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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zinplava

bezlotoxumab

Procedure no: EMEA/H/C/004136/P46/004

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	28 Oct 2022	28 Oct 2022	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2023	12 Dec 2022	☐
☐	CHMP members comments	16 Jan 2023	16 Jan 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	19 Jan 2023	19 Jan 2023	☐
☒	CHMP adoption of conclusions:	26 Jan 2023	26 Jan 2023	☐

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1. Introduction

On 24 October 2022, the MAH submitted a completed paediatric study for Zinplava (Study P001), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study P001 (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)) is part of a clinical development programme. An extension application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by Q1/2023. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Paediatric participants in P001 were administered bezlotoxumab identical in formulation to commercially available bezlotoxumab:

Zinplava 25 mg/mL concentrate for solution for infusion. Each mL of concentrate contains 25 mg bezlotoxumab. One 40 mL vial contains 1,000 mg of bezlotoxumab.

CHMP comment

The planned variation will also include an update to the smaller volume single does vial containing 625 mg/25 mL (25mg/mL). The vial size contains the same concentration of the currently marketed vial (1000mg/ mL) [25mg/ mL)] with the only difference between the smaller and larger vials being the total volume held (25mL and 40mL, respectively).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study P001.

2.3.2. Clinical 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)

Description

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.

Treatments

Bezlotoxumab 10 mg/kg or placebo.

Objective(s)

Outcomes/endpoints

Participants were followed for 12 weeks 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

The planned sample size was 192 participants, which was reduced to a minimum of 140 participants based on a review of blinded safety data that supported the determination that enrolment of additional

participants was not needed to characterize the safety and tolerability of MK-6072 in paediatric patients.

Table 2.5: 1
Definitions of the Populations Analyzed in P001

Analysis Population	Definition
Per-protocol	Randomized participants who received a dose of bezlotoxumab, and who had ≥4 postdose evaluable PK samples and who complied with the protocol sufficiently to ensure their data show the effects of study intervention
Modified Intent-to-Treat	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.
All Participants as Treated	A subset of all randomized participants who received any amount of study intervention.
CDI=*C. difficile* infection; PK=pharmacokinetics.	

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

Randomisation and blinding (masking)

Eligible participants were stratified by age at randomization (Age Cohort 1: 12 to <18 years of age, Age Cohort 2: 1 to <12 years of age).

Statistical Methods

The primary population for noncompartmental PK analysis was the per-protocol population (PP), which consisted of a subset of 91 participants who received bezlotoxumab and who had at least 4 post-dose PK samples. AUC0-inf data were natural log transformed and compared to historical adult data using an analysis of variance model with a factor for group (paediatric participants and adults). Separate models were used for each paediatric cohort. A point estimate of the GMR (pediatric participants/adults) of bezlotoxumab AUC0-inf with 90% confidence interval (CI) was generated from the model for each cohort. The 90% CIs of the GMRs were compared using prespecified clinical comparability bounds (0.6, 1.6), to determine if the AUC0-inf of bezlotoxumab in each cohort was similar to the AUC0-inf in adults.

Safety analyses were performed on the APaT population, which included all randomized participants who received study intervention. The primary safety objective was addressed by the Tier 2 endpoints: proportion of participants with any adverse event (AE), any intervention-related AE, any serious adverse event (SAE), any intervention-related SAE, infusion-related reactions; the proportion of participants who discontinued study intervention due to an AE; AE (specific preferred terms), system organ classes with frequency ≥12 participants in the bezlotoxumab arm and or ≥2 participants in the placebo arm. These analyses were performed using the Miettinen and Nurminen asymptotic method (1985) and 95% CIs were provided.

Secondary efficacy analyses were performed using a 2-sided 95% CI based on the Miettinen and Nurminen method stratified by age cohort (12 to <18 years of age, 1 to <12 years of age) using a Cochran-Mantel-Haenszel weight to evaluate the treatment differences for (1) CDI recurrence, (2) sustained clinical response, and (3) CDI recurrence among participants at high risk of CDI recurrence within 12 weeks of study medication infusion.

Results

Participant flow

Participant Disposition:

Participant Disposition				
	Age Cohort 1		Age Cohort 2	
	12 to <18 Years		1 to <12 Years	
	Bezlotoxumab	Placebo	Bezlotoxumab	Placebo
All Randomized population	46	16	65	21
APaT population, N	44	16	63	20
Received Intervention, n (%)[a]	44 (100)	16 (100)	63 (100)	20 (100)
Completed Intervention, n (%)[a]	44 (100)	16 (100)	63 (100)	20 (100)
Completed Study, n (%)[a]	42 (95.5)	16 (100)	61 (96.8)	19 (95.0)
Discontinued From Study, n (%)[a]	2 (4.5)	0 (0.0)	2 (3.2)	1 (5.0)
N=number of participants in APaT population; n=number of participants in the specific population. [a] % of APaT population				

Baseline data

Demographic and baseline characteristics were generally comparable between study intervention groups.

Six participants 1 to <2 years of age were enrolled; 4 received a single IV infusion of bezlotoxumab

Table 10-5
Participant Characteristics
All Participants as 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	

	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]

Pharmacokinetics

To address the primary objective of the study, the PK of bezlotoxumab 10 mg/kg was characterized in paediatric participants in 2 age cohorts.

Serum samples of bezlotoxumab were collected following a single IV dose from samples at Day 1, Day 10, Week 4 (±3 days), and Weeks 8 and 12 (±5 days) after the end of infusion and analysed using a validated assay to measure bezlotoxumab concentration. Exposure (AUC0-inf) in paediatric participants were considered to be similar to those in adults if the observed GMR (paediatric participants/adults) for AUC0-inf of bezlotoxumab contained in the clinical comparability bounds of (0.6, 1.6). Other PK endpoints of interest were Cmax, Tmax, t1/2, Vd and CL. PK sampling was planned for all participants (Panels A and B) and confirmation of dose selection for paediatric patients (1 to <18 years) was based on the final PK analysis population, including those evaluated in each of the IAs. The recommended adult dose of 10 mg/kg was initially evaluated for both age cohorts in Panel A of P001. Once Panel A was completed for each age cohort, an interim PK analysis was performed to confirm the dose for Panel B.

Table 2.5: 2
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						

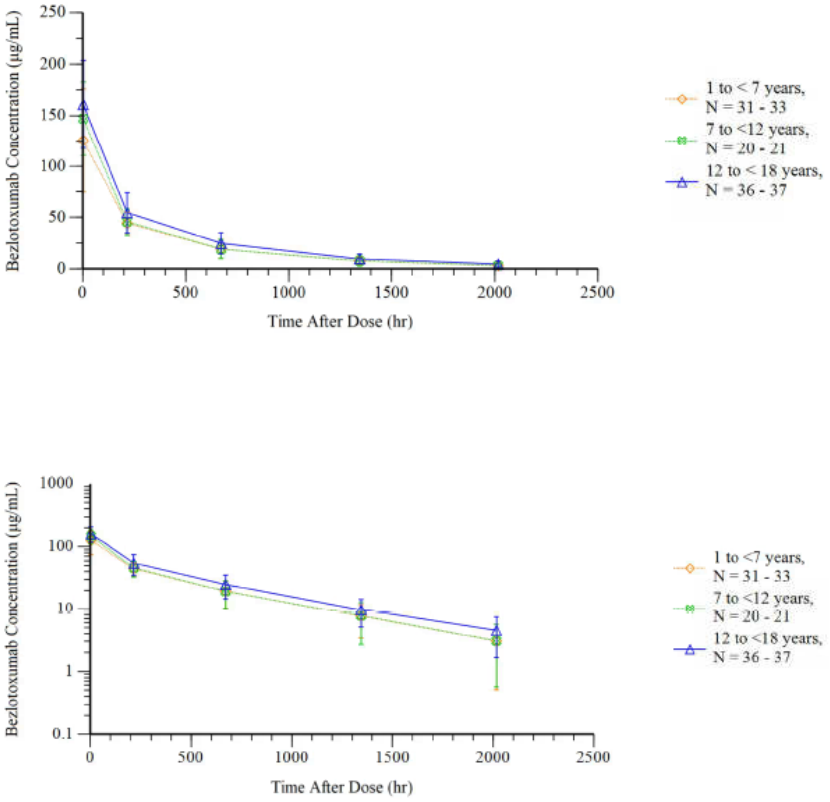
[a]rMSE: Square root of conditional mean squared error (residual error) from the linear fixed-effect model. rMSE*100% approximates the between-subject percent CV on the raw scale.
[b]Back-transformed least-squares mean and confidence interval from fixed effects model performed on natural log transformed 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.
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.
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.

Source: [P001MK6072: adam-adsl; adpp] [P001MK3415A: ppext P002MK3415A: ppext]

The results of this analysis supported the use of the 10 mg/kg dose in Panel B. The 90% CI of paediatric/adult GMR AUC0-inf was within the prespecified clinical comparability bounds (0.6, 1.6) for each age cohort in Panel A. At the completion of the study, PK across Panels A and B was assessed relative to the clinical comparability bounds established for AUC0-inf in adults. The 90% CIs of paediatric/adult GMRs serum bezlotoxumab AUC0-inf were within the prespecified clinical comparability bounds of (0.6, 1.6) for each of the paediatric age cohorts, supporting the primary hypothesis that AUC0-inf in paediatric participants is similar to that in adults following administration of a 10 mg/kg dosage regimen [Table 2.5: 2].

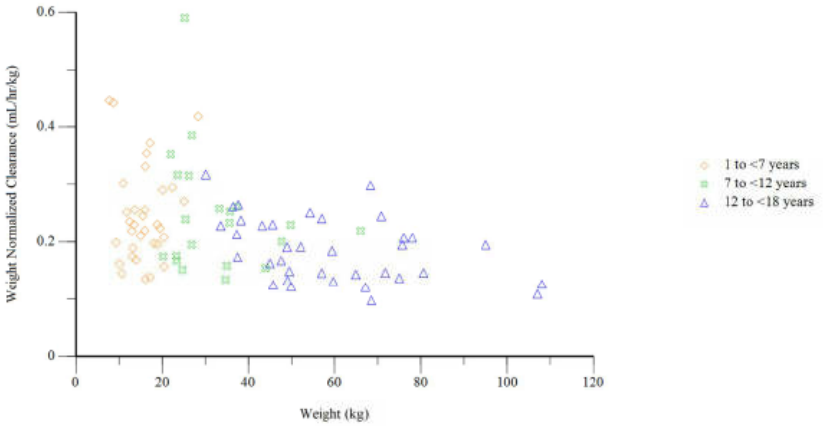
The recommended adult dose of 10 mg/kg was initially evaluated for both age cohorts in Panel A of P001. Once Panel A was completed for each age cohort, an interim PK analysis was performed to confirm the dose for Panel B. The results of this analysis supported the use of the 10 mg/kg dose in Panel B. The 90% CI of paediatric/adult GMR AUC0-inf was within the prespecified clinical comparability bounds (0.6, 1.6) for each age cohort in Panel A. At the completion of the study, PK across Panels A and B was assessed relative to the clinical comparability bounds established for AUC0-inf in adults. The 90% CIs of paediatric/adult GMRs serum bezlotoxumab AUC0-inf were within the prespecified clinical comparability bounds of (0.6, 1.6) for each of the paediatric age cohorts, supporting the primary hypothesis that AUC0-inf in paediatric participants is similar to that in adults following administration of a 10 mg/kg dosage regimen [Table 2.5: 2]. PK data and non-compartmental PK analysis indicate a slightly lower exposure in each paediatric age cohort compared to the adult population. This is likely to be attributed to the higher weight-normalized clearance in children (see figures below).

Figure 14.2.1-14
Arithmetic (SD) Mean Serum Concentration of Bezlotoxumab Vs. Time Profile Following Administration of Single Infusion of 10 mg/kg Bezlotoxumab in the Age Cohorts of Pediatric Participants, Age Cohort 2 Split Into Two Subsets (Top=Linear Scale; Bottom=Semi-log Scale)



Source: [001MK6072: adam-adpc]

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)



Immunogenicity:

Two participants (2%) had a low magnitude titre (≤25x) ADA positive response to bezlotoxumab and no samples were positive for Nab.

Efficacy results

Efficacy outcomes were secondary endpoints in P001; 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 [Table 2.5:1]. The main analysis for CDI recurrence was based on a subset of the mITT population consisting of participants who achieved an 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 2.5: 3].

Table 2.5: 3
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 when analysed across subgroups (i.e., subgroups of age cohort, sex, race, primary treatment for baseline CDI episode, or adjunctive treatment [metronidazole IV] for baseline CDI episode) compared with the overall population.

Further findings were:

- The percentage of participants in the mITT population with initial clinical response who had CDI recurrence was comparable between intervention groups (bezlotoxumab: 11.2%); placebo: 14.7%).
- The percentage of participants in the mITT population who had sustained clinical response was comparable between intervention groups (bezlotoxumab: 83.7%; placebo: 82.9%). There were no clinically meaningful differences observed in sustained clinical response across the subgroups analysed 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 were at high risk for CDI recurrence was comparable between intervention groups (bezlotoxumab: 82.5%; placebo: 82.4%).

Assessor's comment

Efficacy outcomes were secondary endpoints in P001: the study was not powered for formal hypothesis testing of between-intervention group comparisons. Nevertheless, the outcome is unexpected and sheds some doubts on the efficacy in the target population and the validity of the assumed extrapolation concept that is based on exposure matching. The data will be scrutinised in the context of the forthcoming type II variation.

Safety results

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

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).

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.

Table 2.5: 4
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]

Adverse events

Most participants experienced AEs during the 12-week follow-up period and most of these AEs were considered not related to study intervention by the investigator [Table 2.5: 4].

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. Most of these intervention-related AEs were mild in intensity and resolved.

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 12-2].

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)**

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

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)

	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]

No participant discontinued study intervention due to an AE.

Serious adverse events and death

The most frequently reported SAEs (reported for ≥5% 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%) [Table 14.3-12].

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]

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

There were 2 intervention-related SAEs (both in the bezlotoxumab group); intussusception and nausea (each reported in 1 participant) and both events resolved.

Two participants (1 in each intervention group) experienced a protocol-defined infusion related AE; both AEs were of decreased blood pressure, were mild in intensity and resolved.

No participant discontinued study intervention due to an AE.

Laboratory findings

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

Table 14.3-14
Participants With Chemistry Laboratory Findings That Met Predetermined Criteria
Study Intervention Through 12 Week Follow-up
All Participants as Treated

Test Name (Unit)	Criterion	Bezlotoxumab		Placebo	
		n/m	(%)	n/m	(%)
Participants in population		**107**		**36**	
Albumin (g/dL)	Post Baseline < 2.5 g/dL	4/72	(5.6)	2/24	(8.3)
Calcium (mg/dL)	Decrease ≥ 1 mg/dL and value < LLN	3/74	(4.1)	3/26	(11.5)
	Increase ≥ 1 mg/dL and value > ULN	5/74	(6.8)	1/26	(3.8)
Chloride (mmol/L)	Decrease ≥ 10 mmol/L and value < LLN	3/71	(4.2)	1/25	(4.0)
	Increase ≥ 10 mmol/L and value > ULN	2/71	(2.8)	0/25	(0.0)
Creatinine (mg/dL)	Increase ≥ 0.3 mg/dL	4/79	(5.1)	5/28	(17.9)
	Post Baseline > 2.0 mg/dL	3/79	(3.8)	0/28	(0.0)
Potassium (mEq/L)	Decrease ≥ 1 mEq/L and value < LLN	9/84	(10.7)	6/29	(20.7)
	Increase ≥ 1 mEq/L and value > ULN	2/84	(2.4)	0/29	(0.0)
	Post Baseline < 3.3 mEq/L	20/84	(23.8)	9/29	(31.0)
	Post Baseline > 5.4 mEq/L	2/84	(2.4)	0/29	(0.0)
Sodium (mEq/L)	Decrease ≥ 10 mEq/L and value < LLN	5/82	(6.1)	0/27	(0.0)
	Increase ≥ 10 mEq/L and value > ULN	1/82	(1.2)	0/27	(0.0)

The analysis includes local laboratory records collected after the first dose of study intervention through Week 12 (Day 85 ±5 days).
Baseline measurements are defined as the Day 1 value for each participant. In the event that data for this visit are missing, the value obtained at the most recent screening visit is used as the baseline value, when available.
m = Number of participant with at least one post baseline test results.
n = Number of participants with post baseline test results that met criteria at any point.

Source: [P001MK6072: adam-adsl; adlb]

Table 14.3-15
Participants With Hematology Laboratory Findings That Met Predetermined Criteria
Study Intervention Through 12 Week Follow-up
All Participants as Treated

Test Name (Unit)	Criterion	Bezlotoxumab		Placebo	
		n/m	(%)	n/m	(%)
Participants in population		**107**		**36**	
Eosinophils (10^9/L)	Increase ≥ 20% and value > ULN	2/76	(2.6)	2/29	(6.9)
	Post Baseline > 5.0 10^9/L	1/76	(1.3)	0/29	(0.0)
Hemoglobin (g/dL)	Decrease ≥ 5 g/dL	1/86	(1.2)	2/30	(6.7)
	Post Baseline: Male < 10.5 g/dL or Female < 9.5 g/	57/86	(66.3)	24/30	(80.0)
Leukocytes (10^9/L)	Decrease ≥ 50% and value < LLN	31/87	(35.6)	16/32	(50.0)
	Increase ≥ 20% and value > ULN	14/87	(16.1)	5/32	(15.6)
	Post Baseline < 1.5 10^9/L	39/87	(44.8)	18/32	(56.3)
	Post Baseline > 20 10^9/L	10/87	(11.5)	4/32	(12.5)
Lymphocytes (10^9/L)	Post Baseline < 0.5 10^9/L	36/78	(46.2)	14/28	(50.0)
Neutrophils (10^9/L)	Decrease ≥ 20% and value < LLN	35/84	(41.7)	16/29	(55.2)
	Post Baseline < 1.0 10^9/L	42/84	(50.0)	17/29	(58.6)
Platelets (10^9/L)	Decrease ≥ 25% and value < LLN	34/89	(38.2)	13/30	(43.3)
	Post Baseline < 100 10^9/L	44/89	(49.4)	17/30	(56.7)

The analysis includes local laboratory records collected after the first dose of study intervention through Week 12 (Day 85 ±5 days).
Baseline measurements are defined as the Day 1 value for each participant. In the event that data for this visit are missing, the value obtained at the most recent screening visit is used as the baseline value, when available.
m = Number of participant with at least one post baseline test results.
n = Number of participants with post baseline test results that met criteria at any point.

Source: [P001MK6072: adam-adsl; adlb]

The percentage of participants who had chemistry and haematology laboratory findings that met predetermined criteria was generally comparable between intervention groups [Table 14.3-14, 14.3-15]. There were no clinically meaningful findings in vital sign measurements for either intervention group.

2.3.3. Discussion on clinical aspects

The primary objective of the study was to characterize bezlotoxumab PK in children and adolescents (1 to < 18 years).

Secondary efficacy endpoints were analysed from study intervention through the 12-week follow-up (Day 85 ± 5 days). The study was not powered for formal hypothesis testing of between-intervention group comparisons.

The exposure (AUC0-inf) of bezlotoxumab, following a single IV infusion of 10 mg/kg in paediatric patients (1 to <18 years of age) is comparable to that in adult patients. Non-compartmental PK analysis and statistical analysis indicate that the observed GMR (paediatric participants/adults) for AUC0-inf of bezlotoxumab in different paediatric age groups was not exceeding the clinical comparability bounds of (0.6, 1.6). There was a trend in decreasing exposure with decrease in age, that might plausibly be attributed to the increase in weight-normalised clearance. Thus, the MAH concluded that the results are supporting the determination that the efficacy conclusion in adults can be extrapolated to the paediatric population (1 to <18 years of age). This conclusion cannot be shared. In principle, given the results of the pk evaluation it could be expected that the paediatric patients show the clinical results as the adult patients. However, all clinical endpoints showed comparable results between the groups. The study failed to demonstrate clinical efficacy of bezlotoxumab in paediatric patients with Clostridium difficile infection. Although the study was not powered for formal hypothesis testing of between-intervention group comparisons, the outcome is unexpected. This sheds some doubts on the efficacy in the target population and on the validity of the assumed extrapolation concept that is currently based on exposure matching and exposure/response similarity between adults and paediatric subjects at all age groups. The data will be scrutinised in the context of the forthcoming type II variation.

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

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 (53.3%) group compared with the placebo (80.6%) group, with a 95% CI for the treatment difference that excluded zero. Most SAEs were considered not related to study intervention. 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). Given the above, the favourable safety profile of bezlotoxumab is confirmed.

Six participant deaths occurred due to AEs that began during the 12-week study period (5 in the bezlotoxumab group, 1 in the placebo group). The MAH claimed that none of the deaths were considered related to study intervention by the investigator.

No action is required, however the MAH intends to submit an EoI to include treatment of paediatric patients. The data will be scrutinised in the context of the extension of indication. Considering the unexpected efficacy outcome, the MAH might consider gaining further evidence to support the paediatric indication.

3. Overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.