14 December 2023
EMA/CHMP/534896/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zinplava

International non-proprietary name: Bezlotoxumab

Procedure No. EMEA/H/C/004136/II/0037

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation/Term	Definition
λz	the first order rate constant associated with the terminal (log-linear) portion of the curve
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANOVA	analysis of variance
APaT	all participants as treated
AST	aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-inf	area under the concentration-time curve from 0 to infinity
Bezlo	bezlotoxumab, MK-6172
BMI	body mass index
BP	blood pressure
CDI	*Clostridium (Clostridioides) difficile* infection
C. difficile	*Clostridium (Clostridioides) difficile*
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CLSI	Clinical and Laboratory Standards Institute
Cmax	maximum observed concentration
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	case report form
CSR	clinical study report
CV%	coefficient of variation
DILI	drug-induced liver injury

Abbreviation/Term	Definition
DNA	deoxyribonucleic acid
ECG	electrocardiograms
ECI	events of clinical interest
ECL	electrochemiluminescence
ECV	epidemiological cutoff value
EE	efficacy evaluable
EEA	European Economic Area
EMA	European Medicines Agency
ERC	ethics review committee
EUCAST	European Committee on Antimicrobial Susceptibility Testing
Exp	experimental
FBR	future biomedical research
FDA	Food and Drug Administration
FPE	first participant enrolled
GCP	Good Clinical Practice
GM	geometric mean
GMR	geometric mean ratio
GPvP	Good Pharmacovigilance Practice
HR	heart rate
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immune globulin
LAR	legally acceptable representative
LLOQ	lower limit of quantitation
LPLV	last participant last visit
mAb	monoclonal antibody
Max	maximum
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation/Term	Definition
mITT	modified intent-to-treat
Min	minimum
MODIFY I	Phase 3 study (MK-3415A P001)
MODIFY II	Phase 3 study (MK-3415A P002)
MODIFY III	Phase 3 study (MK-6072 P001)
MSD	Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA
N	number of observations
NAb	neutralizing antibody
NIMP	noninvestigational medicinal product
pAb	polyclonal antibody
PCR	polymerase chain reaction
PI	principal investigator
PK	pharmacokinetic(s)
PP	per-protocol (population)
QA	quality assurance
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
SDR	source data review
SE	standard error
SOC	standard of care
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
Tmax	time to maximum concentration
t1/2	terminal half-life
UBM	unformed bowel movements
ULN	upper limit of normal
US	United States
Vd	apparent volume of distribution during elimination phase
WOCBP	Woman of childbearing potential

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 7 March 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of the paediatric population (1 to 18 years of age) for ZINPLAVA, based on final results from study MK-6072-001 (MODIFY III) listed as a category 3 study in the RMP; this is a phase 3, randomised, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of a single infusion of bezlotoxumab in paediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for *Clostridioides difficile* infection (CDI). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.3 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0135/2022) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP

was completed. The PDCO issued an opinion on

compliance for the PIP P/0135/2022.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	7 March 2023
Start of procedure	25 March 2023
CHMP Rapporteur Assessment Report	17 May 2023
PRAC Rapporteur Assessment Report	24 May 2023
PRAC members comments	31 May 2023
Updated PRAC Rapporteur Assessment Report	1 June 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	16 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	14 September 2023
PRAC Rapporteur Assessment Report	15 September 2023
PRAC members comments	20 September 2023
Updated PRAC Rapporteur Assessment Report	21 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	2 October 2023
Updated CHMP Rapporteur Assessment Report	5 October 2023
Request for supplementary information (RSI)	12 October 2023
PRAC Rapporteur Assessment Report	20 November 2023
PRAC members comments	22 November 2023
Updated PRAC Rapporteur Assessment Report	23 November 2023
CHMP Rapporteur Assessment Report	29 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	4 December 2023
Updated CHMP Rapporteur Assessment Report	7 December 2023
Opinion	14 December 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Clostridioides difficile, is an anaerobic, spore-forming gram-positive bacillus. Strains that cause disease in humans produce toxins, in particular *C. difficile* toxins A and B. CDI occurs when toxigenic strains proliferate in the lower gastrointestinal tract after disruption of the normal bacterial colonic flora, typically after exposure to antibiotics.

State the claimed the therapeutic indication

Bezlotoxumab is indicated to prevent the recurrence of CDI in adult patients who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence. This application provides data to support expanding the use of bezlotoxumab to include paediatric patients one year of age and older. The approved dosage regimen of bezlotoxumab in adult patients is 10 mg/kg administered as a single IV infusion. The proposed dosage regimen for paediatric patients is the same as for adults.

The proposed amended indication statement reads:

> *ZINPLAVA is indicated for the prevention of recurrence of* Clostridioides difficile *infection (CDI) in adult* ***and paediatric patients 1 year of age and older*** *at high risk for recurrence of CDI (see sections 4.2, 4.4 and 5.1).*

Epidemiology and risk factors

The incidence, severity, rate of complications (e.g., ileus, toxic megacolon), and mortality of CDI in adults have increased dramatically in the US, Canada, and Europe over the last 10-15 years [Goorhuis, Abraham, et al 2008] [Gravel, Denise, et al 2009] [Loo, Vivian G., et al 2005] [Loo, Vivian G., et al 2006][McDonald, L. Clifford, et al 2005] [Pepin, Jacques, et al 2005]. Similarly, CDI incidence rates in paediatric patients have increased over time [Kim, Jason, et al 2008] [Zilberberg, M. D., et al

The risk factors for CDI in paediatric patients appear similar to those for adults (e.g., antibiotic use, multiple antibiotics use, and longer duration of hospital stay). In paediatric patients, CDI is also strongly associated with additional factors, namely malignancy, inflammatory bowel disease (IBD), and immune suppression [Pant, Chaitanya, et al 2013] [Hojsak, I., et al 2012] [Banaszkiewicz, Aleksandra, et al 2012] [Enoch, D. A., et al 2011]. The CDI risk appears to be highest in paediatric patients with malignancy [Enoch, D. A., et al 2011] [de Blank, P., et al 2013] [Price, Victoria, et al 2013] [Tai, E., et al 2011]. A case control study identified additional risk factors for paediatric CDI that include solid organ transplant, presence of gastrostomy or jejunostomy tube, receipt of fluoroquinolones, and lack of prior hospitalization; however, the last of these may be a result of control subjects who were hospitalized [Sandora, T. J., et al 2011]. In children, the majority of cases of CDI are community-onset or community-acquired [McFarland, L. V., et al 2016] [Lo Vecchio, A., et al 2016].

Aetiology and pathogenesis

CDI occurs when toxigenic strains of *C. difficile*, either endogenous to the colon or exogenously acquired, flourish after disruption of the normal bacterial colonic flora, typically following exposure to antibiotics that alter the endogenous micro-ecology of the gut, and thus lead to clinically significant disease.

Clinical presentation, diagnosis and prognosis

Symptoms of paediatric CDI include fever, profuse diarrhoea, abdominal tenderness, abdominal distension, leucocytosis, volume depletion, electrolyte imbalance, and occasionally, pseudomembranous colitis. Most cases of paediatric CDI are typically mild in severity and self-limiting in nature. However, moderate to severe CDI does occur in paediatric patients and accumulating evidence indicates that hospital-onset paediatric CDI is associated with increased risk of death, longer length of stay, and higher costs as compared to community-onset CDI in children.

Similar to adults, rCDI occurs in paediatric patients. This is typically due to further acquisition of another strain of *C. difficile* or persistence of the same pathogenic strain in the gut despite treatment, in particular in the form of highly antibiotic-resistant bacterial spores. RCDI within 8 weeks of a previously successfully treated CDI has been reported in 10.8 to 34.4% of paediatric cases.

The laboratory diagnosis of CDI requires the demonstration of toxigenic *C. difficile* or its toxins in stool. A number of different tests are used, including enzyme-linked immunoassays (EIAs) for toxins A and B; cell culture cytotoxicity assay; anaerobic culture followed by toxin detection; nucleic acid amplification tests using polymerase chain reaction (PCR), which detects the gene for toxin B; and EIA for the *C. difficile* common antigen glutamate dehydrogenase, which is typically followed by either a toxin test or a PCR test [Crobach, M. J., et al 2016].

Management

Treatment of paediatric patients with moderate to severe CDI typically involves discontinuation of predisposing antibiotics, supportive measures, and initiating antimicrobial therapy directed against *C. difficile* [Cooperstock, M. S., et al 2012]. Both metronidazole and oral vancomycin have been used as standard-of-care regimens to treat paediatric CDI [McFarland, L. V., et al 2016] [American Academy of Paediatrics 2015]. Fidaxomicin is a newer antibiotic, which received approval in 2011 in the US and other countries for treatment of CDI in adults; however, its safety and efficacy have not yet been established in paediatric patients.

One of the key challenges in the clinical management of CDIs in adults and children is to reduce the incidence of recurrent CDI; such recurrences in paediatric patients have been treated with tapered/pulsed administration of oral vancomycin, vancomycin followed by rifaximin, intravenous (IV) immunoglobulin, and therapy with other microorganisms, including fecal microbiota transplantation (FMT) [Kelly, Ciaran P. and LaMont, J. Thomas 2008]. The available limited data for paediatric CDI recurrence rates ranges from 7.5% to 38%, which is similar to that seen in adults [Lo Vecchio, A., et al 2016] [Kelsen, J. R., et al 2011] [Mezoff, E., et al 2011].

2.1.2. About the product

Bezlotoxumab (MK-6072) is a fully human monoclonal antibody (mAb) that binds to and neutralizes *C. difficile* toxin B.

Bezlotoxumab is currently approved for use in adults for the reduction (United States) or prevention (European Union) of CDI recurrence in patients who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

Bezlotoxumab does not have antimicrobial activity and does not take the place of antibiotic therapy for CDI. Moreover, bezlotoxumab does not impact the initial efficacy of the antibiotics that are used to treat CDI because it is administered after the toxins have already caused damage to the gut lining and after antibiotics have already significantly reduced the amount of toxin present in the colon. When administered concurrently with antibacterial drug treatments for CDI (metronidazole, oral vancomycin, or fidaxomicin in adults), bezlotoxumab prevents recurrent infections by providing passive immunity against *C. difficile* toxin B produced by the outgrowth of persistent or newly acquired spores, thereby preventing new or further damage to the gut epithelium.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

According to the PIP requirement, the applicant developed a vial of 25ml of 25mg/ml concentrate for solution. A summary was provided in Module 2.3.P. This new vial is not authorized yet and therefore a separate type II variation is expected.

Regulatory agency advice was obtained at key points throughout the paediatric development program for bezlotoxumab.

The CHMP notes that the clinical development plan was widely discussed with the FDA. Interactions with EMA were limited to the PIP. No CHMP scientific advice was sought.

2.1.4. General comments on compliance with GCP

The MAH provided a statement that clinical trials carried out outside of the European Union meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The paediatric clinical development program included a single study (MK-6072-001, also referred to as P001). The rationale for the paediatric clinical study was to obtain PK and safety information to support the selection of a dose for paediatric patients that would achieve bezlotoxumab exposures similar to those obtained in adults at the recommended dose (as a single IV infusion at 10 mg/kg). This dose in adults was shown to be efficacious and generally well tolerated in 2 pivotal Phase 3 studies. A paediatric dosing regimen that would provide bezlotoxumab exposures (AUC0-inf) within the clinical comparability bounds (0.6, 1.6) established in adults would, therefore, support extrapolation of adult efficacy to paediatric patients 1 year of age and older based on similarities in disease pathogenesis, the pharmacology of bezlotoxumab, and response to bezlotoxumab infusion

across these age groups.

P001 was a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multisite study evaluating the PK, safety, tolerability, and efficacy to prevent CDI recurrence after a single infusion of bezlotoxumab or placebo in paediatric participants from 1 to <18 years of age, who were receiving antibacterial drug treatment for CDI.

Primary and key secondary endpoints include complete PK, immunogenicity, efficacy, and safety results, which were provided.

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Summary of Clinical Efficacy Studies with Bezlotoxumab

Table 2.7.3-rcdi-peds: 2
Summary of Clinical Efficacy Studies with Bezlotoxumab

<table>
<tr><th>Study Number (Status) [CTD Location] Number of Study Sites (Regions)</th><th>Design</th><th>Number of Participants by Intervention Group</th><th>Study Population (N)</th><th>Efficacy Endpoints[c]</th></tr>
<tr>
<td>P001 (completed) [Ref. 5.3.5.1: P001MK6072]
75 sites (17 countries)</td>
<td>Phase 3, randomized, double-blind placebo-controlled, parallel, multisite study, randomized 3:1 (bezlotoxumab: placebo) and stratified by age cohort to receive a single IV infusion of bezlotoxumab (10 mg/kg) or placebo</td>
<td>Modified intent-to-treat population participants by intervention group

Overall:
Bezlotoxumab: (104 randomized / 104 treated / 100 completed)
Placebo: (35 randomized / 35 treated / 34 completed)
By Age Cohort:
Cohort 1: 12 to <18 years of age
Cohort 2: 1 to <12 years of age
<table>
<tr><th>Age Cohort</th><th>Bezlotoxumab: randomized / treated / completed</th><th>Placebo: randomized / treated / completed</th></tr>
<tr><td>1</td><td>43 / 43 /41</td><td>16 / 16 / 16</td></tr>
<tr><td>2</td><td>61 / 61 / 59</td><td>19 / 19 / 18</td></tr>
</table>
</td>
<td>Male and female participants between the ages of 1 and <18 years with CDI who were receiving antibacterial drug treatment for CDI
Modified intent-to-treat population by intervention group:
<u>Median age (range) years:</u>
Overall bezlotoxumab group: 10.0 (1 to 17)
Overall placebo group: 9.0 (1 to 17)
<u>Sex (M/F):</u>
Overall bezlotoxumab group: 52.9% / 47.1%
Overall placebo group: 51.4% / 48.6%
<table>
<tr><th>Age Cohort</th><th>Bezlotoxumab Median age (range) years</th><th>Placebo Median age (range) years</th></tr>
<tr><td>1: 12 to <18</td><td>15.0 (12 to 17)</td><td>15.0 (12 to 17)</td></tr>
<tr><td>2: 1 to <12</td><td>4.0 (1 to 11)</td><td>4.0 (1 to 11)</td></tr>
</table>
<table>
<tr><th>Age Cohort</th><th>Bezlotoxumab Sex (M / F)</th><th>Placebo Sex (M / F)</th></tr>
<tr><td>1: 12 to <18</td><td>48.8% / 51.2%</td><td>56.3% / 43.8%</td></tr>
<tr><td>2: 1 to <12</td><td>55.7% / 44.3%</td><td>47.4% / 52.6%</td></tr>
</table>
</td>
<td>CDI recurrence[a] within 12 weeks of study medication infusion.

Sustained clinical response[b] over 12 weeks; defined as initial clinical response of the baseline CDI episode AND no CDI recurrence through Week 12.

CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study infusion in the subset of participants at high risk of CDI recurrence.</td>
</tr>
</table>

CDI=*C. difficile* infection; CTD=common technical document; IV=intravenous; M/F = male/female.
[a] CDI recurrence is defined as the development of diarrhea recurrence 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.
[b] Sustained clinical response is defined as a composite of initial clinical response of the baseline CDI episode AND no CDI recurrence through Week 12.
[c] Efficacy endpoints were secondary endpoints.
Source: [Ref. 5.3.5.1: P001MK6072: Table 14.1-3, 14.1-18, 14.1-20] [Ref. 5.3.5.1: P001MK6072: 16.1.1, 16.1.3]

2.3.2. Pharmacokinetics

<u>Bioanalytics</u>

The IV formulation proposed for use in paediatric patients 1 to <18 years of age and used in P001 is identical to that commercially available for use in adults. The bioanalytical method used to assess bezlotoxumab concentrations in P001 was the same as that submitted in the original marketing application. Anti-bezlotoxumab antibodies and NAb were assessed in P001 using validated

bioanalytical methods.

Study P001

Data relevant for this II-procedure informing PK resulted from one Phase 3, randomized, placebo-controlled, parallel group, multisite, double-blind study (P001) evaluating the PK, safety, tolerability, and efficacy in preventing CDI recurrence after a single infusion of bezlotoxumab or placebo in paediatric patients from 1 to <18 years of age who were receiving antibacterial drug treatment for CDI.

The primary PK objective was to characterize the PK of bezlotoxumab in 2 age cohorts of paediatric participants to support dosing recommendations in the paediatric population.

Eligible participants were assigned randomly in a 3:1 ratio to bezlotoxumab 10 mg/kg (N=107) or placebo (N=36), respectively, and were stratified by 2 age cohorts according to the participant's age at the time of randomization (Age Cohort 1: 12 to <18 years of age, Age Cohort 2: 1 to <12 years of age).

The recommended adult dose of 10 mg/kg was evaluated in a two-step procedure. Initially, the dose was evaluated for both age cohorts in Panel A of P001. Secondly, an interim PK analysis was performed to confirm the dose for Panel B. Consequently, all paediatric participants in P001 received a single infusion of bezlotoxumab 10 mg/kg.

A summary of participants included in the per protocol population by panel and age cohort for the prespecified interim PK analyses (Panel A) and final analysis (Panels A and B) and the number of participants in subsets of Age Cohort 2 are provided in the Table 2 below.

Table 2: Summary of P001 Study Participants Included in Pharmacokinetic Analysis

Table 2.7.2-rcdi-peds: 2
Summary of P001 Study Participants Included in Pharmacokinetic Analysis

Age Cohort	Subgroup	Panels A and B		Panel A	
		Participants who received study drug	Participants included in PK analysis	Participants who received study drug	Participants included in PK analysis
1 12 to <18 years	All	45	37	11	9
2 1 to <12 years	All	63	54	17	13
	1 to <7 years	40	33	11	9
	7 to <12 years	23	21	6	4
	1 to <6 years	37	30	11	9
	6 to <12 years	26	24	6	4
Total		108	91	28	22

A total of 17 participants were excluded from the per protocol population including 15 participants who had 3 or less PK samples and 2 participants who only missed the first sample at 2 hour post dose on Day 1

The CHMP noted that the paediatric study P001 included overall N=108 participants who received bezlotoxumab, of whom N=91 were available for PK analysis (4 PK samples per subject). Most of the participants in age cohort 2 (N=63) were aged below 7 years of age (N=40) at a comparable sample size to age cohort 1 (N=45). This imbalance is agreed by the CHMP as most uncertainty in PK is in the youngest age cohort.

Rationale for dose selection and recommendation for the paediatric population

The dose of 10 mg/kg bezlotoxumab applied IV approved for adults was supported by evidence of efficacy and a favourable safety profile demonstrated in 2 Phase 3 studies in adults and was assessed in the context of the original marketing application.

Since bezlotoxumab is acting on an exogeneous target only, it was expected that the exposure range identified as safe and efficacious in adults will result in a similar clinical response in paediatric age groups. The dosing rationale further relied on the assumption that the pathogenesis of CDI, namely overgrowth of toxin-producing *C. difficile* bacteria, is the same in both adult and paediatric patients.

Exposure bridging was focussing on comparison of AUC0-inf (to be in comparability bounds) as the exposure-response relationship between bezlotoxumab AUC0-inf and CDI recurrence in adults was characterized by an Emax relationship, in which exposures achieved following the 10 mg/kg dose are on the maximal response plateau of the exposure-response curve (see Section 5.3.4 for information).

The comparability bounds of (0.6, 1.6) for bezlotoxumab are based on the 10th and 90th percentiles of observed bezlotoxumab AUC0-inf values following administration of a single 10 mg/kg IV infusion of bezlotoxumab alone or as actoxumab + bezlotoxumab in the adult Phase 3 studies. This lower bound is derived from the ratio of MK-6072 AUC0-inf values at the 10th percentile (31,700 µg.h/mL) relative to the median (54,700 µg.h/mL) in a pooled population of CDI patients from the Phase 3 trials. The upper bound is similarly derived from the ratio of MK-6072 AUC0-inf values at the 90th percentile (85,600 µg.h/mL) of the same population relative to the median AUC0-inf.

10 mg/kg dose was anticipated to be appropriate for children and to result in exposures similar to those observed in adults, as being weight adapted and no major additional effects due to age affects or differences in mode of action and pathogenesis of CDI were anticipated.

The rationale for the MAH's chosen extrapolation concept based on exposure bridging is agreed by the CHMP. The pre-specified boundaries of the chosen PK measure (AUC0-inf) were previously agreed.

Exposure bridging was focussing on comparison of AUC0-inf (to be in comparability bounds) as the exposure-response relationship between bezlotoxumab AUC0-inf and CDI recurrence in adults was characterized by an Emax relationship, in which exposures achieved following the 10 mg/kg dose are on the maximal response plateau of the exposure-response curve.

10 mg/kg dose was anticipated to be appropriate for children and to result in exposures similar to those observed in adults, as being weight adapted and no major additional effects due to age affects or differences in mode of action and pathogenesis of CDI were anticipated. This was partly agreed by the CHMP. Since authorization is planned for paediatric subjects down to one year of age, maturation effects might affect the PK of very young patients in addition to weight. This is also indicated in the data and PK analyses conducted and reported. Mean and median exposure including Week 12 observations are below the adult value for all paediatric age/weight groups except for adolescents, with lowest observed exposure for the age group 4 to <7 (47.2% of adult median value) and for the weight group 30 to < 40 kg (52.5% of adult median value). Of note, the age group 4 to <7 would more fit to the weight group 20 to <30 kg. These results and non-linear relationship indicate that weight alone (and per kg dosing) is not predictive of exposure following 10 mg/kg of bezlotoxumab, but there might other factors impacting PK. This is also reflected in the high CV% characterizing adult and paediatric PK metrics. In order to reflect the amount and information content of paediatric PK data, that would serve as confirmation of the extrapolation concept (exposure bridging), Section 5.2 of the SmPC was amended.

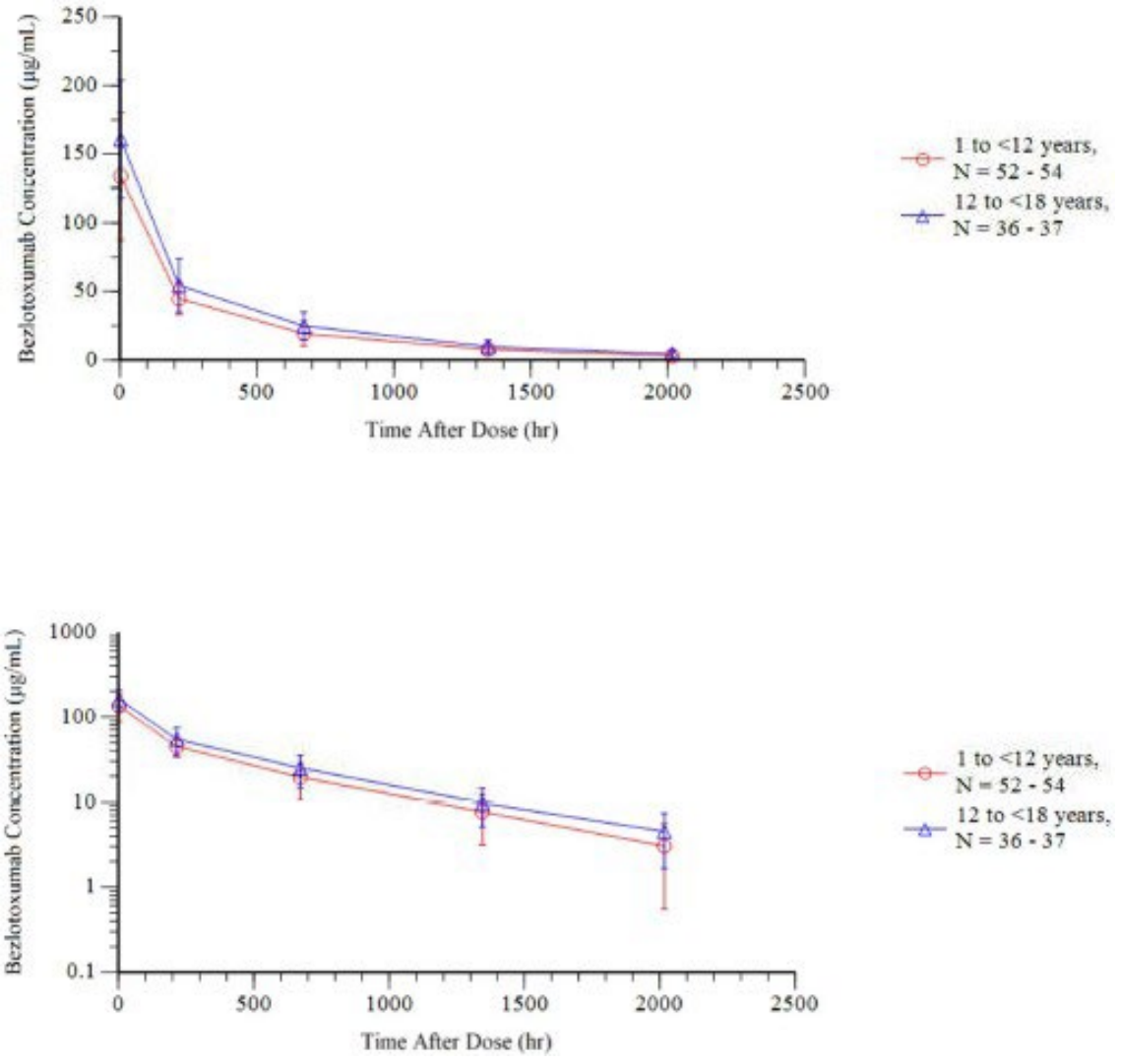
Non-compartmental PK Analysis (NCA)

NCA was based on the per protocol population defined as randomized participants who received a dose of bezlotoxumab and who had ≥4 post-dose evaluable PK samples and who complied with the protocol sufficiently to ensure their data show the effects of study intervention.

The mean concentration-time profiles per age cohort are provided in the figures below. Mean bezlotoxumab serum concentration time profiles following a single IV infusion of 10 mg/kg indicate no apparent differences between age cohorts of paediatric participants, stratified by two age cohorts, from the maximum serum concentration following the infusion on Day 1 through the last serum sample on Day 84.

Figure 1

Figure 2.7.2-rcdi-peds: 2
Arithmetic (SD) Mean Serum Concentration-Time Profiles of Bezlotoxumab Following Administration of a Single Infusion of 10 mg/kg Bezlotoxumab in Pediatric Participants (Top=Linear Scale; Bottom=Semi-log Scale



Based on the NCA, mean AUC0-inf, Cmax, and t1/2 were generally comparable for each age cohort, as presented in the Table 3 below.

Table 3: Summary Statistics for Serum Bezlotoxumab Pharmacokinetic Parameter Values Following Administration of a Single Infusion of 10 mg/kg Bezlotoxumab in Each Age Cohort of Pediatric Participants

Table 2.7.2-rcdi-peds: 3
Summary Statistics for Serum Bezlotoxumab Pharmacokinetic Parameter Values Following Administration of a Single Infusion of 10 mg/kg Bezlotoxumab in Each Age Cohort of Pediatric Participants

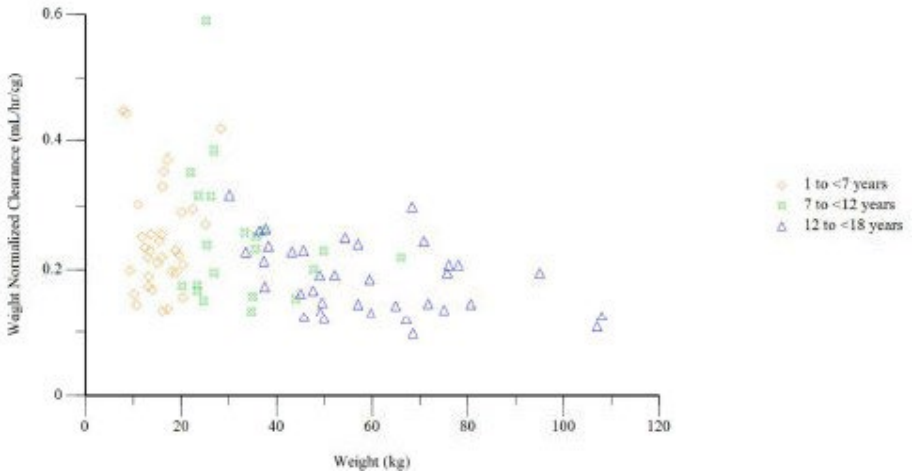
		Age 1 to <12 years		Age 12 to <18 years	
PK Parameter	**Units**	**N**	**GM (%CV)**	**N**	**GM (%CV)**
Cmax	µg/mL	54	129 (32.9)	37	155 (28.2)
Tmax[a]	hr	54	3.00 (2.67 - 285)	37	3.00 (2.67 - 3.47)
AUCinf	hr*µg/mL	54	43200 (35.1)	36	56100 (30.7)
t1/2	day	54	18.1 (33.8)	36	21.7 (22.1)
CL	mL/hr	54	4.66 (59.6)	36	9.99 (33.7)
Vd	L	54	2.93 (54.6)	36	7.50 (33.3)
CL_WN	mL/hr/kg	54	0.233 (34.5)	36	0.178 (31.0)
Vd_WN	L/kg	54	0.146 (28.9)	36	0.134 (29.9)

a= Median (min-max);
CV= Geometric coefficient of variation; GM= Geometric mean; N= Number of participants;
AUCinf= Area under the curve from time zero to infinity; AUClast= Area under the curve from time zero to last quantifiable concentration; AUC0-84D= Area under the curve from time zero till day 84; CL= Clearance; CL_WN= Weight normalized clearance; Cmax= Maximum concentration; Tmax= Time of maximum concentration; t1/2= Terminal half-life; Vd= Volume of distribution; Vd_WN= Weight normalized volume of distribution;

Mean CL and Vd across age groups increased with increasing age, consistent with expectations based on allometric scaling concepts. These differences are reduced with values overlapping when CL and Vd are normalized by bodyweight.

Figure 2

Figure 14.2.1-7
Bezlotoxumab Weight Normalized Clearance vs Body Weight Following Administration of Single Infusion of 10 mg/kg Bezlotoxumab in Pediatric Participants, Age Group 1 to <7 Years (N= 33), 7 to <12 years (N= 21), 12 to <18 years (N=36)



The CHMP noted that Bezlotoxumab pharmacokinetics following a single 10 mg/kg IV infusion in both adult and paediatric populations exhibit characteristics typical for a monoclonal antibody including low clearance and a limited volume of distribution resulting in a predominant elimination phase with terminal half-life of approximately three weeks. The concentration time-profiles for both paediatric age cohorts are considered comparable by the CHMP, with lower exposure indicated for the younger age cohort.

As expected, mean CL and Vd across age groups increased with increasing age, with a remaining trend in higher weight-normalized CL with decreasing age. The CHMP considers that this may be attributed to maturation effects, in particular for the youngest age cohort (1-7 years of age). NCA indicated thus an increasing exposure with age over the paediatric age range.

Population PK Analyses

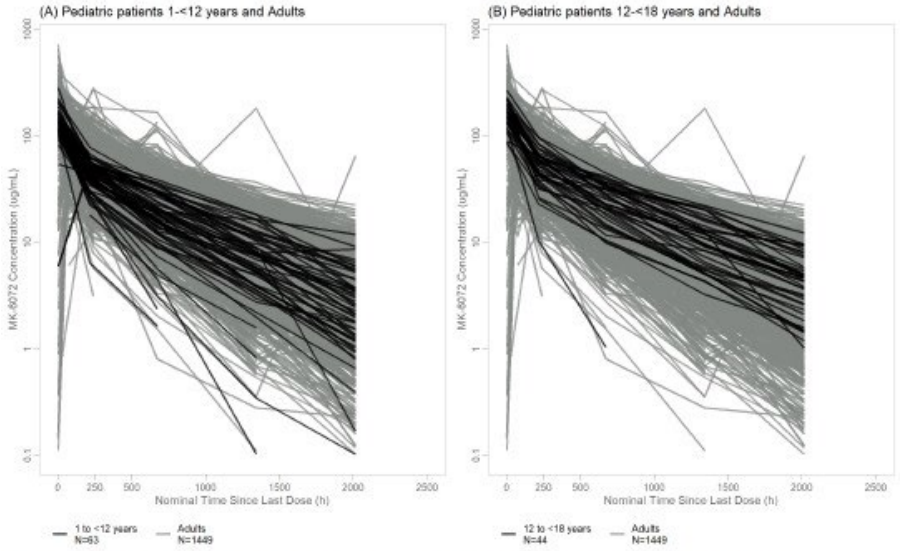
A population modelling approach was used to evaluate the PK of bezlotoxumab in the paediatric patient population, based on a population PK model used previously to support registration of bezlotoxumab in adults. The objective was to characterize bezlotoxumab PK across adult and paediatric CDI patients and support confirmation of paediatric doses that result in PK exposures similar to adults across the range of age and body weight in the intended paediatric population (1 to <18 years).

In the previous analysis, adult data (from N=1622 HV and CDI participants) were described by a 2-compartment model with linear elimination. Weight was included on clearance (CL, Q) and volume (Vc, Vp) terms following an allometric relationship with an estimated exponent of 0.447 for both. Baseline albumin level, sex, and Japanese origin were included as covariates on both CL and Vc. An additional effect of race was identified on CL only.

For the intended analysis, 641 bezlotoxumab serum concentration observations from 107 paediatric participants in P001 following 10 mg/kg were available (see figure below), with no observed bezlotoxumab concentrations from P001 excluded from the analysis.

Figure 3

Figure 3 MK-6072 Concentration versus Nominal Time since Last Dose by Age Group



Notes: 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.
Source: eda-poppk-v5.Rmd

First, external validation of the existing population PK model developed in adults for the newly available paediatric PK data was performed with optional consecutive model-refinement.

Baseline values of continuous and categorical covariates are summarized in the table below for the adult CDI patients who are included in the population PK analysis (Study MK-3415A-P001, Study MK-3415A- P002) as the reference population for exposure comparison, and paediatric patients (Study MK-6072- P001).

Table 4: Summary of Continuous and Categorical 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 (m2)			
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: eda-poppk-v5.Rmd
Note: Numeric columns formatted as mean (SD) and median (CV%) [range].
Abbreviations: CV% = coefficient of variation; GFR = glomerular filtration rate; Max = maximum; Min = minimum; N=number of subjects with available information; SD=standard deviation

A summary of continuous and categorical covariates included in the PK dataset for paediatric participants stratified by age groups (i.e., 1-<7 years, 7-<12 years and 12-<18 years) is provided below.

Table 5: Summary of Continuous and Categorical Covariates for Pediatric Participants Stratified by Age Groups

	1 to < 7 years (N=40)	7 to < 12 years (N=23)	12 to < 18 years (N=44)
CV=coefficient of variation; Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.			
Body weight (kg)			
Mean (SD)	15.7 (4.43)	31.4 (11.8)	56.9 (19.5)
Median (CV%)	15.8 (28.3)	26.9 (37.4)	49.7 (34.3)
[Min, Max]	[7.80, 28.4]	[17.0, 66.0]	[30.1, 108]
Body surface area (m^2)			
Mean (SD)	0.650 (0.140)	1.08 (0.231)	1.60 (0.286)
Median (CV%)	0.654 (21.5)	1.04 (21.3)	1.55 (17.9)
[Min, Max]	[0.414, 0.986]	[0.738, 1.65]	[1.07, 2.22]
Missing	1 (2.5%)	1 (4.3%)	0 (0%)
Sex			
Male	21 (52.5%)	14 (60.9%)	22 (50.0%)

Female	19 (47.5%)	9 (39.1%)	22 (50.0%)
Race			
White	31 (77.5%)	15 (65.2%)	37 (84.1%)
Black or African American	1 (2.5%)	3 (13.0%)	2 (4.5%)
Asian	3 (7.5%)	0 (0%)	0 (0%)
Other	5 (12.5%)	5 (21.7%)	5 (11.4%)
Ethnicity			
Hispanic or Latino	12 (30.0%)	9 (39.1%)	7 (15.9%)
Not Hispanic or Latino / Missing	28 (70.0%)	14 (60.9%)	37 (84.1%)
Albumin (g/dl)			
Mean (SD)	36.4 (7.14)	34.3 (7.26)	37.7 (7.04)
Median (CV%)	38.0 (19.6)	35.0 (21.2)	37.6 (18.7)
[Min, Max]	[25.0, 50.0]	[14.0, 47.0]	[20.0, 48.5]
Missing	3 (7.5%)	2 (8.7%)	4 (9.1%)
Estimated GFR (ml/min/1.73m²)			
Mean (SD)	141 (97.3)	179 (108)	140 (51.4)
Median (CV%)	109 (69.1)	156 (60.3)	117 (36.6)
[Min, Max]	[16.8, 637]	[21.1, 562]	[72.6, 325]
Missing	2 (5.0%)	2 (8.7%)	0 (0%)

Source: eda-poppk-v5.Rmd
Note: Numeric columns formatted as mean (SD) and median (CV%) [range].
Abbreviations: CV% = coefficient of variation; GFR = glomerular filtration rate; Max = maximum; Min = minimum; N=number of subjects with available information; SD=standard deviation

In total, 641 bezlotoxumab serum concentration observations from 107 paediatric participants in P001 following 10 mg/kg were available for model-based PK analyses, with no observed bezlotoxumab concentrations from P001 excluded from the analysis. The CHMP noted that the collected PK data from P001 to confirm the paediatric dose equal to the adult dose are overall highly overlapping with adult observed data regarding both paediatric age cohorts, while observations from the younger age cohort are approaching the lower adult range.

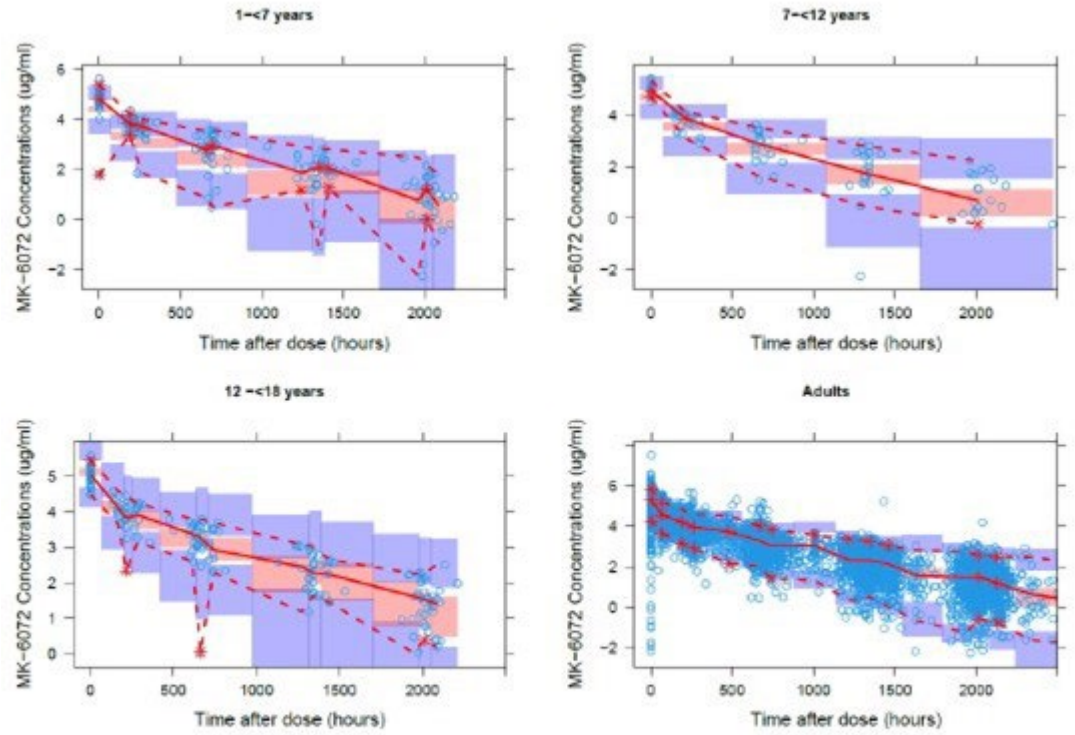
Besides age- and size-related covariates, the paediatric population is regarded overall comparable to the adult subjects in terms of continuous and categorical covariates investigated, however sample sizes are partly low. Gender was balanced also among the different paediatric age cohorts.

Results

- External validation

VPC plots representing the results of external validation using the previous population PK model developed for adults are shown below.

Figure 4: VPC plots for the original Pop PK model by age groups including observations



Notes: Red solid line is the observed median; red dashed lines are observed p5 and p95. The pink area is the 95% PI of the simulated median, and purple areas are the 95% PI of the simulated p5 and p95. The red asterisk indicates where the observed summaries exceed the predicted 95% PI
Abbreviations: p5=5th percentile; p95=95th percentile; PI=prediction interval; VPC=visual predictive check
Source: vpc_run14-vpc-agegrp \PsN_vpc_plots.R

- Parameter re-estimation

As external validation indicated a tendency towards under-prediction in the youngest paediatric group (in particular age group 1 to <7 years), PK parameter were re-estimated (see table below), as prespecified in the Modelling and Simulation Analysis Plan.

Table 6: Parameter Estimates for the Original and Updated Pop PK Models

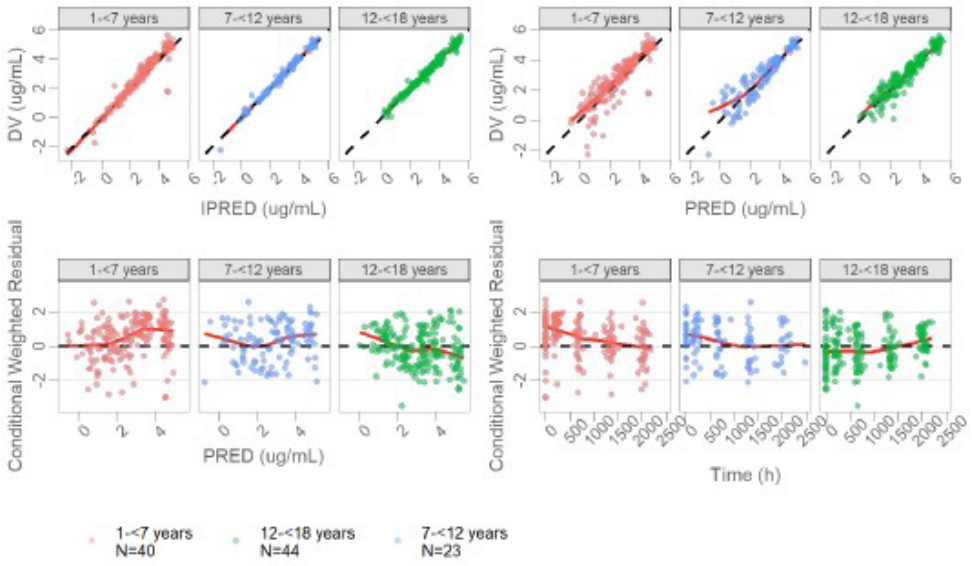
Parameter (unit)	Previous Parameter estimates	Updated Parameter Estimates	RSE (%)	Shrinkage (%)
V1 (L)	3.42	3.46	0.81	
V2 (L)	3.56	3.55	1.17	
CL (L/h)	0.01168	0.0118	0.21	
Q (L/h)	0.02305	0.0226	0.87	
Error model				
W ERR1-LOGADD	0.182	0.19	2.36	
Covariate effects				
WT on V1, V2	0.477	0.59	3.87	
WT 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: bezlo-poppk-diagnostics-v5.Rmd
Notes: Fixed effects parameters were exponentiated during the analysis. Transformed fixed effects parameters are provided here. IIV is reported as CV%; ALB=Albumin; CL=Clearance; JAPAN = Japanese; Q = intercompartmental clearance; RACE = Race; SEX = Sex; V1 = volume of distribution; V2 = peripheral volume of distribution; WT= bodyweight;
Abbreviations: CI=confidence interval; CL=clearance; CV=coefficient of variation; EPS=proportional residual error; IIV=inter-individual variability; Q=inter-compartmental clearance; RSE=relative standard error; V1=central volume of distribution; V2=peripheral volume of distribution

Goodness-of fit plots and VPC plots of the updated pop PK model (re-estimation of all parameters using paediatric PK data) are shown below.

Figure 5

Figure 5 GOF Plots for the Final Model by Pediatric Age Groups



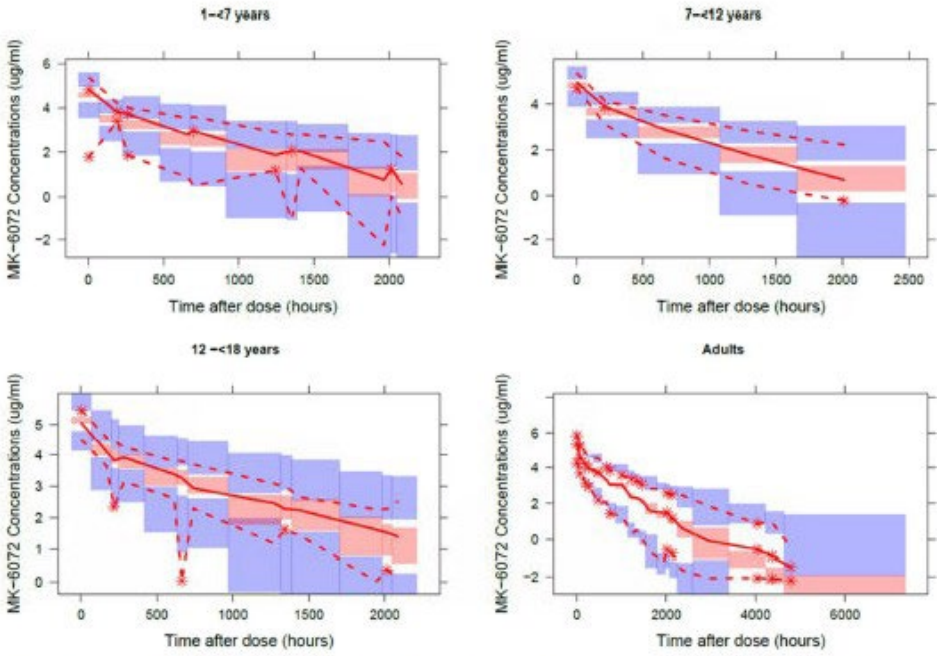
Source: bezlo-poppk-diagnostics-v5.Rmd

Notes: Dots are individual data points and solid lines are smoothed LOESS lines. In the plots in the first row, dashed lines are lines of identity, while in the plots in the second row, dashed lines show the zero-line of the CWRES

Abbreviations: CWRES=conditional weighted residuals; DV=dependent variable (usually observation); GOF=goodness-of-fit; IPRED=individual predictions; LOESS=locally weighted scatterplot smoothing; PRED=population predictions

Figure 6

Figure 2.7.2-rcdi-peds: 4
Prediction-Corrected Visual Predictive Checks by Age Group for the Final Population Pharmacokinetic Model



Notes: Red solid line is the observed median; red dashed lines are observed p5 and p95. The pink area is the 95% PI of the simulated median, and purple areas are the 95% PI of the simulated p5 and p95. The red asterisk indicates where the observed summaries exceed the predicted 95% PI

Abbreviations: p5=5th percentile; p95=95th percentile; PI=prediction interval; VPC=visual predictive check

Goodness-of-fit plots and VPC plots indicate that after re-estimating the model parameters based on the combined adult and paediatric data set under-prediction remained. In consequence, model refinements were conducted on the updated model. First, fixed allometry with standard coefficients of 0.75 for clearance (CL, Q) and 1 for volume (Vc, Vp) parameters was assessed instead of the estimated exponents. Applying these standard allometric exponents resulted in a decline in the fit of the data (dOFV = 890 points increase from the re-estimated model).

Additionally, several maturation functions were assessed on CL (see table below).

Table 7: Summary of Pivotal Runs for Bezlotoxumab Base Model Development

Run No.	Description	OFV	Comments
run14	Original PopPK model in adults	NA	OFV is not comparable as the dataset includes adults only
run007	As run 14;re-estimated parameters	-12322.31	Updated model
run015	As run 007; Fixed exponents to 0.75 and 1 for CL, Q and V1,V2, respectively	-11422.8	The fit of the younger age groups was over-predicted
run008	Exponents for CL,Q,V1,V2 fixed to results of run14. Sigmoid maturation function is implemented on CL	-12261	
run009	Exponents for CL fixed according to Mahmood et al.	-12192	
run010	Exponents for CL,Q,V1,V2 fixed to results of run14. Sigmoid maturation function is implemented on CL with hill coefficient fixed to 1	-12250.2	
run011	Exponents for CL, Q,V1,V2 fixed to results of run14. Exponential maturation function is implemented on CL	-12246	
run012	A separate CL was estimated for the youngest age group (1-<7 years)	-12256.2	

Source: pirana_run_summary_24-AUG-2022.csv (sheet 1)
Abbreviations: CL = clearance, Q = intercompartmental clearance; V1 = central volume of distribution; V2 = peripheral volume of distribution; IIV=inter-individual variability; OFV=objective function value;

The CHMP noted that external validation indicated that the previous model (based on adult data only) was capable to capture the median trend and variability of the paediatric data but there was clear trend towards under-prediction in the youngest paediatric group (i.e., 1 to <7 years).

This finding required further model refinement in order to potentially result in an adequate model-based description of paediatric PK over the entire age range.

In this regard, as a next step, the MAH re-estimated all pop PK parameters based on the extended

PK data set, indicating that the largest difference is that related to the allometric exponent for body weight. The estimates of allometric exponents for scaling CLs and Vs based on the overall weight distribution were both equally increased from 0.477 to 0.59 with an comparable 95% CI for weight effects on CL, Q and V1, V2 (0.54-0.65), being both below the fix allometric exponents (0.75, 1). These updated estimates are based on a very wide adult body weight range (32 kg -194 kg), partly overlapping with the weight range for paediatric patients (7.8-108 kg).

No additional significant covariates were identified for inclusion in the updated model. The relevance of race effects (in particular Japanese effect) for the description of (paediatric) PK in CDI patients is questioned. Median values following bootstrapping with or without the inclusion of the terminated runs were very similar to the parameter estimates of the updated model, the 95% CIs overlapped.

For the model fit based on the combined adult and paediatric dataset, all parameters were overall estimated with acceptable precision (relative standard error [%RSE] < 50%) and condition number (22.3). The η-shrinkage for the re-estimated model was < 30% for all parameters, the ε-shrinkage was low (4%). Goodness-of-fit plots by age category and overall indicate no strong biases or trends. ETA and CWRES distributions indicate some deviation from the horizontal line over all considered paediatric age cohort.

However, still, goodness-of-fit plots and VPC plots indicate that after re-estimating the model parameters based on the combined adult and paediatric data set under-prediction of the median exposure remained in the youngest age cohort. As this may be attributed to age-related effects (maturation). In addition to weight, age-related maturation effects are expected to impact PK below a certain age (as detailed in the M&S Q&A on paediatrics, https://www.ema.europa.eu/en/human-regulatory/research- development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation- questions-answers).

Fix allometry and several maturation functions were tested on CL. Those tested by the MAH did not lead to a significant improvement of the model fit in the youngest age group according to the MAH. This may also be attributed to the fact that the relevant young age group has limited representation in the dataset, preventing to reliably estimate a maturation function for CL but also to exclude this possibility. While some but not all plausible combination of weight exponents accounting for weight-related effects and maturation function were tested for model refinement (e.g. fix allometry (0.75, 1) in combination with additional maturation was not considered), maturation was ultimately not retained by the MAH in the final model used for exposure predictions for all age groups. The updated pop PK model assuming equal weight effects on CL and V (0.59) is indicated to underpredict the median exposure (AUC0_inf) especially for the youngest age group below 7 years of age and considered as the appropriate final pop PK model by the MAH. No paediatric pop PK model has been established, that would include maturation effects, while exclude some adult PK data e.g. at extreme body weight levels.

Thus, model-based conclusions regarding ADME, the CHMP is of the view that PK parameters and exposure predictions for all paediatric age and weight groups should be considered with caution, as indicated in the assessment. Section 5.2 of the SmPC was amended to reflect PK data and non-compartmental PK results, accordingly.

Comparison of bezlotoxumab exposure between paediatrics and adult populations

Adult population

In adult patients with CDI, bezlotoxumab PK following a single 10 mg/kg IV infusion of bezlotoxumab exhibited characteristics typical for a monoclonal antibody including low CL and a limited Vd resulting in a predominant elimination phase with a long terminal t1/2. No evidence of TMDD was observed.

Table 8

Table 2.7.2-rcdi-peds: 1
Summary of Bezlotoxumab Pharmacokinetic Parameter Values in Adult Patients with CDI (N=1504) Following Single IV Infusion of 10 mg/kg Bezlotoxumab or 10 mg/kg Actoxumab + Bezlotoxumab Based on Population Pharmacokinetic Analysis

	AUC0-inf (µg.h/mL)	AUC0-84d (µg.h/mL)	C_{max} (µg/mL)	t1/2 (day)	Tmax† (h)	CL (L/day)	Vd (L)
Geometric mean	53000	50400	185	18.7	.	0.317	7.33
Geometric CV%	40.2	36.7	20.7	28.0	.	40.6	16.3
Median	54700	52300	184	18.9	1.00	0.309	7.36
10th percentile	31700	31500	144	13.1	0.50	0.195	5.96
90th percentile	85600	77800	244	26.2	4.73	0.533	8.98

Based on posthoc exposures for patients who received actual doses between 8 – 12 mg/kg
†Only Median and Range reported

Source: Original application CTD Sec. 2.7.2

Between populations

The statistical comparisons of bezlotoxumab PK parameters following the administration of single infusion of 10 mg/kg is presented below.

Table 9

Table 2.5-rcdi-peds: 5
Statistical Comparisons of Bezlotoxumab Pharmacokinetic Parameters Following the Administration of Single Infusion of 10 mg/kg Bezlotoxumab in Two Age Cohorts of Pediatric Participants Versus Adult Participants in Prior Studies
Per-Protocol Population

Pharmacokinetic Parameter	Pediatric Participants			Adult Participants			Pediatric Participants/ Adult Participants		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE[a]
Age Cohort 1: 12 to <18 years									
AUC0_inf (hr*ug/mL)[b]	36	56100	(49400, 63700)	1550	52800	(51800, 53800)	1.06	(0.95, 1.18)	0.388
Cmax (ug/mL)[b]	37	155	(145, 166)	1550	184	(183, 186)	0.84	(0.79, 0.89)	0.217
Tmax (hr)[c]	37	3.00	(2.67, 3.47)	1550	1.00	(0.0667, 4.73)			
t1/2 (day)[d]	36	21.7	22.1	1550	18.7	27.7			
Vd (L)[d]	36	7.50	33.3	1550	7.34	16.3			
CL (mL/hr)[d]	36	9.99	33.7	1550	13.2	40.4			
Weight-normalized Vd (L/kg)[d]	36	0.134	29.9						
Weight-normalized CL (mL/hr/kg)[d]	36	0.178	31.0						
Age Cohort 2: 1 to <12 years									
AUC0_inf (hr*ug/mL)[b]	54	43200	(38900, 47900)	1550	52800	(51800, 53800)	0.82	(0.75, 0.89)	0.388
Cmax (ug/mL)[b]	54	129	(122, 137)	1550	184	(182, 187)	0.70	(0.67, 0.74)	0.220
Tmax (hr)[c]	54	3.00	(2.67, 285)	1550	1.00	(0.0667, 4.73)			
t1/2 (day)[d]	54	18.1	33.8	1550	18.7	27.7			
Vd (L)[d]	54	2.93	54.6	1550	7.34	16.3			
CL (mL/hr)[d]	54	4.66	59.6	1550	13.2	40.4			
Weight-normalized Vd (L/kg)[d]	54	0.146	28.9						
Weight-normalized CL (mL/hr/kg)[d]	54	0.233	34.5						

AUC0-inf=Area under the curve from time zero to infinity; BLOQ=Below assay limit of quantitation; CI=Confidence interval; CL=Clearance; Cmax=Maximum serum concentration; GM=Geometric least-squares mean; t ½=Terminal half-life; Tmax=Time of peak serum concentration; Vd=Volume of distribution.
[a]rMSE: Square root of conditional mean squared error (residual error) from the linear fixed-effect model. rMSE*100% approximates the between-subject percent CV on the raw scale.
[b]Back-transformed least-squares mean and confidence interval from fixed effects model performed on natural log transformed values.
[c]Median (min, max) reported for Tmax.
[d]Geometric mean, percent CV reported for apparent terminal t½, Vss and Cl. The percent CV is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale.
t1/2 could not be calculated for one subject in Cohort 1 who had BLOQ concentrations at the last 2 time points; only Cmax and Tmax were included for that participant.
Historical adult PK data were obtained from MK-3415 A PN001 and PN002.

Results indicate that the 90% CIs of paediatric/adult GMRs for serum bezlotoxumab AUC0-inf are within the prespecified clinical comparability bounds of (0.6, 1.6) for each of the two paediatric age cohorts.

Additionally, the distribution of individual predicted values of AUC0-inf in the paediatric population based on post hoc estimates from the population PK analysis (updated model assuming re-estimated

covariates and allometry excluding maturation functions) are shown below, including a comparison with NCA-derived results.

Figure 7: Distribution of estimated parameter values obtained with the post hocs from the updated model

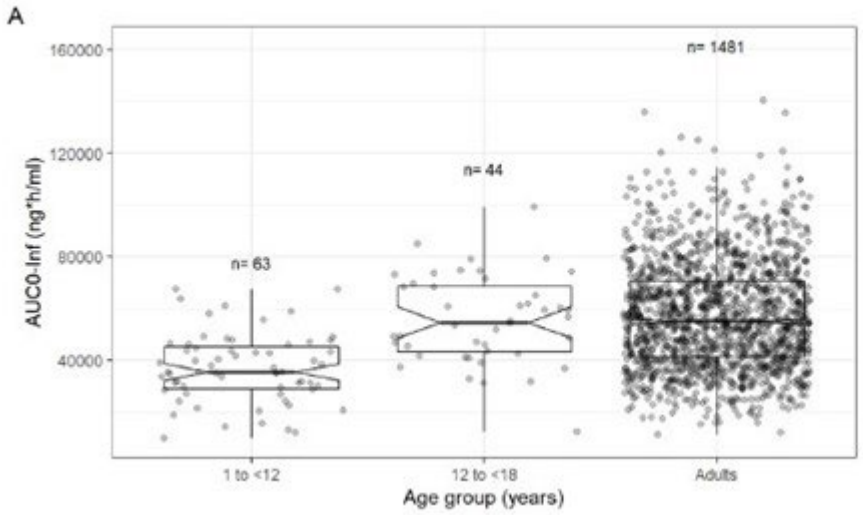


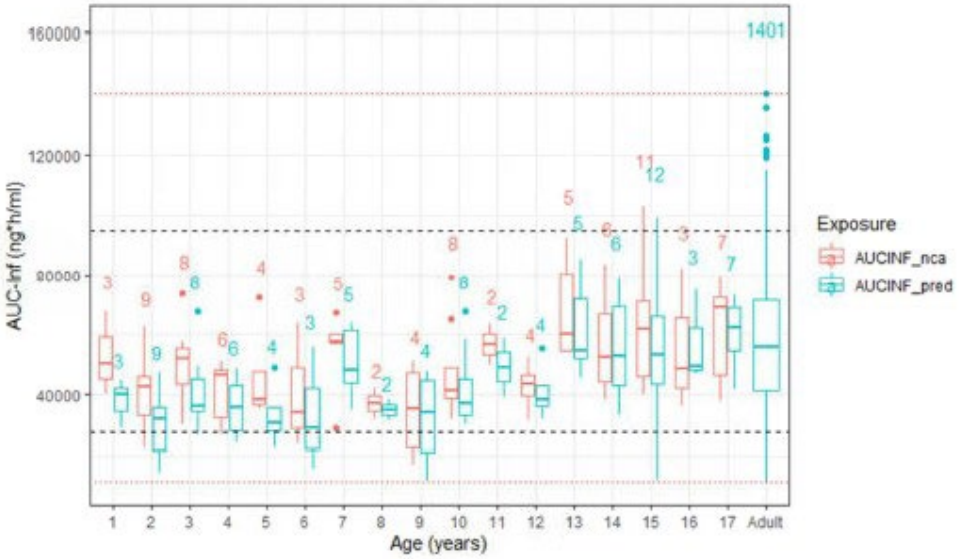
Table 10 Geometric Mean Ratio for AUCinf with 90% CI calculated for the Posthoc Exposures

Exposure Metric	Test Age Group (years)	Reference Age Group	GMR (90%CI)
$AUC_{0\text{-}Inf}$	1 to <7 (n=40)	Adults	0.602 (0.492-0.713)
$AUC_{0\text{-}Inf}$	7 to <12 (n=23)	Adults	0.719 (0.573-0.865)
$AUC_{0\text{-}Inf}$	1 to <12 (n=63)	Adults	0.645 (0.557-0.733)
$AUC_{0\text{-}Inf}$	12 to <18 (n=44)	Adults	0.974 (0.869-1.08)

Source: forest-plot_v1.Rmd
Note: GMR = Geometric mean ratio; CI = confidence int

Figure 8

Figure 2.7.2-rcdi-peds: 7
Comparison of AUC0-inf estimated by Noncompartmental and Population Pharmacokinetic Analyses Stratified by Age

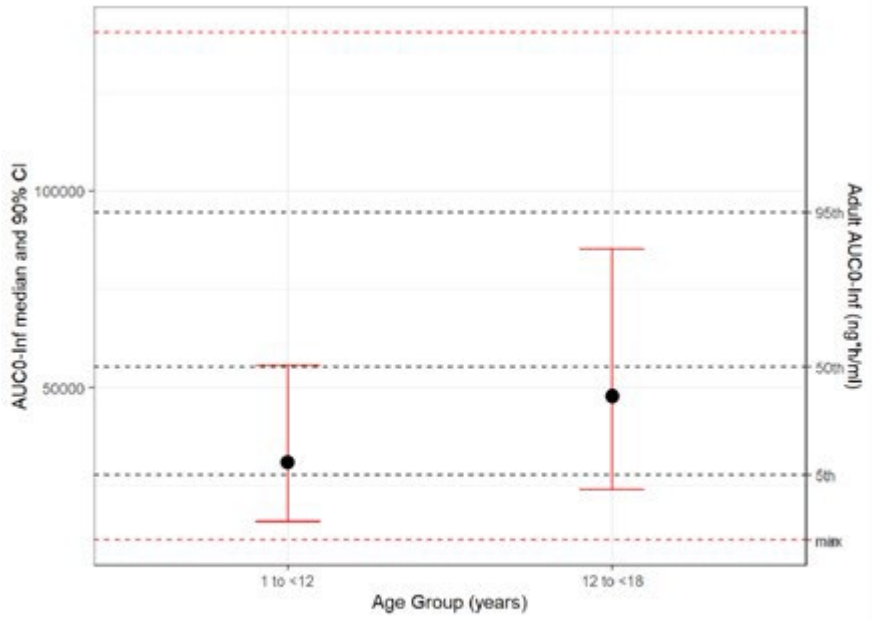


Abbreviations: CL_wt_nca = weight-normalized CL obtained from NCA analysis; CL_wt_pred = weight-normalized CL obtained from PopPK analysis; AUCINF_nca = AUC-Inf obtained from NCA analysis; AUCINF_pred = AUCInf obtained from PopPK analysis
Boxplots summarizing the exposures derived for different age groups after single administration of bezlotoxumab at the sampling timepoints for posthoc simulations (blue) or Non-Compartmental Analysis (red). The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge). Numbers represent the number of individual participants in each age group. Dashed black lines indicate the 5th and 95th percentiles of the adult post hocs exposures while the red dashed lines indicate the minimum and maximum exposure values of adult post hocs exposures

The results of PK simulations based on a virtual paediatric population are shown below.

The median exposures for the two paediatric groups are contained within the 90% CI of the adult reference exposure. The 90% CIs of the simulated paediatric populations are within the entire adult reference exposure.

Figure 9: Results of the Pop PK model simulations in virtual pediatric patients (Scenario 3)

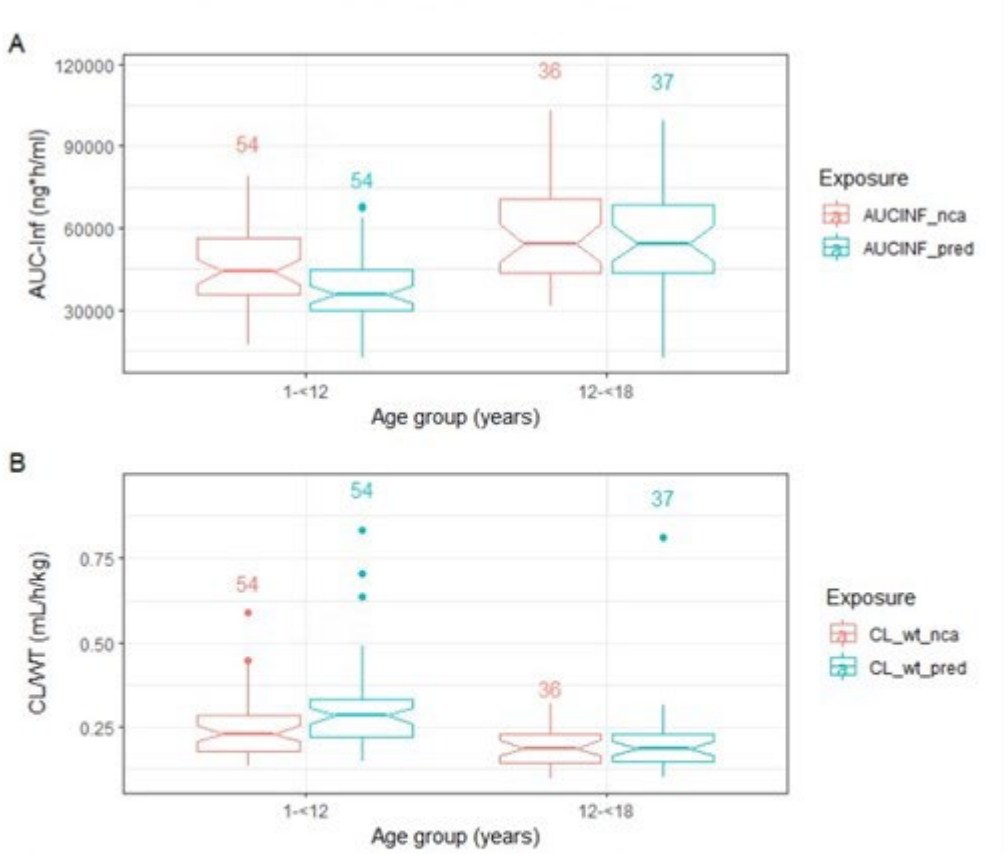


Notes: Error bars represent the 90% CI of the simulated $AUC_{0\text{-}Inf}$ calculated as dose/CL. The median is shown as the black dot. The 5th and 95th percentiles of the adult reference $AUC_{0\text{-}Inf}$ is shown by the black dotted lines. The minimum and maximum adult exposures are shown by the red dotted lines.
Source: mk6072-poppk-sim.v2.R

Within the paediatric age group

NCA-derived PK parameters were based on intensive PK sampling (at least 4 post-dose samples) and reflected in a subset (N=91) of the paediatric dataset integrated into the present analysis. The numerical evaluations were performed between the observed (as derived from the NCA) and predicted AUC0-inf and weight normalized CL (CL/WT). The PK parameters obtained from the NCA and post hocs are summarized in the figure below, stratified by age group.

Figure 10: Boxplots showing the AUCinf and CL/WT as obtained from the NCA and model post hocs stratified by age groups



Boxplots summarizing the exposures derived for different age groups after single administration of MK6072 at the sampling timepoints for posthoc simulations (blue) or Non-Compartmental Analysis (red). The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge). Data beyond the end of the whiskers are called "outlying" points and are plotted as individual values. The notch displays a confidence interval around the median which is based on the median +/- 1.58*IQR/sqrt(n). This gives roughly 95% confidence interval for comparing medians.
Abbreviations: CL_wt_nca = weight-normalized CL obtained from NCA analysis; CL_wt_pred = weight-normalized CL obtained from PopPK analysis; AUCINF_nca = AUC_{Inf} obtained from NCA analysis; AUCINF_pred = AUC_{Inf} obtained from PopPK analysis;
Source: mrk-bezlo-exposures-specifsamptimes-20221012-run007bis.R

The 1 to <7 group leads to the largest difference in geometric means between predicted and observed (i.e., NCA) AUC0-Inf with an RMSE of 22.33 % as compared to less than 10% for the other 2 paediatric groups.

Table 11: Summaries of Posthoc and NCA Results Stratified by Age Group

PK Parameter	Age Group	N	Geometric Mean (NCA)	Geometric Mean (Post hoc)	%Relative Mean SE
$AUC_{0\text{-}Inf}$	1 to <7 years	33	42,852	33,285	22.33
	7 to <12 years	21	43,647	39,425	9.67
	12 to <18 years	37	56,099	52,407	6.58
CL/WT	1 to <7 years	33	0.235	0.302	28.74
	7 to <12 years	21	0.229	0.254	10.71
	12 to <18 years	37	0.178	0.191	7.04

Source: mrk-bezlo-exposures-specifsamptimes-20221012-run007bis.Rs

The CHMP notices that PK estimates based on NCA and following model-based methods are overall in line but diverge with decreasing age. As the pop PK exhibits a clear under-estimation of median exposure in particular for the age cohort 1-7, simulations results are considered inconclusive and are not further discussed in detail. The CHMP considers that exposure predictions based on the updated pop PK model should be considered with caution due to the lack of maturation effects, inclusion of weight effects, and observed divergence to NCA based estimates, in particular for the age group younger than 7 years of age.

While statistical comparisons of bezlotoxumab PK parameters (NCA) following the administration of single infusion of 10 mg/kg indicate that the 90% CIs of paediatric/adult GMRs for serum bezlotoxumab AUC0- inf are within the prespecified clinical comparability bounds of (0.6, 1.6) for each of the two paediatric age cohorts (Cohort 1 and 2), the trend is towards the lower comparability boundary for the youngest patients.

Thus, the MAH was requested by the CHMP to provide a more granular exposure comparison (in terms of paediatric/adult GMRs for serum bezlotoxumab AUC0-inf) by splitting the age groups for comparison, e.g. into the following subcategories 1-3, 4-6, 7-12 years of age. The MAH was further requested to discuss these results in line with the efficacy findings taking the justification of the extrapolation concept (exposure bridging) for the youngest paediatric age cohorts into account. Even a more granular consideration and comparison did not clearly detect consistent and relevant impact of age or weight related impact on PK. Overall, PK results from the paediatric population did not exceed the adult range, however with the outlined limitations and uncertainty in generalizability. It was thus concluded by the CHMP that the information on PK available for the paediatric population, also to support the exposure comparison and extrapolation concept, is best reflected by adequate update of Section 5.2 of the SmPC. Thus, the CHMP is of the view that AUC and concentration on week 12 (non-compartmental analysis) compared between relevant age and weight groups with the adult population were to be reflected in Section 5.2. The MAH updated the section accordingly. (Please cf. also sections Discussion and Conclusions on clinical efficacy in this regard.)

Absorption

Bezlotoxumab is administered intravenously and is 100% bioavailable. Based on NCA, geometric mean (%CV) Cmax following 10 mg/kg was reached after 3 hours (geometric mean) for both paediatric cohorts to 129 (32.9) µg/mL (age cohort 2, 1 to < 12 years of age) and 155 (28.2) µg/mL (age cohort 1, 12 to <18 years of age).

Distribution

For the paediatric population, the volume of distribution (Vd) increased with age. For age cohort 1 to < 12 years of age, the geometric mean (%CV) Vd was derived by NCA to 2.93 (54.6) L. For age cohort 12 to <18 years of age, the geometric mean (%CV) Vd was derived by NCA to 7.50 (33.3) L.

Elimination

For the paediatric population, the mean Clearance (CL) increased with age. For age cohort 1 to < 12 years of age, the geometric mean (%CV) CL was derived by NCA to 4.66 (59.6) mL/hr. For age cohort 12 to <18 years of age, the geometric mean (%CV) CL was derived by NCA to 9.99 (33.7) mL/hr.

Bezlotoxumab is catabolized through protein degradation processes; thus, metabolism does not contribute to its clearance, and it is not eliminated by renal or biliary excretion. Consequently, the clearance of bezlotoxumab was not expected to be different in paediatric patients compared with adults, except based on weight, which is accounted for by weight-based dosing.

In addition to weight, age-related maturation effects are expected to impact PK below a certain age (as detailed in the M&S Q&A on paediatrics, https://www.ema.europa.eu/en/human-regulatory/research- development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation- questions-answers). While some but not all plausible combination of weight exponents accounting for weight-related effects and maturation function were tested for model refinement (e.g. fix allometry (0.75, 1) in combination with additional maturation was not considered), maturation was not retained by the MAH in the final model used for exposure predictions for all age groups. This updated pop PK model assumes equal weight effects on CL and V (0.59) is indicated to underpredict the exposure (AUC0_inf) especial for the youngest age group below 7 years of age. Thus, even after a more granular consideration in terms of age and weight ranges, the CHMP considers that model-based conclusions regarding ADME and PK parameters should be considered with caution. PK results from non-compartmental analysis should be the basis to inform on paediatric PK.

Dose proportionality and time dependencies

As bezlotoxumab is administered via a single IV dose infusion, and no dose ranging studies have been conducted in the target population (paediatric subjects), no conclusions on dose proportionality and accumulation effects can be drawn.

Special populations

In the context of the original MAA, the effects of various covariates on the PK of bezlotoxumab in adults were assessed by population PK analysis. Results indicated that the clearance of bezlotoxumab increased with increasing body weight, which is to some degree accounted for by weight-based dosing. Other than weight, the following factors had no clinically meaningful effect on the exposure of bezlotoxumab in adults and no dose adjustment is required: age (range 18 to 100 years), sex, race, ethnicity, renal impairment, nor hepatic impairment.

Regarding updated pop PK model and covariate selection, no correlations were observed between η-estimates and tested covariates therefore no additional covariates were taken forward in a formal analysis.

It is agreed by the CHMP that no additional covariate in comparison to the adult population may be expected besides maturation effects, that may have a clinically relevant impact on PK. Nevertheless, the predictability and of covariate effects including weight effects from the model is questioned by the CHMP (compare assessment of model performance and model refinement, maturation functions).

Pharmacokinetic interaction studies

Not relevant.

Pharmacokinetics using human biomaterials

Not relevant.

2.3.3. Pharmacodynamics

Mechanism of action

Bezlotoxumab is a human monoclonal antibody that binds to and neutralizes *C. difficile* toxin B.

Primary and secondary pharmacology

The characterization of bezlotoxumab primary and secondary pharmacology in paediatrics compared to adults is assumed unchanged. Primary pharmacology is not expected to be different between paediatric and adult subjects.

Immunogenicity

Serum samples for ADA and NAb analysis were collected in P001 to characterize the immune response to bezlotoxumab. Bioanalysis of ADA was conducted using the standard 3- tiered assay approach. For participants with confirmed ADA positive samples, the ADA titer was determined to characterize the magnitude of the immune response and the presence of NAb was assessed to determine if the antibodies neutralized or blocked binding of bezlotoxumab to *C. difficile* toxin B.

An immunogenicity analysis was conducted for participants who received a dose of bezlotoxumab and who had at least 1 ADA result available post-dose of study intervention.

Following treatment with bezlotoxumab in P001, 2 of the 100 evaluable paediatric participants tested positive for anti-bezlotoxumab antibodies; neither had NAb (see Table 11 below).

Table 12

Table 2.7.2-rcdi-peds: 6
Summary of Participants Anti-bezlotoxumab Antibody Status
All Participants with at Least One ADA Sample Result
Following Treatment with Bezlotoxumab
By Age Cohort

	Age Cohort 1 (12 to <18 years) n (%)	Age Cohort 2 (1 to <12 years) n (%)	Total n (%)
Participants in population	44	62	106
Unevaluable participants	2	4	6
Evaluable participants[a]	42	58	100
Immunogenicity Status			
Negative	41 (97.6)	51 (87.9)	92 (92.0)
Inconclusive[b]	0 (0.0)	3 (5.2)	3 (3.0)
Nontreatment emergent positive[c]	0 (0.0)	3 (5.2)	3 (3.0)
Positive response to Bezlotoxumab	1 (2.4)	1 (1.7)	2 (2.0)
Treatment emergent positive[d]	0 (0.0)	1 (1.7)	1 (1.0)
Treatment boosted positive[e]	1 (2.4)	0 (0.0)	1 (1.0)
Maximum Postdose Titer in Participants with a Positive Response to Bezlotoxumab			
1	0	1	1
25	1	0	1
Neutralizing Antibody Results in Participants with a Positive Response to Bezlotoxumab			
Nontreatment emergent			
Neutralizing negative	0 (0.0)	3 (5.2)	3 (3.0)
Neutralizing positive	0 (0.0)	0 (0.0)	0 (0.0)
Treatment emergent or Treatment boosted			
Neutralizing negative	1 (2.4)	1 (1.7)	2 (2.0)
Neutralizing positive	0 (0.0)	0 (0.0)	0 (0.0)

ADA = antidrug antibody.
[a] Participants with at least one ADA result after treatment with bezlotoxumab. The number of participants evaluable per dose group is the denominator of the percentages in the table.
[b] Participants with a drug concentration in the last sample that exceeds the drug tolerance level of the ADA assay or the drug concentration result is missing.
[c] Participants positive at baseline were considered nontreatment emergent positive if only positive at baseline or if postdose titer increased by less than 2-fold relative to the baseline titer.
[d] Participants who were negative at baseline and positive postdose were considered treatment emergent.
[e] Participants positive at baseline were considered treatment boosted if postdose titer increased by greater than or equal to 2-fold relative to the baseline titer.

The immunogenic potential is indicated to be low (2%) based on the analysis from data resulting von P001. Following bezlotoxumab treatment, 2 of the 100 evaluable paediatric participants were tested positive for ADA without Nab development. This is in line with the low immunogenicity previously assessed for the adult population, based on adult studies MK-3415A P001, MK-3415A P002. From 1515 evaluable participants, 9 (0.6%) were classified nontreatment-emergent positive, with a titre range from 4 to 512. Of these 9 positive nontreatment emergent participants, only one was subsequently shown to be positive for Nab. In light of the above, the CHMP considers the immunogenicity risk, despite the low sample size, is considered low.

2.3.4. PK/PD modelling

As an exposure-response relationship was established based on bezlotoxumab AUC0-inf in adult patients a PK bridging strategy based upon prespecified criteria for AUC0-inf was designed to support extrapolation of efficacy.

Exposure bridging was focussing on comparison of AUC0-inf (to be in comparability bounds) as the exposure-response relationship between bezlotoxumab AUC0-inf and CDI recurrence in adults was characterized by an Emax relationship, in which exposures achieved following the 10 mg/kg dose are on the maximal response plateau of the exposure-response curve.

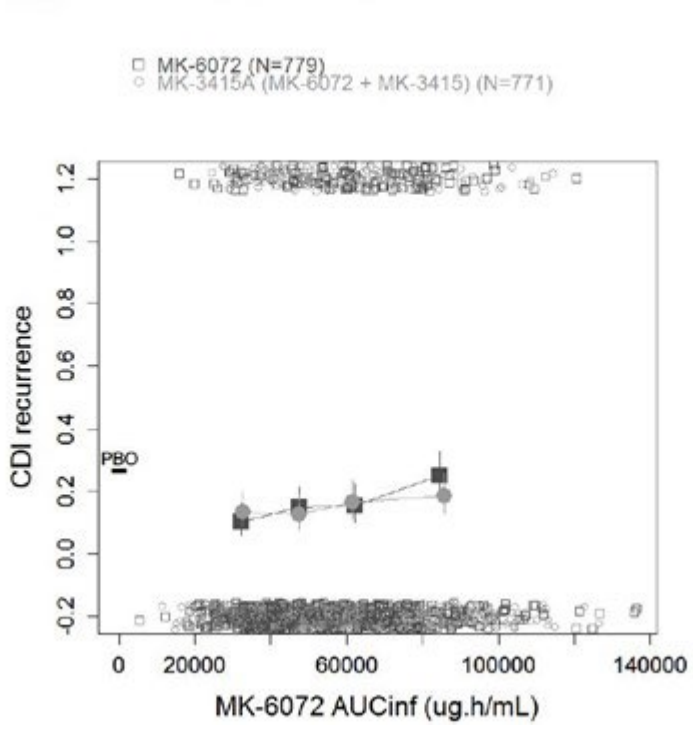
The comparability bounds of (0.6, 1.6) for bezlotoxumab are based on the 10th and 90th percentile of observed AUC0-inf values following administration of a single 10 mg/kg IV infusion in the Phase 3 trials. This lower bound is derived from the ratio of bezlotoxumab AUC0-inf values at the 10th percentile (31,700 µg.h/mL) relative to the median (54,700 µg.h/mL) in a pooled population of CDI patients from the Phase 3 trials. The upper bound is similarly derived from the ratio of bezlotoxumab AUC0-inf values at the 90th percentile (85,600 µg.h/mL) of the same population relative to the median AUC0-inf. These bounds correspond to mean bezlotoxumab exposures anticipated at doses of 6 mg/kg and 16 mg/kg based on dose proportionality observed over the 0.3 – 20 mg/kg dose range.

Results on exposure response with respect to efficacy from the original MAA in adults are provided in the following.

Explorative analysis of exposure effects on CDI recurrence rate (original MAA)

Exposure-response relationships for CDI recurrence in adult patients were explored with quantile plots of binned bezlotoxumab exposure values following administration of bezlotoxumab alone or on combination. The number of bins was set to 4, with the number of observations equally divided over the bins.

Figure 11: Quantile plot for CDI recurrence (Mean and 95% CI) versus MK-6072 AUC 0-inf stratified by treatment



Additionally, to explore potential covariate effects, similar plots were generated stratified by treatment and by covariates that were to be evaluated for impact on the E-R relationship. CDI recurrence rates by MK-6072 exposure bins are also presented in the Table 13 below.

Table 13: CDI Recurrence Rates

Table 32: CDI Recurrence Rates Stratified by Treatment and MK-6072 $AUC_{0\text{-inf}}$ bins, Mean and 95% Confidence Intervals

Treatment	Bin range $AUC_{0\text{-inf}}$	Number of patients	CDI Recurrence Mean (95% CI)
Placebo	-	776	26.7 (23.2 - 30.4)
MK-6072	5329 - 40144	195	10.3 (5.90 - 16.2)
	40276 - 54746	195	14.9 (9.60 - 21.5)
	54838 - 70005	194	15.5 (10.1 - 22.2)
	70037 - 136436	195	25.1 (18.4 - 32.8)
MK-3415A	11238 - 41202	193	13.5 (8.50 - 19.9)
	41294 - 53838	193	12.4 (7.60 - 18.8)
	54073 - 70357	192	16.7 (11.1 - 23.6)
	70739 - 126394	193	18.7 (12.8 - 25.8)

Exposure-response model (original MAA)

Table 14: Parameter estimates for the final E-R model for CDI recurrence

Parameters	Estimate[a]	%RSE[b]	95% CI[c]
Placebo treatment effect (b_0)	-1.15	8.37%	-1.34 ; -0.953
Covariates affecting placebo			
Albumin – continuous	0.318	24.0%	0.172 ; 0.471
Age – continuous	0.0103	31.7%	0.00391 ; 0.0166
History of CDI in past 6 months - Yes	0.707	15.1%	0.513 ; 0.919
Charlson Comorbidity Index – score ≥3	-0.267	42.2%	-0.485 ; -0.0423
MK-6072			
Emax	-0.643	16.0%	-0.844 ; -0.452
EAUC50 (µg.h/mL)	100 Fixed	-	-

[a] final model estimates; [b] %RSE derived from bootstrap analysis, calculated as 100*standard error/median; [c] bootstrap estimates;

The predicted rate of CDI recurrence in patients receiving placebo is 26.2% and upon treatment with bezlotoxumab, the rate of recurrence decreases to 15.9%. Albumin, age, history of CDI in the past 6 months, and the Charlson Comorbidity Index impact the rate of CDI recurrence in patients on placebo.

The CHMP noted that exposure bridging was focussing on comparison of AUC0-inf (to be in comparability bounds) as the exposure-response relationship between bezlotoxumab AUC0-inf and CDI recurrence in adults was characterized by an Emax relationship, in which exposures achieved

following the 10 mg/kg dose are on the maximal response plateau of the exposure-response curve.

While there is an overall trend in decrease in CDI recurrence upon treatment with bezlotoxumab and actoxumab, a counterintuitive upward trend in CDI recurrence rate with increasing bezlotoxumab exposure was detected (exploratory analysis). As exposure is correlated to other factors, in particular albumin, it was argued that these factors may be driving this apparent effect.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Data relevant for this II-procedure informing PK resulted from one Phase 3, randomized, placebo-controlled, parallel group, multisite, double-blind study (P001) evaluating the PK, safety, tolerability, and efficacy in preventing CDI recurrence after a single infusion of bezlotoxumab or placebo in paediatric patients from 1 to <18 years of age who were receiving antibacterial drug treatment for CDI.

No further relevant data on pharmacodynamics or PK/PD have been provided with this application.

The primary PK objective was to characterize the PK of bezlotoxumab in two age cohorts of paediatric participants to support dosing recommendations in the paediatric population.

Paediatric study P001 included overall N=108 participants who received bezlotoxumab, of whom N=91 were available for PK analysis (4 PK samples per subject). Most of the participants in age cohort 2 (N=63) were aged below 7 years of age (N=40) at a comparable sample size to age cohort 1 (N=45). This imbalance is agreed as most uncertainty in PK is in the youngest age cohort.

Bezlotoxumab pharmacokinetics following a single 10 mg/kg IV infusion in both adult and paediatric populations exhibit characteristics typical for a monoclonal antibody including low clearance and a limited volume of distribution resulting in a predominant elimination phase with terminal half-life of approximately three weeks. The concentration time-profiles for both paediatric age cohorts are considered comparable, with lower exposure indicated for the younger age cohort.

As expected, mean CL and Vd across age groups increased with increasing age, with a remaining trend in higher weight-normalized CL with decreasing age. This may be attributed to maturation effects, in particular for the youngest age cohort (1-7 years of age). NCA indicated thus an increasing exposure with age over the paediatric age range.

In total, 641 bezlotoxumab serum concentration observations from 107 paediatric participants in P001 following 10 mg/kg were available for (model-based) PK analyses, with no observed bezlotoxumab concentrations from P001 excluded from the analysis. The collected PK data from P001 to confirm the paediatric dose equal to the adult dose are overall highly overlapping with adult observed data regarding both paediatric age cohorts, while observations from the younger age cohort are approaching the lower adult range.

Besides age- and size-related covariates, the paediatric population is regarded overall comparable to the adult subjects in terms of continuous and categorical covariates investigated, however sample sizes are partly low. Gender was balanced also among the different paediatric age cohorts.

External validation indicated that the previous pop PK model (based on adult data only) was capable to capture the median trend and variability of the paediatric data but there was clear trend towards under- prediction in the youngest paediatric group (i.e., 1 to <7 years).

This finding required further model refinement in order to potentially result in an adequate model-based description of paediatric PK over the entire age range. In this regard, as a next step, the MAH

re- estimated all pop PK parameters based on the extended PK data set, indicating that the largest difference is that related to the allometric exponent for body weight. The estimates of allometric exponents for scaling CLs and Vs based on the overall weight distribution were both equally increased from 0.477 to 0.59 with a comparable 95% CI for weight effects on CL, Q and V1, V2 (0.54-0.65), being both below the fix allometric exponents (0.75, 1). These updated estimates are based on a very wide adult body weight range (32 kg -194 kg), partly overlapping with the weight range for paediatric patients (7.8-108 kg).

No additional significant covariates were identified for inclusion in the updated model. It is agreed that no additional covariate in comparison to the adult population may be expected besides maturation effects, that may have a clinically relevant impact on PK. Nevertheless, the predictability and of covariate effects including weight effects from the model is questioned.

Still, goodness-of-fit plots and VPC plots indicate that after re-estimating the model parameters based on the combined adult and paediatric data set under-prediction of the median exposure remained in the youngest age cohort. This may be attributed to age-related effects (maturation). In addition to weight, age-related maturation effects are expected to impact PK below a certain age (as detailed in the M&S Q&A on paediatrics, https://www.ema.europa.eu/en/human-regulatory/research-development/scientific- guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers).

Fix allometry and several maturation functions were tested on CL. Those tested by the MAH did not lead to a significant improvement of the model fit in the youngest age group according to the MAH. This may also be attributed to the fact that the relevant young age group has limited representation in the dataset, preventing to reliably estimate a maturation function for CL but also to exclude this possibility.

While some but not all plausible combination of weight exponents accounting for weight-related effects and maturation function were tested for model refinement (e.g. fix allometry (0.75, 1) in combination with additional maturation was not considered), maturation was ultimately not retained by the MAH in the final model used for exposure predictions for all age groups. The updated pop PK model assuming equal weight effects on CL and V (0.59) is indicated to underpredict the median exposure (AUC0_inf) especially for the youngest age group below 7 years of age and considered as the appropriate final pop PK model by the MAH. No paediatric pop PK model has been established, that would include maturation effects, while exclude some adult PK data e.g. at extreme body weight levels.

Thus, model-based conclusions (updated pop PK model) regarding paediatric ADME, PK parameters and exposure predictions should be considered with caution. In addition, a more granular consideration of the age range from 1 to <12 years of age is deemed necessary.

Dose recommendation

10 mg/kg dose was anticipated to be appropriate for children and to result in exposures similar to those observed in adults, as being weight adapted and no major additional effects due to age affects or differences in mode of action and pathogenesis of CDI were anticipated. This is partly agreed. Since authorization is planned for paediatric subjects down to one year of age, maturation effects might affect the PK of very young patients in addition to weight. This is also indicated in the data and PK analyses conducted and reported. Thus, while age range from 12 to 18 years of age for the older paediatric age cohort is regarded appropriate, the range for the younger cohort from 1 to 12 years of age is considered too wide to serve for meaningful comparison of exposure resulting from older age groups. Exposure comparability over all age groups following one 10 mg/kg IV is the core of the extrapolation concept towards the paediatric indication.

PK estimates based on noncompartmental analysis (NCA) and following model-based methods are overall in line but diverge with decreasing age. The updated population PK model exhibits a clear under- estimation of median exposure in particular for the age cohort 1-7. Exposure predictions based on the updated pop PK model should be considered with caution for dose justification due to the lack of maturation effects, questioned inclusion of weight effects, and observed divergence to NCA based estimates, in particular for the age group younger than 7 years of age.

While statistical comparisons of bezlotoxumab PK parameters (NCA) following the administration of single infusion of 10 mg/kg indicate that the 90% CIs of paediatric/adult GMRs for serum bezlotoxumab AUC0- inf are within the prespecified and previously agreed clinical comparability bounds of (0.6, 1.6) for each of the two paediatric age cohorts (Cohort 1 and 2), the trend is towards the lower comparability boundary for the youngest patients.

Thus, the MAH was asked to provide a more granular exposure comparison (in terms of paediatric/adult GMRs for serum bezlotoxumab AUC0-inf) by splitting the age groups for comparison, e.g. into the following subcategories 1-3, 4-6, 7-12 years of age. The MAH was further asked to discuss these results in line with the efficacy findings taking the justification of the extrapolation concept (exposure bridging) for the youngest paediatric age cohorts into account. Even after a more granular consideration in terms of age and weight ranges, the CHMP considers that model-based conclusions regarding ADME and PK parameters should be considered with caution. The provided final population PK model is not deemed adequate to serve for simulation of exposure in children, and thus in particular to support dose finding and approval in children <12 years, who are indicated to require a higher mg/kg-dose to reach similar exposures to adults. PK results from non-compartmental analysis should be the basis to inform on paediatric PK and to support the extrapolation concept (exposure bridging).

2.3.6. Conclusions on clinical pharmacology

The data on clinical pharmacology derived from paediatric Study P001 aimed at confirmation of appropriateness of the selected dose (10 mg/kg) administered as a single IV dose, and description of the PK of bezlotoxumab in the paediatric population from 1 to 18 years of age.

Collected PK and conducted PK analyses indicate low immunogenicity risk of bezlotoxumab in paediatrics patients. Observed concentration time-profiles are overall comparable between both paediatric age cohorts and in line with what is expected from a monoclonal antibody and previously observed in the adult population.

Dose confirmation needed a critical consideration and discussion regarding the lowest age range as expected exposure is at the lower limit of previously agreed exposure boundaries resulting from the original MAA in adults. Overall, PK results from the paediatric population did not exceed the adult range, however with the outlined limitations and uncertainty in generalizability. It was thus concluded by the CHMP that the information on PK available for the paediatric population, also to support the exposure comparison and extrapolation concept, is best reflected by adequate update of Section 5.2 of the SmPC. Thus, upon the request of the CHMP, AUC and concentration on week 12 (non-compartmental analysis) compared between relevant age and weight groups with the adult population are now reflected in Section 5.2 of the SmPC. (Please cf. also sections Discussion and Conclusions on clinical efficacy in this regard.)

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was performed.

2.4.2. Main study

Study P001: 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).

Methods

Study participants

Male and female participants aged 1 to <18 years with *C. difficile* infection (CDI) (confirmed presence of
C. difficile toxin in stool) and receiving antibacterial drug treatment were eligible to participate.

The most salient inclusion criteria were:

At the time of randomization/study infusion, participant:

- Had a diagnosis of CDI confirmed by a diagnostic assay, which detected the presence of *C. difficile* toxin in stool, and
- Was still receiving antibacterial drug treatment for CDI (a 10- to 21-day course of antibacterial drug treatment for CDI, which is defined as oral vancomycin, oral metronidazole, or oral fidaxomicin). Additionally, IV metronidazole may be given concurrently with oral vancomycin or oral fidaxomicin

Participant for whom, at the time of randomization, the planned course of antibacterial drug treatment for CDI was longer than 21 days were excluded from the study.

Treatments

Intervention Group Name	Drug	Dose Strength	Dose	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Bezlotoxumab (MK-6072)	Bezlotoxumab (MK-6072)	25 mg/mL	10 mg/kg	Single Infusion	IV infusion	Day 1	Experimental
Placebo	Placebo	Not applicable	Not applicable	Single Infusion	IV infusion	Day 1	Experimental

IV=intravenous.

Objectives

Outcomes/endpoins

Participants were followed up for 12 weeks (i.e., 85 ± 5 days) for PK and immunogenicity collections, monitoring of safety and tolerability parameters, and efficacy outcomes.

Objectives	Endpoints
Primary	
Objective: To characterize bezlotoxumab PK in 2 age cohorts (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) of pediatric participants to support dose selection in this population. Hypothesis: The area under the concentration-time curve from 0 to infinity (AUC0-inf) of bezlotoxumab after treatment of 2 age cohorts of pediatric participants (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) with a single infusion of bezlotoxumab is similar when compared with the AUC0-inf of bezlotoxumab after treatment of adult participants with a single infusion of 10 mg/kg bezlotoxumab, a dose demonstrated to be safe and efficacious in adults. That is, the true geometric mean ratios (GMRs, pediatric participants/adults) for AUC0-inf of bezlotoxumab are contained in the clinical comparability bounds of (0.6, 1.6) in each of the age cohorts.	The AUC0-inf will be determined for each age cohort from bezlotoxumab serum concentration data.
Objective: To evaluate the safety and tolerability of a single infusion of bezlotoxumab as compared with a single infusion of placebo through 12 weeks following infusion.	Proportion of participants experiencing AEs Proportion of participants discontinuing study medication due to AEs
Secondary	
Objective: To estimate the proportion of participants who have a CDI recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo.	Proportion of participants who have a CDI recurrence within 12 weeks of study medication infusion. CDI recurrence is assessed by the investigator.

Objectives	Endpoints
Objective: To estimate the proportion of participants with sustained clinical response over a period of 12 weeks in participants who received a single infusion of bezlotoxumab or placebo.	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.
Objective: 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 bezlotoxumab or placebo.	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).
Objective: To assess the incidence of infusion-related reactions in participants who received a single infusion of bezlotoxumab or placebo.	Proportion of participants experiencing 1 or more infusion-related reactions within 24 hours following the start of the infusion.
Objective: To assess the potential for bezlotoxumab to induce immunogenicity within 12 weeks following administration of a single infusion of bezlotoxumab.	Proportion of participants with treatment-emergent positive antibodies to bezlotoxumab in serum through 12 weeks following a single dose of bezlotoxumab.

Sample size

Originally, the study aimed to randomise 144 paediatric participants in the bezlotoxumab group and 48 in the placebo group, for a total of 192 participants. Although the primary endpoint of the study was for PK, the sample size was chosen also considering safety and efficacy:

- PK: 9 paediatric participants per age and treatment group were considered sufficient for the PK endpoints (supported by formal calculations and using available data from 1400 adults as reference).
- Safety: under the assumption of an incidence of SAE of 1%, there is a 76% chance of observing at least one serious adverse event among 144 subjects in the bezlotoxumab group. This probability was updated to > 99% after eDMC3 (and also taking into consideration the enrolment challenges encountered during the CODIV-19 pandemic)
- Efficacy: "The planned sample size for this study will have limited power to confirm superiority of bezlotoxumab over placebo". No formal power or sample size calculation was provided, but possible scenarios that could be observed in the data:

Table 15: Variability around various possible treatment differences

Bezlotoxumab (n=144)	Placebo (n=48)	Difference (95% CI) (Bezlotoxumab – Placebo)
8% (11/144)	15% (7/48)	-7 (-20, 2)
12% (17/144)	19% (9/48)	-7 (-21, 4)
16% (23/144)	23% (11/48)	-7 (-22, 5)
20% (29/144)	27% (13/48)	-7 (-22, 6)
8% (11/144)	17% (8/48)	-9 (-23, 1)
12% (17/144)	21% (10/48)	-9 (-23, 2)
16% (23/144)	25% (12/48)	-9 (-24, 3)
20% (29/144)	29% (14/48)	-9 (-24, 4)
8% (11/144)	19% (9/48)	-11 (-25, -1)
12% (17/144)	23% (11/48)	-11 (-26, 0)
16% (23/144)	27% (13/48)	-11 (-26, 2)
20% (29/144)	31% (15/48)	-11 (-27, 2)

* Based on the Miettinen and Nurminen method (unstratified)

During the trial, the sample size 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. 202 subjects were screen for inclusion in the trial, 148 were randomized, 143 received study intervention, and 138 completed the study.

Consideration of the sample size regarding safety are acceptable to the CHMP.

Consideration of the sample size regarding efficacy are acknowledged by the CHMP but not considered optimal by the Committee. The presented calculations assume that 100% of the study participants (in either group) reaches initial clinical response (a prerequisite in order to be included in the mITT for efficacy analysis), which was not to be expected in the trial. 132 subjects were eventually analysed for efficacy in the final analysis (98 from bezlotoxumab group and 34 from placebo group). However, since efficacy was not the primary objective of the study, and efficacy data are only to be considered supportive for the scope of this assessment, the sample size is thereof acceptable to the Committee.

Randomisation

Treatment allocation/randomization was planned to occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). The randomisation ratio was 3:1 to bezlotoxumab or placebo, respectively. Randomisation was stratified by age cohort (age cohort 1: 12 to <18 years of age; age cohort 2: 1 to <12 years of age). This was considered acceptable by the CHMP.

Blinding (masking)

The study was planned as double blind. Bezlotoxumab and placebo were planned to be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. Standard procedures in case of unblinding due to welfare of the participant were described in the protocol.

This was considered acceptable by the CHMP.

Statistical methods

Analysis Populations/Sets

Per-Protocol (PP) population: used for PK analyses. Treated participants who complete PK sampling with at least 4 post-dose evaluable samples and comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment.

All Participants as Treated (APaT): used for safety analyses. All randomized participants who receive infusion of study medication, corresponding to the study treatment they actually received. Participants in Panel A to be analysed separately in case of dose modification.

Modified intention to treat (mITT): used for efficacy analyses. All randomized participants with participants excluded for the following reasons:(a) Did not receive any amount of study medication; (b) Did not have a positive local stool test for *C. difficile* toxin to confirm CDI diagnosis of the baseline episode (c) Was not taking a protocol-defined antibacterial drug treatment for CDI on the day of the infusion. Participants in Panel A to be analysed separately in case of dose modification.

Efficacy evaluable (EE) population: used for efficacy analysis. Subset of mITT excluding participants because of (a) important deviations from the protocol that may affect the efficacy results (b) prior or concomitant usage of IV immune globulin (IVIG) (c)Participants who become unblinded for any reason.

Primary Endpoint(s) / Primary Estimand(s)

No primary endpoints for efficacy.

Secondary Endpoints / Secondary Estimand(s)

Three secondary objectives for efficacy:

1. Proportion of participants with CDI recurrence: Proportion of participants who have a CDI recurrence within 12 weeks of study medication infusion. CDI recurrence is assessed by the investigator.
2. Proportion of participants with sustained clinical response: 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.

3. Estimation of 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 bezlotoxumab or placebo.

Data were planned to be analysed using Miettinen and Nurminen's method for stratified data and Cochran-Mantel-Haenszel weights. The 95% CI for the differences in proportions were planned to be presented along with nominal 2-sided p-values (not for inferential purposes).

As a supportive analysis, time to CDI recurrence was planned to be assessed using Kaplan-Meier method and compared between groups using stratified log-rank test.

While not explicitly stated in the methods section, efficacy results were presented in absolute differences.

Missing data

Not described in the protocol or SAP. No missing data for efficacy outcomes were reported in the CSR.

Multiplicity

No multiplicity control.

Interim Analyses

Two planned reviews of safety and tolerability data by the DMC. No interim analyses for efficacy planned.

The CHMP noted that efficacy was only planned as secondary, supportive objective. No formal hypotheses were tested. The methodology is considered appropriate by the CHMP.

Results

Participant flow

Table 16

Table 10-1
Disposition of Participants
All Randomized Participants

	Age Cohort 1 12 to <18 years Bezlotoxumab		Age Cohort 1 12 to <18 years Placebo		Age Cohort 2 1 to <12 years Bezlotoxumab		Age Cohort 2 1 to <12 years Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	46		16		65		21	
Status for Trial								
Completed	42	(91.3)	16	(100.0)	61	(93.8)	19	(90.5)
Discontinued	4	(8.7)	0	(0.0)	4	(6.2)	2	(9.5)
Death	2	(4.3)	0	(0.0)	1	(1.5)	0	(0.0)
Lost To Follow-Up	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)
Protocol Deviation	2	(4.3)	0	(0.0)	2	(3.1)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5)
Status for Study Intervention in Trial								
Completed	44	(95.7)	16	(100.0)	63	(96.9)	20	(95.2)
Status Not Recorded	2	(4.3)	0	(0.0)	2	(3.1)	1	(4.8)

Conduct of the study

There was one amendment of the protocol.

Table 17: Protocol amendments for MK-6072-001

Document	Date of Issue	Rationale
Protocol Amendment 01	07-FEB-2019	Modify the enrollment strategy with the aim of shortening the overall enrollment timelines. Permit dose modification within an age cohort, and therefore the initially planned pause in enrollment after 12 participants have a complete set of PK samples in Panel A of an age cohort has been removed. Patients will continue to be enrolled in Panel A until the PK analysis is completed, and the dose has been confirmed, enrollment in Panel B of the age cohort will commence. Enrollment in Panel A of Age Cohort 2 will commence after the first 12 participants in Panel A of Age Cohort 1 have completed all study visits.
Original Protocol	25-APR-2017	Not applicable.

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 SAE rate was within the range expected given the comorbidities of the study population and supported the determination that enrolment of additional participants was not needed to characterize the safety and tolerability of MK-6072 in paediatric patients.

Baseline data

Table 18: Participant characteristics, All participants treated

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	107		36		143	
Sex						
Male	57	(53.3)	18	(50.0)	75	(52.4)
Female	50	(46.7)	18	(50.0)	68	(47.6)
Age (Years)						
1 to <6	37	(34.6)	13	(36.1)	50	(35.0)
6 to <12	26	(24.3)	7	(19.4)	33	(23.1)
12 to <18	44	(41.1)	16	(44.4)	60	(42.0)
Mean	9.2		9.3		9.2	
SD	5.3		5.3		5.3	
Median	10.0		8.0		9.0	
Range	1 to 17		1 to 17		1 to 17	
Race						
American Indian Or Alaska Native	2	(1.9)	0	(0.0)	2	(1.4)
Asian	3	(2.8)	2	(5.6)	5	(3.5)
Black Or African American	6	(5.6)	1	(2.8)	7	(4.9)
Multiple	9	(8.4)	1	(2.8)	10	(7.0)
Black Or African American, White	9	(8.4)	1	(2.8)	10	(7.0)
White	83	(77.6)	32	(88.9)	115	(80.4)
Missing	4	(3.7)	0	(0.0)	4	(2.8)
Ethnicity						
Hispanic Or Latino	28	(26.2)	8	(22.2)	36	(25.2)
Not Hispanic Or Latino	69	(64.5)	27	(75.0)	96	(67.1)
Not Reported	9	(8.4)	1	(2.8)	10	(7.0)
Unknown	1	(0.9)	0	(0.0)	1	(0.7)
Weight (kg)						
Participants with data	107		36		143	
Mean	36.0		32.9		35.2	
SD	23.0		23.6		23.1	
Median	30.1		24.2		27.0	

Participant Characteristics
All Participants as Treated

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Range	7.8 to 108.0		8.8 to 116.9		7.8 to 116.9	
Body Mass Index (kg/m²)						
Participants with data	105		35		140	
Mean	18.1		16.6		17.7	
SD	4.8		4.9		4.9	
Median	16.6		15.1		16.2	
Range	11.3 to 37.4		9.5 to 36.9		9.5 to 37.4	
Region of Enrollment						
US	22	(20.6)	7	(19.4)	29	(20.3)
Ex-US	85	(79.4)	29	(80.6)	114	(79.7)
Primary Treatment for Baseline CDI Episode						
vancomycin - enteral/oral	44	(41.1)	15	(41.7)	59	(41.3)
fidaxomicin - enteral/oral	14	(13.1)	5	(13.9)	19	(13.3)
metronidazole - enteral/oral	47	(43.9)	16	(44.4)	63	(44.1)
Missing	2	(1.9)	0	(0.0)	2	(1.4)

Source: [P001MK6072: adam-adsl]

Demographic and baseline characteristics were generally comparable between study intervention groups in both the APaT and mITT populations:

- The median age of participants in the APaT population was 10.0 years in the bezlotoxumab group, and 8.0 years in the placebo group. Overall, 52.4% of participants were male and 80.4% of participants were White (race).
- Six participants 1 to <2 years of age were enrolled; 4 received a single IV infusion of bezlotoxumab.

Medical history and concurrent illnesses

The medical history conditions most frequently reported (>20% of participants in either intervention group in the APaT population) were: thrombocytopenia (bezlotoxumab group: 28.0%; placebo group: 44.4%), febrile neutropenia (23.4%; 41.7%), anaemia (35.5%; 58.3%), neutropenia (29.9%; 38.9%), vomiting (19.6%; 27.8%), central venous catheterization (22.4%; 27.8%), abdominal pain (7.5%; 25.0%), nausea (15.9%; 25.0%), mucosal inflammation (12.1%; 22.2%), pyrexia (17.8%; 22.2%), and acute lymphocytic leukaemia (11.2%; 22.2%).

CDI-related medical conditions were generally comparable between intervention groups in the mITT population. The most frequently reported CDI-related medical conditions were: neutropenia (bezlotoxumab group: 52.9%; placebo group: 60.0%), active hematologic malignancy (38.5%; 48.6%), and malignant solid tumour (30.8%; 37.1%).

The CHMP noted that demographic and baseline characteristics as well as medical history conditions were in general between the wo treatment groups.

The MAA reported CDI-related conditions. Among these conditions were active haematologic malignancy (38.5%; 48.6%), and malignant solid tumour (30.8%; 37.1%). This was not comprehensible; the reported conditions seemed rather concurrent illness than CDI-related conditions. Upon CHMP request, the MAH clarified that CDI-related conditions represent conditions that result in significant immunosuppression (due to either the condition itself, its treatment, or both) and therefore increase the risk of CDI and recurrent CDI. This response is acceptable to the CHMP.

Severity of CDI baseline episode

Overall, 18.0% of participants in the mITT population met the criteria for severe CDI (19.2% in the bezlotoxumab group, 14.3% in the placebo group) [Table 14.1-28]. The most frequently reported criteria for severe CDI at baseline episode were bloody diarrhoea (10.1%), fever (7.2%) and diarrhoea accompanied by dehydration.

Severe complicated baseline episode

Three (2.2%) participants in the mITT population presented with severe complicated cases of CDI at the baseline episode. The 3 participants were in the bezlotoxumab group and met the criteria for intensive care unit admission.

CDI antibiotic treatment for baseline episode

All participants in the mITT population were receiving a protocol-defined SOC CDI antibiotic treatment for the baseline CDI episode on the day of intervention.

Specific CDI antibiotic treatment for baseline episode was comparable between the study interventions groups. The most frequently administered concomitant antibiotic treatments for baseline episode were vancomycin (40.3% of participants) and metronidazole (53.2%).

- The mean number of total days on SOC antibiotic treatment for the baseline CDI episode was 14.4 days and was comparable between intervention groups.
- The mean number of days on CDI antibiotic treatment for the baseline episode prior to study intervention was 7.6 days and was comparable between intervention groups.

CDI antibiotic treatment for baseline episode in the mITT population with initial clinical response was consistent with the overall mITT population. The most frequently administered concomitant antibiotic treatments for baseline episode were vancomycin (40.2% of participants in the mITT population with initial clinical response) and metronidazole (51.5%).

Prognostic risk factors

Most participants (94.2%) had 1 or more risk factor for CDI recurrence. The most common risk factors were being immunocompromised (72.7%) and having received treatment with 1 or more systemic antibacterials during treatment for CDI during the baseline episode (62.6%). Approximately one-third of participants in each intervention group had 1 or more episodes of CDI at any point prior to the baseline episode.

The percentage of participants with a prior history of CDI diagnosis and other prognostic risk factors for CDI recurrence (number of prior CDI episodes, etc.) were comparable between intervention groups in both the APaT and mITT populations, respectively. In the mITT population the mean number of prior CDI episodes was 2.7 in the bezlotoxumab group and 3.4 in the placebo group.

Numbers analysed

Table 19

Summary of Participants Included in Analysis Populations
All Randomized Participants

	Bezlotoxumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Included	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)
Had at least one important protocol deviations that have the potential to impact efficacy	22	(19.8)	5	(13.5)	27	(18.2)
Took prior or concomitant IVIG	14	(12.6)	5	(13.5)	19	(12.8)
Participants got unblinded for any reason	4	(3.6)	0	(0.0)	4	(2.7)

Every participant is counted a single time for each applicable row and column.
CDI= *Clostridioides (Clostridium) difficile* infection; IV= intravenous; IVIG=intravenous immune globulin.

Source: [P001MK6072: adam-adsl]

Table 20:Definitions of the efficacy of populations analyzed

Analysis Population / Data Sets	Definition
Modified Intent to Treat (mITT) [a, b]	All participants who received any amount of study intervention, had a positive local stool for *C. difficile* toxin and were taking protocol-defined antibacterial drug treatment for CDI on the day of infusion.
mITT with initial clinical response [a]	A subset of the mITT population who achieved an initial clinical response of the baseline CDI.
mITT with initial clinical response and at high risk[c] for CDI recurrence [a]	A subset of the mITT population who achieved an initial clinical response of the baseline CDI and were at high risk for CDI recurrence.
mITT at high risk for CDI recurrence [b]	A subset of the mITT at high risk for CDI recurrence.
mITT at high risk for CDI recurrence or received 1 or more systemic antibacterials[b]	A subset of the mITT who were at high risk for CDI recurrence or received 1 or more systemic antibacterials.
Efficacy Evaluable (EE)	A subset of the mITT population that excluded participants with important protocol deviations that may affect the efficacy results (determined prior to the final unblinding of the database), all prematurely unblinded participants, and those participants who received prior or concomitant IVIG.

CDI=*C. difficile* infection; EE=efficacy evaluable; IVIG= intravenous immune globulin; mITT=modified intent to treat.
[a] Population analyzed for the CDI recurrence endpoint.
[b] Population analyzed for the sustained clinical response endpoint.
[c] High risk was 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 the 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).

Source: Adapted from [Ref. 5.3.5.1: P001MK6072: Table 10-2] [Ref. 5.3.5.1: P001MK6072: 16.1.1]

Outcomes and estimation

Efficacy outcomes were secondary endpoints in P001 and the study was not powered for formal hypothesis testing of between-intervention group comparisons. The efficacy analyses for this study were conducted using the mITT population. The main analysis for CDI recurrence was based on a subset of the mITT population consisting of participants who achieved an initial clinical response.

Table 21

Table 11-3
Efficacy Populations Associated With Key Endpoints

Key Endpoint	Main Efficacy Population and Subsets
CDI recurrence	• mITT with initial clinical response • mITT • mITT with initial clinical response and at high risk for CDI recurrence • mITT at high risk for CDI recurrence • mITT with initial clinical response and at high risk for CDI recurrence or received 1 or more systemic antibacterials during the 12 week follow-up period
Sustained Clinical Response	• mITT • mITT at high risk for CDI recurrence • mITT at high risk for CDI recurrence or received 1 or more systemic antibacterials during the 12 week follow-up period
CDI=*C. difficile* infection; mITT=modified intent-to-treat.	

Source: [16.1.1]

C. difficile infection recurrence

CDI Recurrence (mITT population with initial clinical response)

The percentage of participants in the mITT population with initial clinical response who had CDI recurrence was low and comparable between intervention groups.

Table 22

Table 11-5
Analysis of CDI Recurrence
Study Intervention Through 12 Week Follow-up
Modified Intent-to-Treat with Initial Clinical Response

Treatment	% (n/N)	Treatment Difference [Bezlotoxumab - Placebo]		
		Unadjusted Difference	Adjusted Difference (95% CI)[a]	p-Value[a]
Bezlotoxumab	11.2 (11/98)	-3.5	-3.7 (-20.0, 8.0)	0.5701
Placebo	14.7 (5/34)			

CDI= *Clostridioides (Clostridium) difficile* infection.
n = Number of participants in the modified intent-to-treat population with initial clinical response of baseline CDI met the criteria for endpoint.
N = Number of participants included in the modified intent-to-treat population with initial clinical response of baseline CDI.
This table considers any CDI recurrence events that occurred from Day 1 through Week 12 (Day 85 ±5 days).
CDI recurrence is defined as participants developed at least one diarrhea recurrence associated with a positive test for the presence of *C. difficile* toxin in stool and for which the participant, in the investigators opinion, requires and receives antibacterial drug treatment for CDI.
[a] 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.

Source: [P001MK6072: adam-adsl; adeff]

- No clinically meaningful differences were observed in the percentage of participants with CDI recurrence in the mITT population with initial clinical response when analysed across subgroups compared with the overall population [Table 14.2.3-5].
- No clinically meaningful differences in CDI recurrence were observed between intervention groups associated with protocol-defined risk factors for CDI recurrence in the mITT population with initial clinical response [Table 14.2.3-6].
- The time to CDI recurrence in participants in the mITT population with initial clinical response was comparable for both intervention groups [Figure 14.2.3-1].
- CDI recurrence rates in the mITT [Table 14.2.3-7] and EE [Table 14.2.3-8] populations were generally consistent with those reported for the mITT population with initial clinical response.
- CDI recurrence subgroup analysis results (i.e., by age cohort, sex, race, primary treatment for baseline CDI episode, or adjunctive treatment for baseline CDI episode) in the mITT [Table 14.2.3-9]. and EE [Table 14.2.3-10] populations were generally consistent with those reported for the mITT population with initial clinical response.
- No clinically meaningful differences in CDI recurrence were observed between intervention groups associated with protocol-defined risk factors for CDI recurrence in the EE population [Table 14.2.3-11].

Sustained clinical response results

The percentage of participants in the mITT population with sustained clinical response was comparable between intervention groups (bezlotoxumab: 83.7%; placebo: 82.9%) [Table 14.2.3-12].

- There were no clinically meaningful differences observed between intervention groups in sustained clinical response across the subgroups analysed (i.e., age cohort, sex, race, primary treatment for baseline CDI episode, or adjunctive treatment for baseline CDI episode) compared with the overall population [Table 14.2.3-13].
- No clinically meaningful differences in sustained clinical response were observed between

intervention groups associated with protocol-defined risk factors for CDI recurrence in the mITT population [Table 14.2.3-14].

- Sustained clinical response rates in the EE population were generally consistent with those reported in the mITT population [Table 14.2.3-15].
- Sustained clinical response subgroup analysis results (i.e., age cohort, sex, race, primary treatment for baseline CDI episode, or adjunctive treatment for baseline CDI episode) in the EE population [Table 14.2.3-16] were consistent with those observed in the mITT population.
- No clinical meaningful differences in sustained clinical response were observed between intervention groups associated with protocol-defined risk factors for CDI recurrence in the EE population [Table 14.2.3-17].

Efficacy in participants at high risk for CDI

recurrence CDI recurrence

The percentage of participants in the mITT population with initial clinical response who had CDI recurrence and were at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 12.1%; placebo: 15.2%) [Table 14.2.3-18].

CDI recurrence rates in the mITT [Table 14.2.3-19] and EE [Table 14.2.3-20] populations at high risk for CDI recurrence were generally consistent with those reported for the mITT population with initial clinical response at high risk for CDI recurrence.

Sustained clinical response

The percentage of participants in the mITT population with sustained clinical response and at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 82.5%, placebo: 82.4%) [Table 14.2.3-21].

Sustained clinical response rates in the EE population at high risk for CDI recurrence were generally consistent with those reported in the mITT population at high risk for CDI recurrence [Table 14.2.3-22].

Sensitivity analysis: Efficacy in participants at high risk for CDI recurrence or who received systemic antibacterials during the 12 Week follow-up Period

In sensitivity analyses listed below, efficacy in participants at high risk for CDI recurrence or who received systemic antibacterials during the 12-week follow-up period was generally consistent with efficacy results reported for participants at high risk for CDI recurrence:

- CDI recurrence (mITT population with initial clinical response) [Table 14.2.3-23].
- CDI recurrence (EE population) [Table 14.2.3-24].
- Sustained clinical response (mITT population) [Table 14.2.3-25].
- Sustained clinical response (EE population) [Table 14.2.3-26].

Tertiary/exploratory endpoint

mITT Population: Diarrhoea recurrence

The percentage of participants in the mITT population with initial clinical response who had diarrhea recurrence was 25.5% in the bezlotoxumab group and 35.3% in the placebo group [Table 14.2.3-27] [16.2.6].

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23: Summary of Efficacy for Study MK-6072-001

<table>
<tr><td colspan="3"><u>Title:</u> A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of a Single Infusion of Bezlotoxumab (P001MK6072, 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)</td></tr>
<tr><td>Study identifiers</td><td colspan="2">Protocol Number: P001MK6072
IND: 12,823
EudraCT: 2017-000070-11
NCT: NCT03182907</td></tr>
<tr><td>Design</td><td colspan="2">A Phase 3, randomized, placebo-controlled, parallel-group, multisite, double-blind study evaluating the pharmacokinetics (PK), safety, tolerability, and efficacy of a single infusion of bezlotoxumab in pediatric participants 1 to <18 years of age with a suspected or confirmed diagnosis of Clostridium difficile infection (CDI) who were receiving a 10- to 21-day course of antibacterial treatment for CDI.

Participants were randomized 3:1 to bezlotoxumab 10 mg/kg or placebo and were stratified by age at randomization (Age Cohort 1: 12 to <18 years of age, Age Cohort 2: 1 to <12 years of age). After receiving a single dose of study intervention, participants were followed up for 12 weeks (ie, 85 ± 5 days) for PK and immunogenicity collections, monitoring of safety and tolerability parameters, and efficacy outcomes.</td></tr>
<tr><td></td><td>Duration of main phase:</td><td>First Participant First Visit: 27-MAR-2018
Last Participant Last Visit: 12-MAY-2022
Approximately 50 months</td></tr>
<tr><td></td><td>Duration of Run-in phase:</td><td>Not applicable</td></tr>
<tr><td></td><td>Duration of Extension phase:</td><td>Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Pharmacokinetic (Primary):
The area under the concentration-time curve from 0 to infinity (AUC0-inf) of bezlotoxumab after treatment of 2 age cohorts of pediatric participants (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) with a single infusion of bezlotoxumab is similar when compared with the AUC0-inf of bezlotoxumab after treatment of adult participants with a single infusion of 10 mg/kg bezlotoxumab, a dose demonstrated to be safe and efficacious in adults. That is, the true geometric mean ratios (GMRs, pediatric participants/adults) for AUC0-inf of bezlotoxumab are contained in the clinical comparability bounds of (0.6, 1.6) in each of the age cohorts.

Efficacy (Secondary):</td></tr>
</table>

Objectives	Primary objective: To characterize bezlotoxumab PK in 2 age cohorts (Age Cohort 1: 12 to <18 years; Age Cohort 2: 1 to <12 years) of pediatric participants to support dose selection in this population. Secondary Objectives: Efficacy outcomes were secondary endpoints. The study was not powered for formal hypothesis testing for efficacy. To estimate the proportion of participants who have a CDI recurrence within 12 weeks following administration of a single infusion of bezlotoxumab or placebo. To estimate the proportion of participants with sustained clinical response over a period of 12 weeks in participants who received a single infusion of bezlotoxumab or placebo. 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 bezlotoxumab or placebo.

Treatment groups	Bezlotoxumab		Bezlotoxumab 10 mg/kg, single intravenous (IV) infusion 104 participants were randomized, 104 (100%) participants completed study intervention, 104 (96.2%) participants completed the study.
	Placebo		Single IV infusion 35 participants were randomized, 35 (100%) participants completed study intervention, 34 (97.1%) participants completed the study.
Endpoints and definitions	Primary Endpoint	Bezlotoxumab Pharmacokinetics	For each age cohort, plasma PK profile, included area under the concentration-time curve from 0 to infinity (AUC0-inf), maximum observed plasma concentration (Cmax), time to maximum concentration (Tmax), terminal half-life (t1/2), volume of distribution (Vdss), and clearance (CL) following administration of bezlotoxumab.
	Secondary Efficacy Endpoint	CDI Recurrence	Proportion of participants who have a CDI recurrence as assessed by the investigator within 12 weeks following administration of a single infusion of bezlotoxumab or placebo. CDI recurrence is defined as the development of diarrhea recurrence 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.
	Secondary Efficacy Endpoint	Sustained Clinical Response	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 as assessed by the investigator AND no CDI recurrence through Week 12.

	Secondary Efficacy Endpoint	CDI Recurrence – Participants at High Risk Sustained Clinical Response – Participants at High Risk	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).
Database lock	14-JUL-2022		

Results and Analysis

The AUC0-inf of bezlotoxumab following a single IV infusion of 10 mg/kg in paediatric patients (1 to <18 years of age) is similar to the historical PK data for AUC0-inf in adult patients with CDI. The PK data support the selection of the adult dose of 10 mg/kg dose for paediatric patients 1 year of age and older and the extrapolation of efficacy and safety established in adults for the prevention of CDI recurrence to the paediatric population.

In paediatric participants (1 to <18 years of age) with CDI who received a single IV dose of bezlotoxumab (10 mg/kg) or placebo, the percentage of participants with CDI recurrence was low and comparable between the bezlotoxumab and placebo groups.

Results for the 3 main efficacy objectives (CDI recurrence, sustained clinical response, and efficacy in participants at high risk of recurrence) were comparable between intervention groups. Despite most participants having protocol-defined risk factors for recurrence, the percentage of participants with CDI recurrence was low in the modified intent-to-treat (mITT) population, with 17 participants experiencing a recurrence.

In sensitivity analyses, the percentage of participants who had a CDI recurrence in the mITT population with initial clinical response and were at high risk for CDI recurrence or who received systemic antibacterials during the 12-week follow-up was comparable between intervention groups and generally consistent with results reported for participants at high risk for CDI recurrence.

In sensitivity analyses, the percentage of participants in the mITT population who had sustained clinical response and were at high risk for CDI recurrence or who received systemic antibacterials during the 12-week follow-up period was comparable between intervention groups and generally consistent with results reported for participants at high risk for CDI recurrence.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study P001 was randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of a single Infusion of bezlotoxumab human monoclonal antibody to *C. difficile* Toxin B) in children aged 1 to <18 years receiving antibacterial drug treatment for *C. difficile* infection.

Male and female participants aged 1 to <18 years with *C. difficile* infection (CDI) (confirmed presence of *C. difficile* toxin in stool) and receiving a 10- to 21-day course of antibacterial drug treatment for

CDI were eligible to participate.

Patients were treated with a single dose of 10mg/kg single dose of bezlotoxumab or placebo on top of adequate CDI treatment. The dose is the same dose as for treatment of adults.

Efficacy outcomes were secondary endpoints and the study was not powered for formal hypothesis testing of between treatment group comparisons. Efficacy endpoints were analysed from the day study intervention was administered through the 12-week follow-up period and point estimates are provided for the efficacy of bezlotoxumab versus placebo. The duration of follow up is adequate.

The efficacy endpoints were:

- CDI recurrence within 12 weeks of study medication infusion.
- Sustained clinical response over 12 weeks; defined as initial clinical response of the baseline CDI episode AND no CDI recurrence through Week 12.
- CDI recurrence and proportion of participants who achieve sustained clinical response within 12 weeks of study infusion in the subset of participants at high risk of CDI recurrence.

Efficacy data and additional analyses

The efficacy analyses for this study were conducted using the mITT population and subsets of the mITT population. The main analysis for CDI recurrence was conducted using a subset of the mITT population, which included participants who achieved an initial clinical response of baseline CDI. The analysis population is acceptable by the CHMP. Of not bezlotoxuab is not expected to have an effect on the current episode, it its aimed to reverent further episodes within 3 months of treatment.

Demographic and baseline characteristics were generally comparable between study intervention groups in both the APaT and mITT populations. The MAA reported CDI-related conditions. Among these conditions were active haematologic malignancy (38.5%; 48.6%), and malignant solid tumour (30.8%; 37.1%). This was not comprehensible; the reported conditions seemed rather concurrent illness than CDI-related conditions. Upon CHMP request, the MAH clarified that CDI-related conditions represent conditions that result in significant immunosuppression (due to either the condition itself, its treatment, or both) and therefore increase the risk of CDI and recurrent CDI. This response is acceptable to the CHMP.

CDI antibiotic treatment for baseline episode in the mITT population with initial clinical response was consistent with the overall mITT population. The most frequently administered concomitant antibiotic treatments for baseline episode were vancomycin (40.2% of participants in the mITT population with initial clinical response) and metronidazole (51.5%).

Most participants (94.2%) had 1 or more risk factor for CDI recurrence. The most common risk factors were being immunocompromised (72.7%) and having received treatment with 1 or more systemic antibacterials during treatment for CDI during the baseline episode (62.6%). Approximately one-third of participants in each intervention group had 1 or more episodes of CDI at any point prior to the baseline episode.

The percentage of participants in the mITT population with initial clinical response who had CDI recurrence was low and comparable between intervention groups (bezlotoxumab: 11,2%; placebo: 14,7%).

The percentage of participants in the mITT population with sustained clinical response was comparable between intervention groups (bezlotoxumab: 83.7%; placebo: 82.9%). There were no clinically meaningful differences observed between intervention groups in sustained clinical response

across the subgroups analysed (i.e., age cohort, sex, race, primary treatment for baseline CDI episode, or adjunctive treatment for baseline CDI episode) compared with the overall population.

The percentage of participants in the mITT population with initial clinical response who had CDI recurrence and were at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 12.1%; placebo: 15.2%).

The percentage of participants in the mITT population with sustained clinical response and at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 82.5%, placebo: 82.4%).

2.4.4. Conclusions on the clinical efficacy

In paediatric participants (1 to <18 years of age) with CDI who received a single IV dose of bezlotoxumab (10 mg/kg) or placebo, the CHMP noted that the percentage of participants with CDI recurrence was low and comparable between the bezlotoxumab and placebo groups. Although the pharmacokinetic evaluation showed comparable exposure between the adult and paediatric population, these results are not reflected in the efficacy data. The treatment group showed comparable results with the placebo group. These cannot be explained in a different pathophysiology in paediatric and adult population. The MAH stated that a lower background incidence of CDI was observed during the study period than in the period prior to MODIFY III. Since study enrolment partly occurred during the COVID-19 era the strict hygiene and cleaning practices were in place in hospitals and communities; this may have contributed to decreased recurrence rates. The simulation exercise presented by the MAH supports the MAH's statement that the efficacy results of the MODIFY III trials, while not compelling, are not unexpected for the given scenario.

2.5. Clinical safety

Introduction

A primary objective of the study was the evaluation of safety and tolerability of bezlotoxumab compared with placebo following a single dose of infusion through 12 weeks.

Safety and tolerability in P001 were evaluated by collection of AE data, clinical laboratory evaluations, and vital sign measurements. Safety analyses were performed on the APaT population. These analyses were performed using the M&N asymptotic method (1985) and 95% CIs were provided.

All participants who received study intervention completed a single infusion of either 10 mg/kg bezlotoxumab or placebo, therefore the extent of exposure was the same for all participants.

Patient exposure

A total of 107 paediatric participants received bezlotoxumab and 36 received placebo.

Table 24

Disposition of Participants
All Participants as Treated

	Total Bezlotoxumab		Total Placebo	
	n	(%)	n	(%)
Participants in population	107		36	
Status for Trial				
Completed	103	(96.3)	35	(97.2)
Discontinued	4	(3.7)	1	(2.8)
Death	3	(2.8)	0	(0.0)
Lost To Follow-Up	1	(0.9)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	1	(2.8)
Status for Study Intervention in Trial				
Completed	107	(100.0)	36	(100.0)

Each participant is counted once for trial disposition and study intervention disposition.
"Status Not Recorded" disposition statuses are for participants who were randomized and never dosed.
There are a total of 7 deaths among all treated participants. Three deaths occurred prior to the completion of the 12-week study follow-up period and are summarized in this table. One participant died after early discontinuation due to withdrawal of parental consent. Three participants died after completing the 12-week follow-up; 1 of these 3 developed a serious adverse event leading to death, which began after the participant completed the 12-week study follow-up period.

Source: [P001MK6072: adam-adsl; adex]

The disposition of participants was generally comparable between study intervention groups (APaT population).

Adverse events

A higher observed incidence of AEs considered related to study intervention by the investigator was reported for the participants in the bezlotoxumab group (15.9%) compared with the placebo group (8.3%), with a 95% CI for the treatment difference that included zero.

There was a lower incidence of SAEs in the bezlotoxumab group (53.3%) compared with the placebo group (80.6%), with a 95% CI for the treatment difference that excluded zero. Most SAEs were considered not related to study intervention by the investigator.

Six deaths occurred due to AEs that began during the 12-week follow-up period (5 in the bezlotoxumab group, 1 in the placebo group). None the deaths were considered related to study intervention by the investigator.

No participant discontinued study intervention due to an AE.

Table 25

Table 2.5-rcdi-peds: 7
Analysis of Adverse Event Summary
Study Intervention Through 12 Week Follow-up
All Participants as Treated

	Bezlotoxumab		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	107		36		
with one or more adverse events	95	(88.8)	34	(94.4)	-5.7 (-14.5, 7.7)
with no adverse event	12	(11.2)	2	(5.6)	5.7 (-7.7, 14.5)
with drug-related[b] adverse events	17	(15.9)	3	(8.3)	7.6 (-7.1, 17.8)
with serious adverse events	57	(53.3)	29	(80.6)	-27.3 (-41.4, -9.3)
with serious drug-related adverse events	2	(1.9)	0	(0.0)	1.9 (-7.9, 6.6)
who died	5	(4.7)	1	(2.8)	1.9 (-9.8, 8.4)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0.0 (-9.7, 3.5)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-9.7, 3.5)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0.0 (-9.7, 3.5)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-9.7, 3.5)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
This table includes adverse events that occurred from Day 1 through Week 12 (Day 85 ±5 days).

Source: [P001MK6072: adam-adsl; adae]

The most frequently reported AEs (reported for ≥20% participants in either intervention group) were: febrile neutropenia (bezlotoxumab: 21.5%, placebo: 30.6%), pyrexia (17.8%, 30.6%), headache (14.0%, 22.2%), and vomiting (13.1%, 22.2%).

Table 26

Table 12-2
Participants With Adverse Events
(Incidence ≥ 10% in One or More Treatment Groups)
Study Intervention Through 12 Week Follow-up
All Participants as Treated

	Bezlotoxumab		Placebo	
	n	(%)	n	(%)
Participants in population	107		36	
with one or more adverse events	95	(88.8)	34	(94.4)
with no adverse events	12	(11.2)	2	(5.6)
Blood and lymphatic system disorders	**37**	**(34.6)**	**17**	**(47.2)**
Anaemia	8	(7.5)	6	(16.7)
Febrile neutropenia	23	(21.5)	11	(30.6)
Gastrointestinal disorders	**49**	**(45.8)**	**14**	**(38.9)**
Abdominal pain	15	(14.0)	6	(16.7)
Diarrhoea	8	(7.5)	5	(13.9)
Nausea	8	(7.5)	4	(11.1)
Vomiting	14	(13.1)	8	(22.2)
General disorders and administration site conditions	**28**	**(26.2)**	**14**	**(38.9)**
Pyrexia	19	(17.8)	11	(30.6)
Hepatobiliary disorders	**6**	**(5.6)**	**4**	**(11.1)**
Infections and infestations	**59**	**(55.1)**	**26**	**(72.2)**
Injury, poisoning and procedural complications	**3**	**(2.8)**	**6**	**(16.7)**
Investigations	**25**	**(23.4)**	**8**	**(22.2)**
Metabolism and nutrition disorders	**20**	**(18.7)**	**9**	**(25.0)**
Hypokalaemia	9	(8.4)	6	(16.7)
Musculoskeletal and connective tissue disorders	**12**	**(11.2)**	**4**	**(11.1)**
Nervous system disorders	**22**	**(20.6)**	**8**	**(22.2)**
Headache	15	(14.0)	8	(22.2)
Respiratory, thoracic and mediastinal disorders	**16**	**(15.0)**	**8**	**(22.2)**
Skin and subcutaneous tissue disorders	**17**	**(15.9)**	**10**	**(27.8)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 was used in the reporting of this study.
This table includes adverse events that occurred from Day 1 through Week 12 (Day 85 ±5 days).

Source: [P001MK6072: adam-adsl; adae]

The most frequently reported AEs considered related to study intervention in the bezlotoxumab group were ALT increased, AST increased, and headache (each for 3 [2.8% participants). The most frequently reported AE related to study intervention in the placebo group was headache (2 [5.6%] participants).

Table 27

Analysis Population / Data Sets	Definition
Modified Intent to Treat (mITT) [a, b]	All participants who received any amount of study intervention, had a positive local stool for *C. difficile* toxin and were taking protocol-defined antibacterial drug treatment for CDI on the day of infusion.
mITT with initial clinical response [a]	A subset of the mITT population who achieved an initial clinical response of the baseline CDI.
mITT with initial clinical response and at high risk[c] for CDI recurrence [a]	A subset of the mITT population who achieved an initial clinical response of the baseline CDI and were at high risk for CDI recurrence.
mITT at high risk for CDI recurrence [b]	A subset of the mITT at high risk for CDI recurrence.
mITT at high risk for CDI recurrence or received 1 or more systemic antibacterials[b]	A subset of the mITT who were at high risk for CDI recurrence or received 1 or more systemic antibacterials.
Efficacy Evaluable (EE)	A subset of the mITT population that excluded participants with important protocol deviations that may affect the efficacy results (determined prior to the final unblinding of the database), all prematurely unblinded participants, and those participants who received prior or concomitant IVIG.

CDI=*C. difficile* infection; EE=efficacy evaluable; IVIG= intravenous immune globulin; mITT=modified intent to treat.
[a] Population analyzed for the CDI recurrence endpoint.
[b] Population analyzed for the sustained clinical response endpoint.
[c] High risk was 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 the 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).

Source: Adapted from [Ref. 5.3.5.1: P001MK6072: Table 10-2] [Ref. 5.3.5.1: P001MK6072: 16.1.1]

Table 28

Table 14.3-8
Participants With Drug-Related Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Study Intervention Through 12 Week Follow-up
All Participants as Treated

	Bezlotoxumab		Placebo	
	n	(%)	n	(%)
Participants in population	107		36	
with one or more drug-related adverse events	17	(15.9)	3	(8.3)
with no drug-related adverse events	90	(84.1)	33	(91.7)
Ear and labyrinth disorders	**1**	**(0.9)**	**0**	**(0.0)**
Vertigo	1	(0.9)	0	(0.0)
Gastrointestinal disorders	**6**	**(5.6)**	**2**	**(5.6)**
Abdominal pain	1	(0.9)	1	(2.8)
Anal inflammation	1	(0.9)	0	(0.0)
Intussusception	1	(0.9)	0	(0.0)
Large intestine polyp	0	(0.0)	1	(2.8)
Nausea	2	(1.9)	0	(0.0)
Vomiting	2	(1.9)	1	(2.8)
General disorders and administration site conditions	**4**	**(3.7)**	**1**	**(2.8)**
Asthenia	0	(0.0)	1	(2.8)
Fatigue	2	(1.9)	0	(0.0)
Infusion site rash	1	(0.9)	0	(0.0)
Pyrexia	2	(1.9)	0	(0.0)
Infections and infestations	**1**	**(0.9)**	**0**	**(0.0)**
Infection	1	(0.9)	0	(0.0)
Investigations	**4**	**(3.7)**	**1**	**(2.8)**
Alanine aminotransferase increased	3	(2.8)	0	(0.0)
Aspartate aminotransferase increased	3	(2.8)	0	(0.0)
Blood bicarbonate increased	1	(0.9)	0	(0.0)
Blood lactate dehydrogenase increased	2	(1.9)	0	(0.0)
Blood pressure decreased	0	(0.0)	1	(2.8)
Blood pressure systolic decreased	1	(0.9)	0	(0.0)
Clostridium test positive	1	(0.9)	0	(0.0)
Metabolism and nutrition disorders	**1**	**(0.9)**	**0**	**(0.0)**
Hyperphagia	1	(0.9)	0	(0.0)

Table 29

Analysis Population / Data Sets	Definition
Modified Intent to Treat (mITT) [a, b]	All participants who received any amount of study intervention, had a positive local stool for *C. difficile* toxin and were taking protocol-defined antibacterial drug treatment for CDI on the day of infusion.
mITT with initial clinical response [a]	A subset of the mITT population who achieved an initial clinical response of the baseline CDI.
mITT with initial clinical response and at high risk[c] for CDI recurrence [a]	A subset of the mITT population who achieved an initial clinical response of the baseline CDI and were at high risk for CDI recurrence.
mITT at high risk for CDI recurrence [b]	A subset of the mITT at high risk for CDI recurrence.
mITT at high risk for CDI recurrence or received 1 or more systemic antibacterials[b]	A subset of the mITT who were at high risk for CDI recurrence or received 1 or more systemic antibacterials.
Efficacy Evaluable (EE)	A subset of the mITT population that excluded participants with important protocol deviations that may affect the efficacy results (determined prior to the final unblinding of the database), all prematurely unblinded participants, and those participants who received prior or concomitant IVIG.

CDI=*C. difficile* infection; EE=efficacy evaluable; IVIG= intravenous immune globulin; mITT=modified intent to treat.
[a] Population analyzed for the CDI recurrence endpoint.
[b] Population analyzed for the sustained clinical response endpoint.
[c] High risk was 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 the 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).

Source: Adapted from [Ref. 5.3.5.1: P001MK6072: Table 10-2] [Ref. 5.3.5.1: P001MK6072: 16.1.1]

Table 30

Participants With Drug-Related Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Study Intervention Through 12 Week Follow-up
All Participants as Treated

	Bezlotoxumab		Placebo	
	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**1**	**(0.9)**	**0**	**(0.0)**
Pain in extremity	1	(0.9)	0	(0.0)
Nervous system disorders	**3**	**(2.8)**	**2**	**(5.6)**
Dizziness	0	(0.0)	1	(2.8)
Dysgeusia	0	(0.0)	1	(2.8)
Headache	3	(2.8)	2	(5.6)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(2.8)**
Dyspnoea	0	(0.0)	1	(2.8)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(2.8)**
Pruritus	0	(0.0)	1	(2.8)
Rash	0	(0.0)	1	(2.8)

Every participant is counted a single time for each applicable row and column.
Relatedness to study drug was determined by the investigator.
Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 was used in the reporting of this study.
This table includes adverse events that occurred from Day 1 through Week 12 (Day 85 ±5 days).

Source: [P001MK6072: adam-adsl; adae]

Serious adverse event/deaths/other significant events

There was a lower incidence of SAEs in the bezlotoxumab group (53.3%) compared with the placebo group (80.6%) with a 95% CI for the treatment difference that excluded zero. Most SAEs were considered not related to study intervention by the investigator.

The most frequently reported SAEs (reported for ≥5% participants in either intervention group) were febrile neutropenia (bezlotoxumab: 20.6%; placebo: 30.6%), pyrexia (3.7%; 8.3%), *C. difficile* colitis (0.9%; 5.6%), and urinary tract infection (2.9%; 5.6%).

SAEs considered related to study intervention by the investigator were reported for 2 participants (intussusception and nausea, 1 participant each), both in the bezlotoxumab group) and both AEs resolved.

Table 31

Listing of Participants With Fatal Outcome Adverse Events
All Participants as Treated

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Maximum Intensity	Serious	Related	Action Taken	Outcome
Bezlotoxumab									
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 1, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 1	FOLLOW-UP 1	28	Bacterial sepsis	3.65 Months	Severe	Y	N	N/A	Fatal
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 2, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 2	FOLLOW-UP 2	43	Venoocclusive disease	1.38 Months	Severe	Y	N	N/A	Fatal
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 3, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 3	LONG-TERM FOLLOW-UP	94	Septic shock	4 Days	Severe	Y	N	N/A	Fatal
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 4, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 4	TREATMENT	2	Septic shock	5 Days	Severe	Y	N	N/A	Fatal
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 5, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 5	FOLLOW-UP 2	41	Leukaemia	23 Hours	Severe	Y	N	N/A	Fatal
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 6, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 6	FOLLOW-UP 2	83	Acute myeloid leukaemia	2 Days	Severe	Y	N	N/A	Fatal
Placebo									
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 7, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Trial Number=6072-001, Site Number=Site X, Unique Subject ID=6072-001_Case 7, Sex=XX, Race=Race X, Age=999 Years, Rel Day of Last Recorded Dose of Study Medication=									
Case 7	TREATMENT	2	Neuroblastoma	2.86 Weeks	Severe	Y	N	N/A	Fatal

Related: Investigator-assessed relationship of the adverse event to study medication. Y = RELATED, N = NOT RELATED

Action Taken: Discontinued = DRUG WITHDRAWN, Interrupted = DRUG INTERRUPTED, Reduced = DOSE REDUCED, Increased = DOSE INCREASED, None = DOSE NOT CHANGED, N/A = NOT APPLICABLE.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

TREATMENT epoch is defined as the period from start of antibody or placebo infusion up to 24 hours after end of antibody or placebo infusion.

FOLLOW-UP 1 epoch is defined as the period from 24 hours after end of antibody or placebo infusion to 31 days after end of antibody or placebo infusion.

FOLLOW-UP 2 epoch is defined as the period from 32 days after end of antibody or placebo infusion to 90 days after end of antibody or placebo infusion.

LONG-TERM FOLLOW-UP epoch is defined as the period beyond 90 days after end of antibody or placebo infusion.

The percentage of participants with intervention-related SAEs was low (2 [1.9%] participants, both in the bezlotoxumab group).

The intervention-related SAEs in the bezlotoxumab group were intussusception and nausea (each for 1 participant) and both AEs resolved.

After the 12-week follow-up period, an additional participant (in the bezlotoxumab group) was reported by the investigator to be an intervention-related SAE of large intestinal obstruction (onset Day 294), which was severe in intensity and resolved after 5 days.

Six participant deaths occurred due to AEs that began during the 12-week follow-up period (5 in the bezlotoxumab group, 1 in the placebo group). None were considered related to study intervention.

One additional participant (in the bezlotoxumab group) died of an SAE that began after the12-week follow-up period. The participant had an SAE of septic shock (onset Day 94) whichwas not considered related to study intervention.

Table 32

Table 14.3-12
Participants With Serious Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
Study Intervention Through 12 Week Follow-up
All Participants as Treated

	Bezlotoxumab		Placebo	
	n	(%)	n	(%)
Participants in population	107		36	
with one or more serious adverse events	57	(53.3)	29	(80.6)
with no serious adverse events	50	(46.7)	7	(19.4)
Blood and lymphatic system disorders	**28**	**(26.2)**	**12**	**(33.3)**
Febrile neutropenia	22	(20.6)	11	(30.6)
Gastrointestinal disorders	**7**	**(6.5)**	**3**	**(8.3)**
General disorders and administration site conditions	**5**	**(4.7)**	**4**	**(11.1)**
Pyrexia	4	(3.7)	3	(8.3)
Infections and infestations	**32**	**(29.9)**	**13**	**(36.1)**
Clostridium difficile colitis	1	(0.9)	2	(5.6)
Urinary tract infection	3	(2.8)	2	(5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(1.9)**	**2**	**(5.6)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 was used in the reporting of this study.
This table includes adverse events that occurred from Day 1 through Week 12 (Day 85 ±5 days).

Source: [P001MK6072: adam-adsl; adae]

Adverse events of special interest

No protocol-specified AEs of special interest were identified for this study.

Cardiac AEs

Cardiac AEs were reported for 4 participants (1 in bezlotoxumab group, 3 in placebo group). None were considered related to study intervention by the investigator or serious.

Predefined laboratory criteria for potential drug-induced liver injury

No participants had laboratory values that met the predefined ECI criteria for hepatic test abnormalities requiring additional evaluation of an underlying aetiology.

Infusion-related reactions

Two participants experienced a protocol-defined infusion-related reaction. Of these, 1 occurred in the bezlotoxumab group (blood pressure systolic decreased) and 1 in the placebo group (blood pressure decreased); both events were of mild intensity and resolved.

Laboratory findings

The percentage of participants who had chemistry and hematologic laboratory findings that met predetermined criteria was generally comparable between intervention groups.

Vital signs, and other observations related to safety

There were no clinically meaningful findings in vital sign measurements for either intervention group.

Safety in special populations

No clinically meaningful differences were observed between intervention groups in the percentages of participants with AEs, intervention-related AEs, or all SAEs by age groups in.

No intrinsic factors other than age were evaluated for this study. No extrinsic factors were evaluated for this study.

Safety related to drug-drug interactions and other interactions

Bezlotoxumab-mediated drug-drug interactions are unlikely, as the target of bezlotoxumab is an exogenous toxin and hence is not likely to directly modulate inflammatory cytokines that affect P450 expression. Because bezlotoxumab is eliminated by catabolism, no metabolic drug-drug interactions are expected.

Discontinuation due to adverse events

No participant discontinued study intervention due to an AE.

Post marketing experience

Bezlotoxumab was first approved in the United States on 21-OCT-2016 and has been approved in adults in 36 countries as of 31-MAY-2022.

A total of 399 reports (242 reports, 60.6% considered serious) containing 985 events (494 events, 50.1% serious) were reported as of 31-MAY-2022 Of the 399 reports, 193 (48.3%) were spontaneous and 206 (51.6%) were non-interventional study reports.

Of the 376 (94.2%) reports that included gender information, 169 (44.9%) were for males and 207 (55%) were for females. The median age was 73 years (range 15 to 98 years).

Table 33

Table 2.7.4-rcdi-peds: 7
SOC for Post marketing AEs Reported for Bezlotoxumab
From 21-OCT-2016 to 31-MAY-2022

SOC	Number Events	Percentage Events	Number Serious Events	Percentage Serious Events
Blood and lymphatic system disorders	27	2.74 %	19	3.85 %
Cardiac disorders	35	3.55 %	33	6.68 %
Endocrine disorders	3	0.30 %	3	0.61 %
Eye disorders	1	0.10 %	0	0.00 %
Gastrointestinal disorders	66	6.70 %	31	6.28 %
General disorders and administration site conditions	259	26.29 %	94	19.03 %
Hepatobiliary disorders	7	0.71 %	2	0.40 %
Immune system disorders	6	0.61 %	6	1.21 %
Infections and infestations	170	17.26 %	166	33.60 %
Injury, poisoning, and procedural complications	142	14.42 %	5	1.01 %
Investigations	98	9.95 %	31	6.28 %
Metabolism and nutrition disorders	33	3.35 %	10	2.02 %
Musculoskeletal and connective tissue disorders	6	0.61 %	4	0.81 %
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	13	1.32 %	13	2.63 %
Nervous system disorders	23	2.34 %	15	3.04 %
Psychiatric disorders	6	0.61 %	0	0.00 %
Renal and urinary disorders	17	1.73 %	16	3.24 %
Respiratory, thoracic, and mediastinal disorders	38	3.86 %	29	5.87 %
Skin and subcutaneous tissue disorders	8	0.81 %	3	0.61 %
Social circumstances	2	0.20 %	1	0.20 %
Surgical and medical procedures	14	1.42 %	7	1.42 %
Vascular disorders	11	1.12 %	6	1.21 %
Grand total	985	100.00 %	494	100.00 %
SOCs not present on this table have 0 postmarketing AEs Reported for Bezlotoxumab				

For the 985 AEs reported, the SOCs with the most commonly reported AEs were General disorders and administration site conditions (259 events), Infections and infestations (170 events), and Injury, poisoning and procedural complications (142 events).

The 5 most commonly reported preferred terms in the General disorders and administration site conditions SOC were drug ineffective (54), no adverse event (53), adverse event (38), treatment failure (22), and death (22). Of the 259 events in this SOC, 94 were considered serious and 165 non serious. The outcomes provided were as follows: fatal (30), not recovered/not resolved (20), recovered or recovering (17), recovered with sequelae and 191 had unknown outcome. Review of the reports did not identify any new safety concerns. The reports coded as "death" had limited information or were confounded by the underlying medical conditions in the context of critically ill

patients.

The most commonly reported PTs in the Infections and infestations SOC were *C. difficile* infection (77), Pneumonia (7), Pneumonia aspiration (6), Septic shock (6), and *C. difficile* colitis (6). Of the 170 events in this SOC, 166 were considered serious and 4 non-serious. The outcomes provided were as follows: unknown outcome (69), recovered or recovering (62), fatal (26), and not recovered/not resolved (13). The fatal reports had limited information or were confounded by the underlying medical conditions in the context of critically ill patients.

The most commonly reported PTs in the Injury, poisoning and procedural complications SOC were overdose (45) under dose (25) and product use in unapproved indication (15). Of the 142 events of the SOC, 5 were serious and 137 non-serious. The outcomes provided were as follows: unknown outcome (138), recovered (3), and fatal (1). The fatal case was a patient with multiple conditions who died due to chronic dysfunction of a renal graft.

Of the 399 reports identified in the safety database, 1 report (0.09%) described the use of bezlotoxumab in a 15-year-old patient (off-label use) with no other co-reported adverse events. The case did not provide additional details. A complete medical assessment cannot be performed with the limited information provided.

2.5.1. Discussion on clinical safety

A primary objective of study P001 was the evaluation of safety and tolerability of bezlotoxumab compared with placebo following a single dose of infusion through 12 weeks.

Safety and tolerability were evaluated by collection of AE data, clinical laboratory evaluations, and vital sign measurements. Safety analyses were performed on the APaT population. These analyses were performed using the M&N asymptotic method (1985) and 95% CIs were provided.

All participants who received study intervention completed a single infusion of either 10 mg/kg bezlotoxumab or placebo, therefore the extent of exposure was the same for all participants. A toatal of 143 patients were evaluated for safety, 107 in the bezlotoxumab group and 36 in the placebo group.

The CHMP noted that a higher observed incidence of AEs considered related to study intervention by the investigator was reported for the participants in the bezlotoxumab group (15.9%) compared with the placebo group (8.3%), with a 95% CI for the treatment difference that included zero. The most frequently reported AEs (reported for ≥20% participants in either intervention group) were: febrile neutropenia (bezlotoxumab: 21.5%, placebo: 30.6%), pyrexia (17.8%, 30.6%), headache (14.0%, 22.2%), and vomiting (13.1%, 22.2%).

The most frequently reported AEs considered related to study intervention in the bezlotoxumab group were ALT increased, AST increased, and headache (each for 3 [2.8% participants). The most frequently reported AE related to study intervention in the placebo group was headache (2 [5.6%] participants).

There was a lower incidence of SAEs in the bezlotoxumab group (53.3%) compared with the placebo group (80.6%) with a 95% CI for the treatment difference that excluded zero. Most SAEs were considered not related to study intervention by the investigator.

The percentage of participants with intervention-related SAEs was low (2 [1.9%] participants, both in the bezlotoxumab group).

The intervention-related SAEs in the bezlotoxumab group were intussusception and nausea (each for 1 participant) and both AEs resolved. After the 12-week follow-up period, an additional participant (in

the bezlotoxumab group) was reported by the investigator to be an intervention-related SAE of large intestinal obstruction (onset Day 294), which was severe in intensity and resolved after 5 days.

Six participant deaths occurred due to AEs that began during the 12-week follow-up period (5 in the bezlotoxumab group, 1 in the placebo group). None were considered related to study intervention. One additional participant (in the bezlotoxumab group) died of an SAE that began after the12-week follow-up period. The participant had an SAE of septic shock (onset Day 94) which was not considered related to study intervention. The relatively large number of deaths in this small study sheds some doubts that the selected population i.e. paediatric patients with severe underlying disease adequate population for performing a PK study.

No protocol-specified AEs of special interest were identified for this study.

Cardiac AEs were reported for 4 participants (1 in bezlotoxumab group, 3 in placebo group). None were considered related to study intervention by the investigator or serious.

No participants had laboratory values that met the predefined ECI criteria for hepatic test abnormalities requiring additional evaluation of an underlying aetiology.

Two participants experienced a protocol-defined infusion-related reaction. Of these, 1 occurred in the bezlotoxumab group (blood pressure systolic decreased) and 1 in the placebo group (blood pressure decreased), both events were of mild intensity and resolved.

The percentage of participants who had chemistry and hematologic laboratory findings that met predetermined criteria was generally comparable between intervention groups.

There were no clinically meaningful findings in vital sign measurements for either intervention group.

No clinically meaningful differences were observed between intervention groups in the percentages of participants with AEs, intervention-related AEs, or all SAEs by age groups in.

No participant discontinued study intervention due to an AE.

The CHMP also noted that a review of cumulative post-marketing adverse events was conducted from market introduction (21-OCT-2016) through 31-MAY-2022 and did not identify any new safety issues. The available post-marketing data in adult patients (and a single case of off-label use in a paediatric patient), are consistent with the known safety profile of bezlotoxumab.

2.5.2. Conclusions on clinical safety

The CHMP is of the opinion that the overall incidence of AEs in the bezlotoxumab group was generally comparable with the placebo group regardless of age cohort, demographics, or other risk factors. The incidence of study drug related events is low.

The observed AEs and SAEs and death are rather related to the significant comorbidities of the selected patient population than to the study drug.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated version 2.3 of the RMP within this application; version 3.0 was endorsed by the Committee.

The main proposed RMP changes were the following (text copied without references in the RMP):

- PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Epidemiology of the indications and target population CDI epidemiology among adults was updated

up to date.

CDI epidemiology among paediatric populations was added:

"Incidence of CDI:

Incidence of CDI among paediatric patients increased in the US from 1991 to 2009, rising from 2.6 to 32.6 infections per 100,000 person-years. In the US hospital setting specifically, incidence increased from
4.4 per 10,000 patient-days in 2001 to 6.5 per 10,000 patient-days in 2006, with a similar incidence rate in 2013 (7.1 cases per 10,000 patient-days) as in 2006. CDI incidence among paediatric inpatients in the Netherlands was also stable over approximately the same time period of 2009-2015. Incidence among paediatric inpatients in the US declined to 4.9 cases per 10,000 patient-days by 2019.

Prevalence of CDI and CDI recurrence:

In the US, there are approximately 16,900 paediatric CDI cases annually. Approximately 10-30% of paediatric patients with a case of CDI are expected to have a recurrent episode. Among all paediatric CDI cases, approximately three-quarters are community-acquired, while the remainder are acquired in a healthcare setting. Globally, asymptomatic colonization of C. difficile is common among infants, occurring in 41% of those aged 6 months to 1 year, compared with 12% in those aged 5-18 years. Despite relatively high prevalence of C. difficile colonization, clinically relevant CDI is rare in infants aged <1 year.

Severe outcomes of CDI are uncommon among paediatric cases and include toxic megacolon (0.1%), colectomy (0.3%), gastrointestinal perforation (0.4%), and pseudomembranous colitis (1.1%). Global estimates of all-cause mortality among paediatric patients with CDI range from 2-5%.

Risk factors for CDI and CDI recurrence:

Paediatric patients are at higher risk of CDI if they have prior antibiotic exposure, prolonged hospitalization, a history of hospitalization, current use of gastric acid suppressants, or have comorbidities, including neoplastic disease, immunodeficiency, solid organ transplantation, and enteral feeding. Among paediatric patients with CDI, 67%-91% are estimated to have comorbidities.

Risk factors for CDI recurrence include malignancy, tracheostomy tube dependence, recent surgery, and antibiotic use in the 30 days before symptom onset. As with initial cases of CDI, comorbidities are common among paediatric patients with recurrent CDI. Among paediatric patients with recurrent CDI in a Swedish hospital, 97% had an underlying comorbidity.

Demographics of the population in the authorized indication:

The target population is paediatric patients 1 year of age and older with an acute episode of primary or recurrent CDI and who are at high risk for recurrence of CDI.

Main existing treatment options:

Vancomycin and metronidazole are commonly used for treatment of paediatric CDI. Limited observational data suggest that vancomycin may result in higher rates of clinical improvement than metronidazole and that recurrence is more likely following metronidazole than vancomycin treatment. Fidaxomicin is an oral, narrow-spectrum antibiotic that has activity against both C. difficile and its spores, thereby treating both initial episodes of CDI and reducing recurrence [Ref. 5.4: 080Z6N]. In a randomized controlled clinical trial among paediatric patients aged <18 years with CDI, fidaxomicin was non- inferior to vancomycin for treatment of CDI and also resulted in higher rates of global cure (68% vs. 50%) and longer time to recurrence."

- PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Changes regarding paediatric population was introduced. The following text was added:

"The acceptable safety profile of bezlotoxumab alone and in combination with actoxumab defined in nonclinical studies has been confirmed in clinical trials in adult and paediatric patients. Therefore, additional nonclinical toxicity studies for the express purpose of evaluating effects in juvenile animals were not considered of value for establishing safety in the paediatric population and in accordance with ICH M3(R2) and ICH S11 recommendations, no studies in juvenile animals were conducted."

"Overall, the non-clinical profile supports the use of bezlotoxumab for the prevention of CDI recurrence in adult and paediatric patients 1 year of age and older."

- PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Changes regarding paediatric population was introduced. The following text was added:

"The paediatric clinical development program included a single Phase 3 clinical trial (MK- 6072 -001). The rationale for the paediatric clinical trial was to obtain PK and safety information to support the selection of a dose for paediatric patients over 1 year of age that would achieve bezlotoxumab exposures similar to those obtained in adults at the recommended dose (as a single IV infusion at 10 mg/kg). Safety and PK data of a single IV infusion of bezlotoxumab (10 mg/kg) in paediatric participants were consistent with data in adults. Given these findings, bezlotoxumab (10 mg/kg) has a favorable benefit/risk profile in paediatric patients over 1 year of age."

"In addition to the adult clinical trials, MK-6072 P001 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 paediatric participants 1 to <18 years of age receiving antibacterial drug treatment for CDI. Participants were randomized 3:1 to bezlotoxumab 10 mg/kg or placebo and were stratified by age at randomization (Age Cohort 1: 12 to <18 years of age, Age Cohort 2: 1 to <12 years of age). Participants were followed up for 12 weeks (ie, 85 ± 5 days) for PK and immunogenicity collections, monitoring of safety and tolerability parameters, and efficacy outcomes. The final sample size was 143 participants (107 treated with bezlotoxumab; 36 placebo). Although efficacy was a secondary objective, the study was not powered for the analysis of efficacy and an extrapolation approach incorporating the adult data was used."

The study MK-6072 P001 was added to table "Summary of the Clinical Development Program".

Clinical trial exposure in pediatric population was added.

- PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Exclusion Criteria in Pivotal Clinical Studies Within the Development Program was updated. The information "Animal reproduction studies have not been conducted with bezlotoxumab." was removed.

Limitations of Clinical Trial Program was updated, points regarding limitation "due to prolonged

exposure" and "paediatric population".

- PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

Minor changes – this section was updated.

- PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

- ***Safety***

concerns

Safety concerns

were reclassified.

Important

Potential Risks:

„Based upon EMA GVP Module V (Rev 2) guidance, 'Immunogenicity' previously classified as an important
potential risk, is removed from the list of RMP risks. This risk was maintained as the study MK-6072 001 was considered an additional pharmacovigilance activity for bezlotoxumab. As study MK-6072 001 is now completed, no new safety concerns were identified, no additional pharmacovigilance activities are planned to further characterize it, and immunogenicity following administration of bezlotoxumab is described in the label, this risk was removed from the list of Important Potential Risks. Routine risk minimization measures remain adequate for maintaining the positive benefit risk profile for the product use in the targeted indications."

The missing information:

"Exposure in paediatric patients, previously identified as missing information, is removed from the list of safety concerns. The paediatric clinical trial MK-6072-001 (MK-6072 P001) demonstrated that the safety profile in paediatric participants is consistent with that observed in adults. No new safety concern was identified."

Table 34: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

- PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST - AUTHORISATION SAFETY STUDIES)

Section „Additional Pharmacovigilance Activities" was updated, as MK-6072-P001 trial was completed.

- PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Section was updated. In line with the new safety concern and EMA GVP Module V (Rev 2) guidance.

- PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Section was updated. In line with the new safety concern and EMA GVP Module V (Rev 2) guidance.

Conclusion

Overall, the changes regarding the list of safety concerns and Pharmacovigilance Plan in the RMP (version 3.0) are acceptable to the Committee, and in line with EMA GVP Module V (Rev 2) guidance. The MAH should take the following point into consideration at the next RMP update:

1. The sentence in section II PART VI, *"If important information that may affect the safe use of bezlotoxumab is not yet available, it is listed under 'missing information' below."*, should be erased as there are no missing information.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to reflect the paediatric indication. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reason:

In this submission, applying for the modification of the approved therapeutic indication for ZINPLAVA 25 mg/mL concentrate for solution for infusion to include paediatric patients, the changes to the package leaflet for ZINPLAVA are limited. The only changes in the patient leaflet text are revisions of the paragraphs concerning the paediatric indication, i.e. section "1. What ZINPLAVA is and what it is used for" and "2. What you need to know before you take ZINPLAVA", subsection "Children and adolescents". There are no other proposed changes to the content of the package leaflet; in particular, the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

Therefore, neither a consultation with target patient groups nor a focus test should be performed. The justification submitted by the company is acceptable by the CHMP.

2.7.2. Additional monitoring

N/A.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Clostridioides difficile, is an anaerobic, spore-forming gram-positive bacillus. Strains that cause disease in humans produce toxins, in particular *C. difficile* toxins A and B. CDI occurs when toxigenic strains proliferate in the lower gastrointestinal tract after disruption of the normal bacterial colonic flora, typically after exposure to antibiotics. CDI results in a wide spectrum of clinical disease ranging from mild diarrhoea to severe illness with complications (e.g., ileus, toxic megacolon, or death).

Although CDI more frequently affects adults and is strongly associated with advanced age, a minority of cases occur in susceptible paediatric patients.

Many of the risk factors for CDI in paediatric patients are similar to those in adults (e.g., use of broad- spectrum antibiotics, or longer duration of hospital stay). In paediatric patients, CDI is also strongly associated with additional factors, including malignancy, inflammatory bowel disease, and immune suppression.

Similar to adults, rCDI occurs in paediatric patients. This is typically due to further acquisition of another strain of *C. difficile* or persistence of the same pathogenic strain in the gut despite treatment, in particular in the form of highly antibiotic-resistant bacterial spores. RCDI within 8 weeks of a previously successfully treated CDI has been reported in 10.8 to 34.4% of paediatric cases [Ref. 5.4: 082D8R, 080Z6L, 055T9Z] [Ref. 5.4: 082XYP, 05CYZL].

Risk factors for rCDI in paediatric patients are less well established compared with adults, but considered broadly similar to adults and include malignancy, recent surgery, exposure to multiple antibiotic classes, immunosuppressive medications, continued systemic antibacterial exposure during initial CDI illness, severe initial CDI, and infection with ribotype 027.

3.1.2. Available therapies and unmet medical need

A key component of the clinical management of CDI is to reduce the risk of recurrent CDI, especially in patients who have already experienced one or more recurrent episodes. RCDI is challenging and associated with a higher risk of further recurrence; various clinical management strategies may be used including tapered/pulsed administration of oral vancomycin, vancomycin followed by rifaximin, fidaxomicin, IV immunoglobulin, or therapy with other microorganisms, including faecal microbiota transplant [Ref. 5.4: 03QVFH]. The intention of these therapies is two-fold: treatment of the recurrent CDI episode and prevention of further recurrence.

Bezlotoxumab is currently the only approved therapy specifically for the prevention of recurrent CDI in adults. Bezlotoxumab does not have antimicrobial activity and is administered concurrently with antibacterial drug treatments for CDI. Bezlotoxumab prevents recurrence by providing passive immunity against *C. difficile* toxin B produced by the outgrowth of persistent or newly acquired spores.

3.1.3. Main clinical studies

The paediatric clinical development program included a single study (P001). The rationale for the paediatric clinical study was to obtain PK and safety information to support the selection of a dose for paediatric patients that would achieve bezlotoxumab exposures similar to those obtained in adults at the recommended dose (as a single IV infusion at 10 mg/kg). The efficacy data are considered supportive by the CHMP.

3.2. Favourable effects

Statistical analyses indicate that the 90% CIs of paediatric/adult GMR of serum bezlotoxumab $AUC_{0\text{-}inf}$

(but not C_{max}) are overall within the prespecified bounds for each age or weight cohort examined, supporting the extrapolation concept based on exposure bridging.

In paediatric participants (1 to <18 years of age) with CDI who received a single IV dose of bezlotoxumab (10 mg/kg) or placebo, the percentage of participants with CDI recurrence was low and comparable between the bezlotoxumab and placebo groups.

The percentage of participants in the mITT population with initial clinical response who had CDI recurrence was low and comparable between intervention groups (bezlotoxumab: 11,2%; placebo: 14,7%). The percentage of participants in the mITT population with sustained clinical response was comparable between intervention groups (bezlotoxumab: 83.7%; placebo: 82.9%).

The percentage of participants in the mITT population with initial clinical response who had CDI recurrence and were at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 12.1%; placebo: 15.2%) [Table 14.2.3-18].

The percentage of participants in the mITT population with sustained clinical response and at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 82.5%, placebo: 82.4%)

3.3. Uncertainties and limitations about favourable effects

There remains some uncertainty in the underlying assumption of PK similarity between paediatric subjects at all age or weight cohorts/bins and the adult population.

For monoclonal antibodies, C_{trough} is often considered the most appropriate PK metric to correlate with efficacy. Treatment with Zinplava is intended as a single dose treatment, i.e., there is no C_{trough} to correlate with efficacy. No data are available to date which indicate that the drug concentration in paediatric patients doesn't decrease to potentially inefficacious levels earlier than in adults. While it is formally agreed that bezlotoxumab AUC and Week 12 serum concentration are within the adult range, sample sizes for the paediatric age/weight groups are low and a one-to-one comparison between paediatrics and adult patient population is seen critical (e.g. in terms of accompanying diseases). Mean and median exposure including Week 12 observations are below the adult value for all paediatric age/weight groups - except for adolescents (at or above 40 kg) - with lowest observed exposure for the age group 4 to <7 years of age (47.2% of adult median value) and for the weight group 30 to < 40 kg (52.5% of adult median value). Of note, the age group 4 to <7 would more fit to the weight group 20 to <30 kg. These results and non-linear relationship indicate that weight alone is not predictive of exposure following 10 mg/kg of bezlotoxumab, but there might other factors impacting PK. This is also reflected in the high CV% characterizing adult and paediatric PK metrics. As the amount and information content of paediatric PK data is critical to support the extrapolation concept (exposure bridging).

The percentage of participants with CDI recurrence was low and comparable between the bezlotoxumab and placebo groups. RCDI within 8 weeks of a previously successfully treated CDI has been reported in 10.8 to 34.4% of paediatric cases. In the current study the incidence of RCDI was in the placebo group at the lower end the expected cases. Thus, a difference between the two groups could not be established in the small study.

3.4. Unfavourable effects

A higher observed incidence of AEs considered related to study intervention by the investigator was reported for the participants in the bezlotoxumab group (15.9%) compared with the placebo group

(8.3%), with a 95% CI for the treatment difference that included zero. The most frequently reported AEs considered related to study intervention in the bezlotoxumab group were ALT increased, AST increased, and headache (each for 3 [2.8% participants). The most frequently reported AE related to study intervention in the placebo group was headache (2 [5.6%] participants).

There was a lower incidence of SAEs in the bezlotoxumab group (53.3%) compared with the placebo group (80.6%), with a 95% CI for the treatment difference that excluded zero. Most SAEs were considered not related to study intervention by the investigator.

The most frequently reported SAEs (reported for ≥5% participants in either intervention group) were febrile neutropenia (bezlotoxumab: 20.6%; placebo: 30.6%), pyrexia (3.7%; 8.3%), *C. difficile* colitis (0.9%; 5.6%), and urinary tract infection (2.9%; 5.6%).

SAEs considered related to study intervention by the investigator were reported for 2 participants (intussusception and nausea, 1 participant each), both in the bezlotoxumab group).

3.5. Uncertainties and limitations about unfavourable effects

Serious and non-serious AEs were common however the study was performed in a population with significant comorbidities consistent with a paediatric population with CDI. The data rather reflect the comorbidities in the trial population than the safety profile of bezlotoxumab.

3.6. Effects Table

Table 35: Effects Table for [bezlotoxumab; prevention of C. difficile recurrence]

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CDI recurrence	mITT population with initial clinical response	%	11,2	14,7	No effect	Table 11-5
Sustained clinical response	mITT population	%	83,7	82,9	No effect	Clinical study report
CDI recurrence	mITT population with initial clinical response at high risk for CDI recurrence	%	12,1	15,2	No effect	[Table 14.2.3-18
Sustained clinical response	mITT population at high risk for CDI recurrence was comparable	%	82,5	82,4	No effect	Clinical study report
Unfavourable Effects						

AEs		%	15,9	8,3	95% CI for the treatment difference that included zero	Clinical study report
SAEs		%	53,3	80,6	95% CI for the treatment difference that excluded zero	Clinical study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

PK data of a single IV infusion of bezlotoxumab (10 mg/kg) in paediatric participants are consistent with data in adults.

The clinical efficacy demonstrated following a single IV infusion of 10 mg/kg, in paediatric CDI patients a comparable response in both intervention groups. The incidence of CDI recurrence was low in both groups.

The safety data confirmed the favourable safety profile of bezlotoxumab observed in adult patients. No new safety concerns were identified based on findings from P001.

3.7.2. Balance of benefits and risks

Safety and PK data of a single IV infusion of bezlotoxumab (10 mg/kg) in paediatric participants are consistent with data in adults.

A clinical benefit over placebo could not be demonstrated. This might be attributed to the small sample size and low CDI in the study population. A lower background incidence of CDI was observed during the study period than in the period prior to MODIFY III. Since study enrolment partly occurred during the COVID-19 era, strict hygiene and cleaning practices were in place in hospitals and communities; this may have contributed to decreased recurrence rates. The MAH provided upon request comparison of observed bezlotoxumab concentration at week 12 in adults and paediatrics – statistics were stratified by age and weight groups, which is acknowledged.

Results indicate that observed concentrations are within the range of those observed in adult patients.

While it is formally agreed that bezlotoxumab AUC and Week 12 serum concentration are within the adult range, it is pointed out that sample size for the paediatric age/weight groups are low and a one-to-one comparison between paediatrics and adult patient population is seen as critical (e.g. in terms of accompanying diseases). Mean and median exposure including Week 12 observations are below the adult value for all paediatric age/weight groups except for adolescents, with lowest observed exposure for the age group 4 to <7 (47.2% of adult median value) and for the weight group 30 to < 40 kg (52.5% of adult median value). Of note, the age group 4 to <7 would more fit to the weight group 20 to <30 kg.

These results and non-linear relationship indicate that weight alone (and per kg dosing) is not predictive of exposure following 10 mg/kg of bezlotoxumab, but there might other factors impacting PK. This is also reflected in the high CV% characterizing adult and paediatric PK metrics. In order to reflect the amount and information content of paediatric PK data, that would serve as confirmation of the extrapolation concept (exposure bridging), Section 5.2 of the SmPC was amended accordingly.

3.8. Conclusions

The overall benefit-risk of Zinplava is positive in the new population applied for (paediatric, 1 to 18 years of age).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the marketing authorisation, concerning the following changes:

Variation(s) agreed		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II	I, IIIA and IIIB

Extension of indication to include treatment of the paediatric population (1 to 18 years of age) for ZINPLAVA, based on final results from study MK-6072-001 (MODIFY III) listed as a category 3 study in the RMP; this is a phase 3, randomised, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of a single infusion of bezlotoxumab in paediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for *Clostridioides difficile* infection (CDI). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. A revised RMP version 3.0 has been approved. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).