If vancomycin is used, a tapered and pulsed regimen can be considered, with an initial 10 to 14 day course of oral vancomycin dosed 4 times daily followed by a gradual decrease in dosing frequency over several weeks. For second and subsequent CDI recurrences, treatment options include fidaxomicin, tapered and pulsed vancomycin or vancomycin followed by rifaximin. Bezlotoxumab is suggested for adjunctive use in combination with antibacterial drug therapy in patients who had a prior episode of CDI within the last 6 months. In patients who have received appropriate antibacterial drug therapy for at least three CDI episodes and subsequently present with a fourth or further episode, fecal microbiota transplant (FMT) is recommended. Of note, at the time the 2021 IDSA Focused Update Guidelines on the Management of CDI in Adults was published, there were no FDA approved biological agents for FMT. Since the submission of this sBLA, two fecal microbiota products (REBYOTA for fecal administration and VOWST for oral administration) have been approved by FDA to prevent recurrence of CDI in patients 18 years of age or older (Table 2).

Recurrent CDI in pediatric patients is managed per the 2017 IDSA guidelines (McDonald et al. 2018). The first episode of recurrent CDI is typically treated with vancomycin or metronidazole unless the recurrence is deemed severe, in which case oral vancomycin is recommended. Metronidazole is not recommended for prolonged therapy due to the risk of neurotoxicity and is reserved for treatment of initial or first recurrence of disease. For the second CDI recurrence, oral vancomycin is recommended as either a tapered approach or to be followed by rifaximin (currently only approved in children 12 years and older). At the time the 2017 IDSA guidelines were published, fidaxomicin had not been approved in children so it was only recommended for treatment of children with multiple CDI recurrences. In January 2020, fidaxomicin was approved for the treatment of *C. difficile*-associated diarrhea in children >6 months of age (Table 2).

The 2017 IDSA guidelines also recommend FMT in pediatric patients with multiple recurrences of CDI who have failed appropriate antibiotic treatment. However, the guidelines for management of CDI published by the American Society of Clinical Oncology do not recommend routine use of FMT in pediatric patients with cancer and hematopoietic stem cell transplantation. Although this population is at high risk of recurrent CDI, the guidelines cite the limited data evaluating the efficacy of FMT in children, including the virtual absence of randomized data in pediatric patients with neutropenia and those receiving cancer treatments, leading to the designation of low quality evidence and the challenges related to the mode of administration contributing to a strong recommendation against the routine use of FMT in this population (Diorio et al. 2018).

Table 2. Current Approved Treatments to Reduce Recurrent CDI

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Additional Comments
Fidaxomicin (DIFICID)	Treatment of *C. difficile*-associated diarrhea in patients 6 months and older[1]	Adults: 2011 Pediatric patients (≥6 months): 2020	Oral tablets or oral suspension 200 mg BID x 10 days for patients ≥12.5 kg Oral suspension weight based dosing BID for 10 days for patients <12.5 kg	Common adverse reactions in pediatric clinical trial (≥5%): pyrexia, abdominal pain, vomiting, diarrhea, constipation, increased aminotransferases, rash
Bezlotoxumab (ZINPLAVA)	Reduce recurrence of CDI in patients 18 years or older who are receiving treatment for CDI and are at high risk of CDI recurrence	Adults: 2016	IV infusion, 10 mg/kg/dose administered once	No impact on clinical cure of acute infection Increased incidence of heart failure in patients with underlying CHF
Fecal microbiota, live (REBYOTA)	Prevention of recurrence of CDI in individuals 18 years or older, following antibiotic treatment for recurrent CDI	Adults: 2022	150 mL administrated rectally	Not indicated for treatment of CDI; given 24 to 72 hours after completion of treatment regimen Granted orphan designation; pediatric assessment not required
Fecal microbiota spores, live-brpk (VOWST)	Prevention of recurrence of CDI individuals 18 years of age and older, following antibacterial treatment for recurrent CDI	Adults: 2023	Four oral capsules taken once a day for three consecutive days	Not indicated for treatment of CDI; given 2 to 4 days after completion of treatment regimen Granted orphan designation; pediatric assessment not required

Source: Reviewer table
[1] Approved fidaxomicin indication is treatment of *C. difficile*-associated diarrhea; fidaxomicin labeling reports higher rates of sustained clinical response (defined as clinical response at the end of treatment combined with survival without CDI recurrence) at 25 days post-treatment compared to vancomycin in randomized, controlled trials
Abbreviations: BID, twice a day; CDI, *Clostridioides difficile* infection; CHF, chronic heart failure; IV, intravenous

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

ZINPLAVA (bezlotoxumab) injection was initially approved by FDA on October 21, 2016, to reduce the recurrence of 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 (Merck 2016).

At the time of approval, FDA required that a postmarketing study be completed (PMR 3118-1) in the pediatric population 1 to less than 18 years of age and waived the pediatric study requirement for patients <1 year of age because the disease does not commonly occur in this age group. The study was completed in parallel with a response to the PWR issued on April 13, 2020, and revised on April 29, 2022.

This efficacy supplement (S-012) was submitted on November 28, 2022 and provides for the addition of pediatric patients 1 to less than 18 years of age to the approved indication.

This supplemental application was granted a priority review and has a Prescription Drug User Fee Act (PDUFA) due date of May 28, 2023. The applicant submitted a pediatric exclusivity request with this supplement.

3.2 Summary of Presubmission/Submission Regulatory Activity

A summary of the regulatory activity related to the submission of this sBLA is presented in Table 3 below.

Table 3. Regulatory Activity Summary

Date	Meeting/Correspondence/Outcomes
5 January 2015	FDA agreed to the iPSP, which included two pediatric studies. Study 1 (Protocol 015) would study safety, efficacy, tolerability, and pharmacokinetics in pediatric patients aged 24 months to <18 years with a sample size of 184 patients. Study 2 (Protocol 021) planned to evaluate the safety, tolerability, and pharmacokinetics in pediatric patients from birth to <24 months and would be deferred until after data from Study 1 were obtained to confirm safety and efficacy in the older pediatric cohorts and to select the dose for the younger age cohort. A deferral was requested for pediatric trials in patients from birth to <18 years until the safety and efficacy was established in adults and it was determined whether the MK-3415A combination product (consisting of the mAbs actoxumab and bezlotoxumab) would be the final drug product or if the drug product would consist of only a single mAb. The Applicant notified the Division that they were re-evaluating the feasibility of enrolling neonates in Study 2.
06 November 2015	The Applicant submitted an amended iPSP. MK-6072 (bezlotoxumab) was selected as the product to be evaluated in pediatric studies instead of MK-3415A (combination actoxumab and bezlotoxumab) based on the results of the initial phase 3 trial in adults (MODIFY I). The Applicant also updated the clinical data to show the results from the phase 3 adult trials. FDA agreed to the proposed nonclinical and pediatric clinical development plan including study design, endpoints, and study population for evaluating MK-6072 (bezlotoxumab) in pediatric patients.

Date	Meeting/Correspondence/Outcomes
17 November 2015	BLA 761046 was submitted for bezlotoxumab with a request for deferral in all pediatric age groups based on plans to conduct two pediatric studies: a placebo-controlled RCT of safety and efficacy in patients 2 to <18 years of age with confirmed CDI (Study 1) and an uncontrolled, open-label safety/PK study in patients 0 to <2 years of age with confirmed or suspected CDI (Study 2). The application was discussed at the PeRC meeting on June 22, 2016. The Division noted it may be difficult to enroll patients <6 months of age because of the difficulty in diagnosing CDI in infants and because bezlotoxumab is not intended to treat initial infection; they recommended a waiver in patients <12 months. The Division also noted that pediatric patients 1 to less than 18 years of age could be studied in a single trial; they recommended a single deferral to study pediatric patients 1 to less than 18 years of age. The PeRC agreed with these recommendations.
21 October 2016	FDA approved ZINPLAVA (bezlotoxumab, BLA761046) for reduction in recurrence of CDI in adults who are receiving treatment for CDI and are at high risk of CDI recurrence (Merck 2016). FDA issued PMR 3118-1: Conduct a randomized, double-blind, placebo-controlled study of safety, efficacy, and pharmacokinetics of ZINPLAVA in pediatric patients from 1 to <18 years of age receiving antibacterial therapy for *C. difficile* infection. The study was to be completed by May 2022 with final report submission by November 2022. The requirement for pediatric studies in patients <1 year of age was waived because necessary studies are impossible or highly impractical as the disease does not commonly occur in this population.
28 February 2017	Draft protocol for MK-6072-001-00 (MODIFY III) submitted to the FDA. The protocol planned to enroll patients 1 to <18 years with a diagnosis of CDI, randomized 3:1 to bezlotoxumab 10 mg/kg or placebo, stratified into Age Cohort 1 (12-<18 years) and Age Cohort 2 (1-<12 years). Each cohort would enroll in 2 panels: Panel A would consist of the first 12 subjects of the cohort and Panel B would consist of the remainder of the cohort. Enrollment would be initiated with Age Cohort 1 Panel A (first 12 subjects aged 12 to <18 years) followed by an enrollment pause and interim analysis of PK data to confirm the appropriateness of the 10 mg/kg dose. Age Cohort 2 Panel A would be initiated after the first interim analysis and enrollment of this cohort paused after the first 12 subjects aged 1 to <12 years to allow a second interim analysis of PK data. FDA requested that all age groups be adequately represented/distributed in the study, that subjects be monitored in a clinical setting for infusion reactions in the first 24 hours, that sustained clinical response be used as the endpoint to assess CDI recurrence, and that participants be categorized as at high risk for CDI recurrence based only on information obtained at or before randomization.
28 April 2017	Final pediatric protocol MK-6072-001 submitted (MODIFY III).
12 December 2018	Draft protocol amendment submitted for MK-6072-001 (MODIFY III). Amendment intended to remove the planned pause in enrollment after 12 participants completed PK sampling in Panel A of an age cohort. Additionally, enrollment in Panel A of Age Cohort 2 (1 to <12 years) was to commence after the first 12 participants in Panel A of Age Cohort 1 (12 to <18 years) completed all study visits. FDA agreed to proposed amendment on 31 January 2019.
18 December 2019	The Applicant submitted a PPSR proposing that the protocol MK-6072-001-01 form the basis for a PWR.

Date	Meeting/Correspondence/Outcomes
13 April 2020	FDA issued a PWR for bezlotoxumab requesting one randomized double-blind, placebo-controlled study of safety, efficacy, and pharmacokinetics of ZINPLAVA in pediatric patients from 1 to <18 years. The Agency required at least 192 subjects be enrolled in two age cohorts, Cohort 1 (12 to <18 years) and Cohort 2 (1 to <12 years) with a minimum of 24 subjects in each cohort. The Applicant accepted the PWR on 31 July 2020.
05 May 2021	The Applicant requested feedback regarding the proposal to use a non-cell-based assay for the detection of neutralizing ADAs in pediatric participants. FDA agreed to the proposal on 02 July 2021 and noted that the adequacy of the proposed assay and its validation results would be a review issue.
15 October 2021	The Applicant submitted a request for FDA agreement to decrease the planned sample size of MK-6072-001 (MODIFY III) in order to enable trial completion in May 2022 as required by PMR 3118-1. At the time of the request, the Applicant had enrolled 132 participants and estimated enrollment would be approximately 140 participants by February 2022. The Applicant cited declining enrollment rates impacted by the COVID-19 pandemic and estimated that an additional 1-2 years would be required to complete the study at current enrollment rates, without an appreciable improvement in the ability of the study to provide an adequate assessment of safety, PK, and efficacy in the pediatric population.
22 November 2021	FDA requested the Applicant submit a request to amend the PWR to align with the request to decrease enrollment in MK-6072-001 (MODIFY III). The request was submitted on 17 December 2021. Review of blinded safety data was consistent with expectations for a pediatric study population with multiple medical comorbidities and review of common TEAEs in the ongoing study revealed a safety profile comparable to that observed in the adult phase 3 trials of bezlotoxumab. This was discussed with the PeRC as well, who reviewed the PWR and agreed with the proposed enrollment target of 140 participants. FDA issued PWR Amendment 1, which included the revised enrollment target of 140 participants and retained the requirement for a minimum of 24 subjects in each age cohort for PK assessment on 29 April 2022.
28 November 2022	Pediatric efficacy supplement, BLA 761042 S-012, submitted to FDA. This supplement included study data from MODIFY III to support the proposed indication of ZINPLAVA to reduce the recurrence of CDI in pediatric patients ages 1 to <18 years who are receiving antibacterial (b) (4) for CDI and are at high risk for CDI recurrence. The Applicant submitted a pediatric exclusivity request with the supplement.

Source: Reviewer table
Abbreviations: ADA, antidrug antibody; CDI, *Clostridioides difficile* infection; iPSP, initial pediatric study plan; mAb, monoclonal antibody; PeRC, Pediatric Review Committee; PK, pharmacokinetics; PPSR, proposed pediatric study request; PWR, pediatric written request; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations

The review team determined that clinical site inspections were not necessary for this supplement. The number of patients enrolled in each site was small in the single pediatric trial submitted (MODIFY III). Efficacy was extrapolated from the data obtained in the adult phase 3 trials (MODIFY I and MODIFY II); inspections performed as part of the original BLA review found that inspected data were adequately verifiable and appeared reliable.

4.2 Office of Study Integrity and Surveillance

An inspection for the two bioanalytical sites that evaluated the PK and immunogenicity (i.e., antidrug antibody and neutralizing antibody) samples was requested for MODIFY III trial. The Office of Study Integrity and Surveillance (OSIS) declined to conduct an inspection for the two sites for the following reasons. For the first site (Merck Research Laboratories), OSIS declined inspection due to insufficient time for the inspection to be completed and for providing a review to the Division prior to the PDUFA goal date of May 26, 2023 (OSIS memorandum dated February 7, 2023, BLA 761046/S-012). For the second site ([redacted] (b) (4)), OSIS declined inspection since it previously conducted a Remote Regulatory Assessment for this site in [redacted] (b) (4) related to three other submissions: [redacted] (b) (4) (OSIS memorandum on February 1, 2023, BLA 761046/S-012). OSIS observed several objectionable conditions for [redacted] (b) (4) but concluded that the observations were isolated in nature and did not impact data from other reviewed studies.

4.3 Product Quality

Bezlotoxumab is currently commercially available as an intravenous formulation for adults. The pediatric formulation is the same as the adult formulation and no new chemistry, manufacturing, and controls information was submitted.

4.4 Clinical Microbiology

4.4.1 Executive Summary

ZINPLAVA (Bezlotoxumab, MK-6072) is a human mAb that binds to *C. difficile* toxin B. ZINPLAVA prevents binding of toxin B to its target cells. From a clinical microbiology perspective, the previous nonclinical microbiology and clinical microbiology data which were used to support the approval of ZINPLAVA in patients greater than 18 years of age support approval in a pediatric population 1 year of age and older since the mAb targets a bacterial exotoxin and the pathophysiology of recurrent CDI is similar in adults and pediatric patients greater than 1 year of age. Overall, the information is supportive of ZINPLAVA's approval to reduce the recurrence of CDI in pediatric patients 1 year of age and older who are receiving antibacterial drug treatment of CDI and are at high risk for CDI recurrence. No changes are proposed by the Applicant or the Agency to the clinical microbiology sections of the ZINPLAVA labeling.

4.4.2 Nonclinical Microbiology

There were no updates to ZINPLAVA regarding nonclinical microbiology including in vitro and in vivo data. Since the information previously provided is applicable to the microbiology in the pediatric population, this is acceptable. Additionally, no new nonclinical pharmacokinetic or pharmacodynamic studies were submitted to support the intended pediatric population.

4.4.3 Clinical Microbiology

The Applicant has provided the final study report for a phase 3, randomized, placebo-controlled, parallel group, multisite, double-blind study evaluating the PK, safety, tolerability, and efficacy of a single infusion of ZINPLAVA or placebo in pediatric participants 1 to <18 years of age receiving antibacterial drug treatment for CDI. Participants were randomized 3:1 to ZINPLAVA 10 mg/kg or placebo and were stratified by age at randomization. Suspected or confirmed CDI was determined by a set of screening criteria that included a stool sample that had tested positive for toxigenic *C. difficile* according to local diagnostic criteria. At the time of randomization, study participants were required to have CDI confirmed by a diagnostic assay which detected the presence of *C. difficile* toxin in stool and to still be receiving antibacterial drug treatment for CDI. Exclusion criteria related to clinical microbiology included participants that had previously received ZINPLAVA, an experimental mAb against *C. difficile* toxin B, or received a vaccine against *C. difficile* or its toxins.

Objectives and endpoints were evaluated in pediatric participants aged 1 year to <18 years who were receiving antibacterial drug treatment for CDI. The secondary objective was to estimate the proportion of participants who have CDI recurrence and the proportion of participants with sustained clinical response within 12 weeks following administration of a single infusion of ZINPLAVA or placebo. The Applicant also wanted to estimate efficacy (CDI recurrence and sustained clinical response) in the subset of participants at high risk of CDI recurrence within 12 weeks following administration of a single infusion of ZINPLAVA or placebo. As part of the endpoint for this objective, high risk was defined by several criteria including having *C. difficile* ribotype 027 isolated from a stool sample collected during the baseline CDI episode.

Overall, the percentage of participants who had CDI recurrence was reported by the Applicant as low and comparable between intervention groups (see Section 8.1.1.2). The percentage of participants in the modified intent to treat (mITT) population with initial clinical response who had CDI recurrence and were at high risk for CDI recurrence was also comparable between intervention groups.

Microbiology Assessments at Baseline (Central Laboratory Tests)

The percentage of participants with a positive baseline *C. difficile* toxigenic culture as determined by the central laboratory was comparable between intervention groups in the mITT population (ZINPLAVA: 50.0%; placebo: 54.3%). However, the percentages were lower than those from the positive local test results. The Applicant reported the following to explain the discrepancy: due to not all participants having an available stool sample for central laboratory analysis or because the *C. difficile* culture became nonviable after storage and transit. Also, the types of positive local tests permitted for study entry included those that detect toxin directly and were the most frequently used standard of care (SOC) diagnostic methods. *C. difficile* culture is less sensitive and was required at the reference laboratory to perform further analyses. The most common reason for sample nonavailability was a protocol compliant prescreening sample for eligibility that had not been retained locally. Therefore, unless the participant had a further diarrheal episode during screening, there was no baseline sample aliquot available for central laboratory testing. Antimicrobial susceptibility testing was done on isolates and found to be comparable between groups. The most common pathogen DNA detected in stool at baseline other than for *C. difficile* was for Enteropathogenic *E. coli*, Shiga-toxin-producing *E. coli*, and norovirus.

Table 4 and Table 5 include a summary of the baseline stool *C. difficile* test results from the local and central laboratories are below:

Table 4. Summary of Baseline Stool *C. difficile* Test Results From the Local Laboratories mITT

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	104		35		139	
Baseline stool *C. difficile* toxin						
Positive[a]	104	(100.0)	35	(100.0)	139	(100.0)
Negative	0	(0.0)	0	(0.0)	0	(0.0)
Not Performed	0	(0.0)	0	(0.0)	0	(0.0)
No Sample[b]	0	(0.0)	0	(0.0)	0	(0.0)

C. difficile= Clostridioides (Clostridium) difficile.
[a] Results from protocol-approved test for the presence of *C. difficile* toxins A/B in stool.
[b] No sample includes uncollected, damaged or lost samples at the central laboratory.
Source: [P001MK6072: adam-adsl; admb]

Source: This submission.
Abbreviations: mITT, modified intent to treat; n, number of participants in population

Table 5. Summary of Baseline Stool *C. difficile* Test Results From the Central Laboratory mITT

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	104		35		139	
Baseline *C. difficile* culture result at central laboratory						
Positive	55	(52.9)	20	(57.1)	75	(54.0)
Negative	31	(29.8)	7	(20.0)	38	(27.3)
Not Performed[a]	1	(1.0)	3	(8.6)	4	(2.9)
No Sample[b]	17	(16.3)	5	(14.3)	22	(15.8)
Baseline toxigenic *C. difficile* assay result at central laboratory						
Positive	52	(50.0)	19	(54.3)	71	(51.1)
Negative	1	(1.0)	1	(2.9)	2	(1.4)
Not Performed[a]	34	(32.7)	10	(28.6)	44	(31.7)
No Sample[b]	17	(16.3)	5	(14.3)	22	(15.8)

C. difficle= Clostridioides (Clostridium) difficile.
[a] Tests may not be performed due to *C. difficile* not isolated, insufficient sample volume to perform at the central laboratory.
[b] No sample includes uncollected, damaged or lost samples at the central laboratory.
Source: [P001MK6072: adam-adsl; admb]

Source: This submission.
Abbreviations: mITT, modified intent to treat; n, number of participants in population

Reviewer Comment*: On the listing of stool C. difficile tests from the central laboratory, the results included "unable to perform" or "C. difficile not isolated, therefore test not performed". Most tests were for toxigenic C. difficile. The majority of the stool C. difficile tests from the local laboratories included C. difficile toxin by Enzyme Immunoassay and Nucleic Acid Amplification*

Test, but microbial culture was also sometimes listed. Specifics of the tests used were not included.

Table 6 and Table 7 include a summary of the baseline PCR ribotypes in the mITT population:

Table 6. Summary of Baseline PCR Ribotypes mITT

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	104		35		139	
Summary of Ribotype by descending order						
014	8	(7.7)	4	(11.4)	12	(8.6)
106	7	(6.7)	3	(8.6)	10	(7.2)
017	3	(2.9)	1	(2.9)	4	(2.9)
023	4	(3.8)	0	(0.0)	4	(2.9)
027	3	(2.9)	1	(2.9)	4	(2.9)
002	1	(1.0)	1	(2.9)	2	(1.4)
005	2	(1.9)	0	(0.0)	2	(1.4)
012	2	(1.9)	0	(0.0)	2	(1.4)
020	0	(0.0)	2	(5.7)	2	(1.4)
046	2	(1.9)	0	(0.0)	2	(1.4)
057	2	(1.9)	0	(0.0)	2	(1.4)
103	2	(1.9)	0	(0.0)	2	(1.4)
126	2	(1.9)	0	(0.0)	2	(1.4)
220	2	(1.9)	0	(0.0)	2	(1.4)
255	2	(1.9)	0	(0.0)	2	(1.4)
001	1	(1.0)	0	(0.0)	1	(0.7)
018	0	(0.0)	1	(2.9)	1	(0.7)
026	1	(1.0)	0	(0.0)	1	(0.7)
043	0	(0.0)	1	(2.9)	1	(0.7)
045	0	(0.0)	1	(2.9)	1	(0.7)
054	1	(1.0)	0	(0.0)	1	(0.7)
056	1	(1.0)	0	(0.0)	1	(0.7)
070	0	(0.0)	1	(2.9)	1	(0.7)
076	1	(1.0)	0	(0.0)	1	(0.7)
078	0	(0.0)	1	(2.9)	1	(0.7)
097	1	(1.0)	0	(0.0)	1	(0.7)
111	0	(0.0)	1	(2.9)	1	(0.7)
153	1	(1.0)	0	(0.0)	1	(0.7)
154	1	(1.0)	0	(0.0)	1	(0.7)
216	0	(0.0)	1	(2.9)	1	(0.7)
228	1	(1.0)	0	(0.0)	1	(0.7)
244	1	(1.0)	0	(0.0)	1	(0.7)
287	1	(1.0)	0	(0.0)	1	(0.7)
600	1	(1.0)	0	(0.0)	1	(0.7)
987	1	(1.0)	0	(0.0)	1	(0.7)
1001	0	(0.0)	1	(2.9)	1	(0.7)

Source: This submission
Abbreviations: mITT, modified intent to treat; n, number of participants in population; PCR, polymerase chain reaction

***Reviewer Comment**: The Applicant reported that a range of 36 different C. difficile ribotypes were detected from stool samples in Table 6 above but the most common ribotype was 014 in 8.6% of all participants in the mITT population. Participants with 027 ribotype were 2.9% of all participants in the mITT population. More participants with identified C. difficile ribotypes were found in the ZINPLAVA arm than in the placebo arm. Ribotypes that were considered to be from hypervirulent strains of C. difficile included 027, 078 and 244 which were 4.3% of the mITT population. Of the hypervirulent strains identified, C. difficile ribotype 027 is of particular concern. C. difficile ribotype 027 caused higher mortality and severe colitis and the hypervirulence may be attributed to genetic mutations in a toxin regulator gene that causes* *hyperproduction of toxins A and B. It also produces a binary toxin that is associated with severe diarrhea (Clements et al. 2010).*

In the Applicant's summary of risk factors for CDI recurrence in the mITT population, *C. difficile* ribotype 027 was isolated from a stool sample collected during a baseline CDI episode in 3 participants of the ZINPLAVA arm, and 1 participant of the placebo arm. It was not found in 52 participants of the ZINPLAVA arm, and 19 participants of the placebo arm. In the missing category, there were 49 participants in the ZINPLAVA arm, 15 in the placebo arm. See Table 7 below for the summary of PCR ribotypes from samples obtained during recurrent episodes in the mITT population.

Table 7. Summary of PCR Ribotypes From Samples Obtained During Recurrent Episode mITT

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	104		35		139	
Summary of Ribotype by descending order						
014	1	(1.0)	2	(5.7)	3	(2.2)
017	2	(1.9)	1	(2.9)	3	(2.2)
027	2	(1.9)	0	(0.0)	2	(1.4)
001	1	(1.0)	0	(0.0)	1	(0.7)
005	1	(1.0)	0	(0.0)	1	(0.7)
010	1	(1.0)	0	(0.0)	1	(0.7)
012	1	(1.0)	0	(0.0)	1	(0.7)
018	0	(0.0)	1	(2.9)	1	(0.7)
020	0	(0.0)	1	(2.9)	1	(0.7)
023	1	(1.0)	0	(0.0)	1	(0.7)
029	1	(1.0)	0	(0.0)	1	(0.7)
032	1	(1.0)	0	(0.0)	1	(0.7)
045	0	(0.0)	1	(2.9)	1	(0.7)
046	1	(1.0)	0	(0.0)	1	(0.7)
056	1	(1.0)	0	(0.0)	1	(0.7)
070	0	(0.0)	1	(2.9)	1	(0.7)
076	1	(1.0)	0	(0.0)	1	(0.7)
097	1	(1.0)	0	(0.0)	1	(0.7)
103	1	(1.0)	0	(0.0)	1	(0.7)
111	0	(0.0)	1	(2.9)	1	(0.7)
255	1	(1.0)	0	(0.0)	1	(0.7)
410	1	(1.0)	0	(0.0)	1	(0.7)
430	0	(0.0)	1	(2.9)	1	(0.7)
987	1	(1.0)	0	(0.0)	1	(0.7)
027 Ribotype						
Yes	2	(1.9)	0	(0.0)	2	(1.4)
No	17	(16.3)	8	(22.9)	25	(18.0)
Hypervirulent strain (027, 078, or 244 ribotypes)						
Yes	2	(1.9)	0	(0.0)	2	(1.4)
No	17	(16.3)	8	(22.9)	25	(18.0)

This table only includes participants who had at least one diarrhea or CDI recurrence.
PCR=polymerase chain reaction.

Source: [P001MK6072: adam-adsl; admb]

Source: This submission
Abbreviations: CDI, *Clostridioides difficile* infection; mITT, modified intent to treat; n, number of participants in population; PCR, polymerase chain reaction

Table 8 shows the pathogens at baseline that were isolated in the mITT population:

Table 8. Pathogens at Baseline mITT

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	104		35		139	
One or more Pathogens[a] at Baseline						
Bacteria						
Enteroaggregative Escherichia coli DNA	1	(1.0)	0	(0.0)	1	(0.7)
Enteroinvasive Escherichia coli DNA	0	(0.0)	2	(5.7)	2	(1.4)
Enteropathogenic Escherichia coli DNA	7	(6.7)	2	(5.7)	9	(6.5)
Enterotoxigenic Escherichia coli DNA	1	(1.0)	0	(0.0)	1	(0.7)
Salmonella DNA	2	(1.9)	0	(0.0)	2	(1.4)
Shiga-Like Toxin-Producing E coli DNA	1	(1.0)	2	(5.7)	3	(2.2)
Virus						
Astrovirus DNA	2	(1.9)	0	(0.0)	2	(1.4)
Norovirus DNA	3	(2.9)	1	(2.9)	4	(2.9)

Every participant is counted a single time for each pathogen. A participant with multiple positive pathogens is counted a single time for One or more Pathogens at Baseline.
This table includes all pre-treatment microbiology data with positive results from the central laboratory.
[a] Based on the stool sample collected during baseline *Clostridioides (Clostridium) difficile* episode.

Source: [P001MK6072: adam-adsl; admb]

Source: This submission
Abbreviations: mITT, modified intent to treat; n, number of subjects in category

Reviewer Comment*: The Applicant reported that the phase 3 study was not powered for efficacy and had no efficacy hypothesis. However, results for the 3 main efficacy objectives (CDI recurrence, sustained clinical response and efficacy in those at high risk of recurrence) were comparable between intervention groups (see Section 8.1.1.2). Additionally, the Applicant reported that where possible, the overall susceptibility of C. difficile isolates from baseline stool samples to the baseline CDI episode antibacterial therapy was below the recognized breakpoints for resistance. This reviewer noted that the FDA does not recognize breakpoints for vancomycin for C. difficile. Additionally, there are no breakpoints recognized by FDA for fidaxomicin at this time. FDA recognizes the CLSI breakpoints for anaerobes for metronidazole which are ≤8, 16, ≥32 mcg. MIC summary data is shown in Table 9.*

Table 9. Overall MIC Summary mITT

	Bezlotoxumab n (%)	Placebo n (%)	Total n (%)
Participants in population	104	35	139
Vancomycin			
N	55	20	75
MIC-50	0.5	0.5	0.5
MIC-90	1	0.5	1
MIC range	0.12 - 1	0.25 - 1	0.12 - 1
Metronidazole			
N	55	20	75
MIC-50	0.25	0.25	0.25
MIC-90	0.5	0.25	0.25
MIC range	0.06 - 4	0.06 - 1	0.06 - 4
Fidaxomicin			
N	54	20	74
MIC-50	0.5	0.5	0.5
MIC-90	0.5	1	1
MIC range	0.125 - 1	0.06 - 1	0.06 - 1

mcg = microgram; MIC= minimum inhibitory concentration (mcg/mL).
N=number of isolates
This table includes baseline susceptibility data.
Source: [P001MK6072: adam-adsl; adms]

Source: This submission
Abbreviations: MIC, minimum inhibitory concentration; mITT, modified intent to treat; n, number of subjects in category

***Reviewer Comment**: Overall, the information is supportive of approval of ZINPLAVA to reduce recurrence of CDI in pediatric patients 1 year of age and older who are receiving antibacterial drug treatment of CDI and are at high risk for CDI recurrence. No changes are proposed by the Applicant or the Agency to the clinical microbiology sections of the ZINPLAVA labeling.*

4.5 Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted to the efficacy supplement for review. Animals used in nonclinical studies submitted with the original application for the adult population (2-week toxicity studies in mice with bezlotoxumab alone and in combination with actoxumab) were on average 8 weeks of age at study initiation. Based on prior review of the available nonclinical toxicology data, no additional animal studies were recommended to support the clinical study in pediatric patients conducted to fulfill PMR 3118-1 (see Nonclinical Review [April 29, 2016] and COR-PEDEX-01 (Pediatric-Written Request) [April 13, 2020] and COR-PEDEX-02 (Pediatric-Revised Written Request) [April 29, 2022] in DARRTS). Of note, the area under the concentration-time curve (AUC) exposures and safety margins in pediatric patients receiving a 10 mg/kg dose were similar to those observed in adults (see Table 10 below). The Applicant did not propose any changes to the labeling relevant to Pharmacology/Toxicology.

This efficacy supplement is approvable from a Pharmacology/Toxicology perspective.

Table 10. Bezlotoxumab Systemic Exposure Margins at NOAEL

		Exposure Margin AUC		
			Pediatric[c]	
Test Article(s)[a]	**AUC (mcg*hr/mL)**	**Adult[b]**	**1 to <12 yr**	**12 to 18 yr**
Study TT#15-1015: 12-Day Intermittent-Dose IV Toxicity Study in Mice				
MK-6072 alone	356000	6.7-fold	8.2-fold	6.3-fold
MK-6072 (in MK-3415A)	330000	6.2-fold	7.6-fold	6-fold
Study TT#15-1015: 12-Day Intermittent-Dose IV Toxicity Study in Mice				
MK-6072 alone	370000	7-fold	8.6-fold	6.6-fold
MK-6072 (in MK-3415A)	334000	6.3-fold	7.7-fold	6-fold

Source: Reviewer, adapted from Applicant Table 2.4:1 in Nonclinical Overview
[a] Studies TT #15-1015 and TT #15-1079 were used to calculate exposure margins as they were performed at the highest dose of 125 mg/kg and they reported C_{max} and AUC to allow comparison with clinical data.
[b] Based on bezlotoxumab clinical exposure AUC_{0-inf} (53000 µg*hr/mL) attained at a dose of 10 mg/kg in adult humans [bezlotoxumab PI (rev 10/2016)].
[c] Based on exposure in pediatric subjects: age 1 to <12 years: AUC_{0-inf} =43200 µg*hr/mL and age 12 to <18 years: AUC_{0-inf} =56100 µg*hr/mL [Study Report P001MK6072].
Abbreviations: AUC, area under the curve; AUC_{0-inf}, area under the curve from 0 to infinity; C_{max}, maximum concentration; IV, intravenous; MK-3415A, bezlotoxumab + actoxumab; MK-6072, bezlotoxumab, NOAEL, no-observed-adverse-effect level; PI, prescribing information

6 Clinical Pharmacology

6.1 Executive Summary

The clinical pharmacology information submitted in the BLA supplement supports the approval of ZINPLAVA to reduce recurrence of CDI in pediatric patients who are 1 year of age and older receiving antibacterial drug treatment for CDI and are at high risk for CDI recurrence. See Table 11 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 11. Summary of OCP Recommendations and Comments on Key Review Issues

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	Effectiveness The pivotal evidence of effectiveness for bezlotoxumab for the proposed indication in pediatric patients (≥1 year of age) is based on the extrapolation of effectiveness from adult patients who received the currently approved bezlotoxumab dosage to reduce CDI recurrence by comparing bezlotoxumab exposures from pediatrics (from MODIFY III trial) to adults (from MODIFY I and MODIFY II trials) (see Section 6.2.2). With respect to the bezlotoxumab exposures comparison, pediatric exposures (assessed by noncompartmental analysis) across four age and body weight increment bands were generally comparable to the exposures observed in the adult population. Safety The evidence of safety is derived from the MODIFY III trial safety data that evaluated the proposed pediatric bezlotoxumab dosage, which is same as the approved adult dosage noted above. See Sections 8.2.4 and 8.2.11 for the evaluation of safety findings. No new safety concerns were identified when bezlotoxumab was studied in pediatric patients. Further supportive safety evidence is derived based on the comparison of bezlotoxumab exposures in pediatric patients ≥1 year of age from MODIFY III trial to adults. The MODIFY III trial also evaluated immunogenicity during the 12-week post-treatment period. The incidence of ADA formation post-treatment in the pediatric patients was <5% (2 of 100) and the NAb screening in two patients was deemed inconclusive due to analytical methods related limitations (see Sections 8.2.4 and 14.3.1).
General dosing instructions	The recommended dosing regimen of bezlotoxumab in pediatric patients 1 year to <18 years of age is a one-time IV infusion of 10 mg/kg, given over 1 hour.
Dosing in patient subgroups (intrinsic and extrinsic)	No dose individualization is recommended based on intrinsic and extrinsic factors.
Labeling	The Applicant's proposed labeling was reviewed, and the Review team proposed revisions to the content and format of Clinical Pharmacology Sections 12.3 and 12.6 (see Labeling Recommendations in Section 11.1 of this review).

Source: Reviewer table
Abbreviations: ADA, antidrug antibody; CDI, *Clostridioides difficile* infection; IV, intravenous; NAb, neutralization antibody; OCP, Office of Clinical Pharmacology

6.2 Comprehensive Clinical Pharmacology Review

6.2.1 General Pharmacology and Pharmacokinetic Characteristics

The general pharmacology and PK of bezlotoxumab in adult patients 18 years and older was previously reviewed for the original BLA submission (for additional details, refer to the Clinical Pharmacology Review dated April 28, 2016).

6.2.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness for the proposed indication of reducing the recurrence of CDI in pediatric patients 1 year to less than 18 years who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

The clinical pharmacology program consists of 1) safety, tolerability, PK, and immunogenicity data from a phase 3, randomized placebo-controlled trial (MODIFY III trial) in pediatric patients 1 to less than 18 years of age receiving antibacterial therapy for CDI, and 2) bezlotoxumab population PK analyses. Overall, findings from the clinical pharmacology program based on bezlotoxumab exposure comparison between adult and pediatric CDI patients (summarized below in the next question) supported the extrapolation of effectiveness from adult to pediatric patients. This bezlotoxumab exposure comparison-based extrapolation is supported based on the assumptions that 1) bezlotoxumab has the same mechanism of action in adults and pediatric patients in which the drug binds to *C. difficile* produced toxin B, and 2) the pathogenesis of CDI (i.e., overgrowth of toxin-production by *C. difficile* bacteria) is similar between adults and pediatric patients.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

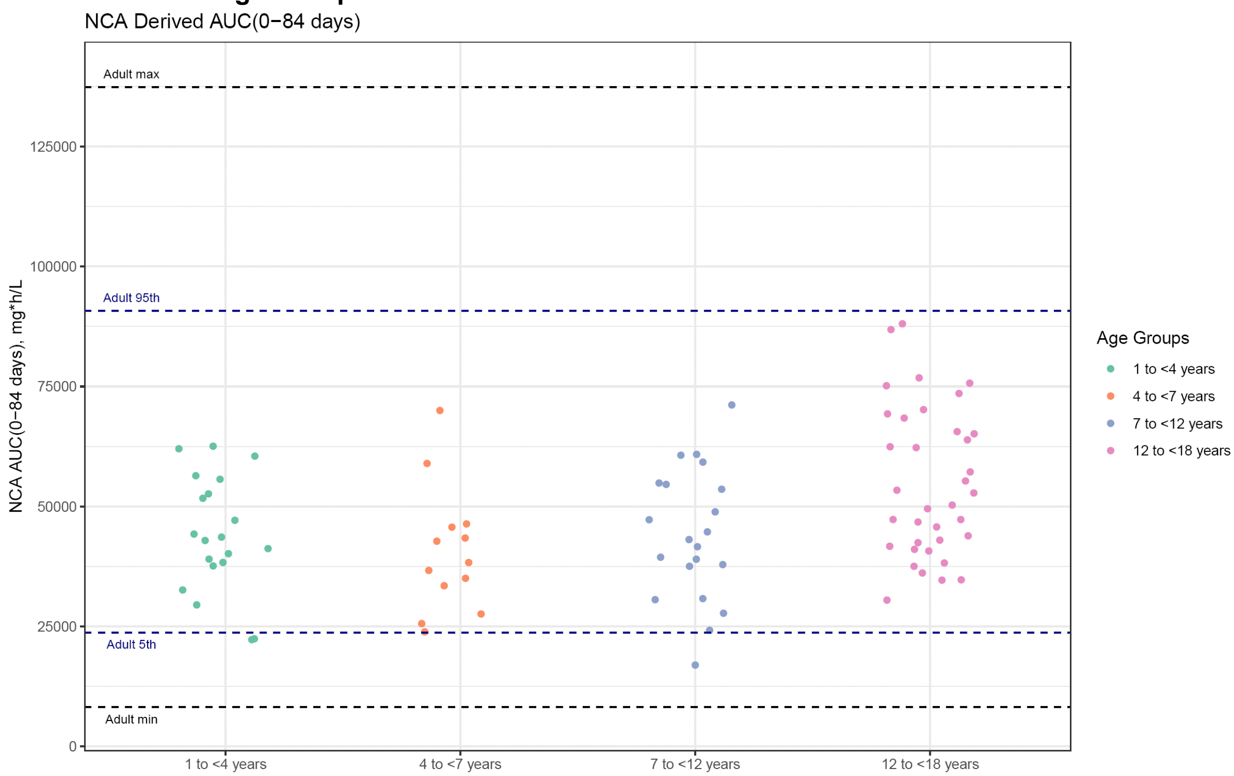
Yes, the proposed dosing regimen of bezlotoxumab is acceptable for the proposed indication in pediatric patients aged 1 years and older. Specifically, it is acceptable primarily based on the findings related to exposure comparison (summarized below) between pediatric and adult patients (for additional details, refer to the Clinical Pharmacology and Pharmacometrics Appendix Section 14.3).

Comparison of Bezlotoxumab PK Between Pediatric and Adult CDI Patients:

The Applicant's analysis relied on noncompartmental analyses (NCA) and population PK (popPK) modeling analyses to support the proposed pediatric dosage. Specifically, utilizing pre-specified comparability bounds of 0.6 and 1.6 around 90% CIs for pediatric/adult geometric mean ratio (GMR) for serum bezlotoxumab $AUC_{0\text{-inf}}$, the Applicant concludes that the results, combined with the acceptable safety profile observed for pediatric participants in the MODIFY III trial, support the appropriateness of the currently approved adult dosage of 10 mg/kg dose for pediatric patients. The Applicant selected the comparability bounds for 90% CIs of GMR (0.6, 1.6) based on the quotient of 10^{th} and 90^{th} percentiles of observed bezlotoxumab $AUC_{0\text{-inf}}$ values to the median $AUC_{0\text{-inf}}$ following administration of a single 10 mg/kg IV infusion of bezlotoxumab alone or as actoxumab+bezlotoxumab in the adult phase 3 studies (see Clinical Pharmacology Appendix Section 14.3 for more information).

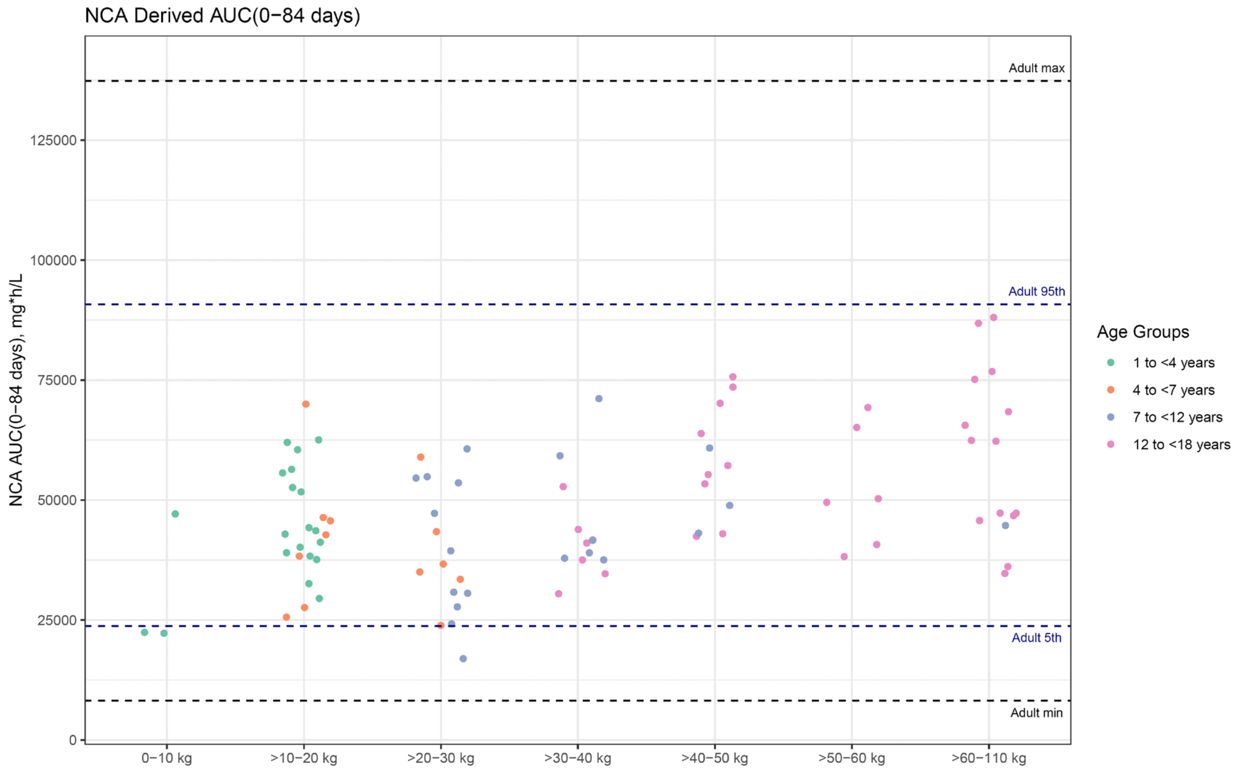
The Clinical Pharmacology Review Team utilized a different approach/criterion for comparing bezlotoxumab PK between pediatric and adult CDI patients. The Review Team performed independent analyses utilizing NCA estimates to compare bezlotoxumab exposures ($AUC_{0\text{-inf}}$, $AUC_{Days0\text{-}84}$, concentration at Day 84 [C_{Day84}]) of pediatric patients to those of historical adult patients from the two phase 3 trials. For these analyses, bezlotoxumab exposures in pediatric patients were compared based on four age cohorts and body weight bands to the exposures of the adult patient population (e.g., the fold-change from adults and 5th and 95th percentiles). The findings are presented in Figure 1, Figure 2, and Figure 3, as well as Table 12.

Figure 1. Comparison of NCA Derived Bezlotoxumab $AUC_{0\text{-}84days}$ Among Pediatric CDI Patients Across Different Age Groups



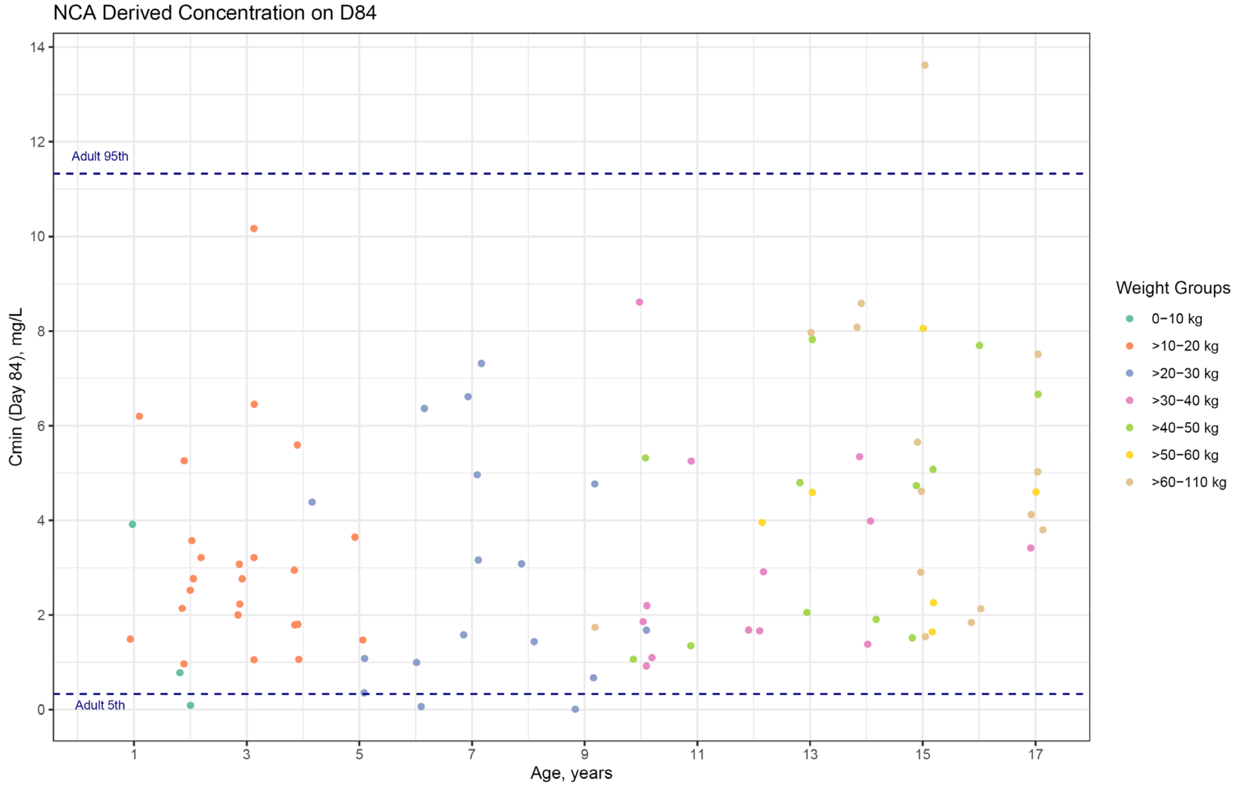
Source: Reviewer's analysis using the Applicant's datasets
Note: Navy dashed lines represent NCA derived 5th and 95th percentile of adult exposures; for NCA exposures derivation, only subjects with 4 or more PK samples and at least 1 measurable [non-below limit of quantification] drug concentration observed on Day 1 were retained for NCA analysis and to derive $AUC_{0\text{-}84days}$
Abbreviations: $AUC_{0\text{-}84days}$, AUC from time zero to day 84; CDI, *Clostridioides difficile* infection; max, maximum; min, minimum; NCA, noncompartmental analyses; PK, pharmacokinetics

Figure 2. Comparison of NCA Derived Bezlotoxumab $AUC_{0\text{-}84\ days}$ Values Among Pediatric CDI Patients Across Different Age and Weight Groups



Source: Reviewer's analysis using the Applicant's datasets
Note: Navy dashed lines represent NCA derived 5th and 95th percentile of adult exposures; for NCA exposures derivation, only subjects with 4 or more PK samples and at least 1 measurable [non-below limit of quantification] drug concentration observed on Day 1 were retained for NCA analysis and to derive $AUC_{0\text{-}84days}$
Abbreviations: $AUC_{0\text{-}84days}$, AUC from time zero to day 84; CDI, *Clostridioides difficile* infection; max, maximum; min, minimum; NCA, noncompartmental analyses; PK, pharmacokinetics

Figure 3. Comparison of NCA Derived Bezlotoxumab Concentration at Day 84 Among Pediatric CDI Patients Across Different Age and Weight Groups



Source: Reviewer's analysis using the Applicant's datasets
Note: Weight group = actual body weight groups
Note: Navy dashed lines represent NCA derived 5th and 95th percentile of adult exposures; for NCA exposures derivation, only subjects with 4 or more PK samples and at least 1 measurable [non-below limit of quantification] drug concentration observed on Day 1 were retained for NCA analysis and to derive C_{min} (i.e., Day 84)
Abbreviations: CDI, *Clostridioides difficile* infection; C_{min}, individual predicted concentration at Day 84; D, day; NCA, noncompartmental analyses; PK, pharmacokinetics

Table 12. Comparison of NCA Derived Bezlotoxumab Exposures Among Pediatric CDI Patients

		Geometric Mean (%GMCV) [95% Confidence Interval]			
Population	**N**	**$AUC_{Day0-84}$ (µg*h/mL)**	**AUC_{0-inf} (µg*h/mL)**	**C_{max} (µg/mL)**	**C_{Day84} (µg/mL)**
1 to <4 years	20	42371 (31) [22406, 62039]	44534 (33) [22623, 67934]	112 (37) [54, 162]	2.3 (131) [0.7-6.6]
4 to <7 years	13	38788 (32) [24901, 63366]	40388 (34) [25702, 67104]	136 (32) [97, 243]	1.5 (192) [0.2-5.9]
7 to <12 years	21	41747 (36) [24193, 60848]	43647 (39) [24524, 67146]	143 (24) [110, 210]	1.9 (258) [0.7-7.3]
12 to <18 years	36	52707 (29) [34687, 79306]	56099 (31) [37364, 85407]	156 (28) [89, 229]	3.9 (68) [1.5-8.2]
Adults	1316	50655 (43) [23735, 90783]	53589 (46) [23940, 100923]	187 (33) [108, 288]	2.7 (153) [0.3-11.3][1]

Source: Reviewer's analysis using the Applicant's datasets
[1] n=1314 (values from 2 adult subjects were excluded from analysis as predicted C_{Day84} were zero)
Abbreviations: $AUC_{Day0-84}$, AUC from time zero to day 84; AUC_{0-inf}, area under the curve from 0 to infinity; CDI, *Clostridioides difficile* infection; C_{Day84}, concentration at day 84; C_{max}, maximum concentration; GMCV, geometric mean coefficient of variation; N, number of subjects; n, number of subjects in category; NCA, noncompartmental analyses

The findings show that the bezlotoxumab exposures for pediatric patients of all age cohorts were generally comparable to the adult patient population, although the adult patient exposures (i.e., $AUC_{Day0\text{-}84}$, $AUC_{0\text{-}inf}$, C_{Day84}) have a relatively wide distribution (CV% estimate of >40% for the geometric means). It is noteworthy that of the pediatric populations with exposures below the 5th percentile of adult exposures, approximately 10% of these patients were younger than 7 years of age. When comparing the NCA derived exposure estimates among the various weight bands, nearly all the body weight bands evaluated exhibited comparable exposures (i.e., $AUC_{Days0\text{-}84}$) except pediatric patients with actual body weight less than 10 kg (Figure 2 and Figure 3). Of the 3 pediatric patients in this population, C_{Day84} estimates for 1/3 (33%) and AUC ($AUC_{Days\ 0\text{-}84}$ and $AUC_{0\text{-}inf}$) estimates for 2/3 (67%) patients were below the 5th percentile of respective exposure estimates from adults. The reason for the observed lower exposures is unclear.

For the completeness of analyses, NCA derived maximum serum concentration (C_{max}) data were also compared between pediatric and adult subjects (data not shown); however, this comparison was not used as an exposure measure for efficacy. C_{max} estimates were generally comparable between pediatric and adult patients. In addition, no pediatric patients had C_{max} estimates above the upper 95% CI bound of geometric mean C_{max} for adults receiving a single bezlotoxumab IV dose of 10 mg/kg.

Exposure-Response Analysis

Exposure-response (ER) analyses were not performed for efficacy or safety in pediatric patients. From the adult data, there was no clinically meaningful ER relationship for efficacy or safety identified during the review of the original BLA submission (for additional details, refer to the Clinical Pharmacology Review dated April 28, 2016).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic or extrinsic patient factors?

The effect of intrinsic and extrinsic patient factors on bezlotoxumab PK was evaluated in adult patients previously during the original BLA submission (for additional details, refer to the Clinical Pharmacology Review dated April 28, 2016). No new information on individualized dosing regimen or management strategy for subpopulation on intrinsic or extrinsic patient factors is submitted. The population PK analysis of the pooled pediatric and adult PK data did not identify additional intrinsic or extrinsic patient factors.

What is the incidence (rate) of formation of the antidrug antibodies (ADA), including the rate of pre-existing antibodies, the rate of ADA formation during and after treatment, time profiles and adequacy of the sampling schedule?

During the conduct of the MODIFY III trial, blood samples were collected pre-dose and on days 28 (Range: 26-52 days) and 84 (Range: 78-104 days) post dose following a single dose of 10 mg/kg 60-minute IV infusion. Considering the proposed treatment is a single dose, the ADA sampling duration and frequency is adequate. ADA assay findings show that ADAs were present in five evaluable subjects, but neutralizing antibody (NAb) results were inconclusive. Among the five patients with ADAs, only two subjects developed an ADA positive response post-treatment: one subject had pre-existing ADAs that increased ≥2-fold post-treatment (treatment boosted), and one subject only had ADA positive response post-dose (treatment emergent). Due to the low occurrence of ADA and NAb results, the effect of ADA on the PK, safety, and effectiveness of bezlotoxumab is unknown (refer to Section 8.2.4 and Appendix Section 14.3.1 for additional information).

Do the ADA have neutralizing activity?

Further screening of ADA positive samples for NAb was inconclusive.

Conclusion

Overall, due to the low occurrence of ADA and NAb results, the effect of ADA on the PK, safety, and effectiveness of bezlotoxumab is unknown (refer to Section 8.1.4 [immunogenicity] and Appendix Section 14.3.1 for additional information).

7 Sources of Clinical Data and Review Strategy

Clinical safety and efficacy data were analyzed from one pediatric study, MODIFY III, designed with primary objectives evaluating safety and PK; efficacy analyses were descriptive. Evidence of efficacy in the pediatric population was extrapolated from efficacy data from two prior phase 3 adult studies (Table 13).

7.1 Table of Clinical Studies

Table 13. Listing of Clinical Trials Relevant to This BLA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
MODIFY III	NCT03182907	Randomized, double-blind, placebo-controlled multicenter	Single IV infusion of bezlotoxumab (Anti-toxin B) 10 mg/kg or saline placebo	Primary: 1. Determine the AUC for each age cohort from bezlotoxumab serum concentration data. 2. Proportion of participants with any AE and proportion of participants who discontinued due to an AE through 12 weeks following infusion. Key Secondary: 1. Efficacy: proportion of participants who have CDI recurrence and sustained clinical response over 12 weeks 2. Safety: proportion of participants experiencing 1 or more infusion-related reaction within 24 hours of infusion	Single dose only, followed patients for 12 weeks	Randomized: 148 Safety: 143 mITT: 139	Children ages 1 to <18 years receiving antibacterials for CDI	75 sites, 17 countries

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
MODIFY I	NCT01241552	Phase III, randomized, double-blind placebo-controlled multicenter	Single IV infusion of 10 mg/kg of either Antitoxin A, Antitoxin B, Antitoxin A+B, or saline placebo	Primary: CDI recurrence through week 12 Secondary: Global cure (clinical cure+no CDI recurrence)	Single dose only Follow-up through Week 12 (day 85)	Randomized: 1452 Safety: 1412 mITT: 1396	Adults ≥18 years of age receiving antibacterials for CDI	184 sites, 19 countries
MODIFY II	NCT01513239	Phase III, randomized, double-blind placebo-controlled multicenter	Single IV infusion of 10 mg/kg of either Antitoxin B, Antitoxin A+B, or saline placebo.	Primary: CDI recurrence through Week 12 of treatment Secondary: global cure (clinical cure+no CDI recurrence)	Single dose only Follow-up through Week 12 (Day 85) Subgroup of 300 patients followed for 9 months after Week 12	Randomized:1203 Safety: 1168 mITT: 1163	Adults ≥18 years of age receiving antibacterials for CDI	200 sites, 18 countries

Source: Reviewer table
Abbreviations: AE, adverse event; AUC, area under the curve; CDI, *Clostridioides difficile* infection; IV, intravenous; mITT, modified intent to treat; NCT, national clinical trial, No., number

7.2 Review Strategy

MODIFY III was designed with a primary objective of evaluating PK, safety and tolerability of bezlotoxumab in pediatric patients from ages 1 to ≤18 years with CDI. Evaluation of efficacy was a key secondary objective; however, efficacy analyses were intended to be descriptive since there was no adequate power for formal statistical testing. Since bezlotoxumab binds to toxin produced by the *C. difficile* organism responsible for CDI and the pathophysiology of CDI in adults and pediatric patients >1 year old is similar, efficacy data from adequate and well-controlled trials in adults (MODIFY I and MODIFY II) can be extrapolated for the proposed pediatric indication.

Safety results are presented using descriptive statistics. As this is a currently marketed product, some sections of the review template will not be applicable to this review. No sections of the template were omitted, but instead, irrelevant sections were noted where appropriate.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 MODIFY III

8.1.1.1 Trial Plan

Trial Design

This was a phase 3, randomized, placebo-controlled, parallel group, multisite, double-blind study evaluating the PK, safety, tolerability, and efficacy of a single infusion of bezlotoxumab or placebo in pediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for CDI.

Male and female participants with CDI who were receiving or planning to receive a 10- to 21-day course of antibacterial treatment were enrolled in the study. Eligible participants (confirmed presence of *C. difficile* toxin in stool and still receiving antibacterial treatment for CDI) were assigned randomly in a 3:1 ratio to bezlotoxumab or placebo, respectively, and were stratified into 2 age cohorts according to the participant's age at the time of randomization (1 to <12 years of age or 12 to <18 years of age).

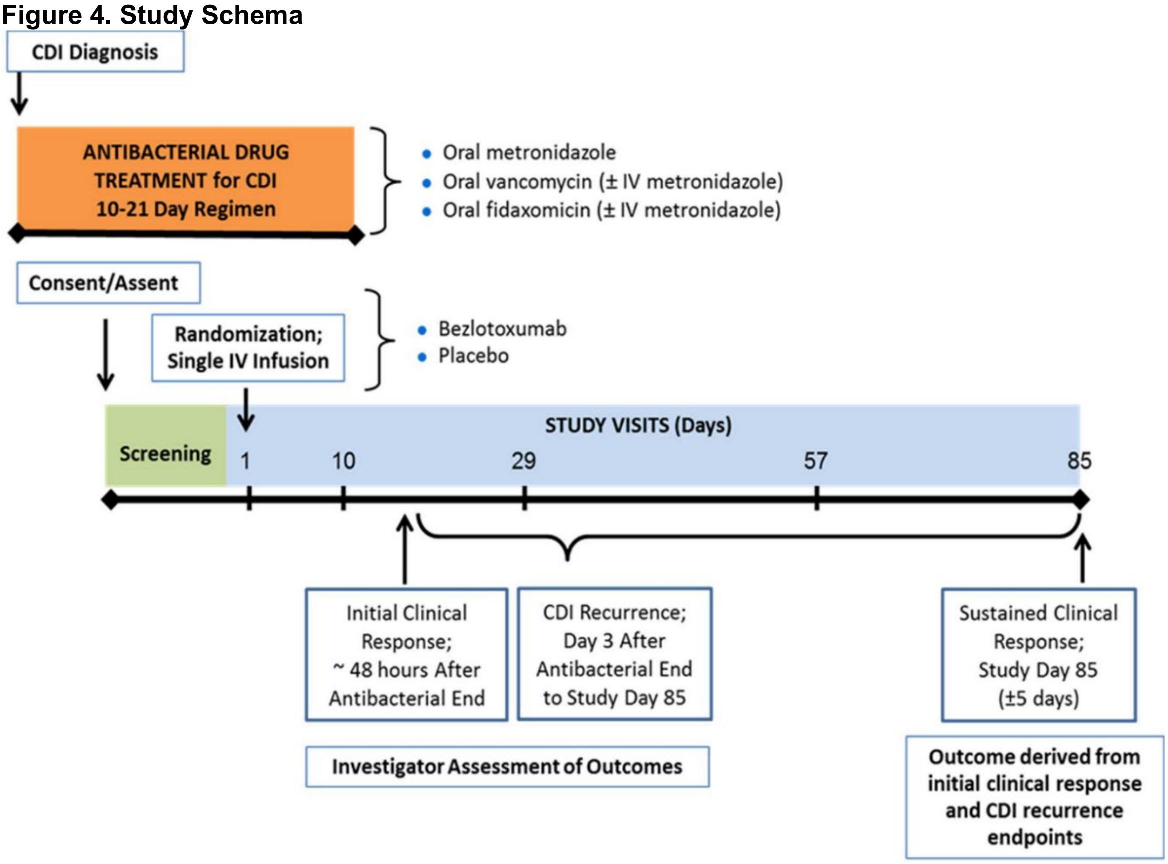
Participants were enrolled by age cohort with sequential enrollment into 2 panels: Panel A and Panel B. Enrollment started with Age Cohort 1 Panel A participants. Enrollment into Age Cohort 2 Panel A began after approximately 12 participants in Age Cohort 1 Panel A completed all study visits. The purpose of Panel A was to determine the dose for each cohort and required a minimum of 12 participants per cohort to complete all study visits through 12 weeks. Enrollment into Panel B of each cohort began after a review of safety and tolerability by an independent Data Monitoring Committee and a review of the PK data by an unblinded designee determined no dose modification was required. A minimum of 24 participants were required to be enrolled in each age cohort at the final age-appropriate dose, as follows:

- Age Cohort 1: 12 to <18 years: 24 participants
- Age Cohort 2: 24 participants
    - Aged 1 to <6 years of age: a minimum of 12 participants
    - Aged 6 to <12 years of age: a minimum of 12 participants

After receiving infusion of study intervention on Day 1, participants were followed up for 12 weeks (i.e., 85±5 days) for collection of blood samples for PK and immunogenicity assessments, monitoring of safety and tolerability parameters, and efficacy outcomes (including CDI recurrence, sustained clinical response, and CDI recurrence among participants with high risk of CDI recurrence within 12 weeks of study intervention infusion).

The study design is depicted in Figure 4.

Figure 4. Study Schema



Source: Partially Adapted from Figure 9-1 of CSR
Abbreviations: CDI, *Clostridioides difficile* infection; CSR, clinical study report; IV, intravenous

Study Endpoints

Primary Endpoints (Safety)

- Proportion of participants experiencing adverse events (AEs)
- Proportion of participants discontinuing study medication due to AEs

Secondary Endpoints (Safety)

- Proportion of participants experiencing 1 or more infusion-related reactions within 24 hours following the start of the infusion.
- Proportion of participants with treatment-emergent positive antibodies to bezlotoxumab in serum through 12 weeks following a single dose of bezlotoxumab.

Secondary Endpoints (Efficacy)

- Proportion of participants who have a CDI recurrence within 12 weeks of study medication infusion. CDI recurrence is assessed by the investigator, as described below.
- Proportion of participants with sustained clinical response over a period of 12 weeks. Sustained clinical response is defined as initial clinical response of the baseline CDI episode (assessed by the investigator) AND no CDI recurrence through Week 12.
- Proportion of participants who have a CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study medication infusion in the subset of participants at high risk of CDI recurrence. High risk is defined as meeting 1 or more of the following criteria at or before randomization:
    - Was immunocompromised
    - Had one or more episodes of CDI at any point prior to the baseline episode
    - Had a baseline CDI episode that met criteria for severe CDI
    - Had *C. difficile* ribotype 027 isolated from a stool sample collected during the baseline CDI episode
    - Had received treatment with 1 or more systemic antibacterials known to increase the risk of CDI (during treatment of the baseline CDI episode).

Response definitions of clinical outcomes related to the investigator assessment of the initial clinical response and new episode of diarrhea is shown in Table 14. Sustained clinical response is defined as participants who had initial clinical response of the baseline CDI episode and no CDI recurrence through Week 12 (Day 85±5 days).

Table 14. Response Definitions of Clinical Outcomes

Clinical Outcome	Response Definition
Investigator assessment of initial clinical response	
Initial clinical response[1]	Improvement in the number and character of bowel movements AND does not require further CDI therapy within 2 days after completion of up to 21 days of antibacterial drug treatment for CDI.
Clinical failure	Initial clinical response not achieved.
Indeterminate	Study data are not available for evaluation of clinical outcome for one of the following reasons: a. Participant was withdrawn for any reason or died before sufficient data had been obtained to permit evaluation; OR b. Extenuating circumstances (e.g., a protocol violation) preclude classification as "initial clinical response" or "clinical failure."
Investigator assessment of new episode of diarrhea	
Diarrhea recurrence	New episode of diarrhea after initial clinical response as defined by a change in normal bowel habits for 2 or more calendar days with either watery diarrhea (for participants using diapers or other type of fecal collection device) or at least 6 unformed bowel movements within a 48-hour period.
CDI recurrence	Diarrhea recurrence (see above definition) associated with a positive test for the presence of *C. difficile* toxin in stool, and for which the participant, in the investigator's opinion, requires and receives antibacterial drug treatment for CDI.

Source: Partially Adapted from Tables 9-2 and 9-3 of CSR
[1] The sustained clinical response is defined as participants who had initial clinical response of the baseline CDI episode and no CDI recurrence through Week 12 (Day 85±5 days).
Abbreviations: CDI, *Clostridioides difficile* infection; CSR, clinical study report

Statistical Analysis Plan

Sample Size

The planned enrollment of 192 participants was reduced to a minimum requirement of 140 participants. The study was not powered for statistical inferences regarding efficacy. The fundamental justification for the sample size was to complete the trial in a timely manner while still providing a sufficient number of participants with bezlotoxumab exposure in this population to assess the safety profile. A 3:1 randomization was used to maximize the number of participants exposed to bezlotoxumab while still maintaining a control arm of reasonable size.

The probability of observing at least one serious adverse event in this study depends on the number of subjects treated and the underlying percentage of subjects with a serious adverse event in the study population. If the underlying incidence of a serious adverse event is 1% (1 of every 100 subjects receiving bezlotoxumab), there is a 76% chance of observing at least one serious adverse event among 144 subjects in the bezlotoxumab group. If no serious adverse events are observed among the 144 subjects in bezlotoxumab group, this study will provide 95% confidence that the underlying percentage of subjects with a serious adverse event is ≤2.6% (<1 in every 38 subjects) in the bezlotoxumab group.

Analysis Methods

Safety analyses of the primary endpoints were performed on the All Participants as Treated (APaT) population, which included all randomized participants who received study intervention. These analyses were performed using the Miettinen and Nurminen asymptotic method (1985) and 95% CIs were provided.

Secondary efficacy analyses were performed using a 2-sided 95% CI based on the Miettinen and Nurminen method stratified by age cohort (12 to <18 years of age, 1 to <12 years of age) using a Cochran-Mantel-Haenszel weight to evaluate the treatment differences for (1) CDI recurrence, (2) sustained clinical response, and (3) CDI recurrence among participants at high risk of CDI recurrence within 12 weeks of study medication infusion. As there are no associated hypotheses to be tested, the p-values are not inferential and are only presented as an additional measure of the effect size.

For the proportion of participants who have CDI recurrence in subsets of participants at high risk of CDI recurrence, the bezlotoxumab versus placebo difference (with a nominal 95% CI) will be estimated using Miettinen and Nurminen's method without stratification. Sustained clinical response in the subset of participants at high risk of CDI recurrence will use the same methodology.

Interim Analyses

An independent, unblinded data monitoring committee (DMC) will be appointed to review safety and tolerability data for Panel A of both Age Cohort 1 and Age Cohort 2. A description of the structure, function, and guidelines for decision-making by the DMC will be outlined in the DMC charter. There are no plans to conduct an interim analysis of unblinded efficacy data in the study.

Protocol Amendments

The original protocol was submitted on April 25, 2017. A protocol amendment was submitted on February 12, 2019. The rationale for the amendment was to modify the enrollment strategy with the aim of shortening the overall enrollment timelines. As a result of this protocol amendment, the enrollment strategy was modified as follows:

- Enrollment into Age Cohort 2 will be initiated after 12 participants in Age Cohort 1 Panel A have completed all study visits. The initial dose for Age Cohort 2 will be 10 mg/kg.
- Enrollment into Panel A of each age cohort will not be paused during the time PK assessments in each age cohort are conducted.

Note that an amendment to the PWR was subsequently issued in 2022 in response to the Applicant's request to decrease the overall size of the study to enable completion of the study by the PREA PMR due date, citing declining enrollment rates impacted by the COVID-19 pandemic. PWR Amendment 1 was issued in April 2022.

The planned sample size was 192 participants which was reduced to a minimum of 140 participants based on a review of blinded safety data. The review showed that the observed serious adverse event (SAE) rate was within the range expected given the comorbidities of the study population and that additional participants were not needed to characterize the safety and tolerability of MK-602 in pediatric patients.

A risk-based approach, consistent with FDA guidance (August 2021) on conducting clinical studies during the COVID-19 pandemic, was used to assess and mitigate the impact of the pandemic on study conduct in order to 1) ensure the safety of study participants, study staff, and health care providers, 2) maintain compliance with good clinical practice principles, and 3) minimize risks to study data integrity.

8.1.1.2 Study Results

Compliance With Good Clinical Practices

The Applicant provided a statement that the study was conducted in accordance with current standards regarding the design, conduct, and analysis of studies. The study was conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants.

Financial Disclosure

The Applicant submitted a certification of financial interest (form 3454) in accordance with 21 CFR part 54. There were no financial arrangements disclosed between principal investigators and the Applicant for the trial.

Patient Disposition

Table 15 shows the patient disposition of all randomized participants. Of the 148 randomized participants, 138 (93.2%) completed the study. The study completion rate was slightly lower in the Bezlotoxumab arm (92.8%) versus the Placebo arm (94.6%) which was influenced by a slightly larger percentage of discontinuations in the Bezlotoxumab arm due to deaths (2.7% versus 0%), protocol deviations (3.6% versus 0%) and those lost-to-follow-up (0.9% versus 0%).

Table 15. Disposition of All Randomized Participants

Randomized Participants	Bezlotoxumab (N=111)	Placebo (N=37)	Total (N=148)
Status for trial			
Completed	103 (92.8)	35 (94.6)	138 (93.2)
Discontinued	8 (7.2)	2 (5.4)	10 (6.8)
Death	3 (2.7)	0	(1.4)
Lost-to-follow-up	1 (0.9)	0	1 (0.7)
Protocol deviation	4 (3.6)	0	(2.0)
Withdrawal by parent/guardian	0	2 (5.4)	2 (1.4)

Source: Partially Adapted from Table 14.1-1 of CSR
Abbreviations: CSR, clinical study report; N, number of participants

Table 16 shows the analysis populations/subsets considered in the study. The main analysis populations/subsets used for evaluating the efficacy endpoints included the mITT population for evaluating sustained clinical response and a subset of the mITT Population consisting of participants who achieved an initial clinical response for evaluating CDI recurrence.

Across both study arms, 139 of 148 (93.9%) of randomized participants were included in the mITT population and 132 (89.2%) were included in the subset of the mITT population consisting of participants with an initial clinical response. Reasons for exclusion from the mITT population included not receiving study drug (3.4%), not having a positive local stool test to confirm CDI diagnosis (4.7%) and not taking antibacterial drug treatment for CDI on day of the infusion (4.7%). Comparing study arms, there were generally no major differences for the percentage of randomized participants included in analysis populations/subsets. Similar percentages of randomized participants were included in the mITT analysis population for each study arm, 104 of 111 (93.7%) in the Bezlotoxumab arm versus 35 of 37 (94.6%) in the Placebo arm. In most analysis populations/subsets considered, the percentages of randomized participants included were slightly lower in the Bezlotoxumab arm. This was most pronounced in the subset of mITT participants with an initial clinical response and high risk for CDI recurrence which included 82.0% of randomized participants in the Bezlotoxumab arm versus 89.2% in the Placebo arm.

Table 16. Randomized Participants Included in Analysis Populations/Subsets

Randomized Participants	Bezlotoxumab (N=111)	Placebo (N=37)	Total (N=148)
All participants as treated population	107 (96.4)	36 (97.3)	143 (96.6)
Excluded	4 (3.6)	1 (2.7)	5 (3.4)
Did not receive study drug	4 (3.6)	1 (2.7)	5 (3.4)
mITT population	104 (93.7)	35 (94.6)	139 (93.9)
Excluded	7 (6.3)	2 (5.4)	9 (6.1)
Did not receive study drug	4 (3.6)	1 (2.7)	5 (3.4)
Did not receive + local stool test to confirm CDI	5 (4.5)	2 (5.4)	7 (4.7)
Did not receive protocol-defined antibacterial for CDI	6 (5.4)	1 (2.7)	7 (4.7)
mITT population with initial clinical response	98 (88.3)	34 (91.9)	132 (89.2)
mITT population with initial clinical response and high risk for CDI recurrence	91 (82.0)	33 (89.2)	124 (83.8)
mITT population with initial clinical response and high risk for CDI recurrence or received systemic antibiotic during 12-week follow-up	95 (85.6)	34 (91.9)	129 (87.2)
mITT population with high risk for CDI recurrence	97 (87.4)	34 (91.9)	131 (88.5)
mITT population with high risk for CDI recurrence or received systemic antibiotic during 12-week follow-up	101 (91.0)	35 (94.6)	136 (91.9)
Efficacy evaluable population	72 (64.9)	26 (70.3)	98 (66.2)
Excluded	39 (35.1)	11 (29.7)	50 (33.8)
Did not meet mITT criteria	7 (6.3)	2 (5.4)	9 (6.1)
Protocol deviation(s) which may impact efficacy	22 (19.8)	5 (13.5)	27 (18.2)
Took prior or concomitant IV immune globulin	14 (12.6)	5 (13.5)	19 (12.8)
Unblinded for any reason	4 (3.6)	0 (0.0)	4 (2.7)

Source: Partially Adapted from Table 10.4 of CSR
Abbreviations: CDI, *Clostridioides difficile* infection; CSR, clinical study report, IV, intravenous; mITT, modified intent to treat; N, number of participants

Protocol Violations/Deviations

Table 17 shows the important protocol deviations considered to be clinically important among all randomized participants. In comparison to the Placebo arm, a slightly larger percentage of participants in the Bezlotoxumab arm had at least one important protocol deviation, 21.6% versus 13.5%. This difference was mainly influenced by 'Use of Concomitant medications (not specified in the protocol) from end of antibacterial drug treatment for the baseline CDI episode through 12-week follow-up' and 'Not receiving protocol specified dosage or duration of antibacterial drug treatment for baseline episode of CDI,' both of which were higher in the Bezlotoxumab arm versus the Placebo arm, 9.0% versus 2.7% and 6.3% versus 0.0% respectively.

Table 17. Important Protocol Deviations Considered to be Clinically Important (All Randomized Participants)

Type of Protocol Deviation Reason	Bezlotoxumab (N=111)	Placebo (N=37)
One or more important protocol deviations	24 (21.6)	5 (13.5)
No important protocol deviations	87 (78.4)	32 (86.5)
Inclusion/exclusion criteria	1 (0.9)	1 (2.7)
Did not have positive local stool test for *C.difficile* toxin to confirm diagnosis of baseline episode	1 (0.9)	1 (2.7)
Prohibited medications	12 (10.8)	2 (5.4)
Use of concomitant medications (not specified in protocol) during 12-week period following drug infusion	2 (1.8)	1 (2.7)
Use of concomitant medications (not specified in the protocol) from end of antibacterial drug treatment for the baseline CDI episode through 12-week follow-up	10 (9.0)	1 (2.7)
Study intervention	1 (0.9)	0 (0.0)
Administered improperly stored study drug deemed unacceptable for use	1 (0.9)	0 (0.0)
Trial procedures	12 (10.8)	2 (5.4)
Not receiving protocol specified dosage or duration of antibacterial drug treatment for baseline episode of CDI	7 (6.3)	0 (0.0)
New episode of diarrhea (6 or more loose stools in 48 hours) after SoC is completed and after resolution of the initial CDI episode but no stool sample collected for either local or central lab	3 (2.7)	1 (2.7)
Unscheduled visit didn't occur within 5 days from the onset of the diarrhea recurrence	3 (2.7)	2 (5.4)

Source: Partially Adapted from Table 14.1-9 of CSR
Abbreviations: CDI, *Clostridioides difficile* infection; CSR, clinical study report; N, number of participants; SoC, standard of care

Demographic characteristics of the participants included in the mITT population are shown in Table 18. Across both study arms, 52.5% of participants were male and 47.5% were female. Participants were mostly white (80.6%) and had mostly originated from sites outside of the U.S. (80.9%). The mean and median age of participants were 9.3 years and 10.0 years, respectively. Comparing study arms, the Bezlotoxumab and Placebo arms were fairly balanced across most demographic parameters. However, a slightly larger percentage of randomized participants in the 6 to <12 years age group was observed in the Bezlotoxumab arm, 25 (24.0%) versus 6

(17.1%). Other notable treatment differences related to race and ethnicity with a slightly smaller percentage of participants in the Bezlotoxumab arm being white (77.9% versus 88.6%) or not Hispanic or Latino (65.4% versus 74.3%). Note that such disparities would be expected given the small sample sizes, especially in the Placebo arm.

Table 18. Demographic Characteristics of the Primary Efficacy Analysis (mITT Population)

Demographic Parameters	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)	Total (N=139) n (%)
Sex			
Male	55 (52.9)	18 (51.4)	73 (52.5)
Female	49 (47.1)	17 (48.6)	66 (47.5)
Age			
Mean years (SD)	9.3 (5.3)	9.3 (5.4)	9.3 (5.3)
Median (range) (years)	10.0 (1,17)	9.0 (1,17)	10.0 (1,17)
Age group			
1 to <6 years	36 (34.6)	13 (37.1)	49 (35.3)
6 to <12 years	25 (24.0)	6 (17.1)	31 (22.3)
12 to <18 years	43 (41.3)	16 (45.7)	59 (42.4)
Race			
White	81 (77.9)	31 (88.6)	112 (80.6)
Black/African American	6 (5.8)	1 (2.9)	7 (5.0)
Asian	3 (2.9)	2 (5.7)	5 (3.6)
American Indian or Alaska Native	2 (1.9)	0	2 (1.4)
Multiple	8 (7.7)	1 (2.9)	9 (6.5)
Missing	4 (3.8)	0	4 (2.9)
Ethnicity			
Hispanic or Latino	26 (25.0)	8 (22.9)	34 (24.5)
Not Hispanic or Latino	68 (65.4)	26 (74.3)	94 (67.6)
Not reported/unknown	10 (9.6)	1 (2.9)	11 (7.9)
Region			
United States	22 (21.2)	7 (20.0)	29 (20.9)
Rest of the world	82 (78.8)	28 (80.0)	110 (79.1)

Source: Partially Adapted from Table 14.1.18 of CSR
Abbreviations: CSR, clinical study report; mITT, modified intent to treat; N of subjects; n, number of subjects in category; SD, standard deviation

Characteristics of prior CDI diagnoses of mITT participants are shown in Table 19. Across both study arms, 43 of 139 (30.9%) participants had a prior history of CDI. Among participants with available data, the mean and median number of episodes were 2.9 and 2 episodes respectively with a range from 1 to 10 episodes. The median number of days from date of onset of the most recent CDI episode to the baseline CDI episode was 76 days in both study arms. The treatment of the most recent prior CDI episode usually consisted of either metronidazole (32.6%) or vancomycin (46.5%) used as monotherapy. Overall, there were no major concerns with treatment imbalances in these characteristics given the high degree of variability that would be expected based on the small numbers of qualifying participants. However, among participants with dates available of the most recent prior CDI episode, the Bezlotoxumab arm was more likely to have a prior episode that was more than 60 days from the baseline episode (59.4%

versus 40.0%) and to have their prior episode treated with only metronidazole (36.4% versus 20.0%).

Table 19. Other Baseline Characteristics: Prior Diagnoses (mITT Population)

Demographic Parameters	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)	Total (N=139) n (%)
Prior history of CDI	N=104	N=32	N=139
Yes	33 (31.7)	10 (28.6)	43 (30.9)
No	69 (66.3)	23 (65.7)	92 (66,2)
Unknown	2 (1.9)	2 (5.7)	4 (2.9)
Number of prior CDI episodes			
Participants with data	33	10	43
Mean (SD)	2.7 (2.3)	3.4 (2.6)	2.9 (2.4)
Median (range)	2 (1, 10)	2.5 (1, 10)	2 (1, 10)
Days from date of onset of most recent prior CDI episodes to baseline CDI episode			
Participants reporting a prior CDI episode	N=32	N=10	N=42
≤60 days	13 (40.6)	6 (60.0)	19 (45.2)
61 to 180 days	12 (37.5)	2 (20.0)	14 (33.3)
181 to 360 days	6 (18.8)	1 (10.0)	7 (16.7)
>360 days	1 (3.1)	1 (10.0)	2 (4.8)
Mean (SD)	118.3 (108.2)	143.6 (265.3)	124.4 (156.3)
Median (range)	76 (15,395)	76 (25,886)	76 (15,886)
Treatment for most recent prior CDI episode			
Metronidazole	12 (36.4)	2 (20.0)	14 (32.6)
Vancomycin	16 (48.5)	4 (40.0)	20 (46.5)
Fidaxomicin	2 (6.1)	2 (20.0)	4 (9.3)
Vancomycin plus metronidazole and/or fidaxomicin	2 (6.1)	1 (10.0)	3 (7.0)
Rifaximin	0	1 (10.0)	1 (2.3)

Source: Partially Adapted from Table 14.1-38 of CSR
Abbreviations: CDI, *Clostridioides difficile* infection; CSR, clinical study report; mITT, modified intent to treat; N of subjects; n, number of subjects in category; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance assessments are not relevant for a single-dose infusion of study intervention. The use of concomitant medications was high overall as shown in Table 20. Across both study arms, 102 (97.8%) participants in the mITT population used one or more concomitant antibacterials systemically. Comparisons between study arms showed that the overall use of concomitant antibacterials was generally balanced, 98.1% in the Bezlotoxumab arm versus 97.1% in the Placebo arm. The most commonly used antibacterials across both study arms were metronidazole (56.8%), vancomycin (56.2%) and sulfamethoxazole/trimethoprim (53.2%). Comparisons by specific antibacterials showed that teicoplanin (8.7% versus 31.4%) and sulfamethoxazole/trimethoprim (46.2% versus 74.3%) were much more commonly used in the Placebo arm.

Table 20. Participants With Specific Antibacterials for Systemic Use, mITT Population

Type of Antibacterial for Systemic Use	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)	Total (N=139) n (%)
Any antibacterial for systemic use	102 (98.1)	34 (97.1)	136 (97.8)
Specific antibacterial for systemic use (incidence >5% overall)			
Amikacin	21 (20.2)	9 (25.7)	30 (21.6)
Amoxicillin Trihydrate; Clavulanate Potassium	6 (5.8)	2 (5.7)	8 (5.8)
Cefepime	30 (28.8)	12 (34.3)	42 (30.2)
Ceftazidime	6 (5.8)	4 (11.4)	10 (7.2)
Ceftriaxone	7 (6.7)	5 (14.3)	12 (8.6)
Ciprofloxacin	8 (7.7)	2 (5.7)	10 (7.2)
Meropenem	25 (24.0)	10 (28.6)	35 (25.2)
Meropenem Trihydrate	6 (5.8)	6 (17.1)	12 (8.6)
Metronidazole	59 (56.7)	20 (57.1)	79 (56.8)
Piperacillin; Tazobactam	21 (20.2)	7 (20.0)	28 (20.1)
Sulfamethoxazole/Trimethoprim	48 (46.2)	26 (74.3)	74 (53.2)
Teicoplanin	9 (8.7)	11 (31.4)	20 (14.4)
Vancomycin	56 (53.8)	22 (62.9)	78 (56.1)

Source: Partially Adapted from Table 14.1-44 of CSR
Abbreviations: CSR, clinical study report; mITT, modified intent to treat; N of subjects; n, number of subjects in category

Efficacy Results – Secondary Endpoints

The key efficacy endpoints of the MODIFY III study included CDI recurrence and sustained clinical response. Results for these analyses are shown in Table 21. Note that although these analyses were specified as key secondary analyses, they were for descriptive purposes only and were not intended to allow for statistical hypothesis testing.

The main efficacy subset for analyzing CDI recurrence was the subset of participants in the mITT population who had an initial clinical response and the main efficacy population used for analyzing sustained clinical response was the mITT population. The initial clinical response summary is shown in Table 21. From this table, the initial clinical response rate is shown to be slightly lower in the Bezlotoxumab arm versus the placebo arm, 98 (94.2%) versus 34 (97.1%).

Reviewer Comments*: From Table 21, the exclusion of participants with less favorable initial clinical responses (i.e., Clinical Failure or Indeterminate) from the analyses of CDI recurrence was higher in the treatment arm (4.8% versus 2.9%). Based on these differences, there are concerns that in evaluating CDI recurrence rates, excluding a larger percentage of participants with less favorable outcomes in the Bezlotoxumab arm can potentially result in a bias favoring the Bezlotoxumab arm.*

Table 21. Initial Clinical Response Summary

Infection Response	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)
Initial clinical response	98 (94.2)	34 (97.1)
No initial clinical response	6 (4.8)	1 (2.9)
Clinical failure	4 (3.8)	1 (2.9)
No improvement	2 (1.9)	0
Antibacterial therapy greater than 21 days	2 (1.9)	1 (1.9)
Indeterminate	2 (1.9)	0
Withdrew or died before data obtained to evaluate	1 (1.0)	0
Extenuating circumstances	1 (1.0)	0

Source: Partially Adapted from Table 11-4 of CSR
Abbreviations: CSR, clinical study report; N of subjects; n, number of subjects in category

In Table 22, findings for the key efficacy endpoints of recurrence rates of CDI and sustained clinical response rates are shown to be generally similar between study arms. Recurrence rates of CDI were 11.2% in the Bezlotoxumab arm versus 14.7% in the placebo arm which resulted in an adjusted difference of -3.7% that did not indicate any trend towards significance (p=0.57). Sustained clinical response rates were also similar between study arms, 83.7% versus 82.9% with an adjusted difference of 0.8% (p=0.92).

Table 22. Key Efficacy Endpoints Evaluated Through 12 Weeks After Infusion, MODIFY III (mITT Population)

Endpoint	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)	Unadjusted Difference (%)	Adjusted Difference (95% CI) p-Value[1]
Recurrence of CDI (mITT population with initial clinical response)	N=98 11 (11.2)	N=34 5 (14.7)	-3.5	-3.7 (-20.0, 8.0) p=0.57
Sustained clinical response (mITT)	N=104 87 (83.7)	N=35 29 (82.9)	0.8	0.8 (-11.8, 17.6) p=0.92

Source: Partially Adapted from Tables 14.2.3-4 and 14.2.3-12 of CSR
[1] Two-sided p-value based on the Miettinen and Nurminen method stratified by age cohort (12 to <18 years of age, 1 to <12 years of age) using a Cochran-Mantel-Haenszel weight.
Abbreviations: CDI, *Clostridioides difficile* infection; CI, confidence interval; CSR, clinical study report; mITT, modified intent to treat; N, number of subjects; n, number of subjects in category

Reviewer Comments: *A limitation with the recurrence of CDI endpoint is that it excludes participants who did not have an initial clinical response. Since this exclusion is based on postbaseline considerations, it may be related to the effect of the treatment received and could therefore be informative. For this reason, the Division prefers the sustained clinical response endpoint which does not require postbaseline exclusions of any of the participants from the mITT population.*

Due to the above limitation with the recurrence of CDI endpoint, the Division recommended in its Written Request that the sustained clinical response be designated as the first primary efficacy endpoint. However, the Applicant did not use that designation and considered both recurrence rates of CDI and sustained clinical response rates as key efficacy endpoints.

Data Quality and Integrity

The statistical and clinical review teams evaluated the data and analysis quality with assistance from the Office of Computational Science (OCS). This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the availability of appropriate variables, variables populated by expected data points and the appropriate use of standard terminology. In general, the data submitted by the Applicant were acceptable and there are no issues noted with regard to the data quality and integrity.

The review team determined that inspection of clinical sites was not necessary for this supplement as noted in Section 4.1 of this review.

Efficacy Results – Other relevant endpoints

In addition to evaluating rates of recurrence of CDI and sustained clinical responses, an important study objective was to evaluate these endpoints specifically in the subset of participants at high risk for CDI recurrence. This subset included 97 of 104 (93.2%) of participants in the Bezlotoxumab arm including 91 (87.5%) with an initial clinical response and 34 of 35 (97.1%) of participants in the Placebo arm including 33 (94.2%) with a clinical response. As shown in Table 23, recurrence rates of CDI in participants at high risk for CDI recurrence were similar between study arms, 12.1% in the Bezlotoxumab arm versus 15.2% in the Placebo arm, an adjusted difference of -3.1% (p=0.65). Sustained clinical response rates in this subset were also similar between study arms, 82.5% versus 82.4%, an adjusted difference of 0.1% (p=0.99). These findings were generally consistent with the findings observed for the key efficacy endpoints.

Table 23. Other Efficacy Endpoints Evaluated Through 12 Weeks After Infusion in Participants at High Risk for CDI Recurrence, MODIFY III (mITT Population)

Endpoint	Bezlotoxumab n (%)	Placebo n (%)	Unadjusted Difference (%)	Adjusted Difference (95% CI) p-Value[1]
Recurrence of CDI (mITT population with initial clinical response AND at high risk for CDI recurrence)	N=91 11 (12.1)	N=33 5 (15.2)	-3.1	-3.1 (-19.9, 9.0) P=0.65
Sustained clinical response (mITT population AND at high risk for CDI recurrence)	N=97 80 (82.5)	N=34 28 (82.4)	0.1	0.1 (-13.0, 17.4) P=0.99

Source: Partially Adapted from Tables 14.2.3-18 and 14.2.3-21 of CSR
[1] Based on the Miettinen and Nurminen method without stratification
Abbreviations: CDI, *Clostridioides difficile* infection; CI, confidence interval; CSR, clinical study report; mITT, modified intent to treat; N, number of subjects; n, number of subjects in category

Dose/Dose Response, Durability of Response and Persistence of Effect

No clear response from treatment was observed in the MODIFY III trial.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

An analysis of sustained clinical response for various subgroups was performed however there were no notable findings as shown in Table 24. Due to small numbers, the confidence intervals for differences in these analyses were very wide and included 0 for all subgroups considered. The differences for all subgroups considered did not appear to approach significance.

Table 24. Sustained Clinical Response Through 12 Week Follow-Up by Subgroups, MODIFY III (mITT Population)

Endpoint	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)	Difference (95% CI)[1,2]
Age cohort			
1 to <12 years	82.0 (50/61)	89.5 (17/19)	-7.5 (-22.1, 15.0)
12 to <18 years	86.0 (37/43)	75.0 (12/16)	11.0 (-9.3, 37.4)
Sex			
Male	87.3 (48/55)	77.8 (14/18)	9.5 (-8.2, 33.9)
Female	79.6 (39/49)	88.2 (15/17)	-8.6 (-25.4, 16.0)
Race			
White	86.4 (70/81)	80.6 (25/31)	5.8 (-8.1, 24.0)
Non-white	73.7 (14/19)	100.0 (4/4)	N/A
Primary treatment for baseline CDI episode			
Metronidazole-enteral/oral	88.6 (39/44)	78.6 (11/14)	10.1 (-9.1, 37.7)
Vancomycin-enteral/oral	78.6 (11/14)	100.0 (5/5)	N/A
Fidaxomicin-enteral/oral	80.4 (37/46)	81.3 (13/16)	-0.8 (-20.0, 25.7)

Endpoint	Bezlotoxumab (N=104) n (%)	Placebo (N=35) n (%)	Difference (95% CI)[1,2]
Adjunctive treatment for baseline CDI episode			
Metronidazole- intravenous	71.4 (5/7)	33.3 (1/3)	N/A
Was immunocompromised			
Yes	86.3 (63/73)	78.6 (22/28)	7.7 (-7.3, 27.2)
No	79.3 (23/29)	100.0 (4/4)	N/A
Missing	50.0 (1/2)	100.0 (2/2)	N/A
Had one or more episodes of CDI at any point prior to the baseline episode			
Yes	78.8 (26/33)	70.0 (7/10)	8.8 (-17.7, 42.2)
No	87.0 (60/69)	87.0 (20/23)	0.0 (-13.6, 20.3)
Missing	50.0 (1/2)	100.0 (2/2)	N/A
Had a baseline CDI episode that met criteria for severe CDI			
Yes	80.0 (16/20)	100.0 (5/5)	N/A
No	85.4 (70/82)	80.0 (24/30)	5.4 (-8.9, 24.0)
Missing	50.0 (1/2)	0	N/A
One or more systemic antibacterial treatment at baseline[3]			
Yes	79.1 (53/67)	85.0 (17/20)	-5.9 (-21.5, 16.9)
No	91.9 (34/37)	80.0 (12/15)	11.9 (-6.8, 38.4)

Partially Adapted from Tables 14.2.3-13 and 14.2.3-14 of CSR
[1] Based on the Miettinen and Nurminen method without stratification
[2] The 95% CIs were calculated if there were 10 or more participants in each intervention group
[3] Had received treatment with 1 or more systemic antibacterials at or before randomization along with standard-of-care treatment for CDI baseline episode.
Abbreviations: CDI, *Clostridioides difficile* infection; CI, confidence interval; CSR, clinical study report; mITT, modified intent to treat; N, number of subjects; n, number of subjects in category

There were no additional analyses conducted on the individual trial. As previously noted, the MODIFY III trial was not designed to make statistical inferences regarding efficacy. In addition, the trial was substantially underpowered for showing a treatment benefit for either of the key secondary efficacy endpoints (i.e., recurrence rates of CDI in mITT participants with an initial response and sustained clinical response rates in mITT participants). For these reasons, additional sensitivity and/or subgroup analyses would not be expected to be informative.

8.1.2 MODIFY I and MODIFY II (Phase 3 Trials in Adult CDI Population)

The safety and efficacy of bezlotoxumab for the approved indication of reduction in recurrence of 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 is supported by two randomized, double-blind, placebo-controlled phase 3 trials in adults, MODIFY I and MODIFY II. The efficacy of bezlotoxumab for the proposed indication in pediatric patients aged 1 to 18 years old is extrapolated from the adult efficacy data from the MODIFY I and II randomized, placebo-controlled trials in adults. Therefore, the design of the MODIFY I and MODIFY II trials and their primary endpoint data will be reviewed below.

8.1.2.1 Trial Plan

Both MODIFY I and II included male and female patients age ≥18 years with a confirmed diagnosis of CDI and a positive stool test for toxigenic *C. difficile*. Subjects needed to be receiving SOC therapy at the time of bezlotoxumab infusion. SOC was defined as metronidazole, vancomycin, or fidaxomicin, with a duration of 10 to 14 days. Both trials specified a primary endpoint of CDI recurrence through Week 12 of the study, which was defined as the development of new symptoms (diarrhea) and a positive stool test for *C. difficile* following clinical resolution of the baseline episode. Clinical resolution was defined as a subject receiving SOC treatment for ≤14 days without diarrhea for the two days immediately following the end of treatment.

During its clinical development, bezlotoxumab (an anti-toxin B mAb) was originally evaluated as part of a combination therapy with actoxumab (an anti-toxin A mAb). MODIFY I compared the efficacy of actoxumab alone, bezlotoxumab alone, actoxumab plus bezlotoxumab combination therapy, and placebo. MODIFY II compared the efficacy of bezlotoxumab alone, actoxumab plus bezlotoxumab, and placebo. The actoxumab-specific arm was discontinued from MODIFY I and not included in MODIFY II due to an increase in mortality and low efficacy in this arm.

8.1.2.2 Study Results

Both MODIFY I and II showed a significantly lower proportion of subjects with CDI recurrence at Week 12 in the bezlotoxumab treatment arms as compared to placebo. However, some imbalances in cure rates were noted in baseline CDI episodes, with higher rates of clinical cure in the placebo arm than the bezlotoxumab arm in MODIFY I. FDA was concerned that, using the protocol-specified endpoint of proportion of subjects with CDI recurrence through Week 12, subjects who failed treatment of the baseline CDI episodes were counted as not having a recurrence (i.e., these subjects were counted as successes for the primary endpoint). FDA considered sustained clinical response, defined as clinical cure of the baseline CDI episode and absence of CDI recurrence, as a more appropriate endpoint to evaluate the efficacy of bezlotoxumab. Subsequent analyses showed that CDI cure rates were balanced between treatment arms by 3 weeks post-study drug infusion, supporting the assessment of recurrence rates. Ultimately, the results of the sustained clinical response and the reasons for failure to achieve sustained clinical response (clinical failure versus recurrence) were reported in the labeling (Table 25).

Table 25. Efficacy Results Through 12 Weeks After Infusion in MODIFY I and II

Trial	ZINPLAVA With SoC n (%)	Placebo With SoC n (%)	Adjusted Difference (95% CI)
MODIFY I	N=386	N=395	
Sustained clinical response	232 (60.1)	218 (55.2)	4.8 (-2.1, 11.7)
Reasons for failure to achieve sustained clinical response			
Clinical failure	87 (22.5)	68 (17.2)	
Recurrence	67 (17.4)	109 (27.6)	

Trial	ZINPLAVA With SoC n (%)	Placebo With SoC n (%)	Adjusted Difference (95% CI)
MODIFY II	N=395	N=378	
Sustained clinical response	264 (66.8)	197 (52.1)	14.6 (7.7, 21.4)
Reasons for failure to achieve sustained clinical response			
Clinical failure	69 (17.5)	84 (22.2)	
Recurrence	62 (15.7)	97 (25.7)	

Source: ZINPLAVA PI
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects in category; PI, prescribing information; SoC, standard of care

In both trials, the rates of death, SAEs and treatment-emergent adverse events (TEAEs) in the bezlotoxumab arms were similar to placebo. None of the 710 subjects evaluated tested positive for treatment-emergent anti-bezlotoxumab antibodies in these trials; however, 28% had inconclusive results in the ADA assay.

There was a greater number of SAEs related to heart failure in the bezlotoxumab arms compared to placebo, and in subjects with baseline congestive heart failure (CHF), there were more deaths compared to placebo. The overall mortality rates between treatment arms were similar. Overall, the results of MODIFY I and II demonstrated an acceptable safety profile with a single 10 mg/kg infusion of bezlotoxumab, with the inclusion of a warning statement that use of ZINPLAVA in patients with a history of CHF be reserved for patients in whom the benefit outweighs the risk.

Integrated Review of Effectiveness

8.1.3 Assessment of Efficacy Across Trials

Integrated analyses of efficacy were not conducted across trials because the efficacy determination was primarily based on extrapolating from adults to pediatrics.

Primary Endpoints

Not applicable.

Secondary and Other Endpoints

Not applicable.

Subpopulations

Not applicable.

Additional Efficacy Considerations

Not applicable.

8.1.4 Integrated Assessment of Effectiveness

Not applicable.

8.2 Review of Safety

8.2.1 Safety Review Approach

This safety review is based on a randomized, double-blind-placebo-controlled, parallel group, multisite study (MODIFY III) evaluating the PK, safety, tolerability, and efficacy of bezlotoxumab to prevent CDI recurrence in patients 1 to <18 years of age who were receiving antibacterial drug treatment for CDI. Patients were divided into two age cohorts: age cohort 1 (age 12 to <18) and age cohort 2 (age 1 to <12).

Safety and tolerability in this study were evaluated by the collection of AE data, clinical laboratory evaluations, and vital sign measurements. Safety analysis was performed on all randomized participants who received study intervention (APaT population, n=143).

Special attention was paid to any reported cardiac adverse events in the pediatric population. In adult phase 3 trials, an increase in heart failure was noted in bezlotoxumab-treated patients compared to controls receiving placebo treatment.

8.2.2 Review of the Safety Database

Overall Exposure

The APaT/safety population (n=143) consisting of all randomized participants who received study intervention was similar to the mITT/efficacy population (n=139) consisting of all randomized participants who received study intervention, had a positive local stool for *C. difficile* toxin, and were taking protocol-defined antibacterial drug treatment for CDI on the date of infusion. Since there were only four patients from the safety population not included in the efficacy population, the summary of demographic information and baseline characteristics is not repeated here; please refer to Table 18 and Table 19 in Section 8.1.1.2.

Of note, within the efficacy population, most participants (131/139, 94.2%) had ≥1 risk factor for CDI recurrence and the most common risk factors were being immunocompromised (101/139, 72.7%) and having been treated with 1 or more systemic antibacterial drug during treatment for CDI during the baseline episode (87/139, 62.6%).

Adequacy of the Safety Database

The safety database for MODIFY III is adequate in terms of size (n=143) and population of interest (pediatric patients aged 1 to <18 years). Safety evaluations included routine examinations, vital sign monitoring, and laboratory tests. Patients were monitored for adverse events at dedicated intervals throughout the 12-week study period. Blood samples were obtained for ADA testing and signs/symptoms of infusion-related reactions were identified as events of clinical interest to assess the potential of bezlotoxumab to induce immunogenicity within 12 weeks post-treatment.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues identified with the integrity or quality of the data for this study. The data were submitted in standardized formats for review.

Categorization of Adverse Events

Safety was assessed by analysis of the proportion of participants with any AE, any intervention-related AE, any SAE, intervention-related SAE, and infusion reactions. Analysis also included the proportion of participants who discontinued study intervention due to an AE.

The study protocol defined an AE as "any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment."

The protocol required study investigators to assess the intensity of each AE and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and does not interfere with everyday activities. For pediatric trials, this is an awareness of symptoms, but symptoms are easily tolerated.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. For pediatric trials, the participant would be acting like something is wrong.
- Severe: An event that prevents normal everyday activities. For pediatric trials, the patient is extremely distressed or unable to do usual activities.

An SAE was defined in the protocol as any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening. This refers to an event that places the participant at risk of death during the event.

- Requires inpatient hospitalization or prolongation of existing hospitalization. The protocol defines hospitalization as any inpatient admission but excludes hospitalization or an elective procedure to treat a pre-existing condition from this category.
- Results in persistent or significant disability/incapacity, defined as a substantial disruption of a participant's ability to perform normal life functions.
- Is a congenital anomaly/birth defect. This applies to offspring of participants.
- Other important medical events. These are events that the protocol states may not be immediately life-threatening but could jeopardize the patient or require interventions to prevent one of the aforementioned outcomes.

Routine Clinical Tests

The protocol's Schedule of Activities (SoA) summarized required clinical laboratory testing and safety monitoring during the 12 weeks of the study. On Day 1, a urine pregnancy test, hematology, and chemistry tests were sent prior to the start of the study infusion. If test were performed as part of routine patient care within 72 hours of drug administration, those results were used. Hematology and chemistry clinical laboratory tests were performed subsequently on Day 10 (+/- 3 days), Day 29 (+/- 3 days), Day 57 (+/- 5 days), and Day 85 (+/- 5 days). The protocol also described two types of unscheduled visits to be conducted; one if the participants experienced new onset diarrhea within 24 hours after completion of antibacterial medications for the baseline episode of CDI, and one for any reason other than new onset diarrhea. Both types of unscheduled visits would include hematology and chemistry clinical laboratory testing.

Clinical laboratory testing included in the safety assessment were:

- Hematology: White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, red blood cell indices (MCV, MCHC, % reticulocytes), platelet count, hemoglobin, hematocrit.
- Chemistry: Alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, bilirubin (total and direct if total is elevated above the upper limit of normal), blood urea nitrogen, calcium, chloride, creatinine, glucose (specified if fasting or nonfasting), phosphorus, potassium, sodium, total protein.
- Immunogenicity assessment: Blood for antidrug antibody levels and neutralizing antibody for bezlotoxumab were collected on screening, and Week 4 and Week 12 visits.
- Stool studies: At the time of screening, a stool sample must have tested positive for toxigenic *C. difficile* by local laboratories. During screening, a new stool sample would be collected if aliquots from the prescreening diagnosis were not available.
- Other labs: urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing age) was to be collected at screening and on Day 1. If results were positive, patients were excluded from trial participation.

The protocol specified that if participants were evaluated at an unscheduled visit for new onset diarrhea the following labs should be obtained:

- Hematology: White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Chemistry: Albumin (serum), C-reactive protein (serum), lactate (plasma)
- Stool sample collected and aliquots sent to both a local and central laboratory

8.2.4 Safety Results

Deaths

Six participant deaths occurred in the 12 weeks following study drug administration. Five deaths occurred in the bezlotoxumab arm (5/107 study participants, 4.9%) and 1 (1/36, 2.8%) occurred in the placebo arm. One additional participant in the bezlotoxumab arm died from an SAE that began after the 12-week follow-up period. The following narratives provide insight into the relevant clinical events that occurred prior to each participant's death in the bezlotoxumab arm. Each participant received the study drug on Day 1, and the timelines are created beginning with that day.

- Participant [redacted] (b) (6) (bezlotoxumab group) was a 15-year-old White female with a history of acute myeloid leukemia (AML). On Day 37, she underwent allogenic bone marrow transplant. On Day 43, the participant had an increased ALT as well as hepatosplenomegaly and free abdominal fluid on ultrasound imaging consistent with a diagnosis of veno-occlusive disease (VOD). The patient demonstrated abnormal liver function tests and had a positive *C. diff* antigen test on Day 44. On Day 76, she again had large volume ascites and portal hypertension consistent with VOD. She was intubated on Day 78 and subsequently died on Day 84. The reported cause of death was VOD. In the opinion of the investigator, the fatal SAE of VOD was not considered related to the study medication.

  Reviewer Comment*: This patient's course is consistent with VOD after transplant. It does not appear that her death was related to the study medication.*

- Participant [redacted] (b) (6) (bezlotoxumab group) was a 17-year-old White female with a history of B-cell acute lymphocytic leukemia (ALL) who had received an allogenic stem cell transplant. On Day 1, the participant experienced the AE of mild vomiting which resolved within 24 hours. On Day 19, the participant was admitted to the hospital for leukocytosis. On Day 20, the participant was diagnosed with leukemia progression. She was discharged on palliative care and died at home on Day 41. In the opinion of the investigator, the fatal SAE of leukemia was considered not related to the study medication.

***Reviewer Comment**: This patient's death seems clearly related to the progression of her leukemia and does not appear to be related to the study medication.*

- Participant (b) (6) (bezlotoxumab group) was a 14-year-old Black Hispanic male with a history of ALL and ongoing *E. coli* bacteremia during the time of study drug administration. Of note, the patient's stool sample from Day 1 was positive for Shiga-like-toxin producing *E. coli*. On Day 2, the participant experienced tachycardia, tachypnea, and desaturations, and was diagnosed with septic shock. The patient required escalation of care to intensive care after a seizure and resuscitation due to cardiac arrest. The patient died on Day 6 and the reported cause of death was septic shock. In the opinion of the investigator, the fatal SAE of septic shock was considered not related to the study medication.

  ***Reviewer Comment:** This patient's death appears consistent with his underlying diagnosis of septic shock related to the ongoing bacteremia he had before receiving the study drug.*

- Participant (b) (6) (bezlotoxumab group) was a 2-year-old White Hispanic female with a history of vertebral defects, anal atresia, cardiac defects, trachea-esophageal atresia, renal anomalies, and limb defects and prior diagnoses of septic shock and UTI. From Days 37 to 50 and Days 54 to 68, she experienced the severe SAE of UTI due to *Klebsiella pneumoniae.* On Day 80, the participant experienced loose stool and mild-moderate dehydration. On Day 81, labs showed a marked leukocytosis and thrombocytosis, and the patient was diagnosed with the SAE of UTI; urine culture was positive for *K. pneumoniae* and the patient received antibacterial therapy. On Day 94, the patient developed septic shock. The participant died on Day 97, and blood culture results from the autopsy were positive for *E. coli*, *K. pneumoni*ae, and *Enterococcus faecalis*. The cause of death was determined to be septic shock. In the opinion of the investigator, the fatal SAE of septic shock was considered not related to the study medication.

  ***Reviewer Comment**: This patient's death appears to be related to septic shock due to overwhelming infection with 3 different organisms and does not appear to be related to the study drug.*

- Participant (b) (6) (bezlotoxumab group) was an 8-year-old Hispanic female with a history of AML. From Days 20 to 28, the participant had the SAE of soft tissue infection (severe). From Days 31 to 41, she had an SAE of nosocomial infection (severe). From Days 69 to 74, the participant had the SAE of sepsis (severe). Of note, the participant had an extremely elevated WBC on Day 69 which was attributed to progression of AML. On Day 84, the patient presented to the ER due to fevers that started on Day 83 and was found to febrile, tachycardic, tachypneic, and had cold extremities. Five minutes after arrival to the ER, the participant went into cardiac arrest and was declared dead after 5 cycles of CPR. The reported cause of death was AML disease progression. In the opinion of the investigator, the fatal SAE of AML was considered not related to the study medication.

Reviewer Comment*: This patient's death seems related to the progression of her AML and does not appear to be related to the study medication.*

- Participant [redacted] (b) (6) (bezlotoxumab group) was a 15-year-old Black female with history of thermal burn and pancytopenia. This participant was found to have anemia and thrombocytopenia on Day 1. She was diagnosed with the SAE of nosocomial pneumonia (severe) on Day 5 and required intubation. Blood cultures from Days 5 and 6 were positive for *K. pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA). Day 7 sputum cultures were positive for *Acinetobacter baumannii* and MRSA. Day 28 blood cultures were positive for MRSA and the patient was again diagnosed with the SAE of bacterial sepsis (severe). Day 34 blood cultures were positive for *A. baumannii,* and abdominal ultrasound was suspicious for a cholangitic abscess. A cholangiostomy was performed on Day 36. Cultures from the fluid were positive for *A. baumannii* and MRSA on Day 40. Blood cultures performed on Day 52 and Day 56 were positive for *A. baumannii* and *Candida auris*. Sputum cultures from Days 57 and 63 were positive for *Pseudomonas aeruginosa* and MRSA. Blood culture from Day 63 was positive for *S. aureus*. On Day 138, the patient died from suspected bacterial sepsis. An autopsy was performed and determined that the primary cause of death was disseminated TB. In the opinion of the investigator, the fatal SAE of bacterial sepsis was considered not related to the study medication.

  Reviewer Comment*: This patient had a complicated course, with multiple infections starting early on in her course. The cause of death appears to be related to bacterial sepsis and overwhelming infection but does not appear related to the study drug.*

Reviewer Summary Comments

All of the participants who died during the study were diagnosed with CDI a minimum of 4 days (range 4 to 21 days) prior to the first dose of the study treatment (Day 1). Most of the participants who died were female, and 4 were White. None of the patients who died had reported CDI recurrence, although one experienced a mild AE reported as "positive C. difficile antigen test." Five of these patients had underlying diagnoses of active malignancy (71.4%). While patients with malignancies are already at an elevated risk for CDI, it appears that each of these patients died as a result of their disease process or due to septic shock from a bacterial pathogen. It does not appear that exposure to the study drug contributed to the cause of death.

Serious Adverse Events

There were 86 study participants who experienced serious adverse events, with 57/107 (53.3%) participants in the bezlotoxumab group and 29/36 (80.6%) in the placebo arm (Table 26).

Table 26. Summary of Treatment-Emergent SAEs Occurring in >2% of Bezlotoxumab-Treated Participants

Systemic Organ Class Preferred Term	Bezlotoxumab (N=107) n (%)	Placebo (N=36) n (%)
Any SAE	57 (53.3)	29 (80.6)
Infections and infestations	32 (29.9)	13 (36.1)
Staphylococcal bacteremia	4 (3.7)	1 (2.8)
Sepsis	3 (2.8)	1 (2.8)
Septic shock	3 (2.8)	0 (0.0)
Urinary tract infection	3 (2.8)	2 (5.6)
Blood and lymphatic system disorders	28 (26.2)	12 (33.3)
Febrile neutropenia	22 (20.6)	11 (30.6)
Thrombocytopenia	3 (2.8)	1 (2.8)
Gastrointestinal disorders	7 (6.5)	3 (8.3)
Abdominal pain	3 (2.8)	0 (0.0)
General disorders and administration site conditions	5 (4.7)	4 (11.1)
Pyrexia	4 (3.7)	3 (8.3)
Nervous system disorders	3 (2.8)	1 (2.8)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "Bezlotoxumab" and TRTFL = "Y" (Bezlotoxumab); TRT01A = "Placebo" and TRTFL = "Y" (Placebo); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).
Note: Percent Threshold: Bezlotoxumab ≥2%.
Abbreviations: N, number of subjects; n, number of subjects in category; SAE, serious adverse event

***Reviewer Comment**: The most commonly reported SAEs by system organ class are infections/infestations, which is to be expected in this clinically ill population. The most commonly reported SAE term in both groups was febrile neutropenia. This appears to be consistent with the underlying medical histories of this study efficacy population, as a significant portion of these participants had active malignancies (57 patients, 41% total), with 40 patients (38.5%) in the bezlotoxumab arm and 17 patients (48.6%) in placebo arm. Many participants also had past episodes of febrile neutropenia. It does not appear that febrile neutropenia is related to the study drug, especially given that this occurred in a higher percentage of placebo-treated patients.*

Three SAEs that were assessed by investigators as related to study treatment were reported during the study in the bezlotoxumab arm. Narratives of these events are provided below:

- Participant (b) (6) was a 14-year-old White Hispanic male with a history of intellectual disability, T-cell ALL, colitis, constipation, and immunodeficiency. The patient was admitted for treatment of his underlying condition during study drug administration. On Day 1, he experienced abdominal pain and had MRI evidence of probable typhlitis/enterocolitis and possible intussusception. An ultrasound on Day 2 showed evidence of intussusception, and the patient underwent a laparotomy that revealed colo-colonic intussusception, which auto-reduced during the procedure. This SAE was considered resolved on Day 2.

  ***Reviewer Comment**: Intussusception is classically seen in children of toddler age.*

Intussusception in older children such as this patient is uncommon but could be triggered by some of the pathologic processes this patient experienced prior to study enrollment. The symptoms started on Day 1, but the narrative does not delineate any temporal association between the receipt of study drug and the onset of symptoms, so it is difficult to know if symptoms had started before study drug administration. Additionally, the participant was receiving concomitant antibacterial drugs at this time and MRI imaging showed evidence of typhlitis and enterocolitis. This could be explained by CDI and/or the underlying diagnosis of malignancy. Review of the CRF shows that his last chemotherapy dose was Day -15, and thus the patient could be experiencing enterocolitis as an adverse reaction to those therapeutic agents. An intussusception could be more likely to happen in a patient with CDI, antibacterial drug therapy, underlying malignancy, typhlitis/enterocolitis and recent chemotherapy as all of those factors could cause enough damage to the intestine to trigger the telescoping event of intussusception. While this reviewer cannot definitively rule out the study drug as contributing to the AE of intussusception, it is unlikely to be the sole cause.

- Participant (b) (6) was a 3-year-old White male with a history of malignant neoplasm. The participant experienced the SAE (severe) of nausea and the AE of vomiting (mild) on Day 4. This resolved within 24 hours and the patient was discharged on Day 5. However, the patient was hospitalized on Day 6 for worsening nausea and upper abdominal pain, which resolved on Day 7 and the patient was discharged in good condition.

  Reviewer Comment: *The patient's nausea and abdominal pain are likely attributed to the study drug, and abdominal pain was noted as a serious AE for more than one patient in the bezlotoxumab arm. However, given that the patient had a prior history of nausea, it is difficult to attribute full causality to the study drug. The patient was also receiving concomitant trimethoprim-sulfamethoxazole and vancomycin, and no further information was provided as to the type of malignancy the patient was diagnosed with. All of these factors may have contributed to the nausea and abdominal pain that he experienced, and it could have been worsened by bezlotoxumab.*

- Participant (b) (6) was a 23-month-old male with a history of ALL. The participant experienced the nonserious AE of constipation (mild) from Days 20 to 58 of the study and required a gastrostomy tube on Day 56. On Day 294, the participant had severe constipation with bowel distention and significant pain, and he was diagnosed with the SAE of large intestinal obstruction (severe). The participant was hospitalized and treated medically. The obstruction resolved without surgical intervention and the patient was discharged on Day 298.

  Reviewer Comment: *This SAE occurred over 9 months after administration of the study drug. The half-life of the study drug is approximately 19 days, so 15 half-lives would have been completed by the time this SAE occurred. The bowel obstruction could have been secondary to many factors, however the role of bezlotoxumab cannot be excluded.*

Given that this event occurred so long after the administration of the study drug, it is unlikely to be related to study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

No participants discontinued the study intervention due to an AE.

Significant Adverse Events

In the safety population, 46 (43%) of participants in the bezlotoxumab group had one or more AEs that were graded as severe compared to 24 (66.7%) in the placebo group. Table 27 below summarizes the AE severity experienced by participants during the study.

Table 27 Summary of Adverse Event Severity by Study Participant

AE Severity	Bezlotoxumab (N=107)	Placebo (N=36)	Total (N=143)
Mild	80 (74.8)	27 (75.0)	107 (74.8)
Moderate	52 (48.6)	22 (61.1)	74 (51.7)
Severe	46 (43.0)	24 (66.7)	70 (49.0)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'.
Abbreviations: AE, adverse event; N, number of subjects

There were two preferred terms reported as severe TEAEs in the mAb arm in >4% of patients, which were neutropenia and febrile neutropenia. However, the proportion of study participants reporting these severe TEAEs was higher in the placebo arm (Table 28). The high incidence of febrile neutropenia in both treatment arms is likely because many study participants had active malignancies (41%, 57/139 in the mITT population) and this is an expected component of the clinical course of these patients.

Table 28. Summary of TEAEs by Maximum Severity-Toxicity Occurring in ≥4% of Patients Receiving Bezlotoxumab

	Bezlotoxumab (N=107)			Placebo (N=36)		
Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Febrile neutropenia	1 (0.9)	8 (7.5)	14 (13.1)	0 (0.0)	3 (8.3)	8 (22.2)
Neutropenia	1 (0.9)	1 (0.9)	6 (5.6)	0 (0.0)	0 (0.0)	2 (5.6)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "Bezlotoxumab" and TRTFL = "Y" (Bezlotoxumab); TRT01A = "Placebo" and TRTFL = "Y" (Placebo); TRTEMFL = "Y" and AESEV = ("Mild", "Moderate", or "Severe") (Adverse Events).
Note: Adverse events missing severity/toxicity grades are not included in the above table.
Note: Percent threshold: Bezlotoxumab - severe ≥4%.
Abbreviations: N, number of subjects; n, number of subjects in category, TEAE, treatment emergent adverse event

Treatment Emergent Adverse Events and Adverse Reactions

The majority of study participants experienced one or more TEAEs during the study period (Table 29). Table 30 below highlights adverse events that occurred in ≥4% of bezlotoxumab-treated patients.

Table 29. TEAEs by System Organ Class

TEAEs	Bezlotoxumab (N=107)	Placebo (N=36)
All TEAEs	95 (88.8)	34 (94.4)
TEAEs by SOC		
Infections and infestations	59 (55.1)	26 (72.2)
Gastrointestinal disorders	49 (45.8)	14 (38.9)
Blood and lymphatic system disorders	37 (34.6)	17 (47.2)
General disorders and administration site conditions	28 (26.2)	14 (38.9)
Investigations	25 (23.4)	8 (22.2)
Nervous system disorders	22 (20.6)	8 (22.2)
Metabolism and nutrition disorders	20 (18.7)	9 (25.0)
Skin and subcutaneous tissue disorders	17 (15.9)	10 (27.8)
Respiratory, thoracic and mediastinal disorders	16 (15.0)	8 (22.2)
Musculoskeletal and connective tissue disorders	12 (11.2)	4 (11.1)
Renal and urinary disorders	8 (7.5)	1 (2.8)
Hepatobiliary disorders	6 (5.6)	4 (11.1)
Vascular disorders	6 (5.6)	1 (2.8)
Immune system disorders	5 (4.7)	1 (2.8)
Ear and labyrinth disorders	4 (3.7)	0
Eye disorders	3 (2.8)	1 (2.8)
Injury, poisoning and procedural complications	3 (2.8)	6 (16.7)
Psychiatric disorders	3 (2.8)	1 (2.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.9)	2 (5.6)
Reproductive system and breast disorders	2 (1.9)	0
Cardiac disorders	1 (0.9)	3 (8.3)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'.
Abbreviations: SOC, system organ class; N, number of subjects; TEAE, treatment emergent adverse event

Table 30. TEAEs Occurring in at Least 4% of Study Participants in the Bezlotoxumab Arm

TEAEs by Preferred Term	Bezlotoxumab (N=107)	Placebo (N=36)
Febrile neutropenia	23 (21.5)	11 (30.6)
Pyrexia	19 (17.8)	11 (30.6)
Abdominal pain	15 (14.0)	6 (16.7)
Headache	15 (14.0)	8 (22.2)
Vomiting	14 (13.1)	8 (22.2)
Thrombocytopenia	10 (9.3)	3 (8.3)
Alanine aminotransferase increased	9 (8.4)	0
Hypokalemia	9 (8.4)	6 (16.7)
Stomatitis	9 (8.4)	3 (8.3)
Anemia	8 (7.5)	6 (16.7)
Aspartate aminotransferase increased	8 (7.5)	0
Diarrhea	8 (7.5)	5 (13.9)
Nausea	8 (7.5)	4 (11.1)
Neutropenia	8 (7.5)	2 (5.6)
Constipation	7 (6.5)	2 (5.6)
Urinary tract infection	7 (6.5)	2 (5.6)
Oral herpes	5 (4.7)	2 (5.6)

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y'. Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >=4%
Abbreviations: N, number of subjects; TEAE, treatment emergent adverse event

Reviewer Comment: *Most of the study participants reported one or more TEAEs in this study, which the reviewer sees as reflective of the population studied. The current labeling for bezlotoxumab notes that the most common adverse reactions (≥4% of patients) within 4 weeks of drug administration in the phase 3 trials conducted in adults were nausea, pyrexia, and headache. These were all reported in ≥4% of patients in the pediatric study as well; however, they occurred at a higher incidence in the placebo arm than in the bezlotoxumab arm (Merck 2016).*

In this study, the most common TEAEs in the bezlotoxumab arm (reported in >10% of bezlotoxumab-treated patients) were febrile neutropenia (23 patients, 21.5%), pyrexia (19 patients, 17.8%), abdominal pain (15 patients, 14%), headache (15 patients, 14%) and vomiting (14 patients, 13.1%). All of these events occurred at lower incidence in the bezlotoxumab arm than in the placebo arm; however, since pyrexia and headache were identified as adverse reactions in bezlotoxumab-treated patients in the MODIFY I and MODIFY II adult CDI trials, these were added to the labeling as the most common adverse reactions observed in the pediatric study.

Elevated ALT and/or AST were only reported as TEAEs in the bezlotoxumab arm. Nine patients (8.4%) who received bezlotoxumab had reported TEAEs of elevations in one or both enzymes:

- Three study participants (Participants [redacted] (b) (6)) had elevated transaminases that were assessed by investigators as being related to the study medication.
  - Participant [redacted] (b) (6), a 6-year-old male with ulcerative colitis, had TEAEs of increased AST and ALT reported on Day 10 assessed as mild. He had only received metronidazole during the study period, so there were no identified alternative causes of the transaminase elevations.
  - Participant [redacted] (b) (6), a 16-year-old female with Crohn's disease, had TEAEs of increased AST and ALT reported on Day 8 assessed as mild. She was receiving ongoing azathioprine treatment, which can cause transient elevations in transaminases.
  - Participant [redacted] (b) (6), a 16-year-old female with Hodgkin's lymphoma, had TEAEs of increased AST and ALT reported on Day 26 assessed as mild. She had received chemotherapy in the two weeks prior to study enrollment, including brentuximab (a mAb conjugated with a toxin that has a hepatotoxicity warning in the labeling, administered on Day -15), cytarabine (Day -14), and cisplatin (Day -15). Collectively, these medications could be responsible for the patient's abnormal transaminases.

- For the other 6 study participants with elevated transaminases reported as TEAEs, the investigators assessed the events as unrelated to study treatment:
  - Three participants (Participants [redacted] (b) (6)) had received chemotherapy in the days prior to the elevation in their transaminases, which likely explain the laboratory abnormalities.
  - One participant (Participant [redacted] (b) (6)) experienced severe elevation in transaminases as the result of veno-occlusive disease, a complication after bone marrow transplant. This patient was described earlier and is one of the patients who died during the study. The elevation of the patient's transaminases is consistent with the pathologic process that led to her death.
  - One participant (Participant [redacted] (b) (6)) appeared to have mild elevations in AST that were labeled as "continuing" from early in the study but did not demonstrate a significant elevation until after receiving chemotherapy later on in the study course.
  - One participant (Participant [redacted] (b) (6)) did not have any other TEAEs around the time of their transaminase elevation on Day 21, and as such this reviewer cannot definitively conclude that this elevation was not due to the study drug. This patient was undergoing chemotherapy for AML, with clofarabine and cytarabine most recently administered on Day -17, and the transaminase elevations peaked at Day 31 with an ALT of 234 IU/mL (assessed as moderate) and an AST of 104 IU/mL.

While elevated transaminases were only reported as TEAEs in the bezlotoxumab arm, the small size of the study with 3:1 randomization to study treatment limits the ability to conclude that these TEAEs were related to bezlotoxumab therapy based on incidence alone, since there were only 36 study participants in the placebo arm. Additionally, when the underlying comorbidities and concomitant medications for each of the 9 study participants reporting elevated transaminase TEAEs in the bezlotoxumab arm are examined, the majority (7/9) have likely alternative causes of elevated transaminases, most commonly receipt of chemotherapy drugs just prior to or during the study period. For the other 2 participants who did not have a clear alternative cause identified, one (Participant [redacted] (b) (6)) had transaminase elevation (assessed as moderate for ALT and mild for AST) starting on Day 21 and lasting for 1.12 months, and one (Participant [redacted] (b) (6)) had transaminase elevations reported on Day 10, assessed as mild and lasting for 3 weeks (AST) and 2.56 months (ALT).

When evaluating potential for hepatotoxicity by reviewing the results of clinical safety laboratory testing throughout the study, there were no patients who met the protocol's definition of abnormal hepatic laboratory results for an Event of Clinical Interest (see below). The incidence of transaminases >3X the upper limit of normal at study follow-up visits was higher in the placebo arm than the bezlotoxumab arm, suggesting that elevated transaminases are more likely to be related to comorbid conditions and concomitant medications in this study population than to bezlotoxumab treatment (see Laboratory Findings and Table 31 below). Additionally, hepatotoxicity would be an unlikely adverse effect of bezlotoxumab givevvvvn that it is mAb to an exogenous target and is not metabolized by the liver.

Events of Clinical Interest

The protocol highlights two adverse events that were defined as Events of Clinical Interest (ECI) and would require expedited reporting by investigators during the study: abnormal hepatic laboratory results meeting Hy's Law laboratory criteria and infusion-related reactions.

The protocol definition of the abnormal hepatic laboratory result ECI was:

> "An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal (ULN) and an elevated total bilirubin lab value that is greater than or equal to 2X ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology."

Reviewer Comment: *One bezlotoxumab-treatment patient had laboratory results that met some of these criteria; however, this patient (Participant [redacted] (b) (6)) was also diagnosed with veno-occlusive disease. Part of the diagnosis of VOD is rising bilirubin above 2 mg/dL and elevated transaminases. The participant likely experienced these laboratory abnormalities because of this disease process, which classically causes damage to hepatic sinusoidal endothelial cells and results in severe liver injury, hepatomegaly, ascites, multisystem organ failure and death. The patient did not have alkaline phosphatase levels consistent with Hy's law, and also had an alternative explanation for her laboratory abnormalities, so the case was not reported as an ECI.*

The protocol definition of the infusion-related reaction ECI included events meeting any of these 3 criteria:

(1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritis or flushing, swollen lips-tongue-uvula) AND at least one of the following:

  (a) Respiratory compromise (dyspnea, stridor, wheezing, bronchospasm, hypoxemia)

  (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (hypotonia, syncope, incontinence)

(2) Two or more of the following that occur rapidly after onset of the study drug infusion (minutes to several hours):

  (a) Involvement of the skin-mucosal tissue (hives, itching, swollen lips-tongue-uvula)

  (b) Respiratory compromise (dyspnea, stridor, wheezing, bronchospasm, hypoxemia, reduced peak expiratory flow)

  (c) Reduced BP or associated symptoms (hypotonia, syncope, incontinence)

  (d) Persistent gastrointestinal symptoms (abdominal pain, vomiting)

(3) Reduced BP after onset of study drug infusion (minutes to several hours):

   (a) Low systolic BP

      – 1 to 10 years: less than (70 mmHg + [2Xage])

      – 11 to 17 years: less than 90 mmHg

   (b) OR greater than 30% decrease in systolic BP from baseline

Participant (b) (6) was the only participant in the bezlotoxumab arm who experienced an event consistent with an infusion-related reaction. This participant experienced a drop in systolic BP from 99/54 mmHg to 70/45 mmHg during administration of the study medication. The patient received no treatment or change in drug infusion rate, and blood pressure resolved within 40 minutes of drug discontinuation.

Reviewer Comment*: Out of 107 pediatric patients who received bezlotoxumab in the MODIFY III trial, only one had an infusion-related reaction meeting the protocol definition. In contrast, 10% of bezlotoxumab-treated patients in adult phase 3 trials experienced one or more infusion-related adverse reaction.*

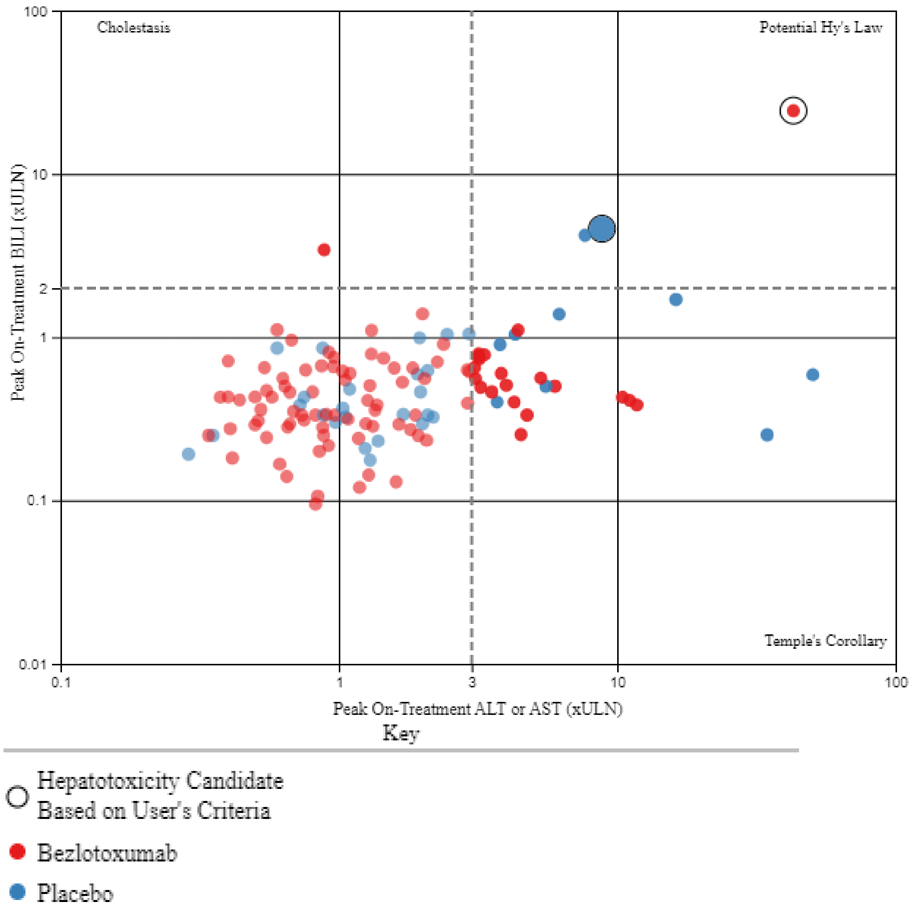
The reviewer also reviewed cardiac adverse events reported in the bezlotoxumab arm since the current labeling contains a warning for heart failure, which was reported more commonly in the adult phase 3 trials in patients treated with bezlotoxumab (2.3%) compared to patients treated with placebo (1.0%). In addition, patients in the adult phase 3 trials with a history of CHF had an increased incidence of heart failure serious adverse reactions and deaths.

Reviewer Comment: *No pediatric patients in the MODIFY III trial had CHF adverse events reported. One patient in the bezlotoxumab arm experienced the AE of cardiogenic shock, but upon further review, this was likely due to multisystem organ failure secondary due to veno-occlusive disease and not related to the study drug. While heart failure was not observed in the bezlotoxumab-treated pediatric patients in this trial, it cannot be excluded as a possibility in pediatric patients given the small size of the study population.*

Laboratory Findings

Given the higher incidence of study participants in the bezlotoxumab arm with elevated transaminases reported as TEAEs, the results of protocol-required hepatic laboratory testing were reviewed in more detail. Review of potential Hy's Law cases identified one bezlotoxumab-treated participant, Participant (b) (6), who had elevated transaminases and bilirubin levels that met criteria but did not have the alkaline phosphatase level to fully meet criteria (Figure 5). As discussed above, this patient was diagnosed with veno-occlusive disease, which causes severe hepatic injury and eventually multi-organ failure and provides a likely explanation for the hepatic laboratory findings.

Figure 5 Liver Function Test Analysis in Safety Population



Source: Reviewer table, OCS Analysis Studio, Hepatic Explorer. Filters: TRTFL = "Y".
Note: Hepatotoxicity Candidates: ALT or AST >=3*ULN; BILI >=2*ULN (0-30 days forward); ALP <2*ULN (0-999 days backward).
Note: Results missing ULN values were imputed using the weighted mean of the lab code.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal

The proportion of study participants with transaminase values at least 3 times the upper limit of normal (>3x ULN) was compared between treatment arms (Table 31). A similar proportion of subjects in both treatment arms had transaminases >3x ULN at the screening visit. At post-treatment follow-up visits where clinical laboratory testing was performed, the proportion of subjects with transaminase values >3x ULN was higher in the placebo arm than the bezlotoxumab arm.

Table 31. Study Participants With Transaminase Value at Least 3x ULN by Treatment Arm

	Bezlotoxumab (N=107)			Placebo (N=36)		
Study Visit	**n**	**N**	**(%)**	**n**	**N**	**(%)**
AST or ALT ≥3x ULN						
Screening[1]	6	102	(5.9%)	3	34	(8.8%)
Follow-Up 1[2]	9	74	(12.2%)	8	27	(29.6%)
Follow-Up 2[3]	7	31	(22.6%)	3	7	(42.9%)

Source: Reviewer table, JMP 15, ADDILI, PARAM = Aminotransferase (ALT or AST), CRIT1FL = Y
[1] Median study day: Day 1 both study arms
[2] Median study day of Follow-Up 1: Day 13 bezlotoxumab, Day 11 placebo
[3] Median study day of Follow-Up 2: Day 55 bezlotoxumab, Day 52 placebo
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of subjects; n, number of subjects in category; ULN, upper limit of normal

Vital Signs

Vital signs were collected at every visit and included heart rate, blood pressure, respiratory rate, body temperature and, on Day 1 only, pulse oximetry. Two participants, one in each arm, were noted to have decreased blood pressure during study drug administration. Neither of these participants required intervention, and their blood pressure normalized quickly.

During the 12 weeks of the study, no clinically significant changes in vital signs were noted in either study arm. Specifically, there was no notable difference in the baseline mean BP in either group (106/64.9 in the bezlotoxumab arm and 102.8/63.5 in the placebo arm) and no significant change in blood pressure after study drug administration (mean BP 105.9/65 in the bezlotoxumab arm versus 103/63.8 in the placebo arm).

Electrocardiograms

The protocol did not include routine electrocardiogram monitoring.

QT

The protocol did not include assessment of QT interval. In the adult phase 3 trials, an electrocardiogram was performed pre-infusion and within 2 hours after the end of the study infusion. There were no significant differences in the number of subjects with QT changes from baseline when comparing the bezlotoxumab and placebo arms of the study.

Immunogenicity

One of the study objectives was to assess the potential for bezlotoxumab to induce immunogenicity within 12 weeks following administration of a single infusion. Blood for ADA and NAb were collected at the screening, Week 4 (Day 28) and Week 12 (Day 84) visits. Post-treatment samples testing positive in the ADA assay were subsequently evaluated for neutralizing activity in the NAb assay. The ADA assay used in the pediatric study was modified from the assay that had been used in the MODIFY I and MODIFY II trials in adults and new non-cell based NAb assay was used in the pediatric study (see clinical pharmacology discussion of these assays in Section 14.3.1).

Two pediatric patients were found to have positive ADA responses after receiving bezlotoxumab in the MODIFY III trial.

- Participant (b) (6) had an antibody titer that increased from a baseline titer of 5 at screening to a titer of 25 at Day 84, deemed "treatment boosted positive." This participant was a 16-year-old male with AML. He did not have any AEs assessed by the investigator or the reviewer as related to study drug. He experienced prurigo on Days 41 and 44, and febrile neutropenia (severe) on Day 46 but was receiving ongoing chemotherapy and in the reviewer's opinion, these are unlikely to have been mediated by ADAs.
- Participant (b) (6) had treatment emergent positive ADA, with an undetectable baseline titer at screening and a titer of 1 at Day 84. This participant was a 3-year-old male with ALL. He had a TEAE of perianal mucositis assessed by the investigator as related to study treatment at Day 61; however, he had multiple additional mucositis TEAEs around the same time and had received chemotherapy in the preceding week. In the reviewer's opinion, there were no TEAEs that were likely to have been mediated by ADAs.

Reviewer Comment*: Because of the low incidence of ADA, the effects of these ADA on the PK, pharmacodynamics, safety and/or effectiveness of bezlotoxumab is not known. In addition, different assays were used to measure ADAs in the adult and pediatric studies of bezlotoxumab. Because the observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay, differences in the assays preclude meaningful comparisons on the incidence of ADAs in the adult and pediatric populations treated with bezlotoxumab.*

8.2.5 Analysis of Submission-Specific Safety Issues

There were no submission-specific safety issues.

8.2.6 Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable

8.2.7 Safety Analyses by Demographic Subgroups

The small size of the study limits the interpretability of safety analyses by demographic subgroups. Given that the randomization was stratified to two age cohorts (Age Cohort 1: 12 to <18 years of age, Age Cohort 2: 1 to <12 years of age), an analysis of TEAE incidence by age was performed (Table 32). Comparing the two age groups, the incidence of TEAEs reported by system organ class in the bezlotoxumab-treated patients in each group was similar. Overall, there were no major differences in reported TEAEs throughout the different age group that would raise concerns for patient use or drug labeling.

Table 32. TEAEs Reported in ≥4% of Study Participants by Age Group

	Age 1 to <12 Years		Age 12 to <18 Years	
TEAEs	**Bezlotoxumab (N=63)**	**Placebo (N=20)**	**Bezlotoxumab (N=44)**	**Placebo (N=16)**
Blood and lymphatic system disorders	23 (36.5)	8 (40.0)	14 (31.8)	9 (56.2)
Cardiac disorders	0	2 (10.0)	1 (2.3)	1 (6.2)
Ear and labyrinth disorders	0	0	3 (6.8)	0
Eye disorders	3 (4.8)	0	0	1 (6.2)
Gastrointestinal disorders	26 (41.3)	6 (30.0)	23 (52.3)	8 (50.0)
General disorders and administration site conditions	16 (25.4)	7 (35.0)	12 (27.3)	7 (43.8)
Hepatobiliary disorders	3 (4.8)	1 (5.0)	3 (6.8)	3 (18.8)
Immune system disorders	4 (6.3)	0	1 (2.3)	1 (6.2)
Infections and infestations	35 (55.6)	13 (65.0)	24 (54.5)	13 (81.2)
Injury, poisoning and procedural complications	1 (1.6)	2 (10.0)	2 (4.5)	4 (25.0)
Investigations	12 (19.0)	2 (10.0)	13 (29.5)	6 (37.5)
Metabolism and nutrition disorders	14 (22.2)	4 (20.0)	6 (13.6)	5 (31.2)
Musculoskeletal and connective tissue disorders	3 (4.8)	1 (5.0)	9 (20.5)	3 (18.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.6)	2 (10.0)	0	0
Nervous system disorders	10 (15.9)	2 (10.0)	12 (27.3)	6 (37.5)
Psychiatric disorders	0	1 (5.0)	3 (6.8)	0
Renal and urinary disorders	6 (9.5)	0	2 (4.5)	1 (6.2)
Respiratory, thoracic and mediastinal disorders	8 (12.7)	4 (20.0)	8 (18.2)	4 (25.0)
Skin and subcutaneous tissue disorders	9 (14.3)	7 (35.0)	8 (18.2)	3 (18.8)
Vascular disorders	2 (3.2)	1 (5.0)	4 (9.1)	0

Source: OCS Analysis Studio, Custom Table Tool. Columns - Dataset: Demographics; Filter: TRTFL = 'Y', AGEGR2 = '1 to <12'. AGEGR2 = '12 to <18'. Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >=4%.
Abbreviations: N, number of subjects; TEAE, treatment emergent adverse event

8.2.8 Specific Safety Studies/Clinical Trials

Not applicable

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Bezlotoxumab has not been found to have mutagenic potential. There have been no safety signals related to human carcinogenicity. This drug is administered as a single course of treatment with a one-time dose. Therefore, a prolonged duration of exposure leading to carcinogenicity is not anticipated.

Human Reproduction and Pregnancy

There are no new studies on reproductive and developmental toxicology effects of bezlotoxumab.

Pediatrics and Assessment of Effects on Growth

The study under review is a pediatric study. In this study, patients were not followed long-term to determine effects of the drug on growth or other developmental parameters. This drug is not intended for long-term use.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

ZINPLAVA and its components are not known to be associated with abuse, withdrawal, or rebound effects. This drug is administered in a hospital setting and is a one-time dose, making the possibility of overdose unlikely.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

A review of post marketing adverse events was conducted by the Applicant from the market introduction of bezlotoxumab (October 21, 2016) through May 31, 2022. Total cumulative patient exposure is estimated at approximately 20,506 vials of drug used during this time. A total of 399 reports containing 985 events were reported. The most commonly reported events included general disorders and administration site conditions (259 events), infections and infestations (170 events), and injury, poisoning, and procedural complications (142 events). Review of these reports did not identify any new safety concerns. The safety profile remains adequately described in the product labeling.

Expectations on Safety in the Postmarket Setting

No new safety concerns were identified when bezlotoxumab was studied in pediatric patients; therefore, similar postmarket events are expected with extension of the approved indication to pediatric patients aged 1 year to less than 18 years of age.

8.2.11 Integrated Assessment of Safety

A total of 143 patients participated in this pediatric study in patients aged 1 to <18 years. There were no deaths associated with ZINPLAVA, and no new safety signals were identified in the study. The most common adverse reactions reported in >10% of patients treated with bezlotoxumab were pyrexia (19 patients, 18%), and headache (15 patients, 14%). This is similar to what has been reported in adult trials. Elevations of transaminases were reported as TEAEs in some bezlotoxumab-treated patients, but transaminase elevations >3x ULN did not occur more frequently in study participants in the bezlotoxumab arm compared with the placebo arm and most of the TEAEs appeared attributable to underlying comorbidities or concomitant medications. There are now new concerns identified from post-marketing reports.

8.3 Statistical Issues

Since the MODIFY III trial did not plan to draw statistical inferences with regard to efficacy and only considered descriptive analyses, there were not many major statistical concerns. The MODIFY III trial did not demonstrate any differences between the Bezlotoxumab arm and the Placebo arm with regard to efficacy, which was not unexpected given the limited sample size of the study. The following points were also noted:

- A limitation with the recurrence of CDI endpoint is that it excludes participants who did not have a clinical response. Since this exclusion is based on postbaseline considerations it may be related to the effect of the treatment received and could therefore be informative. For this reason, the Division prefers the sustained clinical response endpoint which does not require post-baseline exclusions of any of the participants of the mITT in order to be evaluated.
- Due to this limitation, the Division recommended in its Written Request that the sustained clinical response be designated as the first primary efficacy endpoint. The Applicant did not use that designation and considered both recurrence rates of CDI and sustained clinical response rates as key efficacy endpoints. However, since the MODIFY III trial was descriptive in nature, this did not raise any serious concerns from a statistical perspective.

8.4 Conclusions and Recommendations

The MODIFY III trial did not detect differences between treatment arms with regard to efficacy for all endpoints and analysis populations/subsets considered. Although a treatment benefit cannot be determined from this study, findings at least do not suggest the possibility of reduced efficacy in pediatric subjects receiving Bezlotoxumab. Evidence of treatment efficacy in pediatric subjects will rely primarily on an extrapolation from the MODIFY I and MODIFY II trials in adult subjects as discussed in Section 6.

Overall, the safety profile of ZINPLAVA in pediatric patients with CDI who are at high risk of recurrence appears similar to the safety profile of that in adults. The safety data supports extension of the approved indication to reduce the recurrence of CDI in pediatric patients aged 1 year and older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence, with the recommended labeling modifications summarized in Section 11 Prescription Drug Labeling.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for this efficacy supplement.

10 Pediatrics

This submission contains the safety, efficacy and PK data from the MODIFY III trial to evaluate ZINPLAVA use in children 1 to <18 years of age. Evidence of efficacy is extrapolated from adequate and well-controlled trials conducted in adults with CDI (MODIFY I and MODIFY II). The extrapolation of effectiveness at the proposed pediatric dosing regimen is supported by the comparison of bezlotoxumab exposures in adult and pediatric CDI patients. A waiver was granted for children <1 year old due to high rates of colonization with *C. difficile* and low likelihood of diagnosing CDI in infants.

This submission fulfills the requirements of PREA PMR 3118-1 to conduct a randomized, double-blind, placebo-controlled study of safety, efficacy, and pharmacokinetics of ZINPLAVA in pediatric patients from 1 to <18 years of age receiving antibacterial therapy for *C. difficile* infection. The Applicant met the dates for study completion (May 2022) and study report submission (November 2022) for the PMR.

The Applicant requested pediatric exclusivity determination based on this submission. The findings from the final clinical study report from the MODIFY III trial, conducted in accordance with the terms of the PWR Amendment 1, were reviewed by the Pediatric Exclusivity Board. The Applicant was granted pediatric exclusivity for studies conducted on bezlotoxumab, effective May 12, 2023, under section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C) Act. The FD&C Act requires FDA to refer to its Office of Pediatric Therapeutics any report of an adverse event associated with the drug granted exclusivity that is received by FDA during the 18 months after a labeling change reflecting the results of the pediatric study submitted to qualify for exclusivity is approved.

No other pediatric studies are planned at this time.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Prescribing Information

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the currently approved PI and the Applicant's draft PI (Table 33). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Other Prescription Drug Labeling that will be attached to the Approval Letter

Approved Labeling Types

Upon approval of this application/efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information

- Patient Information

The Patient Labeling Team from the Division of Medical Policy Programs (DMPP) reviewed the ZINPLAVA Patient Package Insert (PPI) and recommended several changes to reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication (see DMPP review in DARRTS dated 4/28/2023) for additional details).

12 Risk Evaluation and Mitigation Strategies

No Risk Evaluation and Mitigation Strategies are recommended. At this time, there are no data to indicate the risks associated with ZINPLAVA use in the pediatric population are different than in the adult population. Any risks can be communicated in the labeling for ZINPLAVA, as is the case for the adult population.

13 Postmarketing Requirements and Commitment

No new PMRs recommended.

14 Division Director (Clinical Comments)

I agree with the review team's assessment and recommendations.

15 Appendices

15.1 References

Literature

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Guidance for Industry

Guidance for Industry *FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency* (August 2021)

Draft Guidance for Industry *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format* (February 2022)

Other

Merck, 2016, ZINPLAVA prescribing information accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761046s000lbl.pdf.

15.2 Financial Disclosure

The Applicant's financial disclosure was reviewed and none of the 204 investigators participating in the MODIFY III pediatric study had disclosable financial interests or arrangements.

Covered Clinical Study (Name and/or Number): A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of a Single Infusion of Bezlotoxumab (MK-6072, Human Monoclonal Antibody to *C. difficile* Toxin B) in Children Aged 1 to <18 Years Receiving Antibacterial Drug Treatment for *C. difficile* Infection **(**MODIFY III)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 204		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: ______		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3 OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1 Clinical Pharmacology Study

Study P001 MK6072 (MODIFY III)

This was a phase 3, double blind, placebo-controlled, clinical study evaluating the PK, immunogenicity, safety, tolerability, and efficacy of a single 10 mg/kg bezlotoxumab IV infusion in pediatric CDI patients ages 1 to less than 18 years of age who were concurrently receiving antibacterial drug treatment for CDI. Subjects were randomized 3:1 to single dose bezlotoxumab 10 mg/kg (infused over 60 minutes) or placebo and were stratified to two age cohorts (Age Cohort 1: 12 to <18 years of age, Age Cohort 2: 1 to <12 years of age) and followed up for 12 weeks (i.e., ~84 days).

For the planned safety, tolerability, and efficacy assessments and findings, see Section 8. For PK assessments, five serum samples were collected at the following time points: on Day 1 (2 hours post infusion), and 9, 28, 56, and 84 days post infusion. For immunogenicity assessments, 3 blood samples were collected at screening (prior to drug administration), and 28 and 84 days post infusion for evaluating ADA levels and NAb for bezlotoxumab.

Bezlotoxumab serum concentrations were analyzed with a validated bioanalytical electrochemiluminescent assay. The original bioanalytical electrochemiluminescent method was validated at Merck, which was then transferred and validated by (b) (4) for sample analysis. This bioanalytical method was used to analyze adult samples and was submitted in the original BLA submission and was deemed appropriate by the Clinical Pharmacology Review team. For the phase 3 pediatric study, a method validation addendum was made to support additional evaluations (frozen standard curves, additional disease state selectivity, prozone effect, dilutional linearity, clinical reference standard, lipemia, and hemolysis). The updated assay met the current standards for bioanalytical assay, and the method performance was satisfactory.

Of note, during method validation a hook effect was observed at concentrations above 1048 ng/mL with results re-entering the range of quantification at concentrations above 5250 ng/mL. To address these issues, all samples were tested at 2 different dilution levels.

In the original BLA, a tiered testing approach for ADA and a cell-based NAb assay were in place to support the clinical studies. In this submission to support the pediatric clinical studies, a modified ADA method and a new non-cell based NAb assay were used; the performance of these updated or new assays were evaluated by Dr. Zhuo from the Office of Biological Products (OBP).

In total, 107 enrolled pediatric patients received bezlotoxumab and from which 16 patients were excluded by the Applicant from the NCA because they had less than 4 post dose PK samples or they did not have a measurable drug concentration observation on Day 1. One additional patient was excluded from the Reviewer's analysis due to only having 3 measurable (non-below limit of quantification) drug concentrations (i.e., Days 1, 10, and 29). Overall, 90 pediatric patients were included and the baseline demographics and bezlotoxumab PK parameter estimates from these patients are summarized in Table 34 and Table 35, respectively.

Table 34. Mean (SD) Baseline Demographic Information for Pediatric CDI Patients Included in PK Evaluation of Bezlotoxumab

	Age Cohort 1	Age Cohort 2		
Baseline Demographic Information	12 to <18 yr n=36	7 to <12 yr n=21	4 to <7 yr n=13	1 to <4 yr n=20
Weight (kg)	58.9(19.6)	32.7 (11.4)	19.8 (3.8)	13.2 (3.0)
BMI (kg/m^2)	21.4 (5.7)	17.6 (3.7)	15.1 (1.7)	16.1 (2.0)
Gender (% males)	58.3	66.7	53.8	55.0
Baseline immunocompromised (%)	77.7	90.0	61.5	70.0

Sources: Reviewer's analysis using the Applicant's datasets
Abbreviations: BMI, body mass index; CDI, *Clostridioides difficile* infection; PK, pharmacokinetics; SD, standard deviation; yr, years; n, number of patients in category

Table 35. Geometric Mean (%GMCV) Serum Bezlotoxumab PK Parameters Estimates Following a Single Infusion of 10 mg/kg Bezlotoxumab Across Different Age Cohorts

	Age Cohort 1	Age Cohort 2		
PK Parameters	**12 to <18 yr n=36**	**7 to <12 yr n=21**	**4 to <7 yr n=13**	**1 to <4 yr n=20**
C_{max} (µg/mL)	156 (28.3)	143 (24.0)	136 (32.2)	112 (37.4)
C_{Day84} (µg/mL)	3.9 (68.0)	1.9 (257.8)	1.5 (191.6)	2.3 (131.2)
$AUC_{0\text{-}inf}$ (h*µg/mL)	56099 (30.7)	43647 (38.5)	40388 (33.7)	44534 (33.4)
$AUC_{Days\ 0\text{-}84}$ (h*µg/mL)	52707 (29.0)	41747 (36.0)	38788 (31.9)	42371 (30.9)
$T_{1/2}$ (days)	21.7 (22.1)	18.2 (35.3)	17.6 (36.6)	18.4 (32.0)
CL ((L/day/) kg)	0.178 (31.0)	0.229 (37.6)	0.248 (33.8)	0.227 (33.0)
Vd (L/kg)	0.134 (29.9)	0.145 (27.5)	0.151 (34.2)	0.145 (28.2)

Source: Reviewer's analysis using the Applicant's datasets
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from 0 to infinity; $AUC_{Days0\text{-}84}$, area under the curve from Day 0 to 84; $C_{Day\ 84}$, NCA based predicted concentration at day 84; CL, clearance; C_{max}, maximum concentration; GMCV; percent geometric mean coefficient of variation; n, number of subjects in category; NCA, noncompartmental analyses; PK, pharmacokinetics; $T_{1/2}$, elimination half-life; Vd, volume distr bution; yr, years

With respect to immunogenicity findings, 100 patients were evaluable for ADA analysis. From 100 patients, 4 patients had detectable pre-existing ADAs against bezlotoxumab at the start of therapy, and 2 patients developed an ADA positive response after receiving bezlotoxumab (1 treatment emergent and 1 treatment postdose titer increase by ≥2-fold from baseline titer). None of the patients with ADAs experienced a positive result in the NAb assay. However, the OBP reviewer of the ADA and NAb assays noted that the ADA assay had a drug tolerance of 25 µg/mL with the low positive control of 1.36 ng/mL. A few of the samples were above the validated drug tolerance limit with the low positive control, which may lead to inconclusive ADA results. In addition, the method sensitivity for the NAb assay was low; therefore, the 2 ADA positive patients that were found to have negative NAb results may be inconclusive. Overall, since the ADA occurrence is low, the effect of these ADAs on the PK, pharmacodynamics, safety, and/or effectiveness of bezlotoxumab is unknown.

Reviewer Comment*: As shown in Table 35, compared to adults, younger age groups (less than 12 years of age) exhibited relatively lower exposures, while the geometric mean clearance (CL) and Vd normalized by actual body weight were relatively increased with the younger age groups (see Section 6.2.2 for additional details). Despite these differences, the findings based on the fold-change from adults and 5th and 95th percentiles show that bezlotoxumab exposures among the various age groups administered a single bezlotoxumab 10 mg/kg IV dosage were generally comparable to the adult population on the same weight-based dosage regimen (see Section 6.2.2 for additional details). Subsequently, for the Prescription Drug Label under pediatric patients of Subsection 12.3 Pharmacokinetics, we recommended that the Applicant combine the pediatric PK data of all pediatric age groups (1 to <18 years of age) and summarize the information* [redacted] (b) (4)

With respect to including immunogenicity findings in the Label, based on the OBP Review Teams review conclusions that there may be inconclusive results for ADAs 28 days post infusion of bezlotoxumab [redacted] (b) (4) *the two patients with ADA positive samples,* *we proposed modifications to Section 12 (CLINICAL PHARMACOLOGY) of the proposed ZINPLAVA labeling, indicated as blue font (additions) and strikethrough (deletions).*

- 12.6 Immunogenicity

  ~~Following treatment with ZINPLAVA in~~ Trial 3, 2 of the 100 evaluable pediatric patients developed ADAs through 12 weeks post-treatment [redacted] (b) (4)

15.3.2 Comparison of Bezlotoxumab Pharmacokinetics Across Pediatrics and Adult Patients

For comparing bezlotoxumab PK between pediatrics and adults, the Applicant relied on prespecified comparability bounds. This approach was based on a PK statistical method using analysis of variance to compare NCA estimated and model-predicted bezlotoxumab $AUC_{0\text{-}inf}$ in pediatric patients from the phase 3 trial (MODIFY III) to previously reported adult patient model-predicted bezlotoxumab $AUC_{0\text{-}inf}$ estimates following administration of a single 10-mg/kg IV infusion of bezlotoxumab alone or as actoxumab + bezlotoxumab in the adult phase 3 studies (MODIFY I and MODIFY II). Using these estimates, 90% CIs of the GMRs (pediatric/adult) were determined and compared against a prespecified comparability bounds of 0.6 and 1.6 which were based on the 10^{th} and 90^{th} percentiles of observed bezlotoxumab $AUC_{0\text{-}inf}$ values at bezlotoxumab 10 mg/kg IV in adults from the two phase 3 trials. Therefore, the Applicant postulated that when pediatric-to-adult GMR and 90% CI for serum bezlotoxumab $AUC_{0\text{-}inf}$ were contained within the bounds, bezlotoxumab efficacy in pediatrics is expected to be comparable to that of the efficacy observed in adults following a single 10 mg/kg IV infusion of bezlotoxumab.

As shown in Table 36, the GMR and 90% CI for $AUC_{0\text{-}inf}$ calculated for the two pediatric age cohorts (NCA derived) and adults (model-predicted) were contained in the prespecified clinical comparability bounds established in adults of 0.6 and 1.6 in each of the age cohorts. In contrast, for the GMR of pediatric (model-predicted) and adult exposures bezlotoxumab $AUC_{0\text{-}inf}$ with 90% CI, only Age Cohort 1 (12 to <18 years of age) was comparable to adult exposures while the lower bound of Age Cohort 2 (1 to <12 years of age)-to-adult GMR 90% CI was outside the comparability bounds (GMR 0.65; 90% CI, 0.56 to 0.73). The Applicant states that the $AUC_{0\text{-}inf}$ were under-predicted in Age Cohort 2, and that this was an artifact of an over-prediction of clearance due to model assumptions driven by data of subjects below 3 years old (see Section 14.3.3.4 for additional details).

Table 36. Geometric Mean Ratio (Pediatric/Adult) for Bezlotoxumab $AUC_{0\text{-}inf}$ and 90% CI

PK Parameter	Age Cohort	Derived Estimates	GMR Pediatric/Adult (90% CI)
$AUC_{0\text{-}inf}$	1 to <12 (n=63)	PopPK Model	0.65 (0.56, 0.73)
	12 to <18 (n=44)	PopPK Model	0.97 (0.87, 1.08)
$AUC_{0\text{-}inf}$	1 to <12 (n=54)	NCA	0.82 (0.75, 0.89)
	1 to <18 (n=36)	NCA	1.06 (0.95, 1.18)

Source: P001MK6072- CSR, 084zng- modeling and simulation report, and Reviewer's analysis using the Applicant's datasets
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve 0 to infinity; CI, confidence interval; CSR, clinical study report; GMR, geometric mean ratio; n, number of subjects in category; NCA, noncompartmental analysis; PopPK Model, population pharmacokinetic model

Reviewer Comment: *To evaluate and compare bezlotoxumab exposures between pediatric and adult patients, the Clinical Pharmacology Review Team relied exclusively on an independent analysis using NCA derived bezlotoxumab exposures ($AUC_{0\text{-}inf}$, $AUC_{Days0\text{-}84}$, concentration at Day 84 [C_{Day84}]). Bezlotoxumab exposures in pediatric and adult patients were estimated and compared utilizing similar NCA methodologies. The pediatric PK data used for NCA estimates originated from the phase 3 trial [MODIFY III], while the adult PK data originated from adult patients administered a single 10-mg/kg IV infusion of bezlotoxumab alone or as actoxumab + bezlotoxumab in the two phase 3 studies [MODIFY I and MODIFY II]. For the sample size included in the comparison, a similar criterion used by the Applicant for including pediatric patients in the NCA population was used for the adult population, i.e., 4 or more days of PK sampling time points over 12 weeks, and at least 1 measurable [non-below limit of quantification] drug concentration observed on Day 1. For these analyses, we compared exposures in pediatric patients based on four age increments and body weight bands to the exposures of the adult patient population (e.g., the fold-change from adults and the 5th and 95th percentiles of adult exposures). As detailed in Section 6.2.2, the bezlotoxumab $AUC_{0\text{-}inf}$ and $AUC_{Day0\text{-}84}$ for pediatrics of all age cohorts and body weight bands were generally comparable to the adult patient population with the exception of three subjects (two patients 2 years of age and <10 kg, and one patient 9 years of age and ~25 kg) not contained within the 5th and 95th percentiles of adult exposures.*

15.3.3 Pharmacometrics

15.3.3.1 Review Summary

The bezlotoxumab pediatric efficacy supplement seeks to extend the indication for reduction of CDI recurrence to this pediatric population by extrapolation of efficacy from reference adult data. A population PK (popPK) model was developed previously in the adult population with rich sampling schemes (refer to the Clinical Pharmacology Review dated April 28, 2016). The current submission adopted several approaches for model re-fitting. In general, the Applicant's pooled popPK analysis is reasonable in capturing the central tendency of bezlotoxumab disposition after a single IV dose; however, there is a trend for under-predicting exposures (i.e., posterior predictions) in the younger pediatric cohort of 1 to <7 years of age when compared to those from NCA. The difference of drug CL due to age and maturation could be one factor that accounts for the underpredictions. The Applicant made multiple attempts in popPK model refinement, including modeling maturation function on CL, estimation of CL based on age groups, etc. The reviewer also attempted to incorporate an extra residual noise (i.e., proportional shift of existing error term) for the younger cohort to compensate for a potential difference of total CL of bezlotoxumab that results in underprediction of observed concentrations; however, neither approach improved the model fit (based on the objective function value (OFV) and the condition number). One possible explanation could be the limited sample size of the youngest pediatric subjects with the potential difference in CL.

Considering the tendency of underprediction in the younger age cohort, the popPK model remains a conservative methodology for exposure comparison with the additional support from NCA data. More specifically, the developed model was used to support the current submission as outlined in Table 37.

Table 37. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model			Reviewer Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Section 12.3 Pediatric Patients There is no clinically meaningful relationship between bezlotoxumab exposure and body weight following weight-based dosing of ZINPLAVA in pediatric patients.	The labeling statement is acceptable based on exposure comparison approach using population PK modeling and NCA data.
	Extrinsic factor	N/A	
Derive exposure metrics for exposure-response analyses	N/A		No formal exposure-response analysis was conducted for the pediatric study
Predict exposures at alternative dosing regimen	N/A		

Source: Reviewer analysis
Abbreviations: N/A, not applicable; NCA, non-compartmental analyses; PK, pharmacokinetic

15.3.3.2 Introduction

The primary objectives of the Applicant's popPK analysis were to:

- Characterize bezlotoxumab disposition in pediatric subjects using an existing popPK structural model
- Characterize bezlotoxumab disposition in pediatric subjects in an alternative popPK model (newly developed or modified) if needed
- Support pediatric dosing recommendation by comparison to reference adult exposures via NCA, popPK posterior predictions (post-hoc), and simulation methodologies

15.3.3.3 Model development

Data

Pediatric PK data was pooled with historical adult PK data (three phase 1 and two phase 3 studies) for popPK analysis. Note that all the adult PK data included in PopPK analysis are from clinical studies that evaluated bezlotoxumab treatment in combination with MK-3415 (actoxumab, mAb directed against *C. difficile* toxin A). Treatment with actoxumab in combination with bezlotoxumab did not demonstrate any further reduction in CDI recurrence compared to treatment with bezlotoxumab alone, and treatment with actoxumab alone did not demonstrate a reduction in CDI recurrence relative to placebo (based on the information from original BLA submission). Coadministration of actoxumab with bezlotoxumab did not influence the PK of bezlotoxumab.

In total, the analyses described here are based on PK data from 7 studies. The study design, study population, and timing of PK samples are summarized in Table 38. A total of 107 pediatric subjects were included in the popPK dataset and contributed 595 evaluable bezlotoxumab concentrations; of those, 90 (84.1%) subjects contributed 4 or more evaluable PK samples. Table 39 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 38. Clinical Studies Included in the PopPK Analysis

Study Number, Phase, Type	Subject Population	Number of Subjects	Drug Dose and Regimen	PK Sampling
MK-3415A-P004 Phase 1 Two sequential doses	HV	N=30	10 mg/kg MK-3415 + 10 mg/kg MK-6072, repeated after 12 weeks	Predose, 0.5, 1, 2, 4, 8 hr and 2, 8 and 43 days post first dose. Predose on day 85 and then 0.5, 1,2,4,8 hr post-dose and then days 86, 92, 127, 169 and 253
MK-3415A-P005 Single dose	HV	N=29; (10A + 10B), 6 placebo	10 mg/kg MK-3415 + 10 mg/kg MK-6072	Pre-dose, 0.5, 1, 2, 4, 6, 8, 24, 72 hr and 7, 10, 20, 28, 56 and 84 days post dose
MK-3415A-P006 Japanese, single dose	HV	6 (10A+10B) 7 (20A+20B) 6 placebo	10 mg/kg MK-3415 + 10 mg/kg MK-6072, 20 mg/kg MK-3415 + 20 mg/kg MK-6072, Placebo	Pre-dose, 0.5, 1, 2, 4, 6, 8, 24, 72 hr and 7, 10, 20, 28, 56, 84 and 168 days post dose
MK-3415A-P001 , adaptive design, single dose adjunctive to SOC	Patients with CDI	N=1450 (400 per MK-6072, MK-3415A) and placebo arms, 250 per MK-3415 arm)	10 mg/kg MK-3415, 10 mg/kg MK-6072, 10 mg/kg MK-3415 + 10 mg/kg MK-6072 (MK-3415A), placebo	Pre-dose, 1 hr post infusion and 3, 10, 28, 56 and 84 days post-dose, also unscheduled if CDI recurs
MK-3415A-P002 single dose adjunctive to SOC	Patients with CDI	N=1200 (400 per treatment arm)	10 mg/kg MK-6072, 10 mg/kg MK-3415 + 10 mg/kg MK-6072 (MK-3415A), placebo	Pre-dose, 1 hr post infusion and 3, 10, 28, 56 and 84 days post dose, also unscheduled if CDI recurs
MK-6072-P001	Pediatric patients with CDI	N=140 (at least 36 in each age group and at least 4 patients aged 1-4 years Randomisation ratio 3:1 (bezlotoxumab placebo)	10 mg/kg MK-6072 placebo	Blood samples for PK analysis will be collected in both treatment groups at up to 5 time points, post-infusion, and at follow-up visits planned at 10 days and Weeks 4, 8 and 12 following the study drug administration.

Source: Applicant's PopPK report, Table 1, pages 18-19
Abbreviations: A, actoxumab; B, bezlotoxumab; CDI, *Clostridioides difficile* infection; HV, healthy volunteer; N, number of subjects; PK, pharmacokinetics; PopPK, population pharmacokinetic; SOC, standard of care

Table 39. Summary of Baseline Covariates for Adult and Pediatric Subjects

Baseline Covariates	Study MK-3415A-P001 (N=752)	Study MK-3415A-P002 (N=697)	Study P001 (N=107)
Sex			
Male	321 (42.7%)	307 (44.0%)	57 (53.3%)
Female	431 (57.3%)	390 (56.0%)	50 (46.7%)
Age (years)			
Mean (SD)	61.8 (18.1)	63.0 (17.6)	9.20 (5.33)
Median (CV%)	64.0 (29.3)	66.0 (27.9)	10.0 (57.9)
[Min, max]	[18.0, 100]	[18.0, 93.0]	[1.00, 17.0]
Body weight (kg)			
Mean (SD)	74.3 (20.6)	72.0 (19.9)	36.0 (23.0)
Median (CV%)	71.0 (27.8)	69.3 (27.7)	30.1 (64.0)
[Min, max]	[34.5, 171]	[32.7, 194]	[7.80, 108]
Body surface area (m^2)			
Mean (SD)	1.82 (0.253)	1.80 (0.251)	1.14 (0.482)
Median (CV%)	1.79 (13.9)	1.78 (14.0)	1.16 (42.3)
[Min, max]	[1.24, 2.77]	[1.24, 3.05]	[0.414, 2.22]
Missing	0 (0%)	0 (0%)	2 (1.9%)
Race			
White	675 (89.8%)	598 (85.8%)	83 (77.6%)
Black or African American	43 (5.7%)	35 (5.0%)	6 (5.6%)
Asian	8 (1.1%)	58 (8.3%)	3 (2.8%)
Other	26 (3.5%)	6 (0.9%)	15 (14.0%)
Japanese race			
Other	752 (100%)	697 (100%)	107 (100%)
Japanese	0 (0%)	0 (0%)	0 (0%)
Ethnicity			
Hispanic or Latino	93 (12.4%)	61 (8.8%)	28 (26.2%)
Not Hispanic or Latino / missing	659 (87.6%)	636 (91.2%)	79 (73.8%)
Albumin (g/dl)			
Mean (SD)	34.2 (7.33)	34.0 (7.26)	36.5 (7.17)
Median (CV%)	34.0 (21.4)	34.0 (21.4)	37.0 (19.6)
[Min, max]	[12.0, 52.0]	[15.0, 50.0]	[14.0, 50.0]
Missing	0 (0%)	0 (0%)	9 (8.4%)
Estimated GFR (ml/min/1.73m²)			
Mean (SD)	89.4 (54.8)	88.9 (55.8)	148 (84.1)
Median (CV%)	82.4 (61.3)	81.4 (62.8)	121 (56.7)
[Min, max]	[4.21, 566]	[4.58, 477]	[16.8, 637]
Missing	0 (0%)	0 (0%)	4 (3.7%)

Source: Applicant's PopPK report, Table 3, pages 30-31
Note: Numeric columns formatted as mean (SD) and median (CV%) [range]
Note: eGFR was calculated based on MDRD formula for adults and Schwartz for pediatric subjects
Abbreviations: CV%, coefficient of variation; eGFR, estimated glomerular filtration rate; max, maximum; MDRD, Modification of Diet in Renal Disease equation; Min, minimum; N, number of subjects with available information; PopPK, population pharmacokinetic; SD, standard deviation

Previous popPK Model

A popPK model for bezlotoxumab was previously developed for the adult population in the original BLA submission (refer to the Clinical Pharmacology Review dated April 28, 2016). Briefly, bezlotoxumab PK was best described by a two-compartment model with linear, first-order elimination. Body weight was modeled on CL-related terms (CL and intra-compartmental flow, Q) and volume-related terms (central volume of distribution, Vc; peripheral volume of distribution, Vp) following an allometric relationship with estimated exponents of 0.447. Albumin was a significant covariate for bezlotoxumab PK (i.e., higher levels of albumin led to higher drug exposure). Additionally, gender, and Japanese race were identified as significant covariates on CL and Vc. Race (White versus others) was a significant covariate on CL only. The structural popPK model for the adult population served as the initial step for the popPK model for the combined adult and pediatric population.

Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit (GoF), such as a decrease in the minimum OFV, accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, bootstrap analysis, and visual predictive check (VPC) and GoF plots.

Covariate Analysis

Covariates identified in the adult model were retained with the pediatric data and were re-estimated (since the Applicant deemed this approach necessary after the external validation approach demonstrated under-predictions in the younger age group). Additionally, baseline age and body surface area were examined as additional covariates (Table 40).

Table 40. Covariates to be Evaluated in the PopPK Model

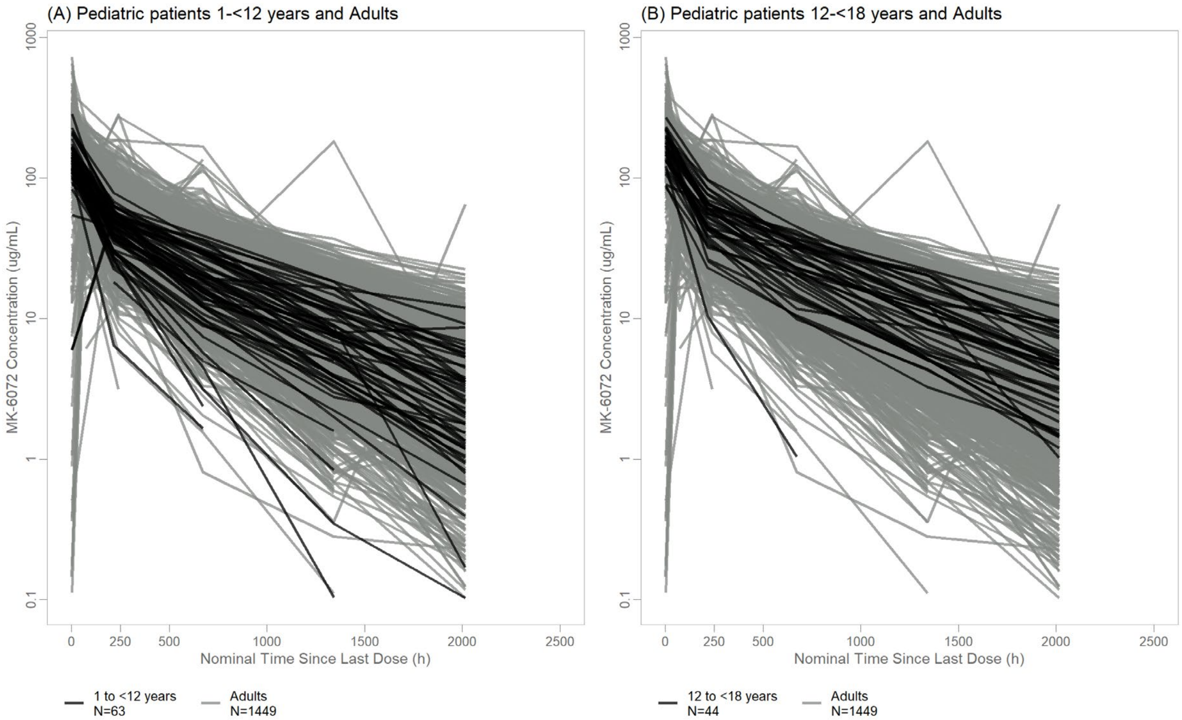
Covariate	Reason for Investigation	Parameter
Baseline age	Potential maturation function	CL, Vc
Baseline BSA	As weight is already included in the model a correlation between the ETAs and BSA, it will be evaluated on CL and/or Vc to assess remaining correlations	CL, Vc

Source: Adapted from Applicant's PopPK Report, Table 2, page 25
Abbreviations: BSA, body surface area at baseline; CL, clearance; ETA, inter-individual random effect; PopPK, population pharmacokinetic; Vc, central volume of distribution

15.3.3.4 Final Model

Bezlotoxumab observations of pediatric subjects from the final popPK dataset are superimposed over historical adult observations in Figure 6. The final popPK model retains the same structural model as the base PK model, and no additional significant covariates were identified. Bezlotoxumab PK is best described by a two-compartment model with linear, first-order elimination. The parameter estimates for the final covariate model and bootstrap analysis results are listed in Table 41 and Table 42, respectively. The GoF and ETA distribution plots for the final covariate model for all data are shown in Figure 7 and Figure 8, respectively. The VPC plots for the final popPK model by age groups are shown in Figure 9.

Figure 6. Bezlotoxumab Concentrations Vs. Nominal TSLD by Age Groups



Source: Applicant's PopPK Report, Figure 3, page 34
Note: Grey solid lines represent the adult profiles on which the pediatric profiles (black solid lines) are superimposed for 1 to <12 years of age (A) and 12 to <18 years of age (B); data is displayed on a log-normal scale
Abbreviations: PopPK, population pharmacokinetic; TSLD, time since last dose

Table 41. Parameter Estimates for the Updated PopPK Model With Pediatric Data

Parameter (unit)	Previous Parameter estimates	Updated Parameter Estimates	RSE (%)	Shrinkage (%)
V1 (L)	3.42	3.46	0.81	
V2 (L)	3.56	3.55	1.17	
CL (L/h)	0.01168	0.0118	0.21	
Q (L/h)	0.02305	0.0226	0.87	
Error model				
W ERR1-LOGADD	0.182	0.19	2.36	
Covariate effects				
WT on V1, V2	0.477	0.59	3.87	
WT on CL, Q	0.477	0.59	4.73	
ALB on CL	-0.897	-0.92	2.74	
JAPAN on CL	-0.0947	-0.06	45.42	
RACE on CL	0.154	0.17	24.22	
SEX on CL	0.219	0.19	9.84	
ALB on V1	-0.124	-0.13	6.66	
JAPAN on V1	-0.144	-0.1	27.65	
SEX on V1	0.243	0.21	8.14	
Interindividual variability				
1 IIV-V1 (%)	10.5	10.1	13.9	28.1
2 IIV-V2 (%)	0	0	FIXED	
3 IIV-CL (%)	28.1	28.3	1.865	3.2
4 IIV-Q (%)	0	0	FIXED	
5 IIV-EPS (%)	57.3	56.9	3.625	0.0

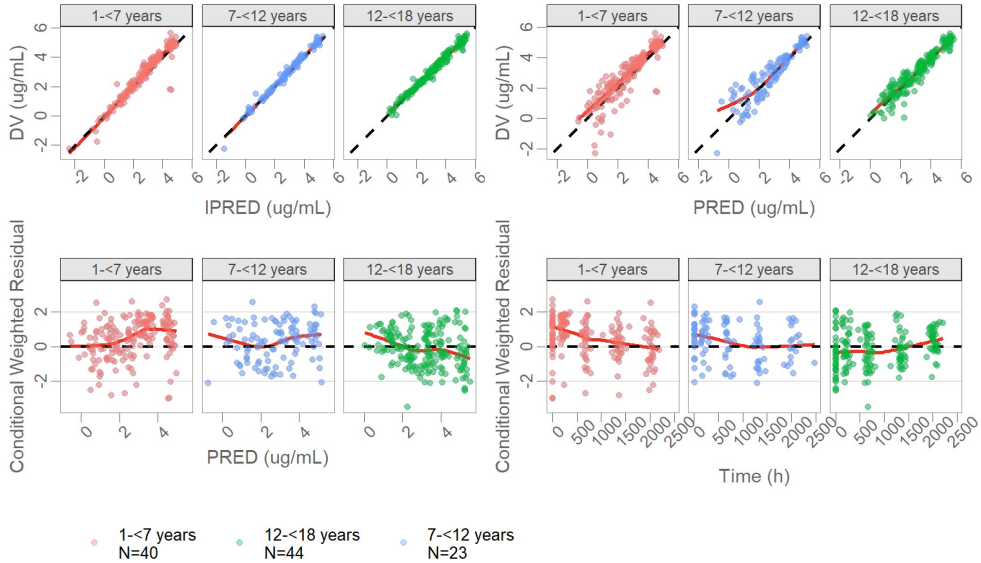
Source: Applicant's PopPK Report, Table 5, page 36
Note: V1 = Vc and V2 = Vp
Abbreviations: ALB, albumin; CL, clearance; EPS, proportional residual error; IIV, inter-individual variability; PopPK, population pharmacokinetic; RSE, relative standard error; Vc, central volume of distribution; Vp, peripheral volume of distribution; WT, weight

Table 42. Parameter Estimates and Bootstrap Analysis Results

Parameter (unit)	Updated Parameter Estimates	Bootstrap Results excluding terminated runs Median [95%CI]	Bootstrap Results including terminated runs Median [95%CI
V1 (L)	3.4600	3.46[3.39-3.53]	3.46[3.39-3.53]
V2 (L)	3.5500	3.55[3.46-3.65]	3.55[3.46-3.65]
CL (L/h)	0.0118	0.0118[0.0115-0.012]	0.0118[0.0115-0.012]
Q (L/h)	0.0226	0.0225[0.0212-0.0241]	0.0226[0.0212-0.0241]
Error model			
W ERR1-LOGADD	0.19	0.19[0.18-0.19]	0.19[0.18-0.19]
Covariate effects			
WT on V1, V2	0.5900	0.59[0.55-0.64]	0.59[0.55-0.64]
WT on CL, Q	0.5900	0.59[0.54-0.65]	0.59[0.53-0.64]
ALB on CL	-0.9200	-0.92[-0.99—0.84]	-0.92[-0.99--0.84]
JAPAN on CL	-0.0600	-0.06[-0.11-0]	-0.06[-0.11-0]
RACE on CL	0.1700	0.17[0.1-0.26]	0.17[0.1-0.25]
SEX on CL	0.1900	0.19[0.15-0.23]	0.19[0.15-0.23]
ALB on V1	-0.1300	-0.13[-0.14—0.11]	-0.13[-0.14--0.11]
JAPAN on V1	-0.1000	-0.1[-0.16—0.04]	-0.1[-0.16--0.04]
SEX on V1	0.2100	0.21[0.17-0.25]	0.21[0.18-0.24]
Interindividual variability			
1 IIV-V1 (%)	0.0100	9.8[7.61-12.88]	9.89[7.61-12.93]
2 IIV-V2 (%)	0.0000	*NA*	NA
3 IIV-CL (%)	0.0800	28.24[27.06-29.78]	28.25[27.12-29.73]
4 IIV-Q (%)	0.0000	*NA*	NA
5 IIV-EPS (%)	0.3200	32.51[27.57-37.13]	32.49[27.69-37.48]

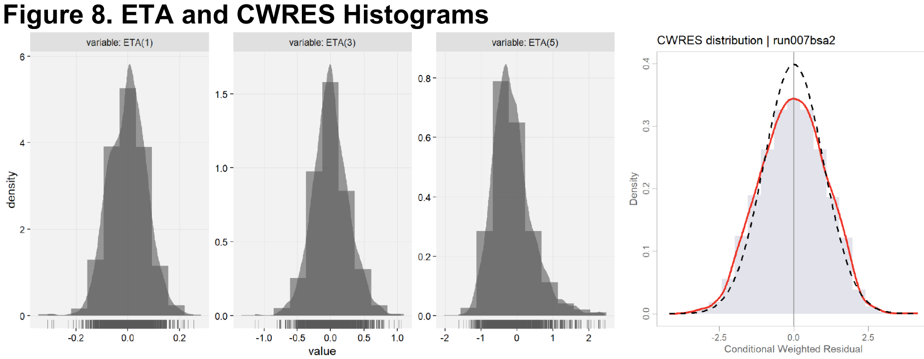
Source: Applicant's PopPK Report, Table 7, page 41
Note: V1 = Vc and V2 = Vp
Abbreviations: ALB, albumin; CI, confidence interval; CL, clearance; EPS, proportional residual error; IIV, inter-individual variability; NA, not applicable; PopPK, population pharmacokinetic; RSE, relative standard error; Vc, central volume of distribution; Vp, peripheral volume of distribution; WT, weight

Figure 7. GoF Plots for the Final PopPK Model by Age Groups



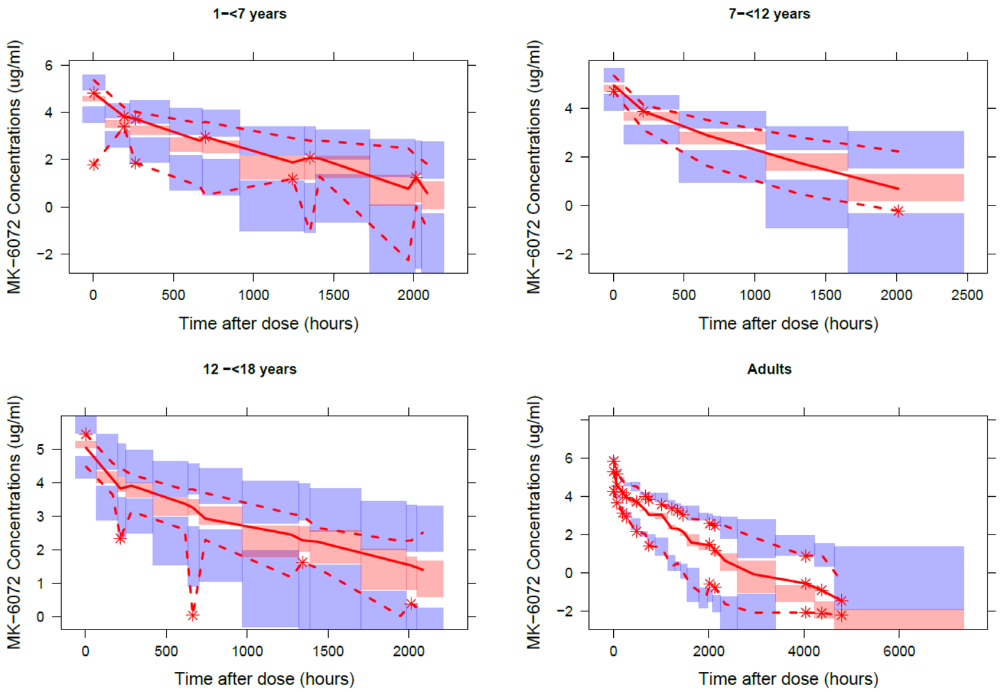
Source: Applicant's PopPK Report, Figure 5, page 39
Note: Dots, data points; solid lines, LOESS lines
Abbreviations: DV, observed serum concentration; GoF, goodness of fit; LOESS, locally estimated scatterplot smoothing; PopPK, population pharmacokinetic; PRED, predicted serum concentration

Figure 8. ETA and CWRES Histograms



Source: Applicant's PopPK Report, Figure 6, page 39
Abbreviations: CWRES, conditional weighted residuals; ETA, inter-individual random effect; PopPK, population pharmacokinetic

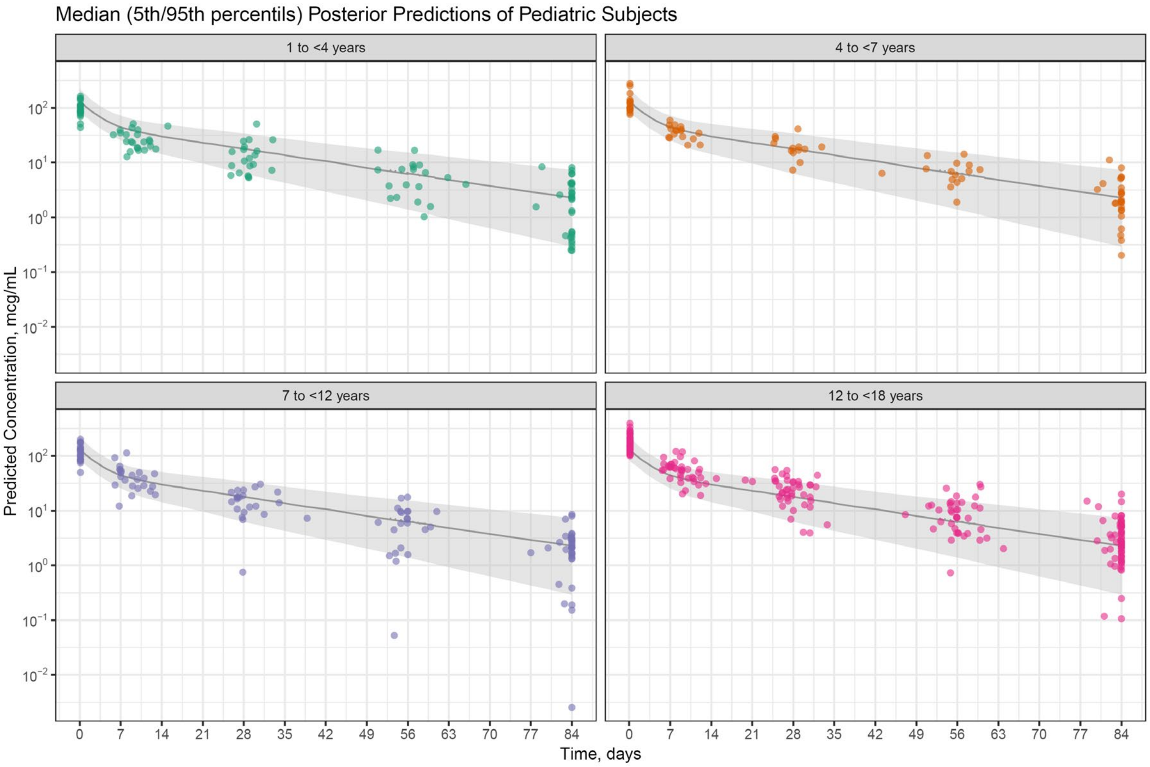
Figure 9. VPC by Age Groups



Source: Applicant's PopPK Report, Figure 7, page 40
Abbreviations: PopPK, population pharmacokinetic; VPC, visual predictive check

Reviewer Comment: *Generally, the final popPK model is acceptable in describing the disposition of bezlotoxumab across pediatric subjects (and adult subjects). This is demonstrated through reasonably precise parameter estimates (all RSEs were below <27.65%; except that Japanese origin on CL had an RSE of 45%) and relatively low between-subject variability (<28.3% except that a relatively high IIV of 56.9% was estimated for the residual error term) for Vc and CL. Parameter estimates are also supported by the bootstrapping procedure (Table 42). GoF plots, ETA distribution, and VPC also supported that the popPK model captures the central tendency of the PK data despite the relatively wide between-subject variability as shown in Figure 6. Lastly, when stratifying by age increments of 1 to <4, 4 to <7, 7 to <12, and 12 to <18 years of age (as shown in Figure 10), the central tendency of model predictions is also shown. However, a trend of slight underprediction (median and lower quantile) is observed in the VPC plot for 1 to <7 years of age.*

Figure 10. Median (5th/95th Percentiles) Bayesian Posterior Predictions of Pediatric Subjects



Source: Reviewer's independent analysis using the final popPK model and individual parameter estimates
Note: Semi-log scale
Abbreviations: popPK model, population pharmacokinetic model

While the general performance of the popPK model is considered reasonable in characterizing bezlotoxumab PK on a population level, issues pertinent to underpredictions in the younger age group warrants further investigation. The following observations are noted and are consistent with the Applicant's reporting:

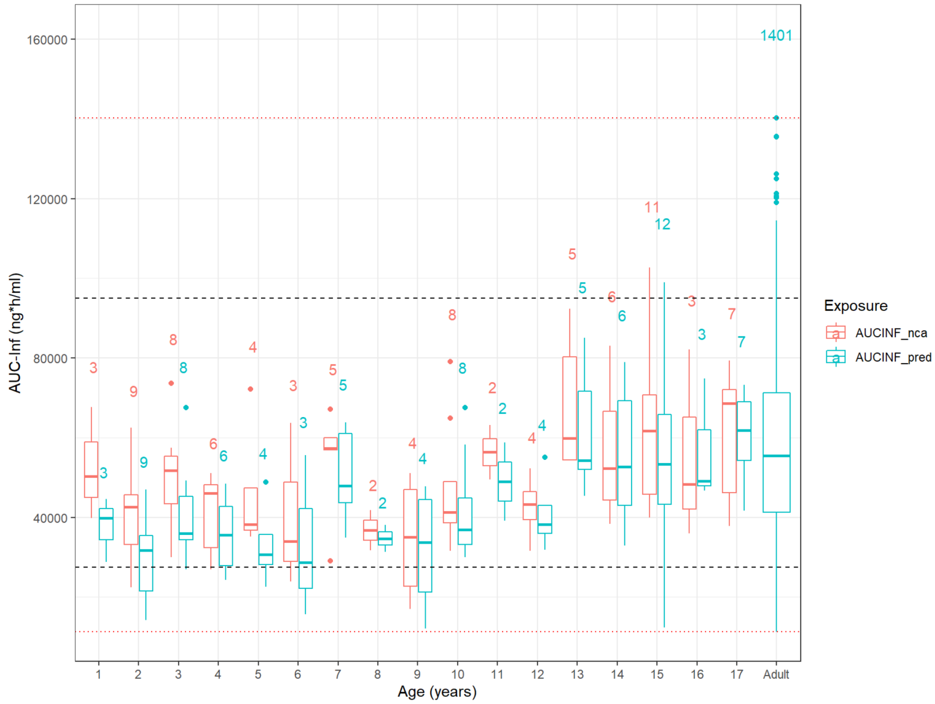
- *As shown in Table 43, the numeric difference of NCA-derived versus model-derived (using individual parameters) is largest in the 1 to <7 years of age group versus other age groups.*
- *Underprediction of popPK model appears more relevant for those 3 years of age or below (Figure 11, Figure 13); when stratifying by weight groups, this trend appears in those weighing at or under 20 kg (Figure 12).*
- *Individual CL parameter from the popPK model is higher than those from NCA methodology*

Table 43. Summaries of PopPK Model and NCA Derived $AUC_{0\text{-}inf}$ by Age Groups

PK Parameter	Age Group (years)	Sample Size	NCA GeoMean	PopPK GeoMean	Relative Mean SE
$AUC_{0\text{-}inf}$ (ng*h/mL)	1 to <7	33	42852	33285	22.3%
	7 to <12	21	43647	39425	9.7%
	12 to <18	37	56099	52407	6.6%

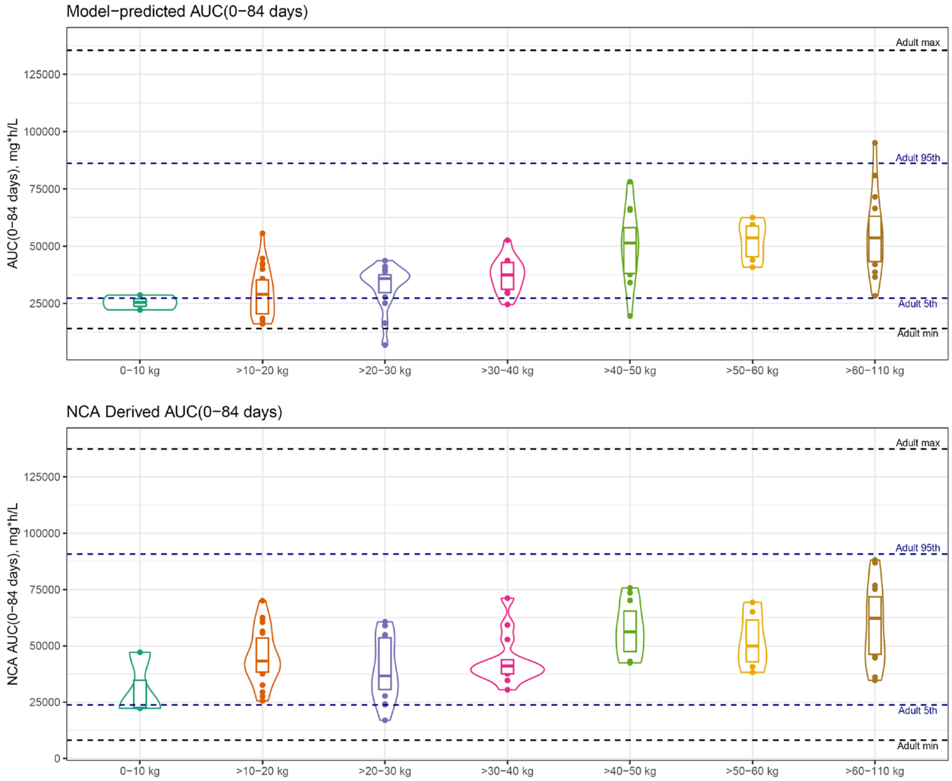
Source: Applicant's PopPK Report, adopted from Table 8, page 43
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from 0 to infinity; GeoMean, geometric mean; NCA, noncompartmental analysis; PopPK, population pharmacokinetic; SE, standard error expressed as a percentage

Figure 11. Boxplots for $AUC_{0\text{-}inf}$ Derived From NCA Vs. Model Predictions by Age



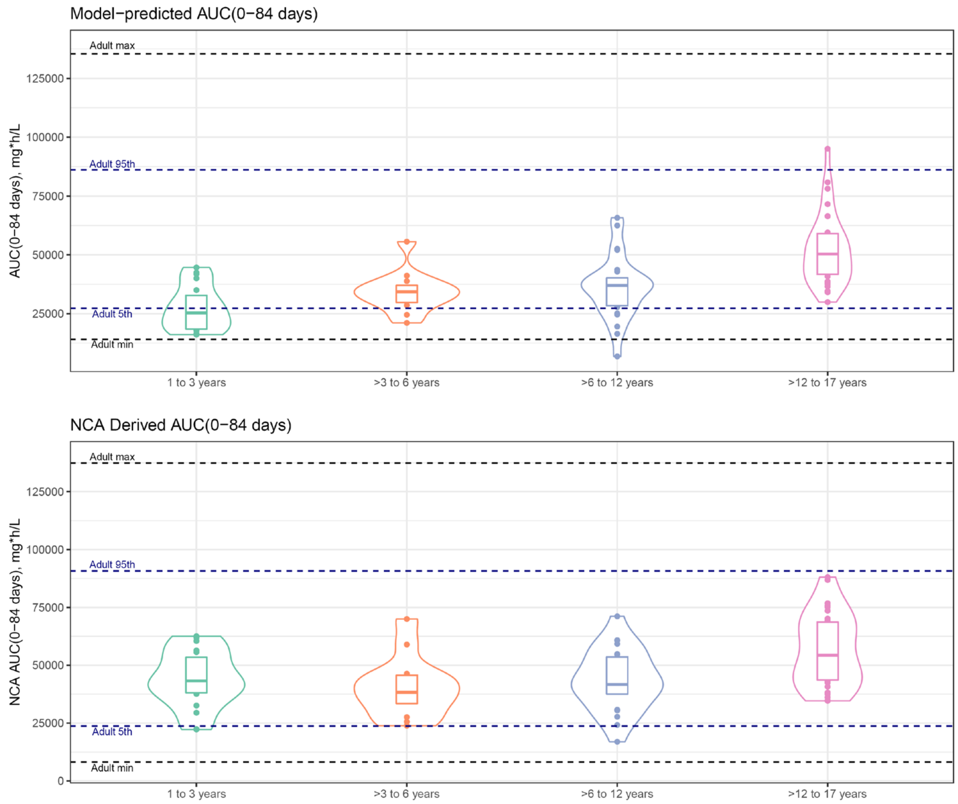
Source: Applicant's PopPK Report, Figure 9, page 45
Note: Black dashed lines represent the 5th and 95th percentiles of the adult post hoc exposures.; red dotted lines represent the minimum and maximum post hoc exposures; for boxplots, the lower, middle, and upper hinges correspond to the 25^{th}, 50^{th} and 75^{th} percentiles.
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from 0 to infinity; NCA, noncompartmental analysis; PopPK, population pharmacokinetic; Pred, predicted serum concentration

Figure 12. Violin Plots for $AUC_{0\text{-}84D}$ Derived From NCA and Model Predictions by Weight Groups



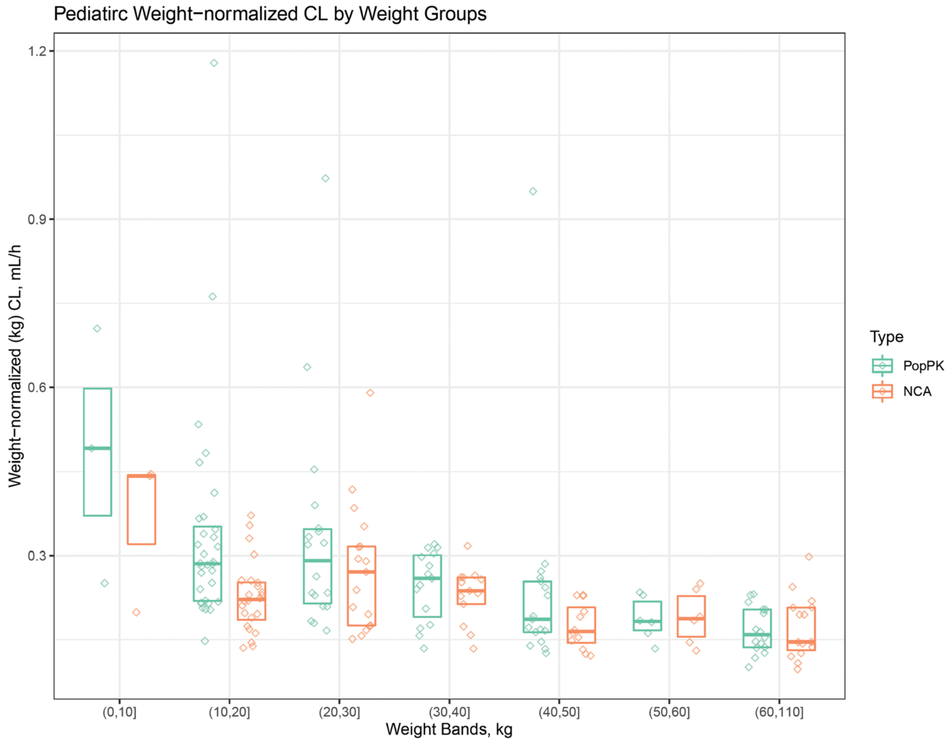
Source: Reviewer's independent analysis
Note: Black dashed lines represent posterior-predicted and NCA derived maximum and minimum of adult exposures; navy dashed lines represent posterior-predicted and NCA derived 5th and 95th percentile of adult exposures; for NCA exposures derivation, only subjects with 4 or more PK samples were retained for NCA analysis and to derive $AUC_{0\text{-}84D}$; for boxplots, the lower, middle, and upper hinges correspond to the 25th, 50th and 75th percentiles.
Abbreviations: $AUC_{0\text{-}84D}$, AUC from time zero to day 84; max, maximum; min, minimum; NCA, noncompartmental analysis

Figure 13. Violin Plots for $AUC_{0\text{-}84D}$ Derived From NCA and Model Predictions by Age Groups



Source: Reviewer's independent analysis
Note: Black dashed lines represent posterior-predicted and NCA derived maximum and minimum of adult exposures; navy dashed lines represent posterior-predicted and NCA derived 5th and 95th percentile of adult exposures; for NCA exposures derivation, only subjects with 4 or more PK samples were retained for NCA analysis and to derive $AUC_{0\text{-}84D}$; for boxplots, the lower, middle, and upper hinges correspond to the 25th, 50th and 75th percentiles
Abbreviations: $AUC_{0\text{-}84D}$, AUC from time zero to day 84; max, maximum; min, minimum; NCA, noncompartmental analysis

Figure 14. Weight-Normalized CL by Weight Groups



Source: Reviewer's independent analysis
Abbreviations: CL, clearance; PopPK, population pharmacokinetics; NCA, noncompartmental analysis

Reviewer Comment: *The Applicant attributed this trend of underprediction in the younger pediatric subjects to CL maturation in the younger participants. As such, variants of maturation functions were modeled in the Applicant's model refinement (methodologies are further detailed in Section 5.2.4 in Applicant's PopPK report). The Reviewer considers this an acceptable approach given the age groups being studied. The Reviewer also conducted additional model analyses by making modifications to the residual error model for the younger subjects (not shown here); however, none of the analyses by the Applicant nor the Reviewer showed an appreciable improvement in model fit (i.e., increase in OFV) compared to the final popPK model. Lastly, the Applicant notes that limited sample size hinders the estimation of precise assessment of CL maturation function, which the Reviewer agrees with. Figure 14 shows that the popPK model tends to estimate higher individual CL values in the younger (and those who weigh less in this study) subjects than those estimated by NCA.*

Overall, available pediatric PK data and analyses support the current dosing regimen for pediatric patients and ultimately the exposure comparison approach and efficacy extrapolation for the pediatric indication of 1 to 17 years of age with the following key points:

- *While underpredictions are observed for the younger pediatric subjects, the popPK model is qualified based on the aforementioned model diagnostics and discussions. As such, model predictions (i.e., individual exposure) serve as a conservative measure for exposure* *comparison approach, and a majority of the pediatric $AUC_{0\text{-}84D}$ fall within 5^{th} to 95^{th} percentiles of the reference adult exposures (derived from model predictions).*

- *NCA data from 90 pediatric subjects serves as an additional layer of confirmation that $AUC_{0\text{-}84D}$ remain comparable between pediatric subjects and historical adults.*
- *A total of 4 pediatric subjects met protocol-defined "clinical failure" in the bezlotoxumab arm of the mITT (modified intent-to-treat) population (n=104 for treatment; n=35 for placebo). Of those subjects, 3 contributed PK data. When plotting NCA derived $AUC_{0\text{-}INF}$ against baseline body weight quartiles as an exploratory measure (not shown), there is no clear relationship between bezlotoxumab exposure and clinical failure (i.e., flat relationship); however, one must cautiously interpret this finding, considering the limited number of events and pediatric subjects.*
- *Given the relatively flat exposure-response relationship established in the adult study (refer to the Clinical Pharmacology Review dated April 28, 2016), a slightly lower exposure that is mostly within the bounds of the reference likely have no meaningfully negative effect of efficacy in the pediatric population in conjunction with appropriate CDI antibiotic therapy.*

Other Evidence to Consider

- *In the pediatric study, the treatment group included subjects with neutropenia (52.9%), active hematologic malignancy (38.5%), and malignant solid tumor (30.8%). These underlying conditions (i.e., inflammatory status) may predispose subjects to an altered proteolytic degradation, a prime elimination pathway for mAbs. Consequently, proteolytic clearance of therapeutically used mAbs may differ depending on protein turnover rate secondary to differences inflammatory status (Ryman and Meibohm 2017).*

15.4 Additional Clinical Safety Analyses

A full listing of the SAEs reported during the MODIFY III is provided in Table 44.

Table 44. Summary of All Treatment-Emergent SAEs

System Organ Class Preferred Term	Bezlotoxumab (N=107) n	(%)	Placebo (N=36) n	(%)
Infections and infestations	32	(29.9)	13	(36.1)
Staphylococcal bacteremia	4	(3.7)	1	(2.8)
Sepsis	3	(2.8)	1	(2.8)
Septic shock	3	(2.8)	0	(0.0)
Urinary tract infection	3	(2.8)	2	(5.6)
Bacteremia	2	(1.9)	0	(0.0)
Candida sepsis	2	(1.9)	0	(0.0)
Covid-19	2	(1.9)	0	(0.0)
Klebsiella bacteremia	2	(1.9)	0	(0.0)
Pneumonia	2	(1.9)	0	(0.0)
Acinetobacter sepsis	1	(0.9)	0	(0.0)

System Organ Class Preferred Term	Bezlotoxumab (N=107) n	(%)	Placebo (N=36) n	(%)
Adenovirus infection	1	(0.9)	0	(0.0)
Bacterial sepsis	1	(0.9)	0	(0.0)
Clostridium difficile colitis	1	(0.9)	2	(5.6)
Coronavirus infection	1	(0.9)	1	(2.8)
Cytomegalovirus infection	1	(0.9)	0	(0.0)
Enterobacter bacteremia	1	(0.9)	1	(2.8)
Escherichia bacteremia	1	(0.9)	0	(0.0)
Fungal sepsis	1	(0.9)	0	(0.0)
Gastroenteritis	1	(0.9)	0	(0.0)
Neutropenic infection	1	(0.9)	0	(0.0)
Neutropenic sepsis	1	(0.9)	0	(0.0)
Nosocomial infection	1	(0.9)	0	(0.0)
Pharyngotonsillitis	1	(0.9)	0	(0.0)
Pneumonia aspiration	1	(0.9)	0	(0.0)
Pseudomonal bacteremia	1	(0.9)	0	(0.0)
Pseudomonal sepsis	1	(0.9)	0	(0.0)
Serratia bacteremia	1	(0.9)	0	(0.0)
Soft tissue infection	1	(0.9)	0	(0.0)
Streptococcal bacteremia	1	(0.9)	0	(0.0)
Urosepsis	1	(0.9)	0	(0.0)
Clostridium difficile infection	0	(0.0)	1	(2.8)
Gastroenteritis sapovirus	0	(0.0)	1	(2.8)
Otitis media acute	0	(0.0)	1	(2.8)
Pharyngitis streptococcal	0	(0.0)	1	(2.8)
Pneumonia fungal	0	(0.0)	1	(2.8)
Respiratory syncytial virus infection	0	(0.0)	1	(2.8)
Staphylococcal sepsis	0	(0.0)	1	(2.8)
Viral infection	0	(0.0)	1	(2.8)
Vulval cellulitis	0	(0.0)	1	(2.8)
Blood and lymphatic system disorders	28	(26.2)	12	(33.3)
Febrile neutropenia	22	(20.6)	11	(30.6)
Thrombocytopenia	3	(2.8)	1	(2.8)
Agranulocytosis	1	(0.9)	0	(0.0)
Bone marrow failure	1	(0.9)	0	(0.0)
Leukocytosis	1	(0.9)	0	(0.0)
Neutropenia	1	(0.9)	0	(0.0)

System Organ Class Preferred Term	Bezlotoxumab (N=107) n	Bezlotoxumab (N=107) (%)	Placebo (N=36) n	Placebo (N=36) (%)
Gastrointestinal disorders	7	(6.5)	3	(8.3)
Abdominal pain	3	(2.8)	0	(0.0)
Anal inflammation	1	(0.9)	0	(0.0)
Intussusception	1	(0.9)	0	(0.0)
Nausea	1	(0.9)	0	(0.0)
Stomatitis	1	(0.9)	1	(2.8)
Pancreatitis	0	(0.0)	1	(2.8)
Vomiting	0	(0.0)	1	(2.8)
General disorders and administration site conditions	5	(4.7)	4	(11.1)
Pyrexia	4	(3.7)	3	(8.3)
Mucosal inflammation	1	(0.9)	0	(0.0)
Asthenia	0	(0.0)	1	(2.8)
Nervous system disorders	3	(2.8)	1	(2.8)
Loss of consciousness	1	(0.9)	0	(0.0)
Neurotoxicity	1	(0.9)	0	(0.0)
Nystagmus	1	(0.9)	0	(0.0)
Seizure	1	(0.9)	0	(0.0)
Headache	0	(0.0)	1	(2.8)
Immune system disorders	2	(1.9)	0	(0.0)
Drug hypersensitivity	1	(0.9)	0	(0.0)
Graft versus host disease	1	(0.9)	0	(0.0)
Investigations	2	(1.9)	0	(0.0)
C-reactive protein increased	1	(0.9)	0	(0.0)
Sars-cov-2 test positive	1	(0.9)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(1.9)	2	(5.6)
Acute myeloid leukemia	1	(0.9)	0	(0.0)
Leukemia	1	(0.9)	0	(0.0)
Neoplasm progression	0	(0.0)	1	(2.8)
Neuroblastoma	0	(0.0)	1	(2.8)
Respiratory, thoracic and mediastinal disorders	2	(1.9)	0	(0.0)
Acute respiratory distress syndrome	1	(0.9)	0	(0.0)
Respiratory tract oedema	1	(0.9)	0	(0.0)
Hepatobiliary disorders	1	(0.9)	1	(2.8)
Biliary-bronchial fistula	1	(0.9)	0	(0.0)
Cholecystitis	0	(0.0)	1	(2.8)
Metabolism and nutrition disorders	1	(0.9)	1	(2.8)
Hypokalemia	1	(0.9)	0	(0.0)
Hyponatremia	1	(0.9)	0	(0.0)
Dehydration	0	(0.0)	1	(2.8)
Musculoskeletal and connective tissue disorders	1	(0.9)	0	(0.0)
Myopathy	1	(0.9)	0	(0.0)

System Organ Class Preferred Term	Bezlotoxumab (N=107) n	(%)	Placebo (N=36) n	(%)
Vascular disorders	1	(0.9)	1	(2.8)
Venoocclusive disease	1	(0.9)	1	(2.8)
Injury, poisoning and procedural complications	0	(0.0)	1	(2.8)
Allergic transfusion reaction	0	(0.0)	1	(2.8)
Renal and urinary disorders	0	(0.0)	1	(2.8)
Hematuria	0	(0.0)	1	(2.8)

Source: OCS Analysis Studio, Safety Explorer. Filters: TRT01A = "Bezlotoxumab" and TRTFL = "Y" (Bezlotoxumab); TRT01A = "Placebo" and TRTFL = "Y" (Placebo); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).
Abbreviations: N, number of subjects; n, number of subjects in category; SAE, serious adverse event

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER W KIM
05/25/2023 02:18:31 PM