22 November 2016
EMA/853812/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zinplava

International non-proprietary name: bezlotoxumab

Procedure No. EMEA/H/C/004136/0000

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
ACV	Arithmetic coefficient of variation
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APaT	All patients as treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BBA`	Brucella blood agar
BBB	Blood-brain barrier
BILI	Bilirubin
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
°C	Degree(s) Celsius
C. difficile	*Clostridium difficile*
CDI	*Clostridium difficile* infection
CDS	Clinical Development Scientist
CFR	Food and Drug Administration Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CMV IgG	Cytomegalovirus immunoglobulin G
CQM	Clinical Quality Management
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
CV	Coefficient of variation
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfated conjugate
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DTL	Drug tolerance level
ECG	Electrocardiogram
ECI	Event of clinical interest
ECL	Electrochemiluminescence
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee

Abbreviation/Term	Definition
EIA	Enzyme Immunoassay
ERC	Ethical Review Committee
EUB	Emergency Unblinding Call Center
°F	Degree(s) Fahrenheit
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	U.S. Food and Drug Administration
FSE	First subject enrolled
FSG	Fasting serum glucose
FSH	Follicle stimulating hormone
GBRC	Genetic and Other Biomedical Research
GCC	Global Clinical Compliance
GC & PVC	Global Clinical and Pharmacovigilance Compliance
GCP	Good Pharmacovigilance Practices
GDH	Glutamate dehydrogenase
GI	Gastrointestinal
GM	Geometric mean
GMR	Geometric mean ratio
GPvP	Good Pharmacovigilance Practice
H	Hour
HA	Hospital acquired
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational new drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
kg	kilogram
KM	Kaplan Meier
LLOQ	Lower limit of quantitation
MED	Minimal effective dose
MedDRA	Medical dictionary of regulatory activities
mg	Milligram
MIC	Minimum inhibitory concentration
mL	milliliter
MOA	Mechanism of action
MRL	Merck Research Laboratories
mRNA	Messenger ribonucleic acid
MRSA	Methicillin-resistant *Staphylococcus aureus*

Abbreviation/Term	Definition
MSD	Meso Scale Delivery
MSE	Mean squared error
NAb	Neutralizing antibody
NC	Negative control
NSAE	Non-serious adverse event
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PK	Pharmacokinetics
PN	Protocol number
PO	By mouth, orally
PP	Per protocol population
PPI	Proton Pump Inhibitor
QA	Quality assurance
QC	Quality control
QTc-B	QT interval corrected-Bazett
QTc-F	QT interval corrected-Fridericia
RBC	Red blood (cell) count
REA	Restriction endonuclease analysis
RNA	Ribonucleic acid
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SIRS	Systemic anti-inflammatory response syndrome
SoC	Standard of Care
SOC	System Organ Class
TE	Tris/EDTA
T_{max}	Maximum time
UK	United Kingdom
ULN	Upper limit of normal
U.S.	United States
WBC	White blood (cell) count
µg	microgram

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 17 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Zinplava, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Zinplava (bezlotoxumab) is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that bezlotoxumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0340/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0340/2014 was not yet completed as some measures were deferred.

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 applicant 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.

New active Substance status

The applicant requested the active substance bezlotoxumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 December 2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 17 November 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 22 October 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 February 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 February 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 March 2016. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 17 March 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 21 March 2016.
- During the meeting on 1 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 1 April 2016. Furthermore, the CHMP considered that the evaluation of the dossier at present is no longer compatible with the previously agreed accelerated assessment procedure and reverted the timetable into a standard timetable
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 June 2016.
- During the PRAC meeting on 7 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 7 July 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 14 October 2016.
- During a meeting of a Scientific Advisory Group on 3 November 2016, experts were convened to address questions raised by the CHMP.
- In the light of the overall data submitted and the scientific discussion within the Committee during the meeting on 10 November 2016, the CHMP issued a positive opinion via written procedure for granting a marketing authorisation to Zinplava on 22 November 2016.

2. Scientific discussion

2.1. Problem statement

C. difficile is an anaerobic, spore-forming gram-positive bacillus that produces two potent toxins: toxin A, an enterotoxin, and toxin B, which is primarily a cytotoxin. Most, if not all, strains isolated from CDI patients have been toxin B (+) strains, with a majority also expressing toxin A. The toxins target the gut epithelium leading to epithelial damage and inflammation in the gut.

C. difficile spores can persist outside the human body on hard surfaces for up to five months. Transmission occurs through the faecal-oral route. *C. difficile* colonises the colon without causing disease in approximately 1% to 3% of adults; the proportion is higher in patients in acute care settings. Disruption of protective colonic microflora results in excessive growth of *C. difficile* and toxin production and development of disease.

A novel approach to the prevention of recurrent CDI is the use of monoclonal antibodies (mAb) directed against the toxins produced by *C. difficile* as a form of passive immunity in patients receiving antibiotic therapy for CDI.

About the product

Bezlotoxumab (MK-6072) is a fully human monoclonal antibody that blocks the action of *Clostridium difficile* toxin B and potentially averts the damage and inflammation that can lead to the symptoms associated with *C. difficile* infection.

Proposed therapeutic indication, posology and mode of administration:

Bezlotoxumab is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in patients 18 years or older receiving antibiotic therapy for CDI. The recommended dose is 10 mg/kg administered as an intravenous (IV) infusion over one hour as a single dose.

Clinical development program

The Applicant pursues the Marketing Authorisation Application (MAA) for bezlotoxumab.

However, the clinical development program is based on studies evaluating the safety and efficacy of a monoclonal antibody (actoxumab) directed against *C.-difficile* toxin A; and a monoclonal antibody (bezlotoxumab) directed against *C.-difficile* toxin B and a combination product containing both, actoxumab and bezlotoxumab.

During the Phase 1 clinical program, conducted in healthy volunteers, all but 30 subjects were exposed to either actoxumab (MK-3415) alone or actoxumab + bezlotuxomab (MK-3415A). The same applies for the Phase 2 studies; subjects received either actoxumab (MK-3415) alone or actoxumab + bezlotuxomab (MK-3415A). The Applicant does not pursue a Marketing Authorisation for actoxumab alone or the combination of actoxumab + bezlotuxomab. Hence, these will not contribute to the efficacy evaluation of bezlotuxumab.

Formally no Scientific Advice was requested on the development program of bezlotoxumab. However on the development program of the combination product MK-3415A (actoxumab + bezlotoxumab), the Applicant obtained Scientific Advice from the CHMP in December 2009.

The scientific principles outlined in the Scientific Advice may apply also for the current application. The main aspects are as follows:

- No further toxicology studies would be required to support the MAA, including agreement that the absence of studies on reproduction and development is justified and that neither genotoxicity nor carcinogenicity studies would be required.
- ADME and mass-balance studies were not required, but that drug-drug interactions should be studied using a population PK approach in Phase 3.
- To ensure that different subgroups of patients with respect to age and renal function status were included in the Phase 3 trials.
- Phase 1 thorough QT studies are not required.
- General agreement was reached on the design of the proposed Phase 3 trials including: patient population; type and duration of standard of care antibiotic therapy (only metronidazole and vancomycin were proposed at that time); stratification by hospitalization status (inpatient versus outpatient) and by standard of care antibiotic therapy; primary efficacy endpoint; dose selection; and adequacy of the size of the safety database to support the MAA.
- The Phase 3 trials include a sufficient number of patients with severe disease and a high risk of recurrence to demonstrate that the drug is efficacious and safe in these subgroups.
- While the time point for assessment of the primary efficacy endpoint was deemed acceptable, the Agency requested an evaluation of duration of protection in an extended trial phase (up to 12 months) in a subset of patients enrolled in Phase 3.
- The design of the planned 2-dose Phase 1 study to evaluate immunogenicity was deemed by the Agency to be acceptable. Additionally, the Agency recommended evaluation of immunogenicity in relation to repeated use in patients (as opposed to healthy volunteers) either in Phase 3 or in a separate post-marketing trial.
- Plans for immunogenicity testing in the Phase 3 trials were deemed acceptable; additionally, the Agency recommended that immunogenicity testing be extended to evaluate the relationship between possible neutralizing antibodies

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on justification brought forward by the Applicant that the demonstration of efficacy and safety of MK-6072 for prevention of the serious condition of CDI recurrence, for which there are no therapies indicated and which represents a critical unmet medical need of major interest from the point of view of public health, is sufficient justification that MK-6072 falls within the scope of an accelerated assessment.

However, during assessment (Day 120 LoQ), the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as major objections and numerous other concerns were identified, which could not be addressed within the accelerated timelines.

2.2. Quality aspects

2.2.1. Introduction

Zinplava finished product (FP) is presented as concentrate for solution for infusion containing 25 mg/mL bezlotoxumab. It is formulated as a sterile, aqueous, preservative-free solution aseptically filled into vials for single use.

Other ingredients are: Citric acid monohydrate (E330), Diethylenetriaminepentaacetic acid (DTPA), Polysorbate 80 (E433), Sodium chloride, Sodium citrate dihydrate (E331), Water for injections and Sodium hydroxide (E524).

No Quality by Design development is claimed by the applicant, however, process characterisation studies for active substance (AS) manufacturing process were executed using a risk-based approach, incorporating quality-by-design principles focused on increased process understanding.

2.2.2. Active Substance

General information

Bezlotoxumab (also referred to as MK-6072 by the Applicant) is a human monoclonal antibody (mAb) that binds with high affinity to Clostridium difficile (C. difficile) toxin B. Bezlotoxumab is a glycoprotein. A Chinese hamster ovary (CHO) host cell line was used for expression of bezlotoxumab. The antibody is heterogeneously glycosylated.

The biological activity of the bezlotoxumab was evaluated by its capacity to bind to C. difficile toxin B fragment using an enzyme-linked immunosorbent assay (ELISA) method. A cell based toxin neutralisation assay is used to measure the ability of the antibody to protect host cells from toxicity of the toxin.

Manufacture, characterisation and process controls

Description of the manufacturing process and process controls

Bezlotoxumab manufacturing is performed at Lonza Biologics, Inc. in Portsmouth, New Hampshire, U.S.A.

The bezlotoxumab commercial manufacturing process has been adequately described. Main steps are expression in cell culture in suspension Chinese hamster ovary (CHO) cell line, harvest and purification.

Manufacture is initiated from a single vial of the working cell bank (WCB) followed by inoculum expansion in shake flasks, roller bottles, and a disposable rocker bag. The harvested cell culture fluid (HCCF) is further processed. Bioprocess container (BPC) bags used comply with *Ph. Eur.* (3.2.2.1) and USP (<87>, <88>, and <661>). Prior to release to manufacturing, the BPC bags are visually inspected and the Certificate of Analysis is checked for conformance to specifications.

Control of materials

A list of non-compendial grade raw materials used to manufacture MK-6072 is provided (Buffers and solutions; chromatography resins and filters). All raw materials used in upstream and downstream operations are animal-component free and provided with TSE/BSE certifications.

The cell bank system, characterisation and testing is sufficiently described and conforms with ICH guideline Q5A/B. cDNA was isolated and transfected into the host cell line. From the Clone a Master cell bank was generated and consequently expanded to a working cell bank. A limit for *in vitro* cell age for production was defined.

Control of critical steps and intermediates

Critical process parameters (CPPs) and key operating parameters (KOPs) are defined throughout the manufacturing process. The CPP classification justifications are based on viral clearance studies, large scale range of experience, process characterisation studies and step-specific verification studies (including bioburden reduction, small scale resin lifetime studies).

The identified CPPs and KOPs are considered adequate to control the upstream and downstream manufacturing process for bezlotoxumab AS.

A hold time study was conducted for process intermediates at defined hold time points. The defined hold times are based on the microbial control qualification studies and biochemical stability data from small-scale studies performed. A cumulative intermediate hold time limit is applied and the Applicant is asked to conduct a small scale study to further confirm the appropriate cumulative hold time as a post-authorisation recommendation.

Re-processing has been successfully validated at small scale. Reprocessing protocols were provided for the full manufacturing scale during processing.

Process validation

For process validation qualification lots were manufactured using the proposed commercial manufacturing process.

All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces bezlotoxumab AS of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development and comparability

The active substance process development, manufacture, and testing of preclinical, clinical and commercial materials was carried out. The process comparability assessments indicate that bezlotoxumab AS manufactured throughout development is comparable. The purification performance attributes displayed similar trends.

Characterisation

Bezlotoxumab AS has been sufficiently characterised.

The characterisation of the bezlotoxumab AS included the determination of physicochemical and immunochemical properties, biological activity, purity, impurities, and quantity. The primary, secondary, tertiary, and quaternary structures of bezlotoxumab were evaluated.

Results indicate that bezlotoxumab exhibits properties representative of a fully human monoclonal antibody containing heavy and light chains bound by disulfide linkages with typical levels of heterogeneity in its mass, glycosylation, and charge profiles.

Specification

Specifications were set in accordance with ICH Q6B. The testing includes identity, purity, content and potency. The batch release data confirm compliance with the proposed commercial specifications.

The applicant is recommended to revisit the criteria after the manufacture of 30 commercial batches and tighten the release criteria accordingly. This recommendation applies to AS and FP.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with guideline ICH Q2(R1). The validation reports are provided and demonstrate that the analytical methods are successfully validated with respect to accuracy, precision, specificity, linearity and robustness.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference material

The establishments and history of in-house reference standard have been outlined for bezlotoxumab.

Stability

An initial shelf life of 24 months is proposed for Bezlotoxumab AS when stored in bags at 2–8 ºC.

Stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Zinplava finished product (FP) is a sterile, aqueous, preservative-free solution. Vials contain a target deliverable dose of 40 mL at 25 mg/mL bezlotoxumab for a total of 1000 mg per vial. The finished product is diluted into a compatible diluent (0.9 % Sodium Chloride Injection or 5 % Dextrose Injection) prior to administration by intravenous infusion.

The finished product is a sterile, clear to moderately opalescent, colourless to pale yellow liquid, free from visible particles. The finished product has a target pH of 6.0. and contains the following excipients: sodium chloride, sodium citrate dihydrate and citric acid monohydrate, polysorbate 80, DTPA and water for injection. Zinplava finished product is supplied in 50 mL vial Type I glass vials with a chlorobutyl stopper and a flip-off cap seal. The material complies with *Ph.Eur.* and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished product does not contain any overages.

Manufacturing history was sufficiently outlined. The results of the comparability assessments demonstrate comparability of FP materials manufactured throughout the development. A risk-assessment approach was used throughout the development of the Zinplava manufacturing process.

The Container Closure integrity (CCI) for the 50-mL container-closure system (glass type I) used for Zinplava finished product liquid is assured. The CCI for the 50-mL container-closure system has been demonstrated and will be monitored as part of the stability protocol.

Bezlotoxumab infusion solution was evaluated for biochemical and physical compatibility with various administration materials. Zinplava FP may be diluted in either 0.9% (w/v) sodium chloride or 5% (w/v) dextrose for infusion solution preparation from 0.9-10 mg/mL. Zinplava infusion solutions are biochemically and physically compatible with a variety of commonly available IV containers, IV-administration sets, IV filters, and IV catheters. The use of an inline or add-on filter is required during administration. These studies support compatibility of the Zinplava infusion solution with commonly available filter materials and pore sizes (0.2-5 µm).

Microbial proliferation studies limit the hold time for the Zinplava infusion solution to 16 hours at room temperature and 24 hours at refrigerated (2-8 °C) temperature.

Manufacture of the product and process controls

For the manufacture of Zinplava bezlotoxumab AS is delivered as formulated bulk solution containing the exact formulation of the finished product from Lonza Biologics (US) to Carlow MSD (Ireland).

Zinplava FP is manufactured and filled. Sterile filtration is performed continuously throughout the filling process and consists of closed system filtration through a 0.2-µm bioburden-reducing filter and a 0.2-µm sterile membrane filter into an intermediate (dosing) vessel within a filling isolator. The sterile-filtered solution is subsequently filled aseptically into vials, closed with stoppers, and sealed with caps.

Adequate in process controls were set.

All excipients used during the AS and FP manufacture have compendial *Ph.Eur.* grade except diethylenetriaminepentaacetic acid for which no *Ph.Eur.* monograph exists but it is conform to USP. No excipients of human or animal origin and no novel excipients are present in Zinplava FP.

Product specification

Finished product specifications were set in accordance with ICH Q6B and the corresponding active substance specifications. Acceptable verification of the methods physical appearance, sub visible particles, extractable volume, endotoxin and sterility was performed for finished product samples.

The method for container closure integrity was validated. The other analytical methods from the specifications were validated for active substance and finished product.

Stability of the product

The agreed shelf life for Zinplava finished product is 18 months at 2-8 °C (refrigerator) for the unopened vial.

Stability studies have been performed using the commercial vial/stopper combination of the Zinplava 1000 mg finished product (FP).

For storage of the solution for infusion, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C or 16 hours at room temperature (at or below 25°C). These time limits include storage of the infusion solution in the IV bag through the duration of infusion. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use

storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours at 2°C – 8°C.

This is acceptable as storage for 24 hours at 2°C – 8°C or for 16 hours at room temperature (at or below 25°C) is supported.

Adventitious agents

TSE compliance

The active substance bezlotoxumab is produced in a serum-free medium and no materials of animal or human origin are used during production (fermentation or purification). Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.

Virus safety

Bezlotoxumab is expressed in cells adapted to serum-free medium. Other than the cells themselves, no material of animal origin is added during fermentation. The cell banking system has been extensively screened for adventitious viruses using a variety of in vitro and in vivo assays. The tests did not reveal any presence of virus contaminants in the cell banks with the exception of intracellular type A and extracellular type C retrovirus-like particles which are well known to be present in rodent cells. This is considered acceptable and it is considered that sufficient capacity within the manufacturing process exists to inactivate/remove such virus particles. At the end of the bezlotoxumab fermentation procedure, general testing for adventitious viruses is performed.

In summary, the TSE and viral safety of bezlotoxumab is considered to be sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

No major concerns were identified during marketing authorisation assessment. Several other concerns pertaining to issues including stability and proposed specifications could be resolved by the Applicant during the procedure. Three recommendations are suggested in order to clarify the step on cumulative hold time of 24 days at the stage of the purification process of the AS, to revise the acceptance criteria for active substance and finished product release specifications after 30 commercial batches have been produced and to implement the process-specific ELISA assay for bezlotoxumab host-cell protein (HCP).

Overall, the dossier is of acceptable quality. The manufacturing of bezlotoxumab AS and Zinplava FP is appropriately described, validated and controlled.

The information presented on adventitious agents is considered acceptable. The manufacturing process has demonstrated good viral removal and/or inactivation capacity.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory manner. Data

has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. No cumulative hold time has been established for bezlotoxumab AS purification process yet. The Applicant will perform a small-scale study to establish the cumulative hold time to ensure that there is no adverse impact to product quality when each process intermediate is held to a proposed maximum hold time. Until the study is complete, a cumulative intermediate hold time limit of 24 days will be applied to future manufacturing batches. The applicant should submit the results of the study as soon as available. If the study suggests a different cumulative intermediate hold time limit the applicant is asked to file a variation.

2. Only slight changes to the acceptance criteria were made for active substance and finished product release specifications. These are based on tolerance intervals for batches produced so far. This is currently acceptable. The applicant should revisit the criteria after the manufacture of 30 commercial batches and revise the criteria accordingly.

3. The Applicant is in the process of developing a process-specific ELISA assay for bezlotoxumab host-cell protein (HCP) determination. The implementation of the assay should be reported to the health authority after successful validation.

2.3. Non-clinical aspects

2.3.1. Introduction

Bezlotoxumab is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI. *Clostridium difficile* (*C. difficile*) is an anaerobic, Gram-positive, spore-forming bacterium that colonizes and infects patients whose normal gut microbiota has been disrupted by treatment with broad-spectrum antibiotics (Bassetti *et al*, 2012). Recurrence is common after antibiotic treatment of *C. difficile* infection (CDI). The symptoms of primary and recurrent CDI are caused by 2 exotoxins, *C. difficile* toxin A (TcdA) and *C. difficile* toxin B (TcdB).
The fully human mAb to *Clostridium difficile* toxin A is designated actoxumab (previously known as CDA1, GS-CDA1 and MK-3415), and the fully human mAb to *C. difficile* toxin B is designated bezlotoxumab (previously known as MDX- 1388, CDB1 and MK-6072). The combined administration of these two fully human mAbs is designated actoxumab+bezlotoxumab (previously known as MK-3415A).

2.3.2. Pharmacology

Bezlotoxumab prevents binding of the toxin B to its target cells by binding to regions of the “combined repetitive oligopeptide” (CROP) domains of the toxin that partially overlap with putative receptor binding pockets. This results in blockade of the cellular intoxication cascade at its first step. The protective effects of bezlotoxumab have been shown *in vitro* in TcdB neutralization assays, and in nonclinical studies in mouse and hamster models of CDI (in combination with actoxumab, since bezlotoxumab alone has poor efficacy in rodent models).

The affinities of bezlotoxumab and actoxumab binding to TcdB and TcdA (from the control *C. difficile* strain VPI 10463), respectively, were determined by surface plasmon resonance (SPR) and revealed Kd values of 19 and 370 pM for bezlotoxumab binding to TcdB (best fit of the data was to a two-site binding model), and 610 pM for actoxumab binding to TcdA. Actoxumab is selective for TcdA and bezlotoxumab is selective for TcdB; no binding of actoxumab to TcdB or of bezlotoxumab to TcdA was observed (Vero cells). A peptide corresponding to the N-terminal half of the CROP domain of TcdB was co-crystalized with Fab fragments of bezlotoxumab and revealed that Fab fragments bind side-by-side to 2 highly homologous epitopes within the CROP domain. This model is in line with binding stoichiometry experiments carried out by size-exclusion chromatography coupled with multi-angle laser light scattering in which the stoichiometry of bezlotoxumab to CROP domain was 1:1 and was independent of the molar ratio of the 2 proteins.

Cellular effects mediated by TcdA and TcdB were investigated such as morphological changes, Rac1 glucosylation, disruption of epithelial integrity, cellular viability, and adhesion of *C. difficile* to Caco-2 cells. These effects were neutralized by actoxumab and bezlotoxumab in a concentration dependent manner. The ability of actoxumab and bezlotoxumab to block binding of TcdA and TcdB to the surface of mammalian cells was assessed by flow cytometry and Western blotting.

Neutralization of *C. difficile* Toxins A and B from genetically-distinct strains of *C. difficile* by actoxumab and bezlotoxumab was investigated by ELISA. *C. difficile* strain VPI 10463 (ribotype 087) was used as a reference strain. Full neutralization of the toxins in culture supernatants of all clinical isolates tested (81 clinical isolates of *C. difficile* from the USA, Canada, Western Europe, and Japan; (ribotypes 001, 002, 003, 012, 014, 017, 018, 023, 027, 053, 063, 077, 078, 081, 087, 106, 198, and 369)) including multiple isolates of the endemic strains of ribotype 027/toxinotype III and ribotype 078/toxinotype V, was achieved by actoxumab and bezlotoxumab. Increase in the EC_{50} values of bezlotoxumab for TcdB of strains of ribotype 027, 036, and 078 are caused by amino acid substitutions at key positions within the epitopes. The results indicate also that for a number of strains, the TcdA concentration was too low to be detected, whereas TcdB was detected in supernatants of all strains tested.

Preclinical *in vivo* efficacy of actoxumab+bezlotoxumab was evaluated in the Golden Syrian hamster model of infection (at doses of 0.5 to 50 mg/Kg) and in the mouse CDI model (at doses of 2, 5, 10 and 50 mg/Kg). Treatment with actoxumab+bezlotoxumab improved animal survival (in mice and hamsters) and decreased morbidity when administered prophylactically or therapeutically, and in both primary and recurrent CDI models. Fc-mediated functions of actoxumab and bezlotoxumab do not appear to play a role in the *in vivo* efficacy, based on the comparison of N297Q mutants to that of wild-type showing they had similar efficacy in both primary and relapse versions of a mouse model of CDI (at a dose of 10mg/Kg).

The ability of actoxumab and bezlotoxumab to directly neutralize TcdA and TcdB *in vivo* was assessed following systemic administration of either TcdA or TcdB in mice. Whereas administration of actoxumab 24 hours before intraperitoneal (IP) challenge with 100ng TcdA increased animal survival, in a similar experiment with TcdB challenge, only a polyclonal goat anti-toxin B serum was protective whereas several monoclonal antibodies (MDX1388 [bezlotoxumab], 2A11, 1G10 and 103-174) were not. However, in a subsequent experiment in mice challenged with a mixture of TcdA and TcdB (25 ng each), the combination of actoxumab+bezlotoxumab was protective.

Although clinical study results suggest that neutralization of toxin B is sufficient to reduce the risk of recurrent disease in humans; the preclinical efficacy data relay on the combination of actoxumab and bezlotoxumab rather than bezlotoxumab alone. From *in vivo* models it is concluded that the combination of actoxumab+bezlotoxumab improves animal survival and decreased morbidity. Treatment with actoxumab might have a minor effect but bezlotoxumab alone seems to be inefficient in hamster models, whereas each antibody alone has partial protective effects in mouse models.

The study performed in piglets by Steele *et al*, JID 2013:207 (15 January) revealed that "piglets treated with anti-TcdB antibodies, whether alone or in addition to anti-TcdA, were completely protected from the development of systemic signs of CDI" and that "Histopathologic lesions in the large intestine were slightly more severe in piglets treated with monoclonal anti-TcdA + anti-TcdB than in those treated with only monoclonal anti-TcdB". Treatment with bezlotoxumab or bezlotoxumab + actoxumab protected the piglets in the same way as mice and hamsters with bezlotoxumab + actoxumab. Data show that both antibodies are transported into the intestinal lumen at the site of infection in piglets and hamsters supporting the suggestion that the general pathogenesis of CDI and mechanisms of protection by bezlotoxumab or by actoxumab + bezlotoxumab are comparable in different hosts, although neutralization of toxin A is not required for efficacy in human and piglet disease. One hypothesis about the cause of this dichotomy is that different host species may express cellular surface receptors with different affinities for the two toxins. Even though the gnotobiotic piglet model has its advantages, it is an exploratory and relatively difficult CDI model to work with. With regard to reproducibility and ability to assess a sufficient number of animals, the rodent model is preferable. However, several aspects of the underlying mechanism of both CDI and the protection offered by anti-toxin antibodies are still unknown. Further development and use of the gnotobiotic piglet model may in future investigations provide valuable knowledge on how the two toxins affect the gut and how anti-toxin treatment can protect against CDI.

As also demonstrated in hamsters and mice, antibody administration did not impact *C. difficile* burden in the intestines of gnotobiotic piglets. Bezlotoxumab is able to prevent recurrence of CDI by neutralizing toxin B produced, thereby preventing intestinal lesions. Recovery of the microbiome over time following the initial infection is associated with clearance of *C. difficile* colonization in mice and hamsters, and may explain why bezlotoxumab prevents recurrence rather than simply delaying it.

2.3.3. Pharmacokinetics

Pharmacokinetic (PK) studies with sparse sampling were conducted in healthy hamsters. Actoxumab and bezlotoxumab median serum concentrations that corresponded to a CDI efficacy survival time point of 48 hr after the last dose were 350 and 320 μg/mL, respectively (PK001) and somewhat higher in another study (PK006: 588 and 493 μg/mL,). *In vivo* tissue distribution studies in hamsters demonstrated that actoxumab and bezlotoxumab reached the site of infection in the lumen of the gut, and were detected at significantly higher levels in hamsters with CDI compared with healthy hamsters. *In vitro* studies using a two-dimensional Caco-2 monolayer culture system demonstrated that antibody applied to the basolateral chamber translocated to the apical chamber to a much greater extent when toxin was added to the apical side.

It can be concluded from these data that systemically administered antibodies localize to the subepithelial space of the gut wall and leak into the lumen via toxin-induced lesions, binding to and neutralizing toxin in this compartment, or any toxin that may have leaked to the basolateral/systemic side.

No formal pharmacokinetic drug interaction studies have been conducted. Since bezlotoxumab is eliminated by catabolism, no metabolic drug-drug interactions are expected.

2.3.4. Toxicology

Nonclinical toxicology studies with bezlotoxumab and actoxumab, alone and in combination as bezlotoxumab + actoxumab were performed in mice. This is acceptable as there is no species in which target-mediated toxicity can be investigated. No findings of toxicological significance were observed in the single (4 weeks) or repeat-dose toxicity studies (2 or 3 weeks studies) performed with bezlotoxumab and/or actoxumab. No anti-bezlotoxumab or anti-actoxumab antibodies were detected in any animals in the test article-treated groups. The no-observed-adverse-effect-level (NOAEL) for bezlotoxumab alone or in combination with actoxumab was ≥125 mg/kg/dose. This is up to 5 fold over the exposure in humans at the clinically recommended dose (10mg/Kg).

Tissue cross-reactivity studies with bezlotoxumab and actoxumab were performed with normal human or Swiss Webster or CD1™ mouse tissues. There were no findings of toxicological significance observed in the *in vitro.*

The provided Toxicology investigation is appropriate for an antibody against foreign target according ICH S6(R1) guidance. “A short-term safety study in one species can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate.” Therefore animal reproduction or developmental toxicity studies have not been conducted with bezlotoxumab.

2.3.5. Ecotoxicity/environmental risk assessment

As stated in the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447), antibodies are unlikely to pose a significant risk to the environment. Based on this, the Applicant’s justification for not submitting an ERA for bezlotoxumab is considered acceptable.

2.3.6. Discussion on non-clinical aspects

In vitro pharmacology, toxicology and pharmacokinetic were appropriately investigated for both antibodies (actoxumab+bezlotoxumab) against foreign targets (*C. difficile* toxin A and toxin B). *In vivo* pharmacology was extensively investigated in mice and hamsters. Although clinical study results suggest that neutralization of toxin B is sufficient to reduce the risk of recurrent disease in humans, the preclinical efficacy data rely on the combination of actoxumab and bezlotoxumab instead of bezlotoxumab alone. The differences in results between the different animal models, with links to the results seen in the clinical setting, was provided and discussed. Data show that both antibodies are transported into the intestinal lumen at the site of infection in piglets and hamsters, supporting the suggestion that the general pathogenesis of CDI and mechanisms of protection by bezlotoxumab or by actoxumab + bezlotoxumab are comparable in different hosts, even though neutralization of toxin A is not required for efficacy in human and piglet disease. A hypothesis about the reason is that different host species may express cellular surface receptors with different affinities for the two toxins. Even though the gnotobiotic piglet model has its advantages, it is an explorative and relatively difficult CDI model to work with. With regard to reproducibility and ability to assess a sufficient number of animals, the rodent model is preferable. However, several aspects of the underlying mechanism of both CDI and the protection offered by anti-toxin antibodies, are still unknown. Further development and use of the gnotobiotic piglet model may in future investigations provide valuable knowledge on how the two toxins affect the gut and how anti-toxin treatment can protect against CDI.

As also demonstrated in hamsters and mice, antibody administration did not impact *C. difficile* burden in the intestines of gnotobiotic piglets. Bezlotoxumab is able to prevent recurrence of CDI by

neutralizing toxin B produced, thereby preventing intestinal lesions. Recovery of the microbiome over time following the initial infection is associated with clearance of *C. difficile* colonization and may explain why bezlotoxumab prevents recurrence. This hypothesis was further substantiated by the demonstration that microbiome recovery was inversely correlated to the *C. difficile* burden.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. Genotoxicity and carcinogenic potential have not been evaluated.

Animal reproduction or developmental toxicity studies have not been conducted with bezlotoxumab. There were no notable effects in the male and female reproductive organs in mice based on repeat dose toxicity studies and no binding to reproductive tissues was observed in tissue cross-reactivity studies. It is unknown whether bezlotoxumab is secreted in human milk. Appropriate statements are added to SmPC, section 4.6 (Fertility, pregnancy and lactation) and 5.3 (Preclinical safety data).

For Zinplava, a marketing authorisation can be granted from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. One US centre was closed to further enrolment as a result of serious GCP non-compliance issues identified by the clinical research associate at the site. The data from this site was excluded from all efficacy analyses, but was retained in safety analyses.

The applicant 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.

Table 1. Tabular overview of clinical studies

Protocol Number	Trial Population	Trial Design	Primary Objective	Number of Subjects Treated
Phase 1				
CA-CDA1-04-01 (Protocol 019)	Healthy subjects	Open-label, dose escalation	To assess the safety and tolerability of escalating doses of actoxumab	Actoxumab: 30
CA-GCDX-05-01 (Protocol 020)	Healthy subjects	Open-label, dose escalation	To assess safety and tolerability of escalating doses of actoxumab and bezlotoxumab	Actoxumab: 6 Bezlotoxumab: 30 Actoxumab + Bezlotoxumab: 24
Protocol 005	Healthy subjects	Randomized, double-blind, placebo-controlled, single dose	To evaluate the safety and tolerability of actoxumab + bezlotoxumab administered over 1 hour†	Actoxumab + Bezlotoxumab: 29 Placebo: 6
Protocol 006	Healthy male Japanese subjects	Randomized, double-blind, placebo-controlled, single dose	To evaluate the safety and tolerability of actoxumab + bezlotoxumab in healthy male Japanese subjects†	Actoxumab + Bezlotoxumab: 13 Placebo: 6
Protocol 004	Healthy subjects	Open-label, two doses 3 months apart	To evaluate the immunogenicity of 2 infusions of actoxumab + bezlotoxumab†	Actoxumab + Bezlotoxumab: 30
Phase 2				
CA-CDA1-05-02 (Protocol 018)	Subjects with CDI receiving SoC antibiotics	Randomized, double-blind, placebo-controlled, single dose	To assess the safety and efficacy of actoxumab for the reduction of CDI recurrence, length of hospital stay, and duration of diarrhea	Actoxumab: 30 Placebo: 17
CA-GCDX-06-02 (Protocol 017)	Subjects with CDI receiving SoC antibiotics	Randomized, double-blind, placebo-controlled, single dose	To determine if actoxumab + bezlotoxumab reduced the proportion of subjects with CDI recurrence	Actoxumab + Bezlotoxumab 101 Placebo: 99
Phase 3				
Protocol 001	Subjects with CDI receiving SoC antibiotics	Randomized, double-blind, placebo controlled, adaptive design, single dose	To determine if actoxumab, bezlotoxumab, and/or actoxumab + bezlotoxumab reduced the proportion of subjects with CDI recurrence†	Actoxumab: 235 Bezlotoxumab: 390 Actoxumab + Bezlotoxumab: 387 Placebo: 400
Protocol 002	Subjects with CDI receiving SoC antibiotics	Randomized, double-blind, placebo controlled, single dose	To determine if bezlotoxumab and/or actoxumab + bezlotoxumab reduced the proportion of subjects with CDI recurrence†	Bezlotoxumab: 396 Actoxumab + Bezlotoxumab: 390 Placebo: 381

† Trial was conducted with a 60 minute infusion duration, as comparison to previous trials (P019, P020, P018 and P017) using no less than a 2 hour infusion. In P004, P005, P006, P001, and P002 infusion was over 60 minutes.
SoC – Standard of Care; CDI – *Clostridium difficile* infection
[Ref. 5.3.3.1: P019, P020, P005] [Ref. 5.3.3.3: P006] [Ref. 5.3.4.1: P004] [Ref. 5.3.5.1: P018, P017, P001, P002]

The development program comprises studies evaluating the safety and efficacy of a monoclonal antibody (actoxumab) directed against *C.-difficile* toxin A; a monoclonal antibody (bezlotoxumab) directed against *C.-difficile* toxin B and a combination product of actoxumab and bezlotoxumab.

Considering the safety and efficacy data, the Applicant concluded that actoxumab alone is not efficacious and actoxumab + bezlotoxumab do not have any safety or efficacy benefit over bezlotoxumab alone. Therefore, the Applicant selected bezlotoxumab for marketing authorisation.

Besides two pivotal Phase 3 trials, the clinical pharmacology program for bezlotoxumab included four Phase 1 trials evaluating the safety, pharmacokinetics (PK), and immunogenicity of bezlotoxumab administered alone or in combination (actoxumab + bezlotoxumab), in healthy adult subjects and one Phase 2 trial in patients with CDI.

2.4.2. Pharmacokinetics

Assays

The screening ADA assay was not sufficiently sensitive and thus inconclusive for about one third of the subjects due to low drug tolerance. In patients with positive/inconclusive ADA result, no potential influence of ADA on PK after the first dose is detectable. The risk of impactful immunogenicity-related effects in CDI patients following a repeated dose is considered low. This is supported by 29 healthy subjects who received two doses of actoxumab + bezlotoxumab, no treatment emergent ADA positive subject has been identified. However, immunogenicity incidence after re-administration in patients remains a potential risk and missing information.

Free bezlotoxumab concentrations in serum were measured using a first and a more specific second generation immunoassay. Due to interference by endogenous anti-toxin B in the first generation assay, only data from those studies using the second generation assay [P004, P005, P006 (Phase 1); P001, P002 (Phase 3)] were included in the population pharmacokinetic analysis.

Semi-quantitative bezlotoxumab detection in stool samples was done in one Phase 3 study using the same immunoassay-design which detects free bezlotoxumab only.

Pharmacokinetics of bezlotoxumab

Non-compartmental PK analysis of Phase 1 PK data in healthy subjects for bezlotoxumab (10 mg/kg) that was administered intravenously either alone or in combination resulted in ranges of characteristic PK parameter values: Cmax (223 – 302 µg/ml), tmax (0.5 – 2 h), AUC0-inf (73300 – 92700 µg*h/ml), half-life t1/2 (18-27 d) as well as values for volume of distribution Vdss (5 – 7 L), and for clearance CL (0.18-0.26 L/d).

Serum concentrations of bezlotoxumab declined in a biphasic manner in the 12 weeks following infusion and did not differ when bezlotoxumab was administered alone or with actoxumab. No evidence of target-mediated drug disposition (TMDD) was observed based on visual inspection of individual concentration time profiles. From study P004, minimal accumulation in bezlotoxumab exposure could be detected, when a second dose of 10 mg/kg of bezlotoxumab in combination 84 days after the first dose was administered.

In patients, PK profiles after a single dose of 10 mg/kg IV were available from two Phase 3 trials and characterized by predicted AUCinf of 53.000 µg*h/ml, Cmax of 185 µg/ml and t1/2 of 18.7 days. It is obvious that AUC exposure in healthy subjects is 43% higher compared to patients. The difference in bezlotoxumab exposures between the healthy subject and patient populations is mainly attributed to differences in baseline albumin level. The general health of patients with CDI is poorer and is reflected in lower albumin levels than healthy subjects. Despite the differential exposures of bezlotoxumab, the shapes of the concentration-time profiles in healthy subjects and patients appear to be similar.

Characterization of bezlotoxumab PK is supported by population PK analysis based on pooled data obtained from Phase 1 (P004, P005, and P006) and Phase 3 (P001 and P002) trials. Therefore, a dataset based on data from administration of bezlotoxumab (monotherapy and combination) in healthy volunteers (72 subjects) and patients (1515 subjects) was created. In total, 8784 evaluable bezlotoxumab concentrations were included in the population PK analysis. Regarding the patient population, 381+ 386 = 767 subjects (50.6%) had evaluable bezlotoxumab PK for the population PK analysis resulting from monotherapy.

Population PK estimation for patients resulted in a low clearance of 0.317 L/day and a limited volume of distribution of 7.33 L), respectively. These typical values are consistent with those of other human monoclonal antibodies.

As a protein product, bezlotoxumab is not expected to be eliminated by renal or biliary excretion but through protein catabolism. Of note, bezlotoxumab appears to be excreted in faeces by direct “transport” across disrupted epithelium into the gut lumen, the location of infection. However, bezlotoxumab was detected in only a low fraction of stool samples and this proportion was higher in the combination MK-3415 treatment arm. Relationship between mAb detection on stool and its effects on serum concentrations is not clearly understood. Due to assay limitations, care should be taken in interpreting the qualitative results. Stool bezlotoxumab data were intended to be supportive of the mechanism of action whereby systemically available bezlotoxumab was shown reach the gut lumen and be detected in stool. As the MAH agrees, stool sample results cannot be used to draw any quantitative conclusions. The key reason for the discrepancy between combination therapy and monotherapy in the proportion of stool samples with bezlotoxumab detected is still unknown. From study P004 (29 healthy volunteers) giving two sequential doses, a low intra-individual variability was derived for healthy subjects (< 10 %CV). Population PK simulations result in PK parameter AUC0-inf

and Cmax with low to moderate inter-individual variability in healthy subjects (17.8 %CV, 14.0 %CV) and within the target patient population (40.2 %CV, 20.7 %CV), respectively.

Dose proportionality and time dependencies

Deviation from dose proportionality was not observable in healthy subjects (study P020, range 0.3 mg/kg – 20 mg/kg), albeit using a first generation assay and a formulation different with that intended for the market. The applicant has described the assessment of comparability between three bezlotoxumab drug substance manufacturing processes demonstrating that the different formulations are comparable. However, there are no patient PK data after other doses than 10 mg/kg. Therefore, no conclusion on dose proportionality in patients can be drawn. The range of AUC in patients overlaps with the range of AUC of healthy subjects receiving 10 mg/kg. Given that the influence of albumin is accounted for by population PK analysis, extrapolation of dose proportionality from healthy subjects to the patient population is possible.

Special populations

Evaluation of pharmacokinetics of bezlotoxumab in special populations has been based on population PK analysis. In total, 17 covariates have been statistically tested and addressed. Albumin, gender (male), Japanese were identified as significant covariates on both Cl and Vdss, and race (black) additionally on clearance. Bodyweight was included as structural covariate on both clearance and volume. The allometric exponents for CL and Vc were both 0.477, which is supportive for body-weight based dosing regimen. No significant effects of impaired renal and hepatic function, gender, race, age, comorbid conditions, endogenous IgG to toxin B on bezlotoxumab PK were observed. Albumin level (range: 1 to 6 g/dL) and body weight (range: 30-194 kg) explained most of the inter-patient-variability in bezlotoxumab PK.

In phase 3 trials, half of the patients (51%) were elderly (≥ 65 years), 29% were older than 75 years. The small decrease in AUC in patients older than 65 years is explainable by both the association of age to albumin and high age to relatively lower level of weight. Age distribution is homogenous; no age influence could be detected.

Table 2. Number of elderly subjects in Phase 3 trials

	Age 65-74 (Older subjects number /total number)	**Age 75+** (Older subjects number /total number)
Phase 3 trials 001/002	344/1504	459/1504

Pharmacokinetic interaction studies

The effect of bezlotoxumab on co-administered drugs is not expected. Population PK analysis did not indicate that concomitant use of Standard of care (SoC) therapy (oral metronidazole, oral vancomycin, and oral fidaxomicin), non-SoC antibiotics and proton pump inhibitors have effects on bezlotoxumab PK. Furthermore, population PK analysis could not detect a significant impact of possible interaction by co-administered actoxumab on bezlotoxumab PK.

Overall, PK characterization in patients is limited. Only data after one dose (10 mg/kg) are available, and the new excretion pathway into the gut and its effects are not fully clear.

2.4.3. Pharmacodynamics

Mechanism of action and primary pharmacology

Bezlotoxumab is a fully human mAb of the immunoglobulin G1 isotype with two κ light chains (IgG1κ), which binds with high affinity to *C. difficile* toxin B. Bezlotoxumab was developed for the adjuvant treatment (in addition to standard of care antibiotics) of recurrence of *C. difficile* infection (CDI) in patients that are 18 years or older.

The two main virulence factors of *C. difficile* are the large toxins, TcdA and TcdB, which enter colonic epithelial cells and cause fluid secretion, inflammation, and cell death, as stated in a recent publication in PNAS (La France *et al*., 2015). The applicant discussed if bezlotoxumab enters colonic epithelial cells to bind and neutralise toxin B and has not rejected the possibility that bezlotoxumab can enter the colonic epithelial cells. The applicant further discussed the above-mentioned article and stated that there are no data to suggest that the interaction of bezlotoxumab with toxin B can occur anywhere but outside the cells, or indeed that bezlotoxumab enters mammalian cells at all as part of the mechanism of toxin neutralization.

Bezlotoxumab is able to bind to toxin B that is produced in case of CDI, blocking its binding and neutralizing the bioactivity of the toxin. However, data is lacking regarding the activity of bezlotoxumab against toxin B from *C. difficile* of food/animal origin, and regarding cross-reactivity against large clostridial glucosylating toxins other than toxin B. No relevant PD biomarker (e.g. toxin B concentration) was evaluated in the Phase 1 and Phase 2 program in order to prove this mode of action in patients. Given the clinical endpoint which is based on a relative simple outcome measures (diarrhoea), the absence of evaluation of pharmacodynamic measures the Phase 1 and Phase 2 is acceptable.

However, the exact mode of action and site of effect are not completely understood. It is unclear whether bezlotoxumab has to be excreted into the gut to be effective or toxin inhibition also occurs on the interstitial site of the gut epithelium. From the presented stool data, no conclusion for a relationship between AUC and the proportion of subjects with bezlotoxumab detected in stool can be drawn. Thus, the relevance of exposure parameter (AUC serum or stool) for PK/PD relationship remains unclear.

As the goal of bezlotoxumab therapy is to prevent the recurrence of an intestinal infection, the presence of bezlotoxumab in stool was assessed in Study P002 to inform if bezlotoxumab could reach the intestinal lumen, the site of infection in humans. The results are inconclusive.

Secondary pharmacology

Monoclonal antibody therapeutics have very low potential to interact with the extracellular or intracellular (pore) domains on the hERG ion channel and, therefore, are highly unlikely to inhibit hERG channel activity based on their targeted, specific binding properties. Per ICH guidelines, a clinical study of the effect of monoclonal antibodies on the QT interval is not required and based on these considerations, a dedicated clinical evaluation of the effects of actoxumab and bezlotoxumab on QTc prolongation was not performed as part of the clinical development program. Instead, ECGs were collected as part of the Phase 3 studies (P001, P002); ECG measurements were taken at 2 time points on Day 1: pre infusion and within 120 minutes post infusion. It should be noted that subjects were not

excluded from the study if they had abnormal ECG findings at baseline. Likewise, subjects receiving medications known to prolong QT were not excluded. Bezlotoxumab is not associated with clinically relevant QTc prolongation.

Immunogenicity

The immunogenicity potential of bezlotoxumab was evaluated in two Phase 1 trials (P004, P006) and the two pivotal Phase 3 trials (P001 and P002). In the Phase 1 trials, no healthy subjects had samples which tested positive for anti bezlotoxumab antibodies. This includes subjects dosed repeatedly (Day 1 and Day 85) with actoxumab + bezlotoxumab. In the Phase 3 trials, there were no bezlotoxumab treatment-emergent positive subjects (i.e., first identified as positive after treatment), although there were 9 of 1414 (0.6%) non treatment- emergent positive subjects (i.e., already positive at baseline). In the Phase 3 trials, bezlotoxumab serum concentrations decreased below the DTL as measured in the last available serum concentration sample such that 1013 of the 1414 subjects (71.6%) were reported as negative and 392 of the 1414 subjects (27.7%) were reported as inconclusive.

ADA assays were not suitable to detect ADAs in one third of the subjects due to low drug level tolerance. Since multiple repeat re-treatments with bezlotoxumab over the years cannot be ruled out, the applicant was requested to address the question of inadequate ADA assay performance (~30% inconclusiveness) as well as the potential risk in case of bezlotoxumab re-administration in ADA-positive patients. There is no indication that inconclusive patients would differ in immunogenicity incidence from ~70% conclusive patients.

Based on data from a single administration, bezlotoxumab seems to have a low potential for immunogenicity. However, no confirmative data are available concerning multiple administrations of bezlotoxumab in patients (who could be older and immunocompromised, compared to healthy subjects); therefore it is important that post-marketing adverse event reports of patients with repeated administration of Bezlotoxumab are thoroughly monitored and analysed in the future. In addition, in order to inform the physicians, it should be clearly stated in the SmPC that there is no experience with multiple administrations in CDI patients. The immunogenicity incidence after re-administration in patients remains a potential risk and missing information. The lack of experience with repeated administration in CDI patients is stated in the SmPC.

Relationship between plasma and effect

Exposure-efficacy analysis results indicate that History of CDI in the past 6 months, baseline albumin level, age, and a Charlson Comorbidity Index $\geq$ 3 were significantly associated ($p < 0.05$) with the rate of CDI recurrence for patients treated with placebo. There is no clear relationship between exposure and response for patients that received bezlotoxumab treatment. Any association between CDI recurrence and bezlotoxumab AUC is attributed to albumin level, rather than a direct relationship between exposure and CDI recurrence.

Concerning exposure-safety relationship, no connection between the incidence of adverse events (AE) and exposure could be detected, but a markedly inverse relationship between severe AE (SAE) incidence and exposure was observed. Higher incidence of SAE at lower AUC levels could be attributed to patients' health status, as patients of poor health tend to have lower albumin and AUC levels as compared to healthy subjects. After albumin-normalization the inverse relationship disappeared, confirming this assumption.

2.4.4. Discussion on clinical pharmacology

The package on pharmacodynamics to support the MAA is limited. No pharmacodynamic measures were evaluated in the Phase 1 and Phase 2 program. Given the clinical endpoint which is based on a relative simple outcome measures (diarrhoea), the absence of evaluation of pharmacodynamic measures the Phase 1 and Phase 2 is acceptable.

As the goal of bezlotoxumab therapy is to prevent the recurrence of an intestinal infection, the presence of bezlotoxumab in stool was assessed in Study P002 to inform if bezlotoxumab could reach the intestinal lumen, the site of infection in humans. The results remain inconclusive and do not allow any quantitative conclusions. The levels of bezlotoxumab required for inactivation of toxin B in the gut lumen to prevent CDI recurrence are not known. Moreover, data regarding the activity of bezlotoxumab against toxin B from *C. difficile* of food/animal origin, and data regarding cross-reactivity against large clostridial glucosylating toxins other than toxin B are still lacking.

Bezlotoxumab is not associated with clinically relevant QTc prolongation

Bezlotoxumab belongs to the class of therapeutic antibodies that are primarily eliminated by protein catabolism, and, thus, concomitant medication use is not anticipated to influence the exposure of bezlotoxumab. Drugs that affect the cytochrome P450 family and other metabolizing enzymes are not expected to interfere with the catabolism of immunoglobulins.

Furthermore, bezlotoxumab is not expected to directly affect cytochrome P450 family members or transporters typically affected by small molecules. In addition, bezlotoxumab targets toxin B of C. difficile, an exogenous target, and therefore its target is not a component of the immune system or of any other pathway potentially involved in drug metabolism or the immune response. These properties make it unlikely that bezlotoxumab will mediate clinically meaningful pharmacodynamic drug-drug interactions with medications that are highly metabolized or transported.

Bezlotoxumab has a low potential to elicit the formation of anti-drug-antibodies after single dose application. Limited data on repeat application (Day 1 and Day 85) in healthy subjects also are available and no signal on ADA development was observed. Since multiple repeat re-treatments with bezlotoxumab over the years cannot be ruled out, the Applicant should further address the potential for immunogenicity, post-marketing (RMP measure).

2.4.5. Conclusions on clinical pharmacology

Considering the nature of the product and the mode of action, the clinical pharmacology is deemed acceptable. Limitations in the knowledge of the product's clinical pharmacology are reflected in the SmPC.

The effect of repeated administration of bezlotoxumab with potential for immunogenicity is stated as an RMP safety concern.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response studies were performed. The target dose for bezlotuxomab of 10 mg/kg was selected based on data from non-clinical studies (in a hamster model of CDI) and clinical trials in healthy subjects and patients.

The 10 mg/kg dose in healthy subjects led to median serum levels that were approximately equivalent to the levels that provided protection from acute CDI in a hamster model.

The efficacy data observed in Study P017 supported the continued evaluation of 10 mg/kg actoxumab +bezlotoxumab in the two pivotal Phase 3 trials (Study P001, Study P002). Although doses lower and higher than 10 mg/kg were studied in healthy volunteers, only a 10 mg/kg dose was tested in Phase 2 and 3 trials. Because of the large magnitude of reduction in CDI recurrence observed in Phase 2 with 10 mg/kg dose, the applicant did not expect that higher doses would add clinically meaningful benefit. Conversely, lower doses were not studied in Phase 3, as acceptable safety was demonstrated at 10 mg/kg in the Phase 1 and Phase 2 trials.

2.5.2. Main studies

Trial P001: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415 (Human Monoclonal Antibody to *Clostridium difficile* toxin A), MK-6072 (Human Monoclonal Antibody to *Clostridium difficile* toxin B), and MK-3415A (Human Monoclonal Antibodies to *Clostridium difficile* toxin A and toxin B) in Patients Receiving Antibiotic Therapy for *Clostridium difficile* Infection (MODIFY I).

Trial P002: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to *C. difficile* toxin B), and MK-3415A (Human Monoclonal Antibodies to *C. difficile* toxin A and B) in Patients Receiving Antibiotic Therapy for *C. difficile* Infection (MODIFY II).

Throughout nonclinical and clinical development, changes to the bezlotoxumab DS manufacturing process were introduced. In the Phase 3 studies, bezlotoxumab DS manufactured with the same manufacturing process intended to be the source for manufacturing of the commercial product was used.

Legend:

MK-6072 = bezlotoxumab

MK-3415A = bezlotoxumab + actoxumab

MK-3415= actoxumab

Methods

Both **P001** and **P002** were Phase 3, randomised, double-blind, placebo-controlled and multicentre studies conducted to evaluate the efficacy, safety, and tolerability of the mAb bezlotoxumab in adult subjects 18 years of age and older with CDI who were receiving standard of care antibiotic therapy for a primary or recurrent episode of CDI. The intended sample size was 400 subjects in each treatment group; thus, ~1600 subjects were enrolled in **P001** (~400/group for the 4 treatment groups), and ~1200 subjects were enrolled in **P002** (~400/group for the 3 treatment groups).

P001 had an adaptive design whereby one or both of the individual mAb treatment groups (actoxumab and/or bezlotoxumab) could be dropped based on the results of an interim analysis if there was a significant difference in the reduction of CDI recurrence when compared to actoxumab + bezlotoxumab.

P002 did not have an interim analysis; however, an adaptation was permitted if the bezlotoxumab alone arm was dropped in **P001** based on recommendations of the eDMC at the time of the interim analysis.

Study **P002** is identical to **P001** in design and conduct (see figure below), with the following three major exceptions:

- P002 contained three treatment groups (bezlotoxumab, actoxumab + bezlotoxumab, and placebo)
- No interim analysis was planned for study P002
- P002 had an extended follow-up period of 9 months conducted in a subset of subjects to assess for CDI recurrence through Month 12.

  Overall, this extension phase was conducted in a subset of ~300 subjects who completed the primary 12-week study period. Study visits occurred on Month 6 (± 10 days), Month 9 (± 10 days), and Month 12 (± 10 days) during which a stool or rectal swab sample was collected for testing of carriage of toxigenic *C. difficile*. Anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) were performed on the stool or swab samples at a central laboratory. Subjects were also contacted every month by phone to assess for CDI recurrence. A stool sample was to be collected at the time of a new episode of diarrhea and tested for toxigenic *C. difficile* locally at the central laboratory. Serum samples were collected during the scheduled and unscheduled visits per the Extended Follow-up Period (“extension phase”) study flow chart; such sera were used for post-infusion PK assessment of MK-3415 and MK-6072 as well as measuring levels of ADA and endogenous anti-toxin A and anti-toxin B antibodies. Safety was assessed through the end of the 12-month follow-up period for any AEs with an outcome of death as well as any SAEs considered to be related to the study infusion. The extension phase did not contribute to the protocol primary, secondary or exploratory objectives. Due to the small number of subjects in the extension phase, subjects were evaluated for these endpoints separately.

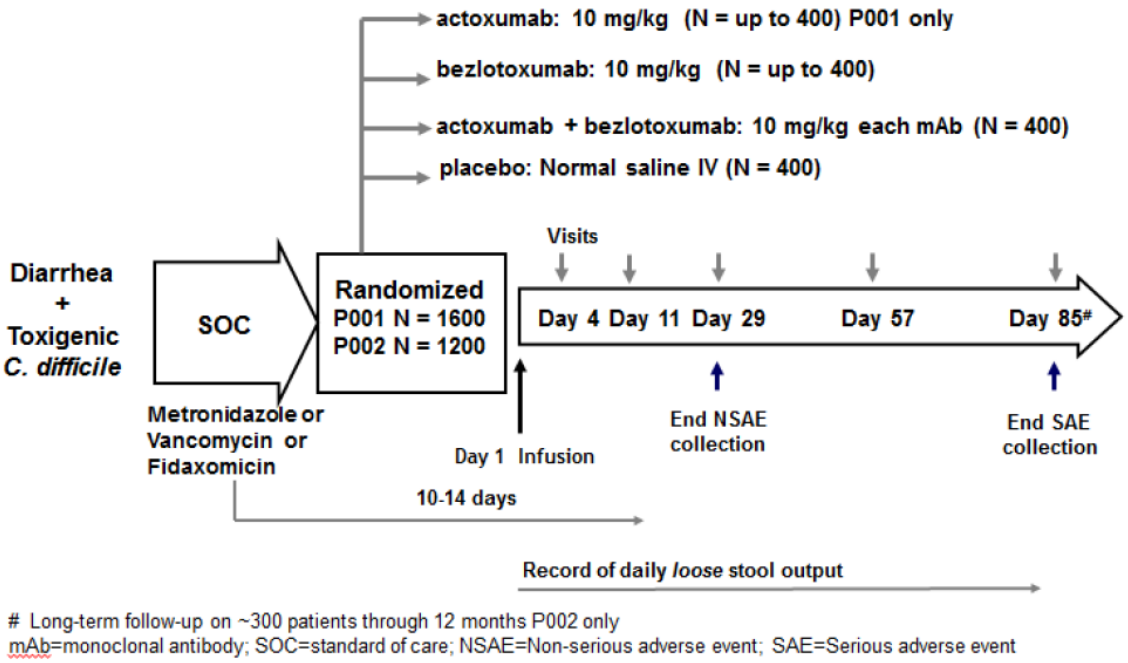


Figure 1: Trial design for protocols 001 and 002

The daily count of loose stools (defined as Type 5 through Type 7 on the Bristol Stool Chart) was recorded by the subject (or designee) by the use of a stool count log. The study personnel were to contact the subject every day through Day 14 for loose stool counts, body temperature, and compliance with standard of care (SoC) medications and to ensure they are being recorded on the log. Thereafter, study personnel was to contact the subject twice weekly Week 3 through Week 12. The information communicated by the subject during the contact was to be recorded in the source documentation

Study Participants

Subjects with confirmed CDI were eligible for enrolment, including those with multiple previous episodes of CDI. Diagnosis of the baseline episode required a positive stool test for toxigenic *C. difficile* within 7 days prior to study infusion. All subjects were required to be receiving oral standard of care antibiotic therapy for the presenting episode of CDI.

Pertinent inclusion criteria

- Subject must be 18 years of age or older.
- Subject has a confirmed diagnosis *of C. difficile* infection (CDI) as defined by:

a. Diarrhoea (passage of 3 or more loose stools in 24 or fewer hours)

and

b. A positive stool test for toxigenic *C. difficile* from a stool samples collected no more than 7 days before the study infusion (allowed stool test methods and kits are listed in respective study protocols)

Diarrhoea is not required to be present on the day of infusion.

- Subject must be receiving or planning to receive a 10- to 14-day course of standard of care therapy for CDI. A subject who is planning to initiate standard of care therapy on the same day as the infusion is eligible for participation. The first dose of standard of care therapy must have been administered prior to or within a few hours following the infusion.

Pertinent exclusion criteria

- Subject with an uncontrolled chronic diarrheal illness such as, but not limited to, uncontrolled ulcerative colitis or Crohn's disease or with a condition such that their normal 24–hour bowel movement habit is 3 or more loose stools as defined by the Bristol Stool Chart Types 5, 6, or 7. Subjects with a history of inflammatory bowel disease who are controlled (i.e., had no recent active diarrhoea prior to current *C. difficile* episode at study entry) may be enrolled if in the opinion of the investigator the symptoms are more likely due to CDI than a flare of the inflammatory bowel disease.
- Subject with a planned surgery for CDI within 24 hours.
- Subject plans to take medications which are given to decrease gastrointestinal peristalsis, such as loperamide (Imodium), or diphenoxylate hydrochloride/atropine sulfate (Lomotil), at any time during the 14 days following infusion. Subjects receiving opioid medications at the onset of diarrhoea may be included if they are expected to be on stable doses of these medications, or there is anticipation of a dose decrease or cessation of their use.
- Subject plans to take the probiotic *Saccharomyces boulardii* or plans to receive faecal transplantation therapy, or any other therapies that have been demonstrated to decrease CDI recurrence at any time following infusion (Day 1) and through the completion of the 12-Week study period all such therapies would be allowed if recurrence occurs after study therapy/standard of care has completed.

Treatments

Patients were randomised to receive at Day 1, a single infusion of:

- Actoxumab 10 mg/kg (Study P001 only)
- Bezlotoxumab 10 mg/kg
- Actoxumab + bezlotoxumab 10 mg/kg each
- Placebo (0.9% sodium chloride)

Concomitant medications

In both studies, all subjects were required to receive standard of care antibiotic therapy for treatment of the CDI episode. The standard of care antibiotic was oral metronidazole, vancomycin or fidaxomicin. In addition, subjects receiving vancomycin or fidaxomicin could also receive IV metronidazole.

Medication intended to decrease gastrointestinal peristalsis and other therapies aiming to decrease CDI recurrence were forbidden.

Objectives

The *primary efficacy* objectives of the studies were to assess the following:

- To determine if treatment with a single infusion actoxumab + bezlotoxumab with standard of care therapy and the separate individual mAb therapy (actoxumab or bezlotoxumab) decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo with standard of care therapy.

In addition, the following objective was a primary objective in Study P001 and a secondary objective in Study P002:

- To determine if treatment with a single infusion of actoxumab +bezlotoxumab with standard of care therapy decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of individual mAb therapy (actoxumab or bezlotoxumab) with standard of care therapy.

Of note, in Study P001 the actoxumab arm was dropped at the time of the interim analysis; therefore only the actoxumab + bezlotoxumab and bezlotoxumab treatment groups were assessed for these objectives.

The *secondary objectives* were defined as follows:

- To evaluate, in the subset of subjects who achieve a clinical cure for the baseline CDI episode, if treatment with a single infusion of mAb with standard of care therapy decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo and standard of care therapy;
- To determine the proportion of subjects who achieve global cure in the treatment group receiving a single infusion of mAb with standard of care therapy as compared to the treatment group receiving a single placebo infusion with standard of care therapy, and
- To evaluate if treatment with a single infusion of mAb with standard of care therapy decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo and standard of care therapy in the following subgroups:
    a. Subjects with or without a history of CDI in the 6 months prior to enrolment
    b. Subjects infected with or without the BI/NAP1/027 strain of *C. difficile* at study entry
    c. Subjects infected with or without an epidemic strain of *C. difficile* at study entry
    d. Subjects with or without a clinically severe *C. difficile* infection at study entry
    e. Subjects <65 years of age or ≥ 65 years of age at study entry

f. Subjects with or without compromised immunity at study entry

The *exploratory efficacy* objectives of both trials were focused on the comparison of actoxumab + bezlotoxumab versus placebo. However, these secondary efficacy objectives may also include the individual monoclonal antibody treatment groups i.e. actoxumab or bezlotoxumab provided one (or both) of these regimens are not found to be different from actoxumab + bezlotoxumab and demonstrate superiority versus placebo. Thus the secondary objectives are defined as follows:

- To evaluate the proportion of subjects with clinical cure in the treatment group receiving a single infusion of mAb with standard of care therapy as compared to the treatment group receiving a single placebo infusion with standard of care therapy
- To determine if treatment with a single infusion of mAb with standard of care therapy reduces the time to resolution of the initial CDI episode as compared to treatment with a single placebo infusion with standard of care therapy
- To assess the impact of treatment with a single infusion of mAb or placebo with standard of care therapy on the median number of loose stools per day for the initial CDI episode (day after infusion [Day 2] through Day 14)
- To evaluate the proportion of subjects whose elevated baseline WBC (>10,000 cells/mm3) decreases to ≤ 10,000 cells/mm3 by Day 4 or Day 11 in the treatment group receiving a single infusion of mAb with standard of care therapy as compared to the treatment group receiving a single placebo infusion with standard of care therapy
- To evaluate the proportion of subjects whose elevated baseline body temperature (≥ 101.0° F [38.4° C]) decreases to <101° F [38.4° C] by Day 4 or Day 11 in the treatment group receiving a single infusion of mAb with standard of care therapy as compared to the treatment group receiving a single placebo infusion with standard of care therapy.

Outcomes/endpoints

Primary endpoint

- CDI recurrence: The primary efficacy endpoint was the proportion of subjects with CDI recurrence assessed through the Week 12 (Day 85 ± 5 days) of the primary study period. CDI recurrence was defined as the development of a new episode of diarrhoea (3 or more loose stools in 24 or fewer hours) associated with a positive local or central lab stool test for toxigenic *C. difficile* following clinical cure of the initial CDI episode. Subjects not meeting the clinical cure endpoint were not assessable for the CDI recurrence endpoint and thus were considered as not having CDI recurrence.

The measurement of clinical and laboratory variables supported the evaluation of the primary endpoint. Those variables were (1) diarrhoea, (2) positive stool test for toxigenic C. difficile from the local or the central laboratory, and (3) the type and duration of standard of care antibiotic therapy. Diarrhoea was defined as 3 or more loose stools in 24 hours. Loose stools were defined as Bristol Types 5, 6, and/or 7. Acceptable diagnostic methods in the assessment of subjects who experience new episodes of diarrhoea while on study were listed in the protocol.

Secondary endpoints

- *CDI recurrence in pre-specified subgroups*
  These assessments used the same definition for CDI recurrence as defined for the primary endpoint, but were limited to the following subsets of subjects:

1) subset of subjects with clinical cure of the baseline CDI episode and 2) other subgroups taking into account hospitalisation status, standard of care therapy, C. difficile strain: 027 ribotype versus non-027 ribotype, any epidemic *C. difficile* strain: 027, 014, 002, 001, 106, or 020 ribotypes versus non-epidemic ribotypes, hypervirulent strain of *C. difficile* (ribotypes 027, 078, or 244) versus non-hypervirulent strain, prior history of CDI i.e. presence versus absence of prior CDI episode within the 6 months prior to enrolment, age i.e.<65 years versus ≥ 65 years, CDI severity, and compromised immunity.
CDI severity was defined as diarrhoea and a score of ≥ 2 points based on the presence of 1 or more of the following: 1) age >60 years old (1 point); 2) body temperature >38.3°C (>100°F) (1 point); 3) albumin level <2.5 mg/Dl (1 point); 4) peripheral WBC count >15,000 cells/mm3 within 48 hours (1 point); 5) endoscopic evidence of pseudomembranous colitis (2 points); and 6) treatment in ICU (2 points). Since diarrhoea was not required to be present on the day of infusion, all subjects were assumed to have had diarrhoea at some point during the baseline episode of CDI.

- *Global cure*: Proportion of subjects with global cure defined as clinical cure of the baseline CDI episode and no CDI recurrence through Week 12.

Exploratory endpoints

- *Clinical cure*: Proportion of subjects with clinical cure defined as subject received ≤ 14 day regimen of standard of care therapy and the subject had no diarrhoea (≤ 2 loose stools per 24 hours) for two consecutive days following completion of standard of care therapy for the baseline CDI episode. Subjects requiring >14 day regimen of standard of care therapy for the baseline CDI episode were considered a failure for the clinical cure endpoint.
- *Time to CDI recurrence*. The start date of CDI recurrence was the first date of the new episode of diarrhoea.
- *Resolution of Initial CDI Episode* defined as the time from randomisation to the end of diarrhoea during the initial CDI episode (i.e., time to first of two consecutive days with ≤ 2 loose stools). Patients will be censored at end of SOC window (≤ 14 days) for this endpoint.
- *Stool Counts during Initial CDI Episode*: Defined as the daily number of loose stools reported on the patient stool log. Summary statistics including the median will be provided by study day starting from the day after infusion (Day 2) through Study Day 14.
- *WBC on Days 4 and 11*: Defined as the proportion of patients whose elevated baseline WBC (>10,000 cells/mm3) decreases to ≤ 10,000 cells/mm3 by Day 4 or Day 11.
- *Elevated body temperature on Days 4 and 11*: Defined as the proportion of patients whose elevated baseline body temperature (≥ 101.0° F [38.4° C]) decreases to <101.0° F [38.4° C] by Day 4 or Day 11.
- *Proportion of patients with diarrhoea recurrence* defined as the development of a new episode of diarrhoea (3 or more loose stools in 24 or fewer hours) whether or not a positive stool test for toxigenic C. difficile is available following clinical cure of the initial CDI episode.

Sample size

Based on data from phase 2 and literature recurrence of CDI was expected for about 7 to 10% patients on MK-3145A, while for patients on SOC therapy the incidence of CDI recurrence was assumed to be between 14.3% and 25%. It was calculated that with 400 patients per group, a chi-square test at a 1-

sided alpha of 0.025 provides approximately 95% power to detect the following differences in the incidence of CDI recurrence between monoclonal antibody therapy and placebo: 8% vs. 16.3%, 9% vs. 17.6% or 10% vs. 18.9%. These calculations resulted in 1600 patients to be initially included into study P001 and 1200 patients to be included into study P002.

Randomisation

Patients in study P001 were initially randomized in a 1:1:1:1 ratio (MK-3415A : MK-3415 : MK-6072 : placebo). Following the planned interim analysis the eDMC recommended to discontinue the MK-3415 arm due to safety concerns. Thus following the interim analysis, subjects were randomized using a 1:1:1 ratio (MK-6072, MK-3415A : placebo). In study P002 patients were randomized in a 1:1:1 ratio (MK-3415A : MK-6072 : placebo).

In both studies randomization was stratified according to SoC (metronidazole, vancomycin, fidaxomicin) and hospitalization status (inpatient, outpatient). In each study at least 20% of the total population was required to be from the vancomycin stratum. Randomisation was performed via an Interactive Voice Response System (IVRS).

Blinding (masking)

According protocol, an unblinded pharmacist at each study centre was responsible to prepare and account for the monoclonal antibodies (MK-3415 (study P001), MK-6072 or MK-3415A) and placebo according to pre-specified guidelines provided by the Applicant. The unblinded pharmacist was not involved in any evaluations for the subject. Due to slight differences in appearance for monoclonal antibody solutions compared to normal saline solutions (placebo) all infusion bags were to be covered in an opaque sleeve to ensure that blinded study personnel and subjects remained blinded to clinical material assignment. The IV line (through which the infusion was administered) did not require blinding as the difference between clinical materials was not visually distinguishable within the tubing.

Statistical methods

Efficacy analyses were performed on the Full Analysis Set (FAS) of all randomized patients excluding patients who

- failed to receive infusion of study medication
- had a lack of a positive local stool test for toxigenic *C. difficile*
- failed to receive protocol defined standard of care therapy within a 1 day window of the infusion

Miettinen and Nurminen's method [Miettinen O, Nurminen M: Comparative analysis of two rates. Stat. Med., 4, 213-226 (1985)] applying the same strata as for randomisation was used to compare the proportion of patients with CDI recurrence between treatment groups. For this analysis patients lacking clinical cure or any post randomization endpoint data subsequent to infusion were considered as having no CDI recurrence. In patients with clinical cure who were lost to follow up, the last available stool records was used to assess for CDI recurrence.

According protocols, Study P001 and Study P002 respectively were considered successful, if the combined monoclonal antibody treatment (MK-3415A) was statistically superior when compared to placebo. To control the type I error (at 0.025, 1-sided) the following strategies were applied:

- Study P001 (Amendment 3): Treatment comparisons were grouped into two families. In Family 2, individual monoclonal antibody therapies (MK-3415 and MK-6072) were compared separately to the combined monoclonal antibody therapy (MK-3415A). A Dunnett procedure was to be applied for the comparison of each of the two monotherapies to the combination therapy. A Haybittle-Peto boundary (spending 0.0001 at interim) was planned to account for the interim analysis. In Family 1, the various active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) were compared separately to placebo. An alpha of 0.0125 (1-sided) was allocated to each of the two hypothesis families in order to provide strong control of the studywise Type 1 error at 0.025 (1-sided) for the primary endpoint of CDI recurrence. The comparisons of interest and the associated p-value cut-offs for declaring statistical significance at the final analyses were as follows:

Comparison	*p-value cut-off (1-sided)*
MK-3415A versus MK-6072	0.0066
MK-3415A versus placebo	0.0125
MK-6072 versus placebo	0.0125 (only if MK-3415A vs. placebo significant)

- Study P002: First MK-3415A was compared to placebo. Only in case of a p-value < 0.025 (1-sided) MK-6072 was to be compared to placebo (at alpha = 0.025, 1-sided).

The same analysis method as for the primary endpoint was used to analyse dichotomous secondary and exploratory endpoints. Time to event outcomes (e.g. time to CDI recurrence) was compared between treatment groups by means of the stratified log-rank test.

In general treatment effects were described by means of point estimates including the corresponding 2-sided) 95% confidence intervals.

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary and secondary endpoints (CDI recurrence and Global Cure) were estimated within each category for the subgroups. Amongst others the primary endpoint was assessed among subjects who attained clinical cure.

Interim analysis

For Study P001 one interim efficacy analysis was planned when the first 640 enrolled patients (40% of planned total) had completed week 12 or discontinued prior to week 12 in order to evaluate the individual monoclonal antibody therapies (MK-3415 or MK-6072) relative to the combined monoclonal antibody therapy (MK-3415A). In case of sufficient evidence of superiority for MK-3415A over either MK-3415 or MK-6072, further enrolment in one or both of these study treatment groups should be stopped. It was not planned to stop the trial for overwhelming efficacy at interim. The interim analysis was conducted by an external statistician with no other responsibilities with respect to study P001. Following the interim analysis further enrolment into the MK-3415 group of study P001 was stopped (for safety reason) due to a recommendation by the eDMC.

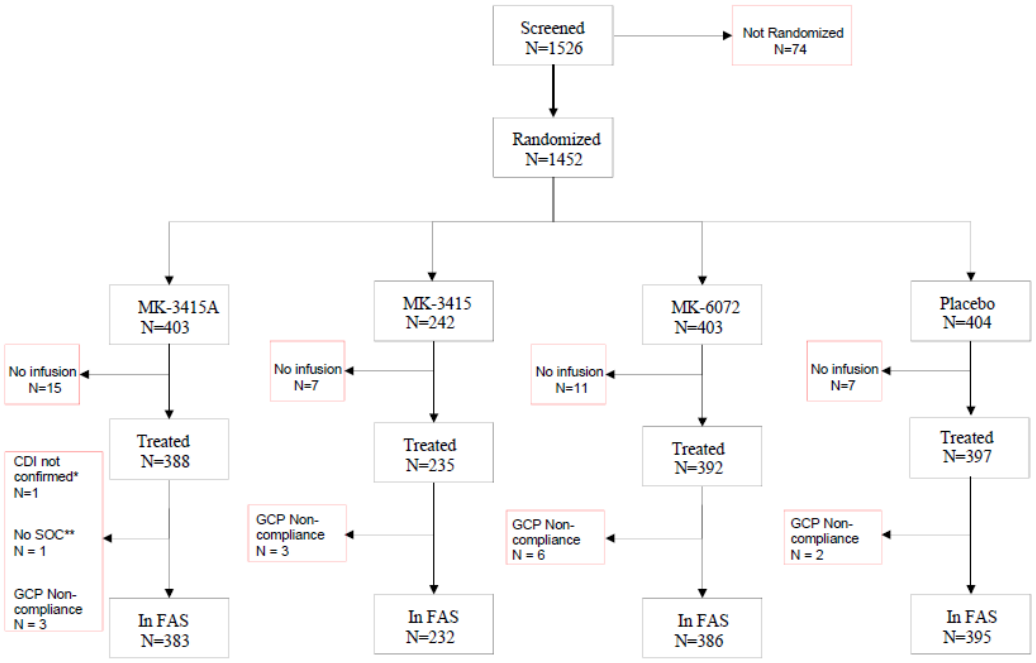
There was no interim analysis for study P002 (neither planned nor performed).

Results

Participant flow

Study P001

Figure 2: Study participant flow



*Subjects with "CDI not confirmed" did not have positive local laboratory test for toxigenic *C. difficile*.
**Subjects with "No SoC" did not receive protocol defined SoC therapy within 1 day window of the infusion.

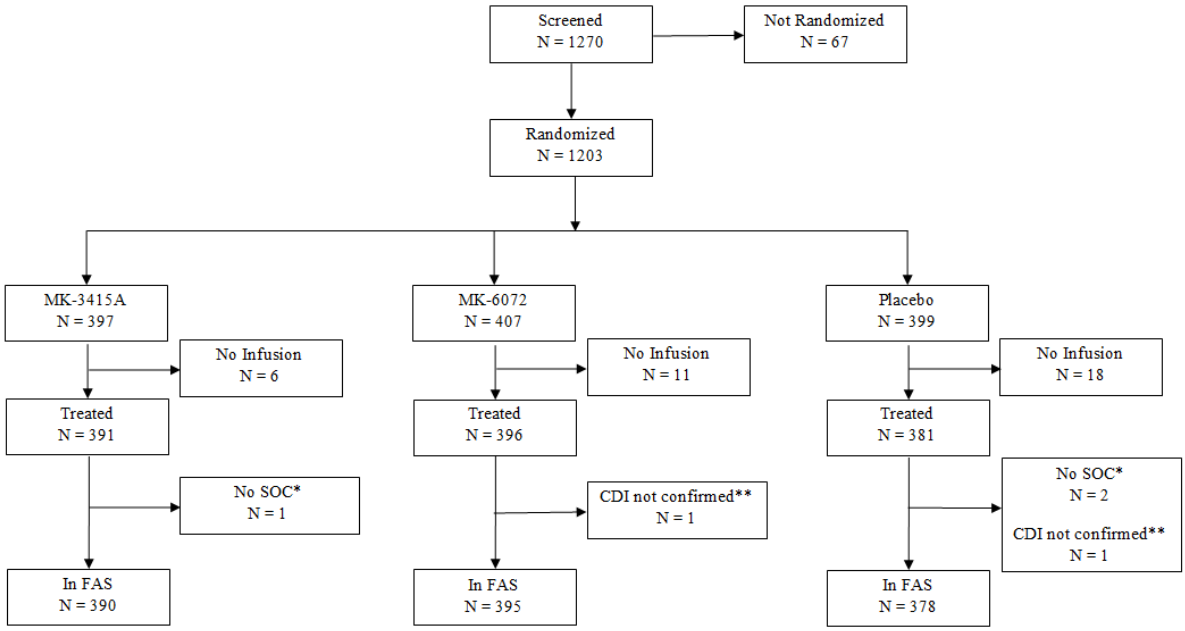
A total of 1526 subjects gave informed consent and were screened for eligibility. Of these, 74 (4.8%) subjects were not randomised.

Table 3: Disposition of subjects (all randomised subjects)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	403		242		403		404		1,452	
Study Disposition										
Completed	343	(85.1)	201	(83.1)	340	(84.4)	340	(84.2)	1,224	(84.3)
Discontinued	60	(14.9)	41	(16.9)	63	(15.6)	64	(15.8)	228	(15.7)
Adverse Event	0	(0.0)	1	(0.4)	1	(0.2)	0	(0.0)	2	(0.1)
Death	20	(5.0)	26	(10.7)	30	(7.4)	25	(6.2)	101	(7.0)
Lack Of Efficacy	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.1)
Lost To Follow-Up	15	(3.7)	2	(0.8)	11	(2.7)	16	(4.0)	44	(3.0)
Physician Decision	2	(0.5)	2	(0.8)	4	(1.0)	3	(0.7)	11	(0.8)
Progressive Disease	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.5)	3	(0.2)
Protocol Violation	6	(1.5)	0	(0.0)	2	(0.5)	1	(0.2)	9	(0.6)
Subject Withdrew Consent	14	(3.5)	7	(2.9)	15	(3.7)	15	(3.7)	51	(3.5)
Technical Problems	2	(0.5)	2	(0.8)	0	(0.0)	2	(0.5)	6	(0.4)
Study Medication Disposition										
Completed	385	(95.5)	229	(94.6)	391	(97.0)	397	(98.3)	1,402	(96.6)
Discontinued	3	(0.7)	6	(2.5)	1	(0.2)	0	(0.0)	10	(0.7)
Adverse Event	0	(0.0)	1	(0.4)	1	(0.2)	0	(0.0)	2	(0.1)
Technical Problems	3	(0.7)	5	(2.1)	0	(0.0)	0	(0.0)	8	(0.6)
Did Not Take Study Medication	15	(3.7)	7	(2.9)	11	(2.7)	7	(1.7)	40	(2.8)
Each subject is counted once for Study Disposition and once for Study Medication Disposition. MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone										

Study P002

Figure 3: Study participant flow



Subjects with "No SoC" did not receive protocol defined SoC therapy within 1 day window of the infusion.
**Subjects with "CDI not confirmed" did not have positive local laboratory test for toxigenic *C. difficile*.

A total of 1270 subjects gave informed consent and were screened for eligibility. Of these, 67 (5.3%) subjects were not randomised.

Table 4: Disposition of subjects

	MK-3415A n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	391	396	381	1168
Main Study Disposition				
Completed	322 (82.4)	337 (85.1)	311 (81.6)	970 (83.0)
Discontinued	69 (17.6)	59 (14.9)	70 (18.4)	198 (17.0)
Adverse Event	1 (0.3)	1 (0.3)	2 (0.5)	4 (0.3)
Death	29 (7.4)	22 (5.6)	32 (8.4)	83 (7.1)
Lost To Follow-Up	11 (2.8)	10 (2.5)	6 (1.6)	27 (2.3)
Physician Decision	3 (0.8)	2 (0.5)	1 (0.3)	6 (0.5)
Protocol Violation	2 (0.5)	0 (0.0)	1 (0.3)	3 (0.3)
Withdrawal By Subject	23 (5.9)	24 (6.1)	28 (7.3)	75 (6.4)
Study Medication Disposition				
Completed Study Medication	390 (99.7)	395 (99.7)	381 (100.0)	1166 (99.8)
Discontinued Study Medication	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Technical Problems	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Withdrawal By Subject	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Each subject is counted once for Trial Disposition and once for Subject Study Medication Disposition MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone				

Data Source: [16.4]

Recruitment

Study P001

Study P001 was initiated in November 2011 and completed December 2014. The trial was conducted at 184 investigator sites: 75 in the United States, 13 in Italy, 11 in Canada, 9 in Spain, 8 in Australia, 8 in the United Kingdom, 7 in Germany, 7 in Portugal, 6 in Chile, 6 in the Czech Republic, 6 in Denmark, 5 in Israel, 4 in Belgium, 4 in Colombia, 4 in New Zealand, 4 in South Africa, 3 in Austria, 3 in Brazil, and 1 in Mexico.

Study P002

Study P002 was initiated in February 2012 and completed May 2015. This trial was conducted at 200 trial centres: United States (47); Japan (35); South Korea (15); Poland (14); France (11); Turkey (10); Argentina (9); Czech Republic (8); Spain (8); Taiwan (8); Germany (7); Russia (7); Canada (6); Sweden (6); Finland (5); Israel (3); and Switzerland (1).

Conduct of the study

Study P001

There were 3 general and one local amendment to the protocol. Amendment 1 and 2 were finalised and approved before any subjects were enrolled into the study. Amendment No.3 was implemented after enrolment of subjects had commenced and before database lock and unblinding. Amendment No. 4 was a local country amendment. The changes were subsequently added to Amendment No. 3, which applied to all sites in all countries.

The percentage of subjects who had at least one major protocol deviation was high, among the 631 (43%) treated subjects who were assessed as having a major protocol deviation, 277 (19.6%) of the 1412 treated subjects had at least one major protocol deviation that could substantially affect the primary efficacy endpoint(s). Sixteen of these subjects were removed from the FAS population. An additional 261 subjects were removed from the PP analysis but retained in the FAS population.

Study P002

There was 1 general and one local amendment to the protocol. Amendment No. 1 was implemented after enrolment of subjects had commenced, before database lock and unblinding. Amendment No. 2 was a local country amendment.

A relative high number of subjects (37.1 %) had at least one or more major protocol deviation. Among the 433 treated subjects who were assessed as having a major protocol deviation, 197 (16.9%) of the 1168 treated subjects had at least one major protocol deviation that could substantially affect the primary efficacy endpoint(s). Five (5) of these subjects were removed from the FAS population. An additional 192 subjects were removed from the PP analysis but retained in the FAS population.

P002 had two planned DBLs with the first one (13-Apr-2015) containing all of the 12-week main study data as well as data from the completed visits for the extension phase. There were major protocol deviations noted after the first database lock but before the second database lock (performed to account for the extension phase data) and occurring months after the first database lock. None of these protocol deviations excluded subjects from an analysis. None of the evaluability assessments changed nor did any of the efficacy database endpoints change between the first and second database locks. Furthermore, the efficacy assessments through Week 12 did not change from the first database lock to the second database lock, with the exception that the amount of available microbiological strain typing data increased between the first and second database locks.

Baseline data

Study P001

Table 5: Baseline characteristics (FAS Population)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	383		232		386		395		1,396	
Gender										
Male	172	(44.9)	102	(44.0)	157	(40.7)	172	(43.5)	603	(43.2)
Female	211	(55.1)	130	(56.0)	229	(59.3)	223	(56.5)	793	(56.8)
Age (Years)										
< 20	2	(0.5)	0	(0.0)	1	(0.3)	7	(1.8)	10	(0.7)
20 to 29	19	(5.0)	6	(2.6)	29	(7.5)	15	(3.8)	69	(4.9)
30 to 39	25	(6.5)	14	(6.0)	22	(5.7)	26	(6.6)	87	(6.2)
40 to 49	45	(11.7)	26	(11.2)	42	(10.9)	40	(10.1)	153	(11.0)
50 to 59	54	(14.1)	39	(16.8)	76	(19.7)	68	(17.2)	237	(17.0)
60 to 69	82	(21.4)	49	(21.1)	81	(21.0)	89	(22.5)	301	(21.6)
70 to 79	89	(23.2)	54	(23.3)	67	(17.4)	63	(15.9)	273	(19.6)
80 to 89	55	(14.4)	33	(14.2)	54	(14.0)	70	(17.7)	212	(15.2)
≥ 90	12	(3.1)	11	(4.7)	14	(3.6)	17	(4.3)	54	(3.9)
Mean	62.7		64.5		61.0		62.7		62.5	
SD	17.7		16.8		18.5		18.4		18.0	
Median	65.0		66.0		63.0		65.0		65.0	
Range	18 to 95		21 to 99		19 to 100		19 to 97		18 to 100	
Race										
American Indian Or Alaska Native	2	(0.5)	0	(0.0)	3	(0.8)	3	(0.8)	8	(0.6)
Asian	4	(1.0)	3	(1.3)	4	(1.0)	1	(0.3)	12	(0.9)
Black Or African American	17	(4.4)	16	(6.9)	28	(7.3)	18	(4.6)	79	(5.7)
Multiple	10	(2.6)	3	(1.3)	13	(3.4)	7	(1.8)	33	(2.4)
White	350	(91.4)	210	(90.5)	338	(87.6)	366	(92.7)	1,264	(90.5)
Ethnicity										
Hispanic Or Latino	52	(13.6)	23	(9.9)	46	(11.9)	56	(14.2)	177	(12.7)
Not Hispanic Or Latino	323	(84.3)	207	(89.2)	323	(83.7)	330	(83.5)	1,183	(84.7)
Not Reported	3	(0.8)	2	(0.9)	6	(1.6)	2	(0.5)	13	(0.9)
Unknown	5	(1.3)	0	(0.0)	11	(2.8)	7	(1.8)	23	(1.6)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Weight (kg)										
≤ 70 kg	200	(52.2)	123	(53.0)	177	(45.9)	191	(48.4)	691	(49.5)
>70 kg	183	(47.8)	109	(47.0)	209	(54.1)	204	(51.6)	705	(50.5)
Subjects with data	383		232		386		395		1396	
Mean	72.8		73.9		75.5		74.0		74.1	
SD	19.1		23.1		21.8		19.2		20.6	
Median	70.0		69.2		72.2		70.8		70.5	
Range	34.5 to 145.0		35.3 to 150.2		39.0 to 171.0		34.0 to 168.3		34.0 to 171.0	
BMI (kg/m^2)										
Subjects with data	375		228		379		385		1367	
Mean	26.2		26.7		26.9		26.4		26.5	
SD	6.7		7.8		6.8		6.4		6.8	
Median	25.1		25.3		25.3		25.4		25.2	
Range	14.9 to 55.2		13.1 to 59.6		14.0 to 59.0		13.7 to 59.1		13.1 to 59.6	
Region of Enrollment										
US	176	(46.0)	120	(51.7)	171	(44.3)	186	(47.1)	653	(46.8)
Ex-US	207	(54.0)	112	(48.3)	215	(55.7)	209	(52.9)	743	(53.2)
Region of Enrollment*										
Africa	2	(0.5)	1	(0.4)	5	(1.3)	2	(0.5)	10	(0.7)
Asia-Pacific	17	(4.4)	10	(4.3)	20	(5.2)	23	(5.8)	70	(5.0)
Latin America	29	(7.6)	9	(3.9)	26	(6.7)	30	(7.6)	94	(6.7)
Europe	131	(34.2)	80	(34.5)	139	(36.0)	132	(33.4)	482	(34.5)
North America	204	(53.3)	132	(56.9)	196	(50.8)	208	(52.7)	740	(53.0)

*Africa includes South Africa. Asia-Pacific includes Australia and New Zealand. Latin America includes Brazil, Chile, Colombia and Mexico. Europe includes Austria, Belgium, Czech Republic, Denmark, Germany, Israel, Italy, Portugal, Spain, and the United Kingdom. North America includes Canada and the United States.

MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

Overall, women constituted 56.8% (n=793) of the FAS population. Race was reported as white for 1264 subjects (90.5%). The median age was 65.0 years, and age ranged from 18 to 100 years. The median weight was 70.5 kg, and weight ranged from 34.0 to 171.0 kg. The median BMI was 25.2 kg/m^2, and BMI ranged from 13.1 to 59.6 kg/m^2.

Study P002

Table 6: Baseline characteristics (FAS Population)

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	390		395		378		1,163	
Gender								
Male	178	(45.6)	182	(46.1)	152	(40.2)	512	(44.0)
Female	212	(54.4)	213	(53.9)	226	(59.8)	651	(56.0)
Age (Years)								
< 20	1	(0.3)	1	(0.3)	1	(0.3)	3	(0.3)
20 to 29	16	(4.1)	20	(5.1)	13	(3.4)	49	(4.2)
30 to 39	20	(5.1)	33	(8.4)	22	(5.8)	75	(6.4)
40 to 49	35	(9.0)	26	(6.6)	29	(7.7)	90	(7.7)
50 to 59	51	(13.1)	66	(16.7)	61	(16.1)	178	(15.3)
60 to 69	68	(17.4)	89	(22.5)	91	(24.1)	248	(21.3)
70 to 79	104	(26.7)	88	(22.3)	96	(25.4)	288	(24.8)
80 to 89	88	(22.6)	64	(16.2)	56	(14.8)	208	(17.9)
≥ 90	7	(1.8)	8	(2.0)	9	(2.4)	24	(2.1)
Mean	65.7		62.7		64.4		64.3	
SD	17.3		17.5		16.4		17.1	
Median	70.0		65.0		66.0		67.0	
Range	19 to 93		18 to 93		18 to 98		18 to 98	
Race								
American Indian Or Alaska Native	0	(0.0)	2	(0.5)	1	(0.3)	3	(0.3)
Asian	65	(16.7)	63	(15.9)	57	(15.1)	185	(15.9)
Black Or African American	18	(4.6)	17	(4.3)	10	(2.6)	45	(3.9)
Multiple	2	(0.5)	2	(0.5)	1	(0.3)	5	(0.4)
White	305	(78.2)	311	(78.7)	309	(81.7)	925	(79.5)
Ethnicity								
Hispanic Or Latino	33	(8.5)	33	(8.4)	45	(11.9)	111	(9.5)
Not Hispanic Or Latino	343	(87.9)	355	(89.9)	318	(84.1)	1,016	(87.4)
Not Reported	8	(2.1)	3	(0.8)	10	(2.6)	21	(1.8)
Unknown	6	(1.5)	4	(1.0)	5	(1.3)	15	(1.3)
Weight (kg)								
≤ 70 kg	225	(57.7)	217	(54.9)	210	(55.6)	652	(56.1)
>70 kg	165	(42.3)	178	(45.1)	168	(44.4)	511	(43.9)
Subjects with data	390		395		378		1163	
Mean	69.8		70.8		70.7		70.4	
SD	19.8		20.1		20.6		20.2	
Median	67.0		67.0		69.0		68.0	
Range	32.7 to 187.3		29.8 to 194.0		28.9 to 163.7		28.9 to 194.0	
BMI (kg/m^2)								

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
BMI (kg/m²)								
Subjects with data	383		390		375		1148	
Mean	25.0		25.5		25.9		25.5	
SD	6.0		6.3		6.7		6.3	
Median	24.0		24.3		24.6		24.3	
Range	11.6 to 57.6		14.6 to 55.5		11.3 to 69.4		11.3 to 69.4	
Region of Enrollment								
US	133	(34.1)	136	(34.4)	131	(34.7)	400	(34.4)
Ex-US	257	(65.9)	259	(65.6)	247	(65.3)	763	(65.6)
Region of Enrollment*								
Asia-Pacific	63	(16.2)	59	(14.9)	54	(14.3)	176	(15.1)
Latin America	8	(2.1)	4	(1.0)	5	(1.3)	17	(1.5)
Europe	161	(41.3)	174	(44.1)	161	(42.6)	496	(42.6)
North America	158	(40.5)	158	(40.0)	158	(41.8)	474	(40.8)

*Asia Pacific includes Japan, Korea and Taiwan. Latin America includes Argentina. Europe includes Czech Republic, Finland, France, Germany, Israel, Poland, Russian Federation, Spain, Sweden, Switzerland, and Turkey. North America includes United States and Canada.

MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Overall, women constituted 56.0% (n=651) of the FAS population. Race was reported as white for 925 subjects (79.5%), and ethnicity was reported as not Hispanic or Latino for 1016 subjects (87.4%). The median age was 67.0 years and age ranged from 18 to 98 years. The median weight was 68.0 kg and weight ranged from 28. 9 to 194.0 kg. The median BMI was 24.3 kg/m^2 and BMI ranged from 11.3 to 69.4 kg/m$^{2.}$

Characteristics of the baseline CDI episode

Key characteristics relating to this baseline CDI episode, include onset of the episode relative to the day of study medication administration, loose stool count which confirmed subjects met the protocol definition of diarrhoea, and the type of test used at the local laboratory to confirm the presence of toxigenic C. difficile in stool.

“Baseline” was defined as the day on which the study medication was administered, and was also identical / synonymous with Day 1. The date of onset of the baseline CDI episode recorded in the case report form may have been interpreted differently across sites. This was generally interpreted as the date symptoms began, but, in some cases, it was the date a patient presented to their physician, or the date of the diagnosis. Hence, the date was obtained from subject recall or based on documentation in hospital records.

The diagnosis of CDI also required a positive stool test for toxigenic C. difficile from a stool sample collected no more than 7 days before study infusion. The permitted methods included cell cytotoxicity assay, anaerobic culture with toxin detection or strain typing, and several commercial test kits. All acceptable methodologies had a specificity of at least 94% and had the capacity to detect the presence of toxin B or the ability to produce toxin B (tcdB gene).

The number and proportion of subjects with elevated temperature (defined as ≥ 38.4° C/101.0° F) or elevated WBC count (defined as >10,000 cells/mm3) at the time of study entry were As previously noted, the study design allowed subjects to enrol any time during treatment with the standard of care

antibiotic, provided that a stool test obtained within the 7 days prior to administration of the study medication was positive for toxigenic C. difficile. Hence, the results for WBC counts and elevated temperature may not reflect what was present at the time of CDI diagnosis.

Pseudomembranous colitis, toxic megacolon, bowel perforation, ileus, or required a colectomy or other surgery due to complications of CDI were considered signs of “severe” or “severe, complicated” CDI during the baseline CDI episode.

Study P001

Table 7: Subjects characteristics –CDI diagnosis (FAS Population)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	383		232		386		395		1,396	
Days Prior to Infusion of Onset of Presenting CDI Episode										
Day of Infusion	1	(0.3)	2	(0.9)	1	(0.3)	0	(0.0)	4	(0.3)
1-2 Days Prior	54	(14.1)	31	(13.4)	51	(13.2)	46	(11.6)	182	(13.0)
3-4 Days Prior	90	(23.5)	67	(28.9)	98	(25.4)	85	(21.5)	340	(24.4)
5-7 Days Prior	134	(35.0)	71	(30.6)	136	(35.2)	144	(36.5)	485	(34.7)
8-10 Days Prior	37	(9.7)	29	(12.5)	36	(9.3)	53	(13.4)	155	(11.1)
11-13 Days Prior	17	(4.4)	9	(3.9)	18	(4.7)	21	(5.3)	65	(4.7)
14+	42	(11.0)	20	(8.6)	42	(10.9)	43	(10.9)	147	(10.5)
Unknown	8	(2.1)	3	(1.3)	4	(1.0)	3	(0.8)	18	(1.3)
Number of Loose Stools at Qualification[‡]										
Unknown[†]	5	(1.3)	1	(0.4)	5	(1.3)	5	(1.3)	16	(1.1)
<3	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
3-6	260	(67.9)	153	(65.9)	273	(70.7)	268	(67.8)	954	(68.3)
7-10	91	(23.8)	50	(21.6)	71	(18.4)	85	(21.5)	297	(21.3)
10+	27	(7.0)	28	(12.1)	37	(9.6)	36	(9.1)	128	(9.2)
Type of Local Laboratory Test Used for Baseline CDI Diagnosis[§]										
EIA	148	(38.6)	90	(38.8)	151	(39.1)	162	(41.0)	551	(39.5)
Cell Cytotoxicity Assay	9	(2.3)	5	(2.2)	1	(0.3)	3	(0.8)	18	(1.3)
Culture	19	(5.0)	10	(4.3)	18	(4.7)	19	(4.8)	66	(4.7)
PCR	207	(54.0)	127	(54.7)	216	(56.0)	211	(53.4)	761	(54.5)

[‡]Subjects were instructed to enter the number of loose stools on the first day on which the number of loose stools met the criteria for diarrhea for the presenting episode of CDI. In the event that the first day on which the number of loose stools meets the criteria for diarrhea as defined by the protocol is the same day of the study infusion, they were instructed to enter the number of loose stools that occurred prior to the infusion of study medication. Please note that this is not necessarily the date of onset of the presenting CDI episode.

[†]Unknown was entered if subject confirmed that they had 3 or more loose stools, but could not provide an exact number of loose stools. This category also includes subjects with fecal collection devices.

[§]Subjects are counted only once in the summary of type of local laboratory test. The order of tests in the table above represents the hierarchy used to assess subjects with more than one type of positive test.

EIA = enzyme immune assay, PCR = polymerase chain reaction assay, Culture = culture with toxin detection or with strain typing

MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

Over one-quarter (27.7%) of subjects in the FAS population had an elevated WBC count at baseline, while only 7 subjects (0.5%) had elevated temperature. In general, the proportion of subjects with elevated WBCs or temperature was similar across treatment groups.

Table 8: Subject characteristics - Clinical characteristics of baseline CDI episode (FAS Population)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	383		232		386		395		1,396	
Endoscopic Evidence of Pseudomembranous Colitis										
Yes	5	(1.3)	2	(0.9)	2	(0.5)	6	(1.5)	15	(1.1)
No	4	(1.0)	2	(0.9)	7	(1.8)	7	(1.8)	20	(1.4)
Unknown	374	(97.7)	228	(98.3)	377	(97.7)	382	(96.7)	1,361	(97.5)
Signs and Symptoms Consistent with Toxic Megacolon										
Yes	4	(1.0)	0	(0.0)	2	(0.5)	1	(0.3)	7	(0.5)
No	365	(95.3)	226	(97.4)	379	(98.2)	383	(97.0)	1,353	(96.9)
Unknown	14	(3.7)	6	(2.6)	5	(1.3)	11	(2.8)	36	(2.6)
Signs and Symptoms Consistent with Bowel Perforation										
Yes	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.1)
No	374	(97.7)	228	(98.3)	383	(99.2)	389	(98.5)	1,374	(98.4)
Unknown	8	(2.1)	4	(1.7)	2	(0.5)	6	(1.5)	20	(1.4)
Signs and Symptoms Consistent with Ileus										
Yes	6	(1.6)	2	(0.9)	2	(0.5)	3	(0.8)	13	(0.9)
No	367	(95.8)	226	(97.4)	380	(98.4)	386	(97.7)	1,359	(97.3)
Unknown	10	(2.6)	4	(1.7)	4	(1.0)	6	(1.5)	24	(1.7)
Required Colectomy or Other Surgical Procedure										
No	377	(98.4)	231	(99.6)	385	(99.7)	392	(99.2)	1,385	(99.2)
Unknown	6	(1.6)	1	(0.4)	1	(0.3)	3	(0.8)	11	(0.8)
MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone										

Study P002

Table 9: Subjects characteristics –CDI diagnosis (FAS Population)

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	390		395		378		1,163	
Days Prior to Infusion of Onset of Presenting CDI Episode								
Day of Infusion	3	(0.8)	0	(0.0)	4	(1.1)	7	(0.6)
1-2 Days Prior	57	(14.6)	63	(15.9)	53	(14.0)	173	(14.9)
3-4 Days Prior	84	(21.5)	82	(20.8)	82	(21.7)	248	(21.3)
5-7 Days Prior	139	(35.6)	138	(34.9)	145	(38.4)	422	(36.3)
8-10 Days Prior	45	(11.5)	47	(11.9)	40	(10.6)	132	(11.3)
11-13 Days Prior	16	(4.1)	18	(4.6)	15	(4.0)	49	(4.2)
14+	39	(10.0)	45	(11.4)	36	(9.5)	120	(10.3)
Unknown	7	(1.8)	2	(0.5)	3	(0.8)	12	(1.0)
Number of Loose Stools at Qualification[‡]								
Unknown[†]	0	(0.0)	0	(0.0)	2	(0.5)	2	(0.2)
<3	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
3-6	271	(69.5)	259	(65.6)	262	(69.3)	792	(68.1)
7-10	83	(21.3)	85	(21.5)	74	(19.6)	242	(20.8)
10+	35	(9.0)	50	(12.7)	40	(10.6)	125	(10.7)
Missing	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Type of Local Laboratory Test Used for Baseline CDI Diagnosis[§]								
EIA	215	(55.1)	221	(55.9)	223	(59.0)	659	(56.7)
Cell Cytotoxicity Assay	7	(1.8)	9	(2.3)	3	(0.8)	19	(1.6)
Culture	30	(7.7)	24	(6.1)	26	(6.9)	80	(6.9)
PCR	138	(35.4)	141	(35.7)	126	(33.3)	405	(34.8)

[‡]Subjects were instructed to enter the number of loose stools on the first day on which the number of loose stools met the criteria for diarrhea for the presenting episode of CDI. In the event that the first day on which the number of loose stools meets the criteria for diarrhea as defined by the protocol is the same day of the study infusion, they were instructed to enter the number of loose stools that occurred prior to the infusion of study medication. Please note that this is not necessarily the date of onset of the presenting CDI episode.

[†]Unknown was entered if subject confirmed that they had 3 or more loose stools, but could not provide an exact number of loose stools. This category also includes subjects with fecal collection devices.

[§]Subjects are counted only once in the summary of type of local laboratory test. The order of tests in the table above represents the hierarchy used to assess subjects with more than one type of positive test.

EIA = enzyme immune assay, PCR = polymerase chain reaction assay, Culture = culture with toxin detection or with strain typing

MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Nearly one-quarter (n=286; 24.6%) of subjects in the FAS population had an elevated WBC count at baseline, while only 7 subjects (0.6%) had elevated temperature. In general, the proportion of subjects with elevated WBCs or temperature was similar across treatment groups.

Table 10: Subject characteristics - Clinical characteristics of baseline CDI episode (FAS Population)

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	390		395		378		1,163	
Endoscopic Evidence of Pseudomembranous Colitis								
Yes	12	(3.1)	7	(1.8)	9	(2.4)	28	(2.4)
No	5	(1.3)	3	(0.8)	4	(1.1)	12	(1.0)
Unknown	373	(95.6)	385	(97.5)	365	(96.6)	1,123	(96.6)
Signs and Symptoms Consistent with Toxic Megacolon								
Yes	1	(0.3)	2	(0.5)	2	(0.5)	5	(0.4)
No	376	(96.4)	378	(95.7)	366	(96.8)	1,120	(96.3)
Unknown	13	(3.3)	15	(3.8)	10	(2.6)	38	(3.3)
Signs and Symptoms Consistent with Bowel Perforation								
Yes	0	(0.0)	0	(0.0)	2	(0.5)	2	(0.2)
No	382	(97.9)	389	(98.5)	371	(98.1)	1,142	(98.2)
Unknown	8	(2.1)	6	(1.5)	5	(1.3)	19	(1.6)
Signs and Symptoms Consistent with Ileus								
Yes	7	(1.8)	6	(1.5)	6	(1.6)	19	(1.6)
No	373	(95.6)	381	(96.5)	370	(97.9)	1,124	(96.6)
Unknown	10	(2.6)	8	(2.0)	2	(0.5)	20	(1.7)
Required Colectomy or Other Surgical Procedure								
Yes	1	(0.3)	1	(0.3)	1	(0.3)	3	(0.3)
No	385	(98.7)	391	(99.0)	375	(99.2)	1,151	(99.0)
Unknown	4	(1.0)	3	(0.8)	2	(0.5)	9	(0.8)

MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Standard of care treatment

The oral standard of care therapy at the time of randomization was one of the stratification variables. It should be noted that a subject may have received an oral standard of care antibiotic either prior to or after trial entry and which differed from that at the time of stratification. A switch in standard of care antibiotic was permitted during the trial if the subject had received at least 3 days of the baseline standard of care therapy and met at least one of the 3 following conditions: (1) continued diarrhoea, (2) presence of ileus, or (3) a body temperature >38.3ºC (>100.9ºF) and peripheral WBC count >15,000 cells/mm3. Additionally, a switch was permitted at any time for emergence of an AE due to the standard of care therapy.

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Table 11: Standard of care antibiotics at baseline (FAS Population):

	MK-3415A n (%)	MK-3415 n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	383	232	386	395	1396
Oral Metronidazole	179 (46.7)	102 (44.0)	179 (46.4)	177 (44.8)	637 (45.6)
Vancomycin	183 (47.8)	110 (47.4)	183 (47.4)	191 (48.4)	667 (47.8)
Oral	158 (41.3)	96 (41.4)	165 (42.7)	171 (43.3)	590 (42.3)
Oral with IV Metronidazole	25 (6.5)	14 (6.0)	18 (4.7)	20 (5.1)	77 (5.5)
Fidaxomicin	12 (3.1)	7 (3.0)	14 (3.6)	17 (4.3)	50 (3.6)
Oral	12 (3.1)	6 (2.6)	14 (3.6)	16 (4.1)	48 (3.4)
Oral with IV Metronidazole	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.1)
Other	9 (2.3)	13 (5.6)	10 (2.6)	10 (2.5)	42 (3.0)
IV Metronidazole	1 (0.3)	1 (0.4)	5 (1.3)	1 (0.3)	8 (0.6)
Oral Fidaxomicin with Oral Metronidazole	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Oral Metronidazole with IV Metronidazole	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.1)
Oral Vancomycin with Oral Metronidazole	6 (1.6)	10 (4.3)	3 (0.8)	8 (2.0)	27 (1.9)
Oral Vancomycin with Oral and IV Metronidazole	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.1)
Oral Fidaxomicin with Oral Vancomycin	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.1)
SoC at baseline differed from SoC stratum	16 (4.2)	9 (3.9)	14 (3.6)	22 (5.6)	61 (4.4)

SoC at baseline is the actual treatment the subject received at the time of the study infusion.
SoC stratum is the antibiotic recorded in the centralized randomization system and was used for stratification.
SoC = Standard of Care Therapy, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

Table 12: Duration of standard of care therapy and days on standard of care therapy prior to infusion (FAS Population)

	MK-3415A n (%)	MK-3415 n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	383	232	386	395	1396
Total Days on SoC Therapy					
1-7 days	9 (2.3)	5 (2.2)	7 (1.8)	5 (1.3)	26 (1.9)
8-9 days	5 (1.3)	11 (4.7)	8 (2.1)	4 (1.0)	28 (2.0)
10-14 days	218 (56.9)	130 (56.0)	233 (60.4)	247 (62.5)	828 (59.3)
15-16 days	108 (28.2)	58 (25.0)	97 (25.1)	107 (27.1)	370 (26.5)
> 16 days	42 (11.0)	26 (11.2)	39 (10.1)	31 (7.8)	138 (9.9)
Unknown	1 (0.3)	2 (0.9)	2 (0.5)	1 (0.3)	6 (0.4)
N	382	230	384	394	1390
Mean	14.6	14.1	13.8	13.8	14.1
SD	7.4	5.2	5.5	4.3	5.8
Median	14.0	14.0	14.0	14.0	14.0
Quartiles	11 to 15	11 to 15	11 to 15	11 to 15	11 to 15
Range	3 to 79	3 to 46	2 to 70	3 to 56	2 to 79
Days on SoC Therapy Prior to Infusion					
SoC Started 1 Day after Infusion	0	1 (0.4)	0	1 (0.3)	2 (0.1)
0 days	29 (7.6)	18 (7.8)	35 (9.1)	27 (6.8)	109 (7.8)
1-2 days	143 (37.3)	81 (34.9)	130 (33.7)	144 (36.5)	498 (35.7)
3-4 days	113 (29.5)	77 (33.2)	122 (31.6)	120 (30.4)	432 (30.9)
5-6 days	78 (20.4)	46 (19.8)	83 (21.5)	81 (20.5)	288 (20.6)
> 6 days	20 (5.2)	9 (3.9)	16 (4.1)	22 (5.6)	67 (4.8)
N	383	232	386	395	1396
Mean	3.1	3.1	3.1	3.2	3.1
SD	2.2	2.1	2.1	2.1	2.1
Median	3.0	3.0	3.0	3.0	3.0
Quartiles	2 to 5	2 to 4	2 to 5	2 to 5	2 to 5
Range	0 to 14	-1 to 14	0 to 13	-1 to 13	-1 to 14

SoC = Standard of Care Therapy, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

The duration of standard of care antibiotic treatment was a part of the definition of the efficacy endpoints. Subjects who received more than a 14-day regimen were counted as failures for the clinical cure endpoint.

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Table 13: Standard of care antibiotics at baseline (FAS Population):

	MK-3415A n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	390	395	378	1163
Oral Metronidazole	187 (47.9)	186 (47.1)	176 (46.6)	549 (47.2)
Vancomycin	183 (46.9)	187 (47.3)	181 (47.9)	551 (47.4)
Oral	156 (40.0)	158 (40.0)	146 (38.6)	460 (39.6)
Oral with IV Metronidazole	27 (6.9)	29 (7.3)	35 (9.3)	91 (7.8)
Fidaxomicin	13 (3.3)	16 (4.1)	13 (3.4)	42 (3.6)
Oral	11 (2.8)	13 (3.3)	13 (3.4)	37 (3.2)
Oral with IV Metronidazole	2 (0.5)	3 (0.8)	0 (0.0)	5 (0.4)
Other	7 (1.8)	6 (1.5)	8 (2.1)	21 (1.8)
IV Metronidazole	4 (1.0)	3 (0.8)	2 (0.5)	9 (0.8)
Oral Vancomycin with Oral Metronidazole	2 (0.5)	2 (0.5)	6 (1.6)	10 (0.9)
Oral Vancomycin with Oral and IV Metronidazole	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Oral Fidaxomicin with Oral Vancomycin	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
SoC at baseline differed from SoC stratum	16 (4.1)	10 (2.5)	16 (4.2)	42 (3.6)

SoC at baseline is the actual treatment the subject received at the time of the study infusion.
SoC stratum is the antibiotic recorded in the centralized randomization system and was used for stratification.
SoC = Standard of Care Therapy, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Table 14: Duration of standard of care therapy and Days on standard of care therapy prior to infusion (FAS Population)

	MK-3415A n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	390	395	378	1163
Total Days on SoC Therapy				
1-7 days	3 (0.8)	6 (1.5)	4 (1.1)	13 (1.1)
8-9 days	7 (1.8)	6 (1.5)	6 (1.6)	19 (1.6)
10-14 days	247 (63.3)	240 (60.8)	235 (62.2)	722 (62.1)
15-16 days	81 (20.8)	110 (27.8)	93 (24.6)	284 (24.4)
> 16 days	50 (12.8)	31 (7.8)	37 (9.8)	118 (10.1)
Unknown	2 (0.5)	2 (0.5)	3 (0.8)	7 (0.6)
N	388	393	375	1156
Mean	14.0	14.1	14.1	14.1
SD	4.4	6.3	5.6	5.5
Median	14.0	14.0	14.0	14.0
Quartiles	11 to 15	11 to 15	11 to 15	11 to 15
Range	6 to 43	4 to 87	4 to 67	4 to 87
Days on SoC Therapy Prior to Infusion				
SoC Started 1 Day after Infusion	3 (0.8)	0	0	3 (0.3)
0 days	31 (7.9)	32 (8.1)	34 (9.0)	97 (8.3)
1-2 days	115 (29.5)	121 (30.6)	125 (33.1)	361 (31.0)
3-4 days	120 (30.8)	117 (29.6)	110 (29.1)	347 (29.8)
5-6 days	94 (24.1)	93 (23.5)	91 (24.1)	278 (23.9)
> 6 days	27 (6.9)	32 (8.1)	18 (4.8)	77 (6.6)
N	390	395	378	1163
Mean	3.3	3.4	3.2	3.3
SD	2.2	2.3	2.1	2.2
Median	3.0	3.0	3.0	3.0
Quartiles	2 to 5	2 to 5	2 to 5	2 to 5
Range	-1 to 9	0 to 14	0 to 13	-1 to 14

SoC = Standard of Care Therapy, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Prognostic risk factors

Study P001

Table 15: Subject characteristics - CDI prognostic risk factors (FAS Population)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	383		232		386		395		1,396	
Age (Years)										
< 65 Years	183	(47.8)	110	(47.4)	201	(52.1)	196	(49.6)	690	(49.4)
≥ 65 Years	200	(52.2)	122	(52.6)	185	(47.9)	199	(50.4)	706	(50.6)
Age (Years)										
< 75 Years	272	(71.0)	164	(70.7)	287	(74.4)	276	(69.9)	999	(71.6)
≥ 75 Years	111	(29.0)	68	(29.3)	99	(25.6)	119	(30.1)	397	(28.4)
History of CDI in Past 6 Months										
Yes	96	(25.1)	69	(29.7)	103	(26.7)	109	(27.6)	377	(27.0)
No	284	(74.2)	162	(69.8)	282	(73.1)	284	(71.9)	1,012	(72.5)
Unknown	3	(0.8)	1	(0.4)	1	(0.3)	2	(0.5)	7	(0.5)
Prior History of CDI (Ever)										
Yes	124	(32.4)	81	(34.9)	124	(32.1)	136	(34.4)	465	(33.3)
No	256	(66.8)	148	(63.8)	260	(67.4)	252	(63.8)	916	(65.6)
Unknown	3	(0.8)	3	(1.3)	2	(0.5)	7	(1.8)	15	(1.1)
Number of Past CDI Episodes (Ever)										
0	256	(66.8)	148	(63.8)	260	(67.4)	252	(63.8)	916	(65.6)
1	74	(19.3)	46	(19.8)	81	(21.0)	62	(15.7)	263	(18.8)
2	22	(5.7)	18	(7.8)	24	(6.2)	38	(9.6)	102	(7.3)
3	18	(4.7)	8	(3.4)	10	(2.6)	22	(5.6)	58	(4.2)
≥ 4	8	(2.1)	8	(3.4)	9	(2.3)	13	(3.3)	38	(2.7)
Unknown	5	(1.3)	4	(1.7)	2	(0.5)	8	(2.0)	19	(1.4)
Clinically Severe CDI										
Yes (Zar Score ≥ 2)	62	(16.2)	31	(13.4)	67	(17.4)	60	(15.2)	220	(15.8)
No (Zar Score < 2)	297	(77.5)	186	(80.2)	303	(78.5)	317	(80.3)	1,103	(79.0)
Unknown	24	(6.3)	15	(6.5)	16	(4.1)	18	(4.6)	73	(5.2)
027 Ribotype										
Yes	37	(9.7)	24	(10.3)	46	(11.9)	36	(9.1)	143	(10.2)
No	188	(49.1)	119	(51.3)	203	(52.6)	207	(52.4)	717	(51.4)
Unknown	158	(41.3)	89	(38.4)	137	(35.5)	152	(38.5)	536	(38.4)
Epidemic Strain (027, 014, 002, 106 or 020 ribotypes)										
Yes	106	(27.7)	57	(24.6)	108	(28.0)	106	(26.8)	377	(27.0)
No	119	(31.1)	86	(37.1)	141	(36.5)	137	(34.7)	483	(34.6)
Unknown	158	(41.3)	89	(38.4)	137	(35.5)	152	(38.5)	536	(38.4)
Hypervirulent Strain (027, 078 or 244 ribotypes)										
Yes	44	(11.5)	30	(12.9)	51	(13.2)	44	(11.1)	169	(12.1)
No	181	(47.3)	113	(48.7)	198	(51.3)	199	(50.4)	691	(49.5)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypervirulent Strain (027, 078 or 244 ribotypes)										
Unknown	158	(41.3)	89	(38.4)	137	(35.5)	152	(38.5)	536	(38.4)
Compromised Immunity										
Yes	78	(20.4)	55	(23.7)	87	(22.5)	92	(23.3)	312	(22.3)
No	305	(79.6)	177	(76.3)	299	(77.5)	303	(76.7)	1,084	(77.7)
Horn's Index										
Level 1 - Low	96	(25.1)	52	(22.4)	109	(28.2)	95	(24.1)	352	(25.2)
Level 2 - Moderate	184	(48.0)	108	(46.6)	174	(45.1)	184	(46.6)	650	(46.6)
Level 3 - Major	102	(26.6)	67	(28.9)	100	(25.9)	115	(29.1)	384	(27.5)
Level 4 - Extreme	1	(0.3)	5	(2.2)	3	(0.8)	1	(0.3)	10	(0.7)
Charlson Comorbidity Index										
< 3	222	(58.0)	126	(54.3)	238	(61.7)	243	(61.5)	829	(59.4)
≥ 3	161	(42.0)	106	(45.7)	148	(38.3)	152	(38.5)	567	(40.6)
Renal Impairment										
Yes (Serum creatinine ≥ 1.5 mg/dL)	49	(12.8)	37	(15.9)	55	(14.2)	61	(15.4)	202	(14.5)
No (Serum creatinine < 1.5 mg/dL)	325	(84.9)	191	(82.3)	321	(83.2)	330	(83.5)	1,167	(83.6)
Unknown	9	(2.3)	4	(1.7)	10	(2.6)	4	(1.0)	27	(1.9)

	MK-3415A		MK-3415		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hepatic Impairment†										
Yes	29	(7.6)	14	(6.0)	23	(6.0)	24	(6.1)	90	(6.4)
No	343	(89.6)	214	(92.2)	350	(90.7)	363	(91.9)	1,270	(91.0)
Unknown	11	(2.9)	4	(1.7)	13	(3.4)	8	(2.0)	36	(2.6)

†Hepatic Impairment defined by two or more of the following: (a) albumin ≤ 3.1 g/dL, (b) ALT ≥ 2X ULN, (c) total bilirubin ≥ 1.3X ULN, or (d) mild, moderate or severe liver disease (as reported on the Charlson Index)

MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

In general, the proportion of subjects for the majority of these prognostic risk factors was balanced across treatment groups; however, there were some notable imbalances. The MK-6072 group had a slightly lower percentage of subjects in the ≥ 75 years age category: 25.6% vs 30.1% placebo group.

The CDI episode at the time of study entry was classified as healthcare facility associated for 52.1% of subjects. Healthcare facility associated refers to those subjects who were in the hospital (or other health care facility, including long term care facility) at the time of onset, or were at home at the time of onset but had been in a healthcare facility within the previous 3 months. In general, the classification of the CDI episode was similar across the treatment groups.

Systemic antibiotic use, PPI use, use of a nasogastric tube, and whether the subject had an appendectomy at any time prior to study entry are considered as additional CDI risk factors. A slightly higher proportion of subjects in the placebo group reported prior systemic antibiotic use than in the other treatment groups (54.9% in the placebo group compared to 51.4%, 51.3%, and 47.2%, for the MK-3415A, MK-3415, and MK-6072 groups, respectively). Prior use of PPIs was generally balanced across treatment groups. Only 4.2% of subjects had a nasogastric tube in place during the month prior to onset of the baseline episode, and the prior presence of a nasogastric tube was generally similar across the treatment groups. Among the 358 subjects for whom a response was given, approximately half had an appendectomy; a numerically higher proportion of subjects in the placebo group had an appendectomy than in the other treatment groups (17.2% in the placebo group compared to 15.4%, 1.7%, and 11.7%, for the MK-3415A, MK-3415, and MK-6072 groups, respectively).

Study P002

Table 16: Subject characteristics - CDI prognostic risk factors (FAS Population)

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	390		395		378		1,163	
Age (Years)								
< 65 Years	149	(38.2)	190	(48.1)	172	(45.5)	511	(43.9)
≥ 65 Years	241	(61.8)	205	(51.9)	206	(54.5)	652	(56.1)
Age (Years)								
< 75 Years	241	(61.8)	281	(71.1)	262	(69.3)	784	(67.4)
≥ 75 Years	149	(38.2)	114	(28.9)	116	(30.7)	379	(32.6)
History of CDI in Past 6 Months								
Yes	104	(26.7)	113	(28.6)	110	(29.1)	327	(28.1)
No	273	(70.0)	274	(69.4)	261	(69.0)	808	(69.5)
Unknown	13	(3.3)	8	(2.0)	7	(1.9)	28	(2.4)
Prior History of CDI (Ever)								
Yes	119	(30.5)	126	(31.9)	123	(32.5)	368	(31.6)
No	256	(65.6)	260	(65.8)	246	(65.1)	762	(65.5)
Unknown	15	(3.8)	9	(2.3)	9	(2.4)	33	(2.8)
Number of Past CDI Episodes (Ever)								
0	256	(65.6)	260	(65.8)	246	(65.1)	762	(65.5)
1	64	(16.4)	69	(17.5)	70	(18.5)	203	(17.5)
2	33	(8.5)	35	(8.9)	32	(8.5)	100	(8.6)
3	13	(3.3)	9	(2.3)	14	(3.7)	36	(3.1)
≥ 4	9	(2.3)	13	(3.3)	7	(1.9)	29	(2.5)
Unknown	15	(3.8)	9	(2.3)	9	(2.4)	33	(2.8)

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Clinically Severe CDI								
Yes (Zar Score ≥ 2)	80	(20.5)	55	(13.9)	65	(17.2)	200	(17.2)
No (Zar Score < 2)	294	(75.4)	326	(82.5)	296	(78.3)	916	(78.8)
Unknown	16	(4.1)	14	(3.5)	17	(4.5)	47	(4.0)
027 Ribotype								
Yes	39	(10.0)	43	(10.9)	64	(16.9)	146	(12.6)
No	212	(54.4)	194	(49.1)	177	(46.8)	583	(50.1)
Unknown	139	(35.6)	158	(40.0)	137	(36.2)	434	(37.3)
Epidemic Strain (027, 014, 002, 001, 106 or 020 ribotypes)								
Yes	116	(29.7)	102	(25.8)	127	(33.6)	345	(29.7)
No	135	(34.6)	135	(34.2)	114	(30.2)	384	(33.0)
Unknown	139	(35.6)	158	(40.0)	137	(36.2)	434	(37.3)
Hypervirulent Strain (027, 078 or 244 ribotypes)								
Yes	46	(11.8)	51	(12.9)	71	(18.8)	168	(14.4)
No	205	(52.6)	186	(47.1)	170	(45.0)	561	(48.2)
Unknown	139	(35.6)	158	(40.0)	137	(36.2)	434	(37.3)
Compromised Immunity								
Yes	75	(19.2)	82	(20.8)	53	(14.0)	210	(18.1)
No	315	(80.8)	313	(79.2)	325	(86.0)	953	(81.9)
Horn's Index								
Level 1 - Low	113	(29.0)	90	(22.8)	108	(28.6)	311	(26.7)
Level 2 - Moderate	167	(42.8)	192	(48.6)	153	(40.5)	512	(44.0)

	MK-3415A		MK-6072		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Horn's Index								
Level 3 - Major	105	(26.9)	111	(28.1)	116	(30.7)	332	(28.5)
Level 4 - Extreme	5	(1.3)	1	(0.3)	1	(0.3)	7	(0.6)
Unknown	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Charlson Comorbidity Index								
< 3	225	(57.7)	224	(56.7)	227	(60.1)	676	(58.1)
≥ 3	165	(42.3)	171	(43.3)	151	(39.9)	487	(41.9)
Renal Impairment								
Yes (Serum creatinine ≥ 1.5 mg/dL)	47	(12.1)	68	(17.2)	49	(13.0)	164	(14.1)
No (Serum creatinine < 1.5 mg/dL)	341	(87.4)	325	(82.3)	322	(85.2)	988	(85.0)
Unknown	2	(0.5)	2	(0.5)	7	(1.9)	11	(0.9)
Hepatic Impairment[†]								
Yes	27	(6.9)	26	(6.6)	20	(5.3)	73	(6.3)
No	359	(92.1)	365	(92.4)	350	(92.6)	1,074	(92.3)
Unknown	4	(1.0)	4	(1.0)	8	(2.1)	16	(1.4)

[†]Hepatic Impairment defined by two or more of the following: (a) albumin ≤ 3.1 g/dL, (b) ALT ≥ 2X ULN, (c) total bilirubin ≥ 1.3X ULN, or (d) mild, moderate or severe liver disease (as reported on the Charlson Index)

MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

The proportion of subjects for the majority of these prognostic risk factors was balanced across treatment groups.

The CDI episode at the time of study entry was classified as healthcare facility associated for 61.2% of subjects. In general, the distribution of CDI episode classifications was generally similar across the treatment groups.

Prior use of a systemic antibiotic or a PPI was recorded for approximately half of the subjects in the FAS population (59.1% for prior systemic antibiotic use; 48.0% for prior PPI use). The proportion of subjects with prior systemic antibiotic use was similar among the treatment groups. The proportion of subjects with prior use of PPIs was slightly higher in the MK-6072 group (50.6%) as compared to the placebo group and the MK-3415A group (46.6% and 46.7%, respectively). Only 4.9% of subjects had a nasogastric tube in place during the month prior to onset of the baseline episode; the proportion of such patients was slightly lower in the MK-6072 group (3.8%) as compared to the MK-3415A group (5.4%) and placebo group (5.6%).

Numbers analysed

Study P001

Table 17: Subject accounting for efficacy analysis (all randomised subjects)

	MK-3415A n (%)	MK-3415 n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	403	242	403	404	1452
Included in All Treated	388 (96.3)	235 (97.1)	392 (97.3)	397 (98.3)	1412 (97.2)
Excluded from All Treated	15 (3.7)	7 (2.9)	11 (2.7)	7 (1.7)	40 (2.8)
Did not receive infusion	15 (3.7)	7 (2.9)	11 (2.7)	7 (1.7)	40 (2.8)
Included in FAS population	383 (95.0)	232 (95.9)	386 (95.8)	395 (97.8)	1396 (96.1)
Excluded from FAS population	20 (5.0)	10 (4.1)	17 (4.2)	9 (2.2)	56 (3.9)
Not in All Treated	15 (3.7)	7 (2.9)	11 (2.7)	7 (1.7)	40 (2.8)
Did not have positive local laboratory test for toxigenic *C. difficile*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Did not receive protocol defined SoC therapy within 1 day window of the infusion	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
GCP Non-compliance	3 (0.7)	3 (1.2)	6 (1.5)	2 (0.5)	14 (1.0)
Included in PP population	324 (80.4)	173 (71.5)	332 (82.4)	306 (75.7)	1135 (78.2)
Excluded from PP population	79 (19.6)	69 (28.5)	71 (17.6)	98 (24.3)	317 (21.8)
Not in FAS	20 (5.0)	10 (4.1)	17 (4.2)	9 (2.2)	56 (3.9)
Prohibited concomitant medication	31 (7.7)	23 (9.5)	26 (6.5)	43 (10.6)	123 (8.5)
No post-infusion loose stool counts recorded after SoC therapy	12 (3.0)	8 (3.3)	12 (3.0)	13 (3.2)	45 (3.1)
Site personnel or sponsor partially or fully unblinded	2 (0.5)	12 (5.0)	4 (1.0)	24 (5.9)	42 (2.9)
SoC route or combination not per protocol	5 (1.2)	12 (5.0)	9 (2.2)	8 (2.0)	34 (2.3)
Baseline toxigenic *C. difficile* test out of window	9 (2.2)	5 (2.1)	8 (2.0)	2 (0.5)	24 (1.7)
Duration of SoC therapy less than 7 days	4 (1.0)	3 (1.2)	3 (0.7)	3 (0.7)	13 (0.9)
Received less than 75% of intended dose	2 (0.5)	6 (2.5)	1 (0.2)	0 (0.0)	9 (0.6)
Wrong treatment administered	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	3 (0.2)
Prohibited prior medication	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)	3 (0.2)
SoC initially prescribed for > 14 days	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.1)
Diarrhea criteria not met for baseline episode	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

Note: Criteria for FAS population was evaluated sequentially (each subject is listed only once across the reasons excluded from the FAS population). Each criterion for the PP population was evaluated for each subject. As such, a subject may have met more than one of the exclusion criteria for the PP population and will be counted once for each exclusion that they met. As such, the sum of the reasons for exclusion may not equal the total number of subjects excluded from the PP population.

† The counts are based on the planned treatment.

All Treated = All Treated Subjects, FAS = Full Analysis Set, GCP = Good Clinical Practice, PP = Per Protocol, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Study P002

Table 18: Subjects accounting for efficacy analysis (all randomised subjects)

	MK-3415A n (%)	MK-6072 n (%)	Placebo n (%)	Total n (%)
Subjects in population	397	407	399	1203
Included in All Treated	391 (98.5)	396 (97.3)	381 (95.5)	1168 (97.1)
Excluded from All Treated	6 (1.5)	11 (2.7)	18 (4.5)	35 (2.9)
Did not receive infusion	6 (1.5)	11 (2.7)	18 (4.5)	35 (2.9)
Included in FAS population	390 (98.2)	395 (97.1)	378 (94.7)	1163 (96.7)
Excluded from FAS population	7 (1.8)	12 (2.9)	21 (5.3)	40 (3.3)
Not in All Treated	6 (1.5)	11 (2.7)	18 (4.5)	35 (2.9)
Did not have positive local laboratory test for toxigenic *C. difficile*	0 (0.0)	1 (0.2)	1 (0.3)	2 (0.2)
Did not receive protocol defined SoC therapy within 1 day window of the infusion	1 (0.3)	0 (0.0)	2 (0.5)	3 (0.2)
Included in PP population	337 (84.9)	331 (81.3)	303 (75.9)	971 (80.7)
Excluded from PP population	60 (15.1)	76 (18.7)	96 (24.1)	232 (19.3)
Not in FAS	7 (1.8)	12 (2.9)	21 (5.3)	40 (3.3)
Prohibited concomitant medication	16 (4.0)	31 (7.6)	26 (6.5)	73 (6.1)
No post-infusion loose stool counts recorded after SoC therapy	20 (5.0)	16 (3.9)	20 (5.0)	56 (4.7)
Site personnel or sponsor partially or fully unblinded	5 (1.3)	6 (1.5)	21 (5.3)	32 (2.7)
SoC route or combination not per protocol	6 (1.5)	6 (1.5)	11 (2.8)	23 (1.9)
Baseline toxigenic *C. difficile* test out of window	6 (1.5)	3 (0.7)	2 (0.5)	11 (0.9)
Duration of SoC therapy less than 7 days	1 (0.3)	2 (0.5)	4 (1.0)	7 (0.6)
Wrong treatment administered	2 (0.5)	1 (0.2)	1 (0.3)	4 (0.3)
Prohibited prior medication	1 (0.3)	1 (0.2)	1 (0.3)	3 (0.2)
Diarrhea criteria not met for baseline episode	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
Unapproved stool test used to confirm subject eligibility	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
Received less than 75% of intended dose	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)

Note: Criteria for FAS population was evaluated sequentially (each subject is listed only once across the reasons excluded from the FAS population). Each criterion for the PP population was evaluated for each subject. As such, a subject may have met more than one of the exclusion criteria for the PP population and will be counted once for each exclusion that they met. As such, the sum of the reasons for exclusion may not equal the total number of subjects excluded from the PP population.

† The counts are based on the planned treatment.

All Treated = All Treated Subjects, FAS = Full Analysis Set, PP = Per Protocol, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

- **Extension study (P002)**

A small cohort of subjects was enrolled in an extension study where subjects were followed for up to 12 months after infusion of the study medication.

There were a total of 295 subjects who completed the main study and subsequently entered the extension phase of the study (MK-3415A group: n=112; MK-6072 group: n=100, and placebo group: n=83). Almost all of these subjects (293 of 295) were included in the FAS in the main study (MK-3415A group: n=112; MK-6072 group: n=99; and placebo: n=82).

Outcomes and estimation

Study P001

Summary of efficacy analysis

Table 19: Summary of efficacy analyses (FAS Population)

	MK-3415A N=383	MK-3415 N=232	MK-6072 N=386	Placebo N=395
Primary Endpoint				
CDI Recurrence	61/383 (15.9%)	60/232 (25.9%)	67/386 (17.4%)	109/395 (27.6%)
Secondary Endpoints				
CDI Recurrence, among subjects who attained clinical cure	61/286 (21.3%)	60/169 (35.5%)	67/299 (22.4%)	109/327 (33.3%)
Global Cure	225/383 (58.7%)	109/232 (47.0%)	232/386 (60.1%)	218/395 (55.2%)
CDI Recurrence by Subgroup†				
SoC Therapy (stratification variable)				
Metronidazole	26/189 (13.8%)	23/112 (20.5%)	32/190 (16.8%)	43/192 (22.4%)
Vancomycin	32/182 (17.6%)	36/113 (31.9%)	31/182 (17.0%)	63/189 (33.3%)
Fidaxomicin	3/12 (25.0%)	1/7 (14.3%)	4/14 (28.6%)	3/14 (21.4%)
Hospitalization Status (stratification variable)				
Inpatient	40/254 (15.7%)	36/158 (22.8%)	40/257 (15.6%)	66/261 (25.3%)
Outpatient	21/129 (16.3%)	24/74 (32.4%)	27/129 (20.9%)	43/134 (32.1%)
History of CDI in the past 6 months				
Yes	24/96 (25.0%)	23/69 (33.3%)	27/103 (26.2%)	43/109 (39.4%)
No	37/284 (13.0%)	36/162 (22.2%)	40/282 (14.2%)	66/284 (23.2%)
Infected with 027 Ribotype				
Yes	4/37 (10.8%)	8/24 (33.3%)	12/46 (26.1%)	13/36 (36.1%)
No	31/188 (16.5%)	33/119 (27.7%)	39/203 (19.2%)	63/207 (30.4%)
Infected with Epidemic‡ Strain				
Yes	21/106 (19.8%)	14/57 (24.6%)	25/108 (23.1%)	38/106 (35.8%)
No	14/119 (11.8%)	27/86 (31.4%)	26/141 (18.4%)	38/137 (27.7%)
Infected with Hypervirulent‖ Strain				
Yes	6/44 (13.6%)	12/30 (40.0%)	13/51 (25.5%)	15/44 (34.1%)
No	29/181 (16.0%)	29/113 (25.7%)	38/198 (19.2%)	61/199 (30.7%)
Severe CDI at study entry				
Yes	8/62 (12.9%)	8/31 (25.8%)	7/67 (10.4%)	15/60 (25.0%)
No	51/297 (17.2%)	49/186 (26.3%)	57/303 (18.8%)	88/317 (27.8%)
Age at study entry				
< 65 Years	27/183 (14.8%)	28/110 (25.5%)	39/201 (19.4%)	43/196 (21.9%)
≥ 65 Years	34/200 (17.0%)	32/122 (26.2%)	28/185 (15.1%)	66/199 (33.2%)
Immunocompromised status				
Yes	9/78 (11.5%)	10/55 (18.2%)	15/87 (17.2%)	26/92 (28.3%)
No	52/305 (17.0%)	50/177 (28.2%)	52/299 (17.4%)	83/303 (27.4%)
Exploratory Endpoints				
Clinical Cure	286/383 (74.7%)	169/232 (72.8%)	299/386 (77.5%)	327/395 (82.8%)
Diarrhea Recurrence	101/383 (26.4%)	81/232 (34.9%)	109/386 (28.2%)	163/395 (41.3%)

† Number of subjects in each subgroup may not add to the total number of subjects with CDI recurrence, as those with unknown responses for each category were excluded from the respective subgroup analysis.

‡ Epidemic strain includes the following: 027, 014, 002, 001, 106, or 020 ribotypes

‖ Hypervirulent strain included the following: 027, 078, or 244 ribotypes

SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

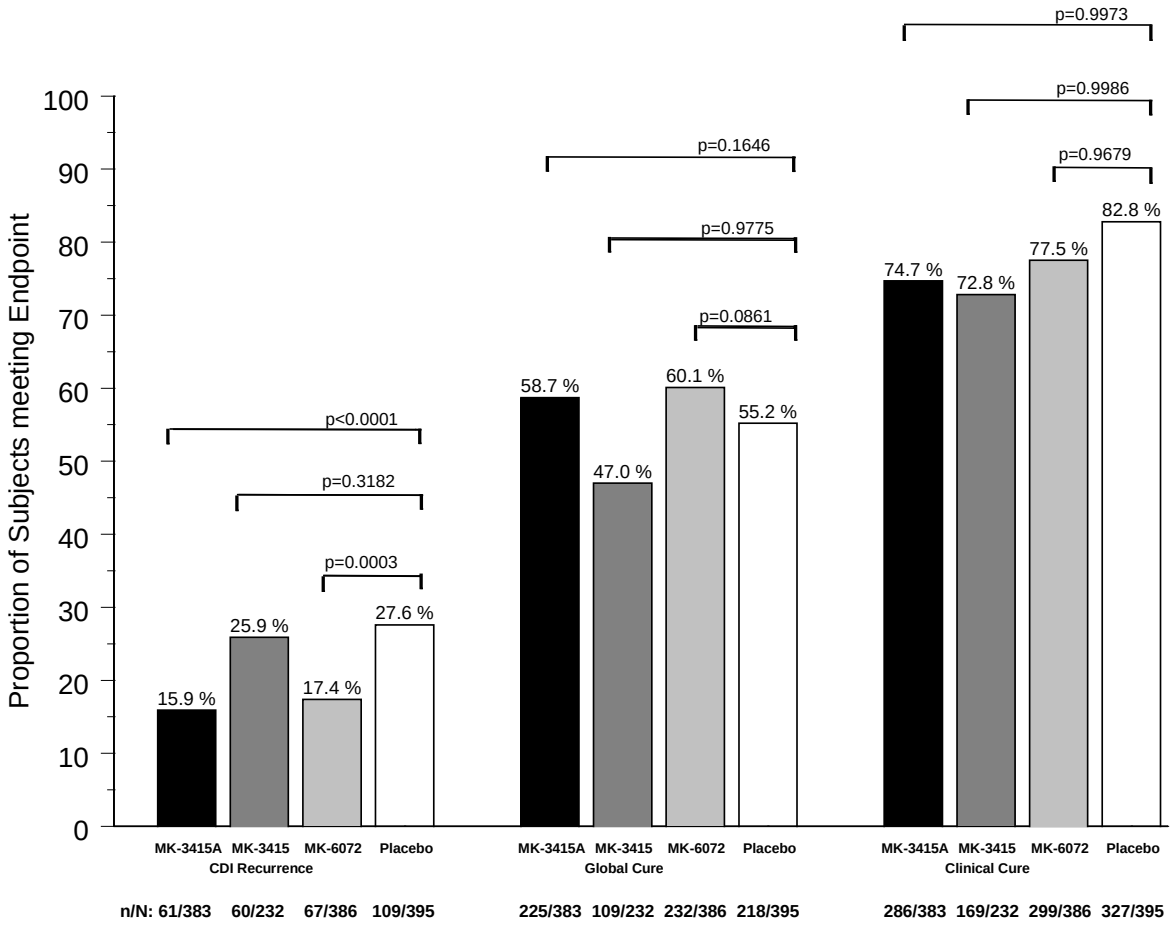


Figure 4: Summary of efficacy analyses for CDI recurrence, global cure, and clinical cure endpoints (FAS Population)

Primary endpoint

- **CDI recurrence**

Table 20: Analysis of the proportion of subjects with CDI recurrence (FAS Population)

Treatment	% (n/N)	Treatment vs. Placebo		
		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A	15.9 (61/383)	-11.7	-11.6 (-17.4, -5.9)	<0.0001
MK-3415	25.9 (60/232)	-1.7	-1.7 (-8.6, 5.5)	0.3182
MK-6072	17.4 (67/386)	-10.2	-10.1 (-15.9, -4.3)	0.0003
Placebo	27.6 (109/395)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A vs. MK-3415		-9.9	-9.9 (-16.9, -3.4)	0.0013
MK-3415A vs. MK-6072		-1.4	-1.4 (-6.7, 3.9)	0.2997

† One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

A lower proportion of subjects had CDI recurrence in the MK-6072 group (17.4%) as compared to the placebo group (27.6%). The estimated difference between the MK-6072 group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -10.1% (95% CI: -15.9% to -4.3%, one-sided p = 0.0003). Given the p-value cut off of 0.0125, these results are considered statistically significant. Though the CDI recurrence rate in the MK-3415A group was slightly lower than the CDI recurrence rate in the MK-6072 group, this difference was not statistically significant (one sided p = 0.2997).

A supportive analysis of CDI recurrence among subjects in the PP population was also performed. Overall, results were similar to those observed among the FAS population. CDI recurrence rates among subjects in the PP population were slightly higher than those observed in the FAS population across all treatment groups. Among subjects in the PP population, the proportion of subjects with CDI recurrence was lower among subjects receiving MK-6072 (19.0%) as compared to that among subjects receiving placebo (31.4%). The estimated differences between the MK-6072 group versus the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, were -12.4% (95% CI: -21.3% to -8.0%). Treatment with a single infusion of MK-6072 given with standard of care antibiotic therapy decreases the proportion of subjects with CDI recurrence as compared with a single infusion of placebo given with standard of care antibiotic therapy among subjects in the PP population (one-sided p = 0.0002, respectively).

Table 21: CDI recurrence by stratification factors (FAS Population)

	MK-3415A n/m (%)	MK-3415 n/m (%)	MK-6072 n/m (%)	Placebo n/m (%)
Subjects in population	383	232	386	395
SoC Therapy Strata				
Metronidazole	26/189 (13.8)	23/112 (20.5)	32/190 (16.8)	43/192 (22.4)
Vancomycin	32/182 (17.6)	36/113 (31.9)	31/182 (17.0)	63/189 (33.3)
Fidaxomicin	3/12 (25.0)	1/7 (14.3)	4/14 (28.6)	3/14 (21.4)
Hospitalization Status Strata				
Inpatient	40/254 (15.7)	36/158 (22.8)	40/257 (15.6)	66/261 (25.3)
Outpatient	21/129 (16.3)	24/74 (32.4)	27/129 (20.9)	43/134 (32.1)
SoC/Hospitalization Status Strata				
Metronidazole/Inpatient	18/124 (14.5)	11/76 (14.5)	21/124 (16.9)	26/126 (20.6)
Metronidazole/Outpatient	8/65 (12.3)	12/36 (33.3)	11/66 (16.7)	17/66 (25.8)
Vancomycin/Inpatient	21/124 (16.9)	24/78 (30.8)	18/126 (14.3)	38/128 (29.7)
Vancomycin/Outpatient	11/58 (19.0)	12/35 (34.3)	13/56 (23.2)	25/61 (41.0)
Fidaxomicin/Inpatient	1/6 (16.7)	1/4 (25.0)	1/7 (14.3)	2/7 (28.6)
Fidaxomicin/Outpatient	2/6 (33.3)	0/3 (0.0)	3/7 (42.9)	1/7 (14.3)

n = Number of subjects within the strata that met the criteria for endpoint.
m = Number of subjects within strata.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

Secondary endpoints

- **CDI recurrence among subjects achieving clinical cure**

Table 22: Analysis of the proportion of subjects with CDI recurrence (FAS Population with clinical cure of the initial episode)

		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A	21.3 (61/286)	-12.0	-11.7 (-18.6, -4.7)	0.0006
MK-3415	35.5 (60/169)	2.2	1.7 (-6.9, 10.7)	0.6505
MK-6072	22.4 (67/299)	-10.9	-10.8 (-17.7, -3.8)	0.0013
Placebo	33.3 (109/327)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A vs. MK-3415		-14.2	-13.7 (-22.5, -5.2)	0.0007
MK-3415A vs. MK-6072		-1.1	-1.0 (-7.7, 5.8)	0.3906

† One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

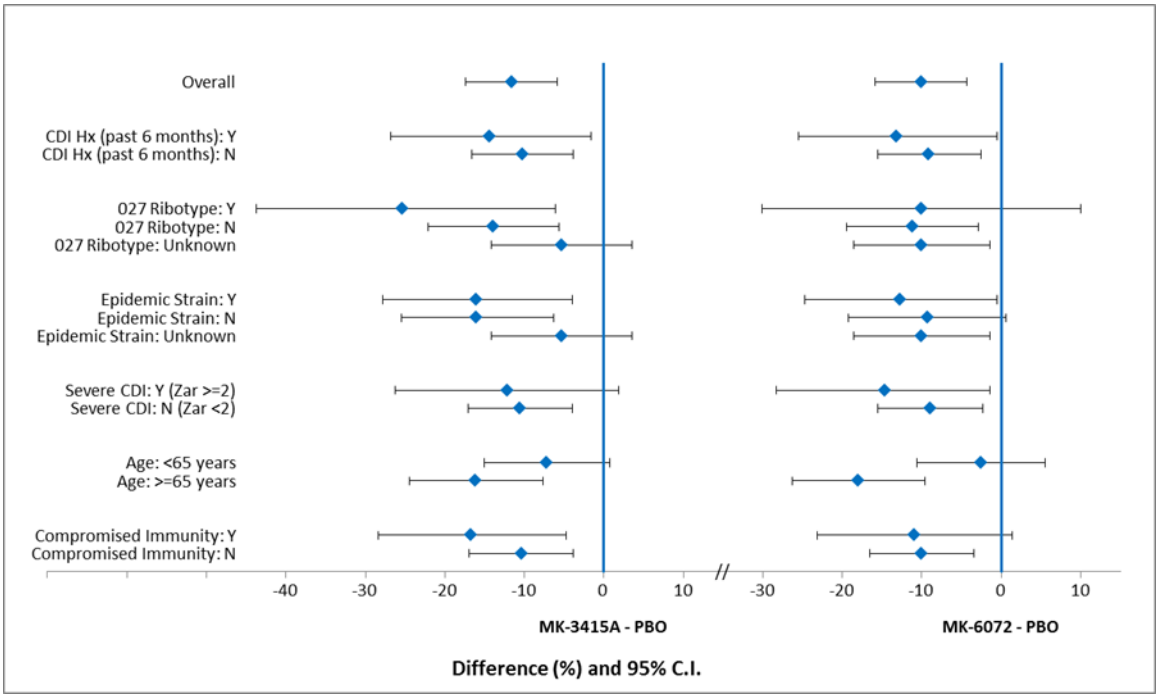
Among subjects with clinical cure of the baseline episode, the proportion of subjects with CDI recurrence was lower among subjects receiving MK-6072 (22.4%) as compared to that among subjects receiving placebo (33.3%)

The estimated difference between the MK-6072 treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -10.8% (95% CI: -17.7% to -3.8%) among subjects with clinical cure of the baseline episode. Treatment with a single infusion of MK-6072 given with standard of care therapy decreases the proportion of subjects with CDI

recurrence as compared with a single infusion of placebo given with standard of care therapy among subjects with clinical cure of their baseline episode (p = 0.0013).

- **CDI recurrence by subgroup**

Figure 5 : CDI recurrence by subgroup (FAS Population)



Subgroup analyses showed consistency of the effect of treatment with MK-6072 (and MK-3415A) versus placebo. The subgroup results were consistent with general conclusions from the primary analysis. Similar trend was observed analysing CDI recurrence for the FAS population who achieved clinical cure (data not shown in this report).

- **Global cure**

Table 23: Analysis of the proportion of subjects with global cure (FAS Population)

		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A	58.7 (225/383)	3.6	3.5 (-3.5, 10.4)	0.1646
MK-3415	47.0 (109/232)	-8.2	-8.3 (-16.3, -0.2)	0.9775
MK-6072	60.1 (232/386)	4.9	4.8 (-2.1, 11.7)	0.0861
Placebo	55.2 (218/395)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A vs. MK-3415		11.8	11.7 (3.5, 19.7)	0.0025
MK-3415A vs. MK-6072		-1.4	-1.4 (-8.3, 5.5)	0.6532

† One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

A numerically higher proportion of subjects achieved global cure in the MK-6072 (60.1%) (and MK-3415A [58.7%]) treatment groups as compared to the placebo group (55.2%). However, differences

between the MK-6072 and MK-3415A groups versus the placebo group did not reach statistical significance (one sided p = 0.0861 and 0.1646, respectively).

Study P002

Table 24: Summary of efficacy analyses (FAS Population)

	MK-3415A N=390	MK-6072 N=395	Placebo N=378
Primary Endpoint			
CDI Recurrence	58/390 (14.9%)	62/395 (15.7%)	97/378 (25.7%)
Secondary Endpoints			
CDI Recurrence, among subjects who attained clinical cure	58/282 (20.6%)	62/326 (19.0%)	97/294 (33.0%)
Global Cure	224/390 (57.4%)	264/395 (66.8%)	197/378 (52.1%)
CDI Recurrence by Subgroup†			
SoC Therapy (stratification variable)			
Metronidazole	28/191 (14.7%)	24/189 (12.7%)	42/182 (23.1%)
Vancomycin	29/187 (15.5%)	36/190 (18.9%)	51/184 (27.7%)
Fidaxomicin	1/12 (8.3%)	2/16 (12.5%)	4/12 (33.3%)
Hospitalization Status (stratification variable)			
Inpatient	35/269 (13.0%)	33/273 (12.1%)	54/259 (20.8%)
Outpatient	23/121 (19.0%)	29/122 (23.8%)	43/119 (36.1%)
History of CDI in the past 6 months			
Yes	21/104 (20.2%)	27/113 (23.9%)	47/110 (42.7%)
No	35/273 (12.8%)	35/274 (12.8%)	48/261 (18.4%)
Infected with 027 Ribotype			
Yes	5/39 (12.8%)	9/43 (20.9%)	21/64 (32.8%)
No	37/212 (17.5%)	26/194 (13.4%)	49/177 (27.7%)
Infected with Epidemic‡ Strain			
Yes	17/116 (14.7%)	19/102 (18.6%)	37/127 (29.1%)
No	25/135 (18.5%)	16/135 (11.9%)	33/114 (28.9%)
Infected with Hypervirulent‖ Strain			
Yes	7/46 (15.2%)	9/51 (17.6%)	22/71 (31.0%)
No	35/205 (17.1%)	26/186 (14.0%)	48/170 (28.2%)
Severe CDI at study entry			
Yes	9/80 (11.3%)	6/55 (10.9%)	13/65 (20.0%)
No	46/294 (15.6%)	53/326 (16.3%)	81/296 (27.4%)
Age at study entry			
< 65 Years	16/149 (10.7%)	30/190 (15.8%)	36/172 (20.9%)
≥ 65 Years	42/241 (17.4%)	32/205 (15.6%)	61/206 (29.6%)
Immunocompromised status			
Yes	11/75 (14.7%)	11/82 (13.4%)	15/53 (28.3%)
No	47/315 (14.9%)	51/313 (16.3%)	82/325 (25.2%)
Exploratory Endpoints			
Clinical Cure	282/390 (72.3%)	326/395 (82.5%)	294/378 (77.8%)
Diarrhea Recurrence	99/390 (25.4%)	104/395 (26.3%)	127/378 (33.6%)

† Number of subjects in each subgroup may not add to the total number of subjects with CDI recurrence, as those with unknown responses for each category were excluded from the respective subgroup analysis.
‡ Epidemic strain includes the following: 027, 014, 002, 001, 106, or 020 ribotypes
‖ Hypervirulent strain included the following: 027, 078, or 244 ribotypes
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Figure 6: Summary of efficacy analyses for CDI recurrence, global cure, and clinical cure endpoints (FAS Population)

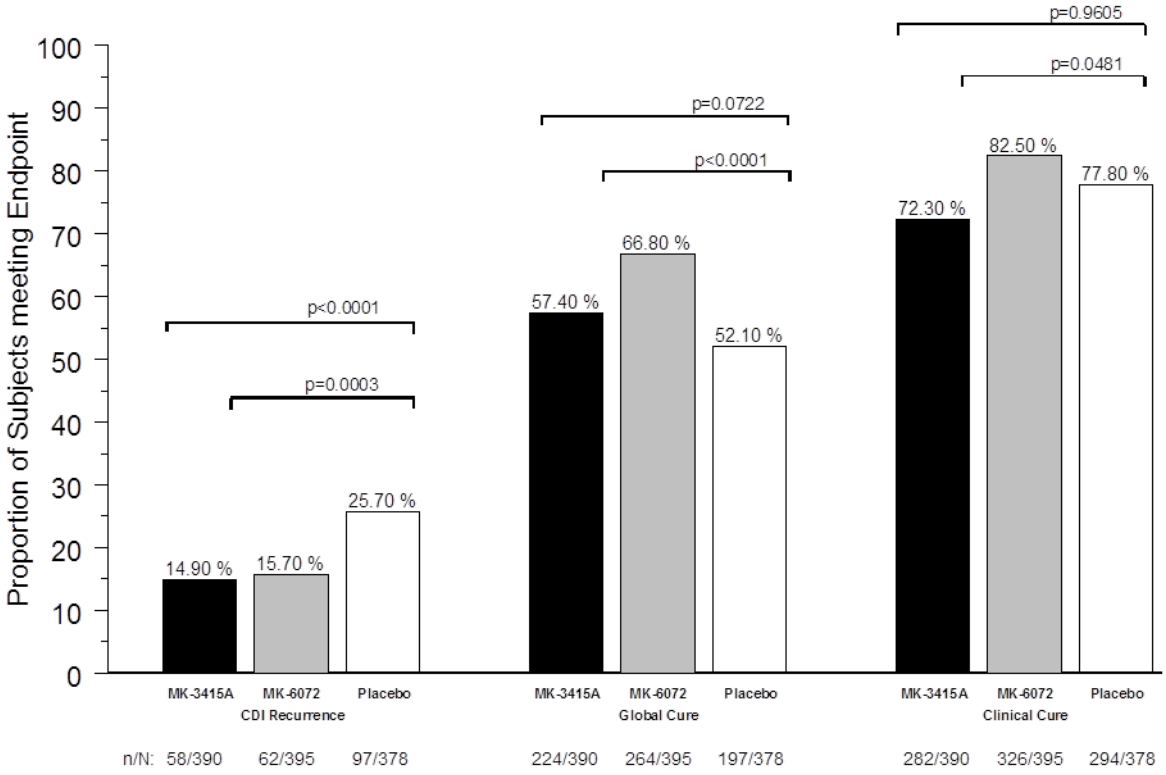


Table 25: Analysis of the proportion of subjects with CDI recurrence (FAS Population)

Treatment	% (n/N)	Treatment vs. Placebo		
		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A	14.9 (58/390)	-10.8	-10.7 (-16.4, -5.1)	<0.0001
MK-6072	15.7 (62/395)	-10.0	-9.9 (-15.5, -4.3)	0.0003
Placebo	25.7 (97/378)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A vs. MK-6072		-0.8	-0.8 (-5.9, 4.2)	0.3718

† One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Inferential testing for the primary endpoint occurred in a pre-specified sequential fashion. The first comparison was the MK-3415A treatment group versus placebo, using a one-sided p-value cut off of 0.025. A lower proportion of subjects had CDI recurrence in the MK-3415A group (14.9%) as compared to the placebo group (25.7%). The estimated difference between the MK-3415A group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care

therapy, was -10.7% (95% CI: -16.4% to -5.1%, one-sided p < 0.0001). Given the p-value cut off of 0.025, these results are considered statistically significant.

The second and final comparison in the sequential testing plan for the primary endpoint was the comparison of the MK-6072 treatment group to the placebo treatment group using a one-sided p-value cut off of 0.025. A lower proportion of subjects had CDI recurrence in the MK-6072 group (15.7%) as compared to the placebo group (25.7%). The estimated difference between the MK-6072 group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -9.9% (95% CI: -15.5% to -4.3%, one-sided p = 0.0003). Given the p-value cut off of 0.025, these results are considered statistically significant.

A secondary objective of this study was to compare the single monoclonal antibody treatment group (MK-6072) to the combined monoclonal antibody treatment group (MK-3415A) with respect to the proportion of subjects with CDI recurrence. There was no statistical difference between MK-3415A and MK-6072 with respect to the proportion of subjects with CDI recurrence.

A supportive analysis of CDI recurrence among subjects in the PP population was also performed. Overall, results were similar to those observed among the FAS population. CDI recurrence rates among subjects in the PP population were slightly higher than those observed in the FAS population across all treatment groups. Among subjects in the PP population, the proportions of subjects with CDI recurrence was lower among subjects receiving MK-3415A (16.0%) and MK-6072 (16.6%) as compared to that among subjects receiving placebo (29.4%). The estimated differences between the MK-3415A group and the MK-6072 group versus the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, were 13.7% (95% CI: -20.2% to -7.3%) and -13.2% (95% CI: -19.6% to -6.8%), respectively.

Table 26: CDI recurrence by stratification factors (FAS Population)

	MK-3415A n/m (%)	MK-6072 n/m (%)	Placebo n/m (%)
Subjects in population	390	395	378
SoC Therapy Strata			
Metronidazole	28/191 (14.7)	24/189 (12.7)	42/182 (23.1)
Vancomycin	29/187 (15.5)	36/190 (18.9)	51/184 (27.7)
Fidaxomicin	1/12 (8.3)	2/16 (12.5)	4/12 (33.3)
Hospitalization Status Strata			
Inpatient	35/269 (13.0)	33/273 (12.1)	54/259 (20.8)
Outpatient	23/121 (19.0)	29/122 (23.8)	43/119 (36.1)
SoC/Hospitalization Status Strata			
Metronidazole/Inpatient	17/121 (14.0)	13/122 (10.7)	21/116 (18.1)
Metronidazole/Outpatient	11/70 (15.7)	11/67 (16.4)	21/66 (31.8)
Vancomycin/Inpatient	17/141 (12.1)	20/143 (14.0)	31/137 (22.6)
Vancomycin/Outpatient	12/46 (26.1)	16/47 (34.0)	20/47 (42.6)
Fidaxomicin/Inpatient	1/7 (14.3)	0/8 (0.0)	2/6 (33.3)
Fidaxomicin/Outpatient	0/5 (0.0)	2/8 (25.0)	2/6 (33.3)

n = Number of subjects within the strata that met the criteria for endpoint.
m = Number of subjects within strata.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Secondary endpoints

- **CDI recurrence among subjects achieving clinical cure**

Table 27 : Analysis of the proportion of subjects with CDI recurrence (FAS Population with clinical cure of the initial episode)

Treatment	% (n/N)	Treatment vs. Placebo		
		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A	20.6 (58/282)	-12.4	-11.9 (-19.0, -4.7)	0.0006
MK-6072	19.0 (62/326)	-14.0	-13.7 (-20.4, -6.9)	<0.0001
Placebo	33.0 (97/294)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
MK-3415A vs. MK-6072		1.5	1.6 (-4.6, 8.0)	0.6962

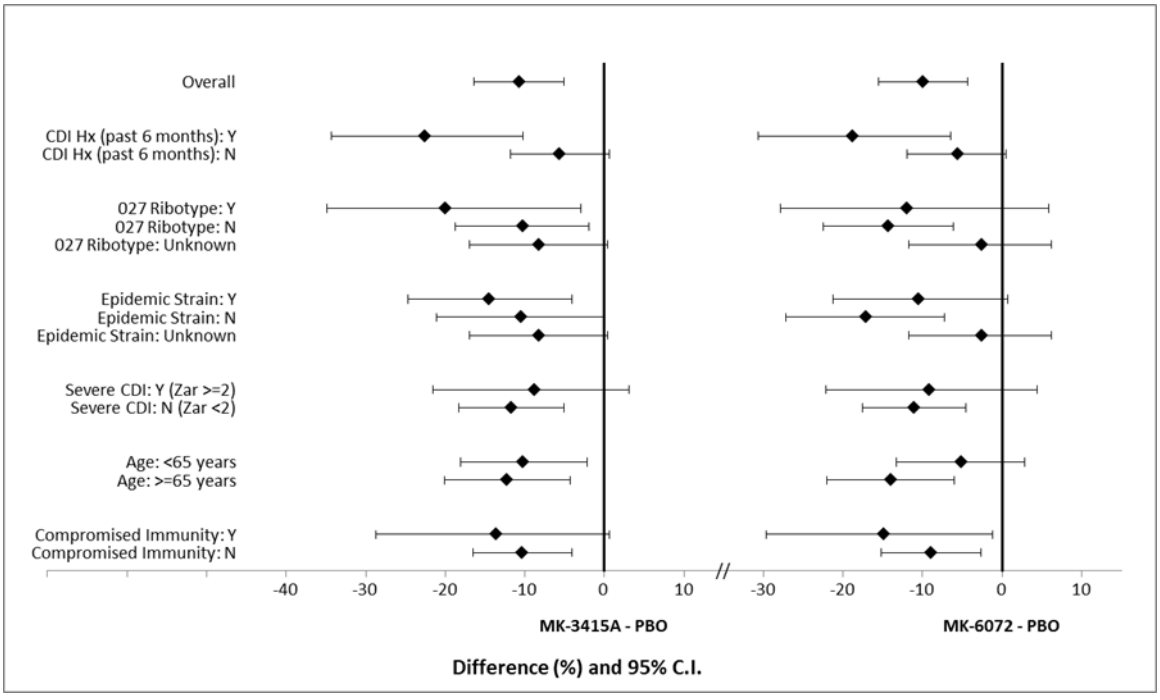
† One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Among subjects with clinical cure of the baseline episode, the proportion of subjects with CDI recurrence was lower among subjects receiving MK-6072 (19.0%) as compared to that among subjects receiving placebo (33.0%). The estimated difference between the MK-6072 treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -13.7% (95% CI: -20.4% to -6.9%) among subjects with clinical cure of the baseline episode. Treatment with a single infusion of MK-6072 given with standard of care therapy decreases the proportion of subjects with CDI recurrence as compared with a single infusion of placebo given with standard of care therapy among subjects with clinical cure of their baseline episode ($p < 0.0001$).

- **CDI recurrence by subgroup**

Figure 7 : CDI recurrence by subgroup (FAS Population)



Subgroup analyses showed consistency of the effect of treatment with MK-6072 (and MK-3415A) versus placebo. Subgroup results were consistent with general conclusions from the primary analysis

- **Global cure**

Table 28: Analysis of the proportion of subjects with global cure (FAS Population)

Treatment	% (n/N)	Treatment vs. Placebo		
		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
MK-3415A	57.4 (224/390)	5.3	5.2 (-1.8, 12.2)	0.0722
MK-6072	66.8 (264/395)	14.7	14.6 (7.7, 21.4)	<0.0001
Placebo	52.1 (197/378)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
MK-3415A vs. MK-6072		-9.4	-9.4 (-16.1, -2.7)	0.9969

[†] One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

Superiority was demonstrated for the secondary endpoint of global cure for the comparison between the MK-6072 group (66.8%) and the placebo group (52.1%, one-sided p <0.0001). A numerical trend favouring the MK-3415A group (57.4%) in comparison to the placebo group (52.1%) was observed; however, the one-sided p-value (p=0.0722) did not reach statistical significance. When comparing MK-3415A to MK-6072 with respect to achieving global cure, superiority of MK-6072 compared to MK-3415A was observed.

A supportive analysis of global cure among subjects in the PP population was also performed (data not shown in this report). Overall, the results were similar to those observed among the FAS population.

Ancillary analyses

Exploratory endpoints

Study P001

- **Clinical cure**

Table 29: Analysis of the proportion of subjects with clinical cure (FAS Set Population)

Treatment	% (n/N)	Treatment vs. Placebo		
		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
MK-3415A	74.7 (286/383)	-8.1	-8.2 (-13.9, -2.4)	0.9973
MK-3415	72.8 (169/232)	-9.9	-10.0 (-17.0, -3.4)	0.9986
MK-6072	77.5 (299/386)	-5.3	-5.3 (-10.9, 0.3)	0.9679
Placebo	82.8 (327/395)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
MK-3415A vs. MK-3415		1.8	1.7 (-5.3, 9.1)	0.3188
MK-3415A vs. MK-6072		-2.8	-2.8 (-8.8, 3.2)	0.8196

[†] One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-3415 = actoxumab alone, MK-6072 = bezlotoxumab alone

A lower proportion of subjects achieved clinical cure of the baseline episode in the MK-6072 (77.5%) (and MK-3415A [74.7%]) treatment groups as compared to the placebo group (82.8%). The estimated difference between the MK-6072 treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -5.3% (95% CI: -10.9% to 0.3%, one sided p= 0.9679). The estimated difference between the MK-3415A treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -8.2% (95% CI: -13.9% to -2.4%, one sided p= 0.9973). Thus, there was not only no evidence that treatment with MK-3415A or MK-6072 provided additional benefit over standard of care antibiotic alone for clinical cure of the baseline episode; the results suggest a more favourable outcome for clinical cure in the placebo group.

- **Diagnosis and severity of new CDI episode**

A total of 297 subjects in the FAS population had a CDI recurrence episode during the 12-week follow-up period

The data suggested that treatment with MK-6072 (and 3415A) appeared to be associated with CDI recurrences of less severity (as evidenced by lower maximum number of loose stool counts) and shorter duration (as evidenced by the time to resolution of the new episode). The majority of subjects on MK-6072 (and MK-3415A) that had a CDI recurrence resolved their episode within 2 days of the start of the recurrent episode (61.2% and 63.9%) as compared with a smaller proportion of placebo subjects (47.7%).

Sensitivity analysis

Table 30: Summary of sensitivity analysis

Sensitivity Analysis Brief Description	Planned vs. Post-hoc	Primary Study Result for Comparison	Key Results from Sensitivity Analysis
Impact of Stratification – no adjustment for stratification factors	Planned	CDI Recurrence MK-6072 vs. Placebo: Diff= -10.1, p=0.0003 MK-3415A vs. Placebo: Diff= -11.6, p<0.0001	CDI Recurrence MK-6072 vs. Placebo: Diff= -10.2, p=0.0003 MK-3415A vs. Placebo: Diff= -11.7, p<0.0001
Subjects with Positive Baseline Culture at Central Laboratory	Planned		CDI Recurrence MK-6072 vs. Placebo: Diff= -11.1, p=0.0022 MK-3415A vs. Placebo: Diff= -15.3, p<0.0001
Impact of Switching Standard of Care Therapy	Planned	rCDI‡: FAS Population MK-6072: 67/386 (17.4%) MK-3415A: 61/383 (15.9%) Placebo: 109/395 (27.6%)	rCDI‡: Subjects with Switch MK-6072: 2/29 (6.9%) MK-3415A: 1/29 (3.4%) Placebo: 2/20 (10.0%)
Impact of Missing Data – discontinue = imputed failure	Planned	CDI Recurrence MK-6072 vs. Placebo: Diff= -10.1, p=0.0003 MK-3415A vs. Placebo: Diff= -11.6, p<0.0001	CDI Recurrence MK-6072 vs. Placebo: Diff= -10.2, p=0.0014 MK-3415A vs. Placebo: Diff= -12.3, p<0.0001
Impact of Missing Data – no post-randomization endpoint data = imputed failure	Planned		CDI Recurrence MK-6072 vs. Placebo: Diff= -10.6, p=0.0002 MK-3415A vs. Placebo: Diff= -11.6, p<0.0001
Propensity Score Analysis	Planned		CDI Recurrence MK-6072 vs. Placebo: Diff= -9.0, p=0.0015 MK-3415A vs. Placebo: Diff= -10.9, p=0.0001
Impact of SOC Duration on Clinical Cure Definition:	Planned	(Clinical cure / rCDI‡ / Global cure) MK-6072: 77.5% / 17.4% / 60.1%	(Clinical cure / rCDI‡ / Global cure) MK-6072: 83.9% / 17.6% / 66.3%

Study P002

- **Clinical cure**

Table 31: Analysis of the proportion of subjects with clinical cure (FAS Set Population)

Treatment	% (n/N)	Treatment vs. Placebo		
		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
MK-3415A	72.3 (282/390)	-5.5	-5.5 (-11.6, 0.6)	0.9605
MK-6072	82.5 (326/395)	4.8	4.8 (-0.9, 10.4)	0.0481
Placebo	77.8 (294/378)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
MK-3415A vs. MK-6072		-10.2	-10.3 (-16.1, -4.4)	0.9997

[†] One sided p-value based on the Miettinen and Nurminen method stratified by SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)
n = Number of subjects in the analysis population meeting the criteria for endpoint.
N = Number of subjects included in the analysis population.
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [16.4]

For the MK-6072 treatment group, the clinical cure rate was higher (82.5%) than in the placebo group. The estimated difference between the clinical cure rates for the MK-6072 treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was 4.8% (95% CI: -0.9% to 10.4%, one sided p= 0.0481). A lower proportion of subjects (72.3%) in the MK-3415A group achieved clinical cure of the baseline episode as compared to the placebo group (77.8%). The estimated difference between the clinical cure rates for the MK-3415A treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -5.5% (95% CI: -11.6% to 0.6%, one sided p= 0.9605). As such, there was no evidence to suggest that treatment with MK-3415A or MK-6072 provided additional benefit over standard of care antibiotic alone for the clinical cure of the baseline episode.

- **Diagnosis and severity of new CDI episode**

A total of 217 subjects in the FAS population had a CDI recurrence episode during the 12- week follow-up period. Treatment with MK-3415A and MK-6072 appeared to be associated with CDI recurrences of less severity (as evidenced by the lower maximum number of loose stool counts) and shorter durations (as evidenced by the time to resolution of the new episode) than the initial CDI episode. A higher proportion of subjects treated with MK-3415A (62.1%) or MK-6072 (56.5%) who experienced a CDI recurrence resolved this episode within 2 days of the start of the recurrent episode, as compared with the proportion of placebo subjects (47.4%).

Among subjects for whom ribotype data were available for both their baseline CDI episode and their recurrent episode, approximately 45.0% had the identical ribotype result for both CDI episodes.

Only a small number of the CDI recurrence episodes were severe as assessed by a Zar score $\geq$ 2 (23 subjects, 10.5% overall). The proportion of severe cases was similar among the MK-3415A, MK-6072, and placebo groups (12.1%, 8.1%, and 11.3%, respectively.

No subjects had toxic megacolon or a colectomy, and 2 subjects (1 each in the MK-3415A and placebo groups) died within 30 days following onset of the CDI recurrence.

The proportion of subjects who received such CDI treatment was higher in the placebo group (71.1%) as compared to the MK-3415A and MK-6072 groups (63.8% and 58.1%, respectively.

- **CDI recurrence and C. difficile colonisation in the extension study (12 month)**

There were no formal statistical analyses conducted for the outcome data collected in these subjects after the end of the main study.

In total, three additional subjects experienced a CDI recurrence during the extension phase of the study (2 subjects from the MK-3415A group and 1 subject from the placebo group). These three events occurred between Months 9 and 12 and occurred (by definition) among subjects who were global cures in the main study

There were an additional 4 subjects who are presumed to have had a recurrence during the extension study (1 subject in the MK-3415A group; 1 subject in the MK-6072 group; 2 subjects in the placebo group). These 4 subjects had a positive stool test for toxigenic *C. difficile* at an unscheduled visit, however loose stool counts were not recorded.

- **C. difficile colonisation at the month 6, month 9, and month 12 visits (extension study)**

Table 32: Colonisation status at the month 6 extension Visit (FAS set extension cohort)

	MK-3415A (N=112) n (%)	MK-6072 (N=99) n (%)	Placebo (N=82) n (%)
Colonization			
Yes†	21 (23.6)	20 (24.4)	23 (32.4)
No	68 (76.4)	62 (75.6)	48 (67.6)
Unknown‡	23	17	11

N = number of subjects on Day 91
†"Yes" = toxigenic *C. difficile* isolated from stool sample collected at Month 6 visit.
‡"Unknown" = no sample provided (includes subjects who discontinued before Month 6 and those who did not provide a sample at Month 6, but continued in the study).
MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone
Note: Percentages were calculated based on the number of subjects with data available.

Data Source: [16.4]

Table 33: Colonisation status at the month 9 extension Visit (FAS set extension cohort)

	MK-3415A (N=112) n (%)	MK-6072 (N=99) n (%)	Placebo (N=82) n (%)
Colonization			
Yes†	16 (18.0)	13 (16.3)	13 (18.8)
No	73 (82.0)	67 (83.8)	56 (81.2)
Unknown‡	23	19	13

N = number of subjects on Day 91
†"Yes" = toxigenic *C. difficile* isolated from stool sample collected at Month 9 visit.
‡ "Unknown" = no sample provided (includes subjects who discontinued before Month 9 and those who did not provide a sample at Month 9, but continued in the study).
MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone
Note: Percentages were calculated based on the number of subjects with data available.

Data Source: [16.4]

Table 34: Colonisation status at the month 12 extension Visit (FAS set extension cohort)

	MK-3415A (N=112) n (%)	MK-6072 (N=99) n (%)	Placebo (N=82) n (%)
Colonization			
Yes†	22 (24.7)	13 (16.9)	14 (21.2)
No	67 (75.3)	64 (83.1)	52 (78.8)
Unknown‡	23	22	16

N = number of subjects on Day 91

†"Yes" = toxigenic *C. difficile* isolated from stool sample collected at Month 12 visit.

‡"Unknown" = no sample provided (includes subjects who discontinued before Month 12 and those who did not provide a sample at Month 12, but continued in the study).

MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Note: Percentages were calculated based on the number of subjects with data available.

Data Source: [16.4]

Sensitivity analysis

Table 35: Summary of sensitivity analysis

Sensitivity Analysis Brief Description	Planned vs. Post-hoc	Primary Study Result for Comparison	Key Results from Sensitivity Analysis
Impact of Stratification – No Adjustment for Stratification Factors	Planned	CDI Recurrence MK-6072 vs. Placebo: Diff= -9.9, p=0.0003 MK-3415A vs. Placebo: Diff= -10.7, p<0.0001	CDI Recurrence MK-6072 vs. Placebo: Diff= -10.0, p=0.0003 MK-3415A vs. Placebo: Diff= -10.8, p<0.0001
Subjects with Positive Baseline Culture at Central Laboratory	Planned		CDI Recurrence MK-6072 vs. Placebo: Diff= -15.0, p<0.0001 MK-3415A vs. Placebo: Diff= -12.9, p=0.0003
Impact of Switching Standard of Care Therapy	Planned	rCDI‡: FAS Population MK-6072: 61/379 (16.1%) MK-3415A: 56/360 (15.6%) Placebo: 92/350 (26.3%)	rCDI‡: Subjects with Switch MK-6072: 1/16 (6.3%) MK-3415A: 2/30 (6.7%) Placebo: 5/28 (17.9%)
Impact of Missing Data – Discontinue = Imputed Failure	Planned	CDI Recurrence MK-6072 vs. Placebo: Diff= -9.9, p=0.0003 MK-3415A vs. Placebo: Diff= -10.7, p<0.0001	CDI Recurrence MK-6072 vs. Placebo: Diff= -11.3, p=0.0005 MK-3415A vs. Placebo: Diff= -10.0, p=0.0020
Impact of Missing Data – No Post-randomization Endpoint Data = Imputed Failure	Planned		CDI Recurrence MK-6072 vs. Placebo: Diff= -8.8, p=0.0011 MK-3415A vs. Placebo: Diff= -10.2, p=0.0002
Propensity Score Analysis for Factors Impacting on Clinical Cure	Planned		CDI Recurrence MK-6072 vs. Placebo: Diff=-9.9, p=0.0004 MK-3415A vs. Placebo: Diff=-10.4, p=0.0002
Impact of Standard of Care Duration on Clinical Cure Definition: Expand Allowable SOC Treatment Duration to 28 Days	Planned	(Clinical cure / rCDI‡ / Global cure) MK-6072: 82.5% / 15.7% / 66.8% MK-3415A: 72.3% / 14.9% / 57.4% Placebo: 77.8% / 25.7% / 52.1%	(Clinical cure / rCDI‡ / Global cure) MK-6072: 86.8% / 16.5% / 70.4% MK-3415A: 80.3% / 16.7% / 63.6% Placebo: 82.8% / 27.0% / 55.8%
Impact of Standard of Care Duration on Clinical Cure Definition: Expand Allowable SOC Treatment Duration 42 Days			(Clin cure / rCDI‡ / Global cure) MK-6072: 87.6% / 16.7% / 70.9% MK-3415A: 81.8% / 16.9% / 64.9% Placebo: 83.3% / 27.0% / 56.3%
Impact of Standard of Care Duration on Clinical Cure Definition: Expand Allowable SOC Treatment Duration to Unlimited Days			(Clinical cure / rCDI‡ / Global cure) MK-6072: 87.8% / 16.7% / 71.1% MK-3415A: 82.1% / 16.9% / 65.1% Placebo: 83.9% / 27.0% / 56.9%
Impact of Clinical Cure Definition and Diarrhea Definition on CDI Recurrence Definition	Post Hoc	CDI Recurrence: Primary Endpoint MK-6072: 15.7% MK-3415A: 14.9% Placebo: 25.7%	rCDI‡: Alternate Definitions 1/2/3† MK-6072: 16.7% / 20.8% / 22.0% MK-3415A: 16.7% / 18.7% / 20.5% Placebo: 26.2% / 31.2% / 32.5%

‡ rCDI = recurrent CDI

† see Table 11-26 for alternative definitions

Summary of main studies

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 36: Summary of efficacy for trial P001

Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415 (Human Monoclonal Antibody to *Clostridium difficile* toxin A), MK-6072 (Human Monoclonal Antibody to Clostridium difficile toxin B), and MK-3415A (Human Monoclonal Antibodies to *Clostridium difficile* toxin A and toxin B) in Patients Receiving Antibiotic Therapy for *Clostridium difficile* Infection			
Study identifier	P001		
Design	Randomized, Double-Blind, Placebo-Controlled, Adaptive		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks not applicable not applicable
Hypothesis	Superiority		
Treatments groups	MK-3415A		A single IV infusion of MK-3415 at a dose of 10 mg/kg and MK-6072 at a dose of 10 mg/kg. N = 403 subjects
	MK-3415		A single IV infusion at a dose of 10 mg/kg. N = 242 subjects
	MK-6072		A single IV infusion at a dose of 10 mg/kg. N = 403 subjects
	Placebo		A single IV infusion of 0.9% sodium chloride. N = 404 subjects
Endpoints and definitions	Primary endpoint	CDI recurrence	CDI recurrence is defined as the development of a new episode of diarrhea associated with a positive local or central stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode
	Secondary endpoint	Global cure	Global cure is defined as clinical cure of the baseline CDI episode and no CDI recurrence through Week 12
Database lock	18-02-2015		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Full analysis set: all randomized patients excluding patients who • failed to receive infusion of study medication • had a lack of a positive local stool test for toxigenic *C. difficile* • failed to receive protocol defined standard of care therapy within a 1 day window of the infusion Within 12 weeks after start of treatment				
Descriptive statistics and estimate variability	Treatment group	Placebo	MK-6072	MK-3415	MK-3415A
	Number of subjects	395	386	232	383
	CDI recurrence n (%)	109 (27.6%)	67 (17.4%)	60 (25.9%)	61 (15.9%)
	95%-CI	23.2% - 32.3%	13.7% - 21.5%	20.4% - 32.0%	12.4% - 20.0%

Effect estimate per comparison	CDI recurrence	Comparison groups	MK-3145A vs. placebo		
		Adjusted difference	-11.7%		
		95%-CI	-17.4% - -5.9%		
		P-value (1-sided)	< 0.0001		
		Comparison groups	MK-6072 vs. placebo		
		Adjusted difference	-10.2%		
		95%-CI	-15.9% - -4.3%		
		P-value (1-sided)	0.0003		
		Comparison groups	MK-3415 vs. placebo		
		Adjusted difference	-1.7%		
		95%-CI	-8.6% - 5.5%		
		P-value (1-sided)	0.3182		
		Comparison groups	MK-3415A vs. MK-3415		
		Adjusted difference	-13.7%		
		95%-CI	-22.5% - -5.2%		
		P-value (1-sided)	0.0007		
		Comparison groups	MK-3415A vs. MK-6072		
		Adjusted difference	-1.1%		
		95%-CI	-7.7% - 5.8%		
		P-value (1-sided)	0.3906		
Notes	The treatment effects for MK-3145A, MK-3145 and MK-6072 vs. placebo have to interpreted with caution as the proportion of patients with clinical cure is relevantly lower in the active treatment groups when compared to placebo [placebo: 82.8%; MK-3145A: 74.7% (p=0.006); MK-3145: 72.8% (p = 0.004); MK-6072: 77.5% (p = 0.073)] and patients without clinical cure were considered as having no CDI recurrence for the primary analysis.				
Analysis description	**Secondary Analysis**				
Descriptive statistics and estimate variability	Treatment group	Placebo	MK-6072	MK-3415	MK-3415A
	Number of subjects	395	386	232	383
	Global cure n (%)	218 (55.2%)	232 (60.1%)	109 (47.0%)	225 (58.7%)
	95%-CI	50.1% - 60.2%	55.0% - 65.0%	40.4% - 53.6%	53.6% - 63.7%
Effect estimate per comparison	Global cure	Comparison groups	MK-3145A vs. placebo		
		Adjusted difference	3.6%		
		95%-CI	-3.5% - 10.4%		
		P-value (1-sided)	0.1646		
		Comparison groups	MK-6072 vs. placebo		
		Adjusted difference	4.8%		
		95%-CI	-2.1% - 11.7%		
		P-value (1-sided)	0.0861		
		Comparison groups	MK-3145 vs. placebo		

		Adjusted difference	-8.3%		
		95%-CI	-16.3% - -0.2%		
		P-value (1-sided)	0.9775		
Analysis description	**Supportive Analysis**				
Analysis population	All patients from the FAS with clinical cure of the initial episode				
Descriptive statistics and estimate variability	Treatment group	Placebo	MK-6072	MK-3415	MK-3415A
	Number of subjects	327	299	169	286
	CDI recurrence n (%)	109 (33.3%)	67 (22.4%)	60 (35.5%)	61 (21.3%)
	95%-CI	28.2% - 38.7%	17.8% - 27.6%	28.3% - 43.2%	16.7% - 26.5%
Effect estimate per comparison	CDI recurrence	Comparison groups	MK-3145A vs. placebo		
		Adjusted difference	-11.7%		
		95%-CI	-18.6% - -4.7%		
		P-value (1-sided)	0.0006		
		Comparison groups	MK-6072 vs. placebo		
		Adjusted difference	-10.8%		
		95%-CI	-17.7% - -3.8%		
		P-value (1-sided)	0.0013		
		Comparison groups	MK-3145 vs. placebo		
		Adjusted difference	1.7%		
		95%-CI	-6.9% - 10.7%		
		P-value (1-sided)	0.6505		

Table 37: Summary of efficacy for trial P002

Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to *C. difficile* toxin B), and MK-3415A (Human Monoclonal Antibodies to *C. difficile* toxin A and B) in Patients Receiving Antibiotic Therapy for *C. difficile* Infection (MODIFY II)		
Study identifier	P002	
Design	Randomized, Double-Blind, Placebo-Controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable 12 months (+ 9 months following main study)
Hypothesis	Superiority of either MK-3415A or MK-6072 over placebo	
Treatments groups	MK-3415A	A single IV infusion of MK-3415 at a dose of 10 mg/kg and MK-6072 at a dose of 10 mg/kg. N = 397 subjects
	MK-607	A single IV infusion at a dose of 10 mg/kg. N = 407 subjects

	Placebo		A single IV infusion of 0.9% sodium chloride. N = 399 subjects
Endpoints and definitions	Primary endpoint	CDI recurrence	CDI recurrence is defined as the development of a new episode of diarrhea associated with a positive local or central stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode
	Secondary endpoint	Global cure	Global cure is defined as clinical cure of the baseline CDI episode and no CDI recurrence through week 12
Database lock	13-04-2015 (main study) / 10-08-2015 (extension study)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set: all randomized patients excluding patients who • failed to receive infusion of study medication • had a lack of a positive local stool test for toxigenic C. difficile • failed to receive protocol defined standard of care therapy within a 1 day window of the infusion Within 12 weeks after start of treatment			
Descriptive statistics and estimate variability	Treatment group	Placebo	MK-6072	MK-3415A
	Number of subject	378	395	390
	CDI recurrence n (%)	97 (25.7%)	62 (15.7%)	58 (14.9%)
	95%-CI	21.3% - 30.4%	12.3% - 19.7%	11.5% - 18.8%

Effect estimate per comparison	CDI recurrence	Comparison groups	MK-3415A vs. placebo
		Adjusted difference	-10.7%
		95%-CI	-16.4% - -5.1%
		P-value (1-sided)	< 0.0001
		Comparison groups	MK-6072 vs. placebo
		Adjusted difference	-9.9%
		95%-CI	-15.5% - -4.3%
		P-value (1-sided)	0.0003
		Comparison groups	MK-3145A vs. MK-6072
		Adjusted difference	-0.8%
		95%-CI	-5.9% - 4.2%
		P-value (1-sided)	0.3718

Analysis description	**Secondary Analysis**			
Descriptive statistics and estimate variability	Treatment group	Placebo	MK-6072	MK-3415A
	Number of subject	378	395	390
	Global cure n (%)	197 (52.1%)	264 (66.8%)	224 (57.4%)
	95%-CI	46.9% - 57.2%	62.0% - 71.5%	52.4% - 62.4%

	Global cure	Comparison groups		MK-3415A vs. placebo
		Adjusted difference		5.3%
		95%-CI		-1.8% - 12.2%
		P-value (1-sided)		0.0722
		Comparison groups		MK-6072 vs. placebo
		Adjusted difference		14.7%
		95%-CI		7.7% - 21.4%
		P-value (1-sided)		< 0.0001
Analysis description	**Supportive Analysis**			
Analysis population	All patients from the FAS with clinical cure of the initial episode			
Descriptive statistics and estimate variability	Treatment group	Placebo	MK-6072	MK-3415A
	Number of subject	294	326	282
	CDI recurrence n (%)	97 (33.0%)	62 (19.9%)	58 (20.6%)
	95%-CI	27.6% - 38.7%	14.9% - 23.7%	16.0% - 25.8%
Effect estimate per comparison	CDI recurrence	Comparison groups		MK-3415A vs. placebo
		Adjusted difference		-11.9%
		95%-CI		-19.0% - -4.7%
		P-value (1-sided)		0.0006
		Comparison groups		MK-6072 vs. placebo
		Adjusted difference		-13.7%
		95%-CI		-20.4% - -6.9%
		P-value (1-sided)		< 0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

Table 38: Summary of efficacy analyses Phase 3 studies (Study P001 + Study P002 Integrated) FAS Population

	MK-3415A (acto/bezlo) N=773	MK-6072 (bezlo) N=781	Placebo N=773
Primary Endpoint			
CDI Recurrence	119/773 (15.4%)	129/781 (16.5%)	206/773 (26.6%)
Secondary Endpoints			
CDI Recurrence, among subjects who attained clinical cure	119/568 (21.0%)	129/625 (20.6%)	206/621 (33.2%)
Global Cure	449/773 (58.1%)	496/781 (63.5%)	415/773 (53.7%)
CDI Recurrence by Subgroup†			
SoC Therapy (stratification variable)			
Metronidazole	54/380 (14.2%)	56/379 (14.8%)	85/374 (22.7%)
Vancomycin	61/369 (16.5%)	67/372 (18.0%)	114/373 (30.6%)
Fidaxomicin	4/24 (16.7%)	6/30 (20.0%)	7/26 (26.9%)
Hospitalization Status (stratification variable)			
Inpatient	75/523 (14.3%)	73/530 (13.8%)	120/520 (23.1%)
Outpatient	44/250 (17.6%)	56/251 (22.3%)	86/253 (34.0%)
History of CDI in the past 6 months			
Yes	45/200 (22.5%)	54/216 (25.0%)	90/219 (41.1%)
No	72/557 (12.9%)	75/556 (13.5%)	114/545 (20.9%)
Infected with 027 Ribotype			
Yes	9/76 (11.8%)	21/89 (23.6%)	34/100 (34.0%)
No	68/400 (17.0%)	65/397 (16.4%)	112/384 (29.2%)
Infected with Epidemic‡ Strain			
Yes	38/222 (17.1%)	44/210 (21.0%)	75/233 (32.2%)
No	39/254 (15.4%)	42/276 (15.2%)	71/251 (28.3%)
Infected with Hypervirulent‖ Strain			
Yes	13/90 (14.4%)	22/102 (21.6%)	37/115 (32.2%)
No	64/386 (16.6%)	64/384 (16.7%)	109/369 (29.5%)
Severe CDI at study entry			
Yes	17/142 (12.0%)	13/122 (10.7%)	28/125 (22.4%)
No	97/591 (16.4%)	110/629 (17.5%)	169/613 (27.6%)
Age at study entry			
< 65 Years	43/332 (13.0%)	69/391 (17.6%)	79/368 (21.5%)
≥ 65 Years	76/441 (17.2%)	60/390 (15.4%)	127/405 (31.4%)
Immunocompromised status			
Yes	20/153 (13.1%)	26/169 (15.4%)	41/145 (28.3%)
No	99/620 (16.0%)	103/612 (16.8%)	165/628 (26.3%)
Exploratory Endpoints			
Clinical Cure	568/773 (73.5%)	625/781 (80.0%)	621/773 (80.3%)
Diarrhea Recurrence	200/773 (25.9%)	213/781 (27.3%)	290/773 (37.5%)

† Number of subjects in each subgroup may not add to the total number of subjects with CDI recurrence, as those with unknown responses for each category were excluded from the respective subgroup analysis.
‡ Epidemic strain includes the following: 027, 014, 002, 001, 106, or 020 ribotypes
‖ Hypervirulent strain included the following: 027, 078, or 244 ribotypes
SoC = Standard of Care, MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [Ref. 5.3.5.1: P001, P002]

Table 39: Clinical cure by baseline endogenous antibody titres Phase 3 Studies (P001 + P002 Integrated) FAS Set Population

	MK-3415A (acto/bezlo) N=773 % (n/m)	MK-6072 (bezlo) N=781 % (n/m)	Placebo N=773 % (n/m)
Overall Clinical Cure	73.5 (568/ 773)	80.0 (625/ 781)	80.3 (621/ 773)
Endogenous Antibody A†			
Low	73.0 (143/196)	81.7 (215/263)	80.2 (227/283)
Medium	74.1 (332/448)	80.9 (338/418)	80.3 (305/380)
High	70.5 (79/112)	72.9 (62/ 85)	79.3 (73/ 92)
Missing	82.4 (14/ 17)	66.7 (10/ 15)	88.9 (16/ 18)
Endogenous Antibody B‡			
Low	74.5 (172/231)	86.9 (213/245)	79.5 (229/288)
Medium	74.3 (266/358)	82.2 (278/338)	81.4 (267/328)
High	70.0 (119/170)	68.3 (123/180)	77.0 (104/135)
Missing	78.6 (11/ 14)	61.1 (11/ 18)	95.5 (21/ 22)

Data in cells: % (n/m) where n = Number of subjects within subgroup and m = Number of subjects within subgroup that met the criteria for endpoint.
† Serum endogenous IgG antibody to *C. difficile* toxin A.
‡ Serum endogenous IgG antibody to *C. difficile* toxin B.
Low = "<=1:1000", Medium = "1:5000", High = ">=1:25000" and Missing = endogenous antibody result is missing.
MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [Ref. 5.3.5.1: P001, P002]

Table 40: Global cure by baseline endogenous antibody titres Phase 3 Studies (P001 + P002 Integrated) FAS Set Population

	MK-3415A (acto/bezlo) N=773 % (n/m)	MK-6072 (bezlo) N=781 % (n/m)	Placebo N=773 % (n/m)
Overall Global Cure	58.1 (449/ 773)	63.5 (496/ 781)	53.7 (415/ 773)
Endogenous Antibody A†			
Low	57.1 (112/196)	66.2 (174/263)	52.7 (149/283)
Medium	59.2 (265/448)	63.2 (264/418)	56.3 (214/380)
High	53.6 (60/112)	57.6 (49/ 85)	43.5 (40/ 92)
Missing	70.6 (12/ 17)	60.0 (9/ 15)	66.7 (12/ 18)
Endogenous Antibody B‡			
Low	61.0 (141/231)	73.5 (180/245)	48.6 (140/288)
Medium	56.4 (202/358)	61.8 (209/338)	54.9 (180/328)
High	57.1 (97/170)	53.9 (97/180)	60.0 (81/135)
Missing	64.3 (9/ 14)	55.6 (10/ 18)	63.6 (14/ 22)

Data in cells: % (n/m) where n = Number of subjects within subgroup and m = Number of subjects within subgroup that met the criteria for endpoint.
† Serum endogenous IgG antibody to *C. difficile* toxin A.
‡ Serum endogenous IgG antibody to *C. difficile* toxin B.
Low = "<=1:1000", Medium = "1:5000", High = ">=1:25000" and Missing = endogenous antibody result is missing.
MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [Ref. 5.3.5.1: P001, P002]

Clinical studies in special populations

Age

Geriatric patients (≥ 65 years) comprised over half (51%) of the analysis population in the Phase 3 trials and included a substantial number (29%) of patients ≥ 75 years of age.

CDI recurrence rates were similar in elderly (≥ 65, 15%), very elderly (≥ 75, 16%), and non-elderly (< 65, 18%) patients treated with 10 mg/kg bezlotoxumab.

Race

CDI recurrence rates were similar in white (17%) patients versus all other races (15%) treated with 10 mg/kg bezlotoxumab.

Renal impairment

Renal impairment was defined as serum creatinine ≥ 1.5 mg/dL at study entry. A lower proportion of subjects with renal impairment experienced a CDI recurrence in the bezlotoxumab group (13.8%, 17/123) as compared to the placebo group (22.7%); the adjusted difference was -8.9% (95% CI: -19.1% to 1.0%). The 95% CI was wide, reflecting the small size of the study population with renal impairment.

CDI recurrence rates were similar regardless of renal function in patients treated with 10 mg/kg bezlotoxumab.

Hepatic impairment

Hepatic impairment was defined as having two or more of the following at study entry: (a) albumin <3.1 g/dL, (b) ALT >2X ULN, (c) total bilirubin >1.3X ULN, or (d) mild, moderate or severe liver disease (as reported in the Charlson Comorbidity Index). Among subjects with hepatic impairment, CDI recurrence rates were 12.2% (6/49) in the bezlotoxumab group versus 11.4% (5/44) in the placebo group; the adjusted difference was -0.9% (95% CI: -13.6% to 14.8%). The small difference was driven by the low CDI recurrence rate in the placebo arm. While CDI recurrence rate remained low in the bezlotoxumab arm of the hepatic insufficiency subgroup, the rate in the placebo arm was substantially lower than that seen in the overall placebo population (26.6%).

Presence of comorbid conditions

The effect of comorbid conditions at the time of study entry as assessed in the Charlson Comorbidity Index was evaluated.

CDI recurrence rates were similar in patients with Charlson Comorbidity Index ≥ 3 (14%) or < 3 (18%).

Supportive studies

Two phase 2 studies (Study P018 and Study P017) either related to monotherapy with actoxumab (Study CA-CDA1-05-02 (Protocol 018)) or combination therapy with actoxumab and bezlotuxumab (Protocol 0017) were included in the application. Since these studies do not contribute to the efficacy evaluation of bezlotuxumab, they are not included in the overview.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two similar Phase 3 studies (Study P001 and Study P002) were submitted to support the efficacy of bezlotoxumab (MK-6072) for the prevention of CDI recurrence. The studies were designed to evaluate two different monoclonal antibodies, actoxumab (MK-3415), directed against *C. difficile* toxin A, bezlotuxumab, directed against *C. difficile* toxin B as well as the combination of the two antibodies (MK-3415A). However based on the results of the clinical studies, the Applicant pursues a MAA for bezlotoxumab only. The two studies included a total of 810 randomised subjects in the bezlotoxumab group and 803 randomised subjects in the placebo group. The aim of the studies was to demonstrate superiority of bezlotoxumab plus standard-of-care antibiotics versus placebo plus standard of care antibiotics in adult subjects with CDI based on the difference in recurrence rates of CDI during a time period of 12 weeks.

The study participants are subjects with confirmed CDI, including those with multiple previous episodes of CDI. However, the majority of the enrolled patients did not have a past history of CDI (approximately 65%). The definition of CDI includes laboratory confirmation of toxigenic *C. difficile* infection. This describes an appropriate target population.

Standard of Care (SoC) antibiotic for the treatment of the baseline episode of CDI was at the discretion of the treating physician. Although the protocol referenced the IDSA/SHEA guidelines regarding the choice of SoC antibiotic, the protocols did not mandate that these guidelines be followed. It was anticipated that North American sites would likely follow the IDSA/SHEA guidelines regarding the choice of SoC antibiotic, while the EU sites would likely follow the ESCMID guidelines. Although the treatment recommendations regarding which SoC antibiotics to use for mild-moderate, severe, and severe-complicated CDI in these two sets of guidelines were generally similar, the Phase 3 protocols allowed flexibility in the choice of doses to account for some differences in local practices, with caveat that the total daily dose and duration of treatment was in accordance with the protocols.

Patients were randomised to receive a single infusion 10 mg/kg infusion of bezlotoxumab or actoxumab or placebo, or actoxumab + bezlotoxumab 10 mg/kg each. No dose response studies were performed. The dose for the early development program was based on non-clinical data. The 10 mg/kg dose selected for the Phase 3 studies is based on data derived from pre-clinical studies, PK-trials in healthy subjects and the Phase 2 clinical trials.

The primary endpoint was CDI recurrence, defined as the development of a new episode of diarrhoea (3 or more loose stools in 24 or fewer hours) associated with a positive local or central lab stool test for toxigenic *C. difficile* following clinical cure of the initial CDI episode. Subjects not meeting the clinical cure endpoint were not assessable for the CDI recurrence endpoint and were considered as not having CDI recurrence.

Secondary endpoints included CDI recurrence in a subset of the FAS population who achieved clinical cure, global cure (clinical cure of the baseline episode and no CDI recurrence) and CDI recurrence in

some chosen subgroups (i.e., with/without history of CDI in the 6 months prior to enrolment, infection with/without 027 strain, with/without hypervirulent strain, with/without clinically severe CDI at study entry, <65 years and ≥ 65 years and with/without compromised immunity). Several exploratory endpoints were also examined.

As part of CDI diagnosis subjects were required to have diarrhoea, defined as at least 3 bowel movements with loose stools (Bristol Stool Charts types 5-7) within a 24-hours period. The Applicant provided evidence that the Bristol Stool Chart is widely used as a tool for CDI diagnostic. The definition for diarrhoea is consistent with the European Society of Clinical Microbiology CDI Treatment Guidance. In the context of the clinical development program the Bristol Stool Form Chart was validated in a pilot study, including patients from 48 to 78 years of age. The patients were to record a stool count log and were contacted every day through Day 14 by study personnel (less frequently after Day 14). The Applicant detailed the measures performed to ensure that the recall bias was minimised and diarrhoea reporting was appropriate. Altogether less than 1% of subjects had < 3 loose stools at qualification or had a response of 'unknown' or 'missing.

CDI severity was defined on basis of data from Zar *et al.* (Clin Infect Disease 2007:45(3):302-7). There is some evidence from literature that the Zar Score is comparable to the CDI severity criteria recommended by the IDSA/SHEA and there is consensus that both scores appropriately measure CDI severity (Gomez-Simmonds *et al.,* 2014).

No literature reports in which a cohort of CDI patients were simultaneously assessed for severity based on the Zar scale and the ESCMID criteria are available, however assessments of CDI patient cohorts using the IDSA/SHEA and ESCMID severity criteria have been reported from two groups (Starzengruber *et al.,* 2014 and Khanafer *et al.,* 2016); both authors comment that the ESCMID definition might lead to a overestimation of severe CDI in their patient collective.

The proportion of P001 and P002 subjects with severe CDI is lower than those described in previously published reports on hospitalized CDI patients. The Applicant relates this finding to the study design *e.g.* many patients were enrolled in the trials after initiation of standard of care (SoC) antibiotic therapy and severity was assessed at the time of randomization into the study. This explanation is accepted.

Analyses of efficacy in patients with Zar Score ≥ 3 vs. patients with Zar Score < 3 and efficacy in patients with severe CDI according to the ESCMID definition were provided:

a) Subjects with Zar Score > 3 showed regarding CDI recurrence among clinical cure subset, Global Cure and Clinical Cure, favourable results in the placebo group, albeit not statistically significant.

b) The analysis of the subgroup of patients with severe CDI or at increased risk of developing severe CDI according to the ESCMID definition suggested that no effect of bezlotoxumab was seen in patients with "no risk" or "unknown risk" (except for Global Cure).

It is acknowledged that to date the Zar scale is an appropriate tool to measure CDI severity; and that the scale defines severe CDI based on a score > 2. The Zar score correlates with severity criteria recommended by the IDSA/SHEA. Although the observed efficacy outcome is to some extent dependent on the definition of CDI, it is accepted that efficacy has been demonstrated in patients with severe CDI (Zar Score >2).

However, it is observed that a limited number of patients having a severe type of CDI or harbouring prognostic risk factors of developing severe CDI were included in the FAS population. Around 80% of the patients had Zar score < 2, indicating a less severe CDI. The design of the studies might possibly have influenced the number of patients with e.g. fever and/or elevated WBC count (factors that are

included in the Zar scale) as it was allowed to start SoC therapy before entering the study and receiving bezlotoxumab. It is also acknowledged, that in addition to the rating of the Zar score, there were patients included who were immunocompromised, infected with hypervirulent strains and who had co-morbidities, which also contribute as factors implying severe CD infection and/or increased risk of severe CD infection.

The applicant provided an analysis of the efficacy of bezlotoxumab by risk groups: analysis for patients with or without pre-defined risk factors, indicating that all patients could possibly be at risk for CDI recurrence and that bezlotoxumab reduces the recurrence rates in all groups. However, for patients with no predefined risk factors, the risk difference for CDI recurrence between bezlotoxumab and placebo groups was marginal (difference of -1.7% vs. placebo and the 95% CI included zero [-9.2, 5.7] indicating no difference between the two treatment groups). The fact that the total number stated by the applicant as having no predefined risk factors is limited (193 patients in the bezlotoxumab group vs. 191 patients in the placebo group) compared to the number of patients having at least 1 pre-defined risk factor (588 in the bezlotoxumab group vs. 582 in the placebo group), makes the analysis concerning patients with “no risk factors” uncertain. The Applicant further argues that although the risk difference for CDI between bezlotoxumab and placebo among patients with no pre-defined risk factors is small, these patients might further benefit from bezlotoxumab treatment by having less severe recurrent CDI episodes. To support this claim a post-hoc analysis on severity was performed (data not shown in this report). However, this analysis is based on very few patients (29 patients in the bezlotoxumab group vs. 32 in the placebo group). Therefore, firm conclusions are not possible to draw based on these limited data. Furthermore, it is only the rate of CDI recurrence that is studied by the primary endpoint and prevention of CDI recurrence that is applied for as an indication. Statements indicating that bezlotoxumab might affect the symptoms of the infection and/or lighten the clinical course of a new episode of CDI, remain speculative.

In general, the statistical analysis methods are considered acceptable. Although there is a concern regarding the chosen primary endpoint (CDI recurrence), additional analyses are re-assuring (concordant with the result of the primary analysis), and thus support the claimed efficacy of bezlotoxumab.

In both studies, a number of subjects (45 % in Study P001 and 37.1 % in Study P002) had at least one or more major protocol deviation. These protocol violations were related to clinical supplies, efficacy assessment, entry criteria, informed consent, prohibited medications and safety assessment. The Applicant provided a detailed assessment of major protocol deviations and the impact on the efficacy. Also GCP findings for a specified site (Study 001, site 0058) and subsequent action were explained, i.e. all subjects from this site were removed from the FAS population and thus not contained within the calculation of the efficacy endpoints.

Efficacy data and additional analyses

The treatment groups were generally well matched with respect to gender, age, ethnicity, race, weight, BMI and disease characteristics. The majority of the enrolled subjects were female, white and recruited from outside the US (whereof 40 % from Europe) and were older than 65 years (however, around 70% was < 75 years) as is expected for subjects with CDI. Regarding the demographic characteristics the target population is well represented.

There was an approximately similar distribution between patients receiving oral metronidazole (around 45-46% in the two treatment groups) and oral vancomycin (ca. 41% in each arm) in both studies. Few patients received fidaxomicin (< 4% in each treatment group). Across the studies and the treatment groups there were few patients who needed to switch antibiotic therapy during the study (< 8 %).

Median and mean duration for SoC therapy were 14 days, which is in line with the protocol. There was a slight trend that patients receiving vancomycin had longer duration of therapy compared to those receiving metronidazole. Days on SoC therapy prior to study drug infusion was median 3 days.

A limited number of patients having a severe type of CDI or harbouring prognostic risk factors of developing severe CDI were included in the FAS population. This was valid for both treatment groups in both studies. The majority of the patients did not have a past history of CDI in the past 6 months (ca. 70%); did not have a prior history of CDI ever: the number of past CDI episodes was 0 in around 65% of the enrolled patients. A percentage of 19.2% in the bezlotoxumab group vs. 17.1% in the placebo group had 1 CDI episode in the past. Around 80% of the patients had Zar score < 2, indicating a less severe CDI. The analyses of different hypervirulent strains, epidemic strains and the 027 ribotype were hampered by large number of unknowns (ca. 38% in both arms for the different categories). Of the known samples, most patients did not have these strains (most evident for the 027 ribotype and hypervirulent strains with approximately 50% of participants in both arms not harbouring these strains). Around 80% of the included patients in both study arms did not have compromised immunity. There were also very few patients with elevated temperature, impaired renal and/or hepatic function and other serious conditions like pseudomembranous colitis, toxic megacolon, bowel perforation, ileus, or who required a colectomy or other surgery due to complications of CDI. Approximately 25-30% of the patients in the two treatment groups had elevated WBC count at baseline. Around 65% of the patients in both arms were categorised with hospitalisation status inpatient. Around half of the patients in the two groups had prior use of systemic antibiotics (> 50%) and proton pump inhibitors (PPIs) (ca. 50%); for concomitant systemic antibiotic use, the proportion was nearly 40 % and for PPIs around 50%.

Overall, these factors indicate that the enrolled patients might constitute a population with mild to moderate CDI.

CDI recurrence

The primary endpoint for both studies is the proportion of subjects with CDI recurrence through the Week 12. In Study P001 a lower proportion of subjects had CDI recurrence in the MK-6072 group (17.4%) as compared to the placebo group (27.6%). The estimated difference between the MK-6072 group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -10.1% (95% CI: -15.9% to -4.3%, one-sided p = 0.0003). In Study P002 a lower proportion of subjects had CDI recurrence in the MK-6072 group (15.7%) as compared to the placebo group (25.7%). The estimated difference between the MK-6072 group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -9.9% (95% CI: -15.5% to -4.3%, one-sided p = 0.0003).

Taken into consideration that it is doubtful whether the included patient population can be claimed to be the main target population, the clinical relevance of the observed difference between bezlotoxumab and placebo is debatable. In addition, subgroup analyses indicate that patients with less severe CDI or with few/no risk factors of developing severe CDI show low or no effect of bezlotoxumab compared to placebo. Although results from subgroup and post-hoc analyses should be interpreted with caution, it seems that the efficacy outcome is to some degree dependent on the severity of the manifested CD infection or the number of risk factors the patient harbours for developing a severe CDI. Thus, the appropriate target population needs to be further elucidated (see further: “Additional Expert Consultation”).

It is also noted that the results are not in favour of bezlotoxumab for the subgroup age < 65 years and men. It is known from several published articles that age ≥ 65 years and also female gender are prognostic factors in regards to both higher incidences of CDI and higher risk of CDI recurrence and this could therefore have had an impact on the results. Notably the known gender and age differences were reflected in the results presented for the placebo groups, but were less pronounced in the new drug investigational groups. These results should however be interpreted with caution.

Global cure

Given the limitation of the primary endpoint, the secondary endpoint "global cure" is deemed more relevant. In Study P001 numerically higher proportion of subjects achieved global cure in the MK-6072 (60.1%) treatment group as compared to the placebo group (55.2%). However, differences between the MK-6072 group versus the placebo group did not reach statistical significance (one sided p = 0.0861).

An improved outcome was obtained in Study P002 for the secondary endpoint of global cure for the comparison between the MK-6072 group (66.8%) and the placebo group (52.1%, one-sided p <0.0001). However, due to the pre-defined testing strategy, this p-value has to be interpreted as a signal only.

Clinical cure

Clinical cure was an exploratory endpoint; however as a pre-requisite for proper assessment of CDI recurrence as well from a patient's perspective the impact on the baseline episode i.e. clinical cure is considered as an important efficacy parameter.

In Study P001, a lower proportion of subjects achieved clinical cure of the baseline episode in the MK-6072 group (77.5 %) and in the MK-3415A group (74.7%) as compared to placebo treated patients (82.2%). The estimated difference between the MK-6072 treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -5.3% (95% CI: -10.9% to 0.3%, one sided p= 0.9679). The estimated difference between the MK-3415A treatment group and the placebo group, adjusted for stratification factors of hospitalization status and standard of care therapy, was -8.2% (95% CI: -13.9% to -2.4%).

In Study P002 the clinical cure rate for MK-6072 treatment (82.5%) was higher than for placebo (77.8 %) without reaching statistical significance.

The study design did not allow a proper assessment of clinical cure. In both studies a considerable number of subjects (i.e. 25.4 % in Study P001 and 30% in Study P002) were already for more than 5 days on SOC prior to study treatment. In previous studies, resolution of diarrhoea by day 6 of treatment and clearance of *Clostridium difficile* toxin at day 6 and 10 was the study endpoint (Zar *et al.,* Clin Infect Disease 2007:45(3):302-7). It might be well possible that bezlotoxumab therapy was initiated after resolution of the baseline episode in some patients while others were still suffering from the baseline episode.

Although no indication is claimed for "clinical cure", nevertheless an effect on the baseline episode is deemed as clinical relevant. Interestingly, presence of endogenous antibodies (eAbs) at baseline, indicate some influence on clinical cure and global cure (Tables 43 & 44). Nevertheless, there seems no obvious biological mechanisms for eAb-B to negatively impact clinical cure and the data have to be interpreted with caution due to methodological constraints (e.g. type of analysis, scope of analysis).

Additional expert consultation

A Scientific Advisory Meeting was organised to address the following concerns:

- Identification of the appropriate target population
- The efficacy results for the primary endpoint, herein, the clinical relevance of the observed difference of 10% between bezlotoxumab and placebo and how these results should be interpreted.
- Place in the therapy given the fact that bezlotoxumab will be administered during a CDI episode without having an influence on the actual episode (the patient even might not survive) and preventing only further episodes up to about 12 weeks afterwards.
- Higher failure rate (clinical cure) in the bezlotoxumab group in subjects with higher baseline endogenous antibody B level

- **Identification of the appropriate target population**

The applicant argued that based on the totality of the data, patients at **high risk** for CDI recurrence are the appropriate target population for bezlotoxumab.

The experts concurred with the applicant that indeed the target population to receive bezlotoxumab in order to prevent relapse in a 12 week period following treatment of CDI episode, constitutes the high risk group as identified by the applicant. However, severity based on Zar score (Zar *et al*. Clin Infect Dis 2007) is considered not universally applied within the EU clinical setting, and severity should not be defined unequivocally as such.
Thus, aimed high risk groups for preventing CDI recurrence would conform with European guidance (ESCMID) on “high risk” categories and the actual population studied in clinical trials:

- age >65 years

- history of previous CDI episode(s)

- immunocompromised population

- hypervirulent strains, also including ribotype 027

- Severe CDI

- **The efficacy results for the primary endpoint, herein, the clinical relevance of the observed difference of 10% between bezlotoxumab and placebo and how these results should be interpreted.**

The applicant concluded that a single dose of 10 mg /kg Bezlotoxumab was efficacious in preventing CDI recurrence through 12 weeks follow-up period, in patients receiving standard of care (SoC) antibiotics

The experts considered the methodological limitations of the trials in receiving this outcome (for primary outcome measure, "recurrence rate", those not initially cured from CDI episode would not relapse and be categorised as a success). A better informed picture emerged from the secondary clinical endpoint, global cure, showing treatment arm difference with borderline statistical significance obtained for one of the two pivotal trials. Nevertheless, experts were united in concluding that meaningful clinical relevant results were obtained in the pivotal trials, although the extent of actual benefit would only be established once the drug has been used more widely.

- **Place in the therapy given the fact that bezlotoxumab will be administered during a CDI episode without having an influence on the actual episode (the patient even might not survive) and preventing only further episodes up to about 12 weeks afterwards.**

The applicant considered that physicians will prescribe bezlotoxumab for patients expected to survive the presenting CDI episode. It was also considered that the risk for recurrence is highest in the period immediately after SoC is completed.

The experts agreed that the administration in great deal will be subject to the physician's professional judgement /discretion. It would be futile to administer bezlotoxumab to a patient hardly expected to survive the initial CDI episode.

No data are however available on future re-administration (2^{nd}, 3^{rd}, 4^{th} course) in subsequent CDI recurrences (after substantial time lapse) and hence it might be helpful to spell out this limitation in the Product Information.

- **Higher failure rate (clinical cure) in the bezlotoxumab group in subjects with higher baseline endogenous antibody B level.**

The experts considered this issue as an area of uncertainty which mechanistically could not be well explained and the data not so robust. In principle, further exploration of the relevance of circulating endogenic Ab against toxin B (IgG type) on clinical cure would be of interest also in light of future possible introduction of vaccines against *C. difficile*. It is however doubtful if conducting any dedicated study at this stage would be feasible or appropriate.

Overall, the group remained divided in its recommendation. Some experts did not support drawing attention of the prescriber to this issue, whilst others supported the idea that the scientific observation would benefit of further exploration (as it may be an early clinical signal of which prescribers should be aware) and thus also to be flagged in the Product Information.

2.5.4. Conclusions on the clinical efficacy

A single dose of 10 mg /kg Bezlotoxumab was efficacious in preventing CDI recurrence through 12 weeks follow-up period, in patients receiving standard of care (SoC) antibiotics. Notwithstanding stated methodological limitations (e.g. enrolled population mainly suffered mild to moderate CDI; responder imputation approach), meaningful clinical relevant results were obtained in the pivotal trials. Based on the totality of the data, and outcome of the additional expert consultation, it is concluded that patients at high risk for CDI recurrence (as identified in the trials, but excluding scoring systems) constitute the appropriate target population to receive bezlotoxumab.

2.6. Clinical safety

Patient exposure

Table 41: Summary of subject exposure with bezlotoxumab, actoxumab + bezlotoxumab, or placebo

Treatment	Phase 1[†]	Phase 2[‡]	Phase 3[§]	Total Number of Subjects[‖]
Bezlotoxumab alone	30	-	786	816
Actoxumab + Bezlotoxumab	96	101	777	974
Placebo	12	99	781	892
Total	138	200	2344	2682

[†] P020, P005, P006, and P004 are included in this safety summary. P019 is not included in this safety summary.

[‡] P017 is included in this safety summary. P018 had 17 subjects in the placebo group that are not included in this safety summary.

[§] P001 and P002 are included in this safety summary.

[‖] Includes healthy volunteers and patients with CDI.

The safety assessment of bezlotoxumab is based on the two phase 3 studies, Study P001 and Study P002.

During the Phase 1 clinical program, conducted in healthy volunteers, all but 30 subjects were exposed either actoxumab (MK-3415) alone or actoxumab + bezlotuxomab (MK-3415A). The 30 subjects enrolled in the Phase 1 Studies received 0.3, 1, 3, 10 and 20 mg/kg bezlotoxumab (N=6/cohort).

The same is true for the Phase 2 studies; subjects were either receiving actoxumab (MK-3415) alone or actoxumab + bezlotuxomab (MK-3415A). In general, these data are not contributing to the safety profile of bezlotuxomab (MK-6072).

In two Phase 3 studies, 786 subjects with a confirmed diagnosis of CDI received a 10 mg/kg dose of bezlotoxumab and 781 received placebo (0.9% NaCl). Additionally, 30 healthy subjects were exposed to bezlotoxumab in a Phase 1 study.

Adverse events

In the Phase 3 trials (Study P001, and Study P002), non-serious AEs were collected from the time of study medication infusion until Week 4 post-infusion

Table 42: Subjects with adverse events during 4 weeks following infusion (incidence ≥ 2% in one or more treatment groups) phase 3 studies (Study P001 + Study P002 integrated) APaT Population

	MK-3415A (acto/bezlo)		MK-6072 (bezlo)		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	777		786		781		2,344	
with one or more adverse events	455	(58.6)	485	(61.7)	478	(61.2)	1,418	(60.5)
with no adverse events	322	(41.4)	301	(38.3)	303	(38.8)	926	(39.5)
Blood and lymphatic system disorders	**31**	**(4.0)**	**31**	**(3.9)**	**26**	**(3.3)**	**88**	**(3.8)**
Cardiac disorders	**29**	**(3.7)**	**29**	**(3.7)**	**39**	**(5.0)**	**97**	**(4.1)**
Gastrointestinal disorders	**176**	**(22.7)**	**191**	**(24.3)**	**161**	**(20.6)**	**528**	**(22.5)**
Abdominal pain	32	(4.1)	34	(4.3)	34	(4.4)	100	(4.3)
Constipation	16	(2.1)	15	(1.9)	10	(1.3)	41	(1.7)
Diarrhoea	46	(5.9)	47	(6.0)	45	(5.8)	138	(5.9)
Nausea	47	(6.0)	52	(6.6)	39	(5.0)	138	(5.9)
Vomiting	24	(3.1)	31	(3.9)	21	(2.7)	76	(3.2)
General disorders and administration site conditions	**108**	**(13.9)**	**118**	**(15.0)**	**101**	**(12.9)**	**327**	**(14.0)**
Fatigue	21	(2.7)	18	(2.3)	12	(1.5)	51	(2.2)
Oedema peripheral	15	(1.9)	19	(2.4)	14	(1.8)	48	(2.0)
Pyrexia	31	(4.0)	36	(4.6)	27	(3.5)	94	(4.0)
Infections and infestations	**139**	**(17.9)**	**154**	**(19.6)**	**183**	**(23.4)**	**476**	**(20.3)**
Clostridium difficile infection	27	(3.5)	23	(2.9)	48	(6.1)	98	(4.2)
Pneumonia	8	(1.0)	14	(1.8)	16	(2.0)	38	(1.6)
Sepsis	3	(0.4)	10	(1.3)	19	(2.4)	32	(1.4)
Urinary tract infection	24	(3.1)	32	(4.1)	35	(4.5)	91	(3.9)
Injury, poisoning and procedural complications	**34**	**(4.4)**	**26**	**(3.3)**	**30**	**(3.8)**	**90**	**(3.8)**
Investigations	**48**	**(6.2)**	**45**	**(5.7)**	**48**	**(6.1)**	**141**	**(6.0)**
Metabolism and nutrition disorders	**51**	**(6.6)**	**40**	**(5.1)**	**51**	**(6.5)**	**142**	**(6.1)**
Hypokalaemia	10	(1.3)	11	(1.4)	19	(2.4)	40	(1.7)

	MK-3415A (acto/bezlo)		MK-6072 (bezlo)		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**53**	**(6.8)**	**45**	**(5.7)**	**42**	**(5.4)**	**140**	**(6.0)**
Nervous system disorders	**81**	**(10.4)**	**83**	**(10.6)**	**75**	**(9.6)**	**239**	**(10.2)**
Dizziness	26	(3.3)	20	(2.5)	23	(2.9)	69	(2.9)
Headache	33	(4.2)	35	(4.5)	24	(3.1)	92	(3.9)
Psychiatric disorders	**29**	**(3.7)**	**29**	**(3.7)**	**29**	**(3.7)**	**87**	**(3.7)**
Renal and urinary disorders	**22**	**(2.8)**	**36**	**(4.6)**	**31**	**(4.0)**	**89**	**(3.8)**
Respiratory, thoracic and mediastinal disorders	**50**	**(6.4)**	**64**	**(8.1)**	**50**	**(6.4)**	**164**	**(7.0)**
Cough	7	(0.9)	17	(2.2)	8	(1.0)	32	(1.4)
Dyspnoea	6	(0.8)	17	(2.2)	13	(1.7)	36	(1.5)
Skin and subcutaneous tissue disorders	**40**	**(5.1)**	**47**	**(6.0)**	**61**	**(7.8)**	**148**	**(6.3)**
Vascular disorders	**31**	**(4.0)**	**31**	**(3.9)**	**31**	**(4.0)**	**93**	**(4.0)**

Every subject 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.
MK-3415A = actoxumab + bezlotoxumab, MK-6072 = bezlotoxumab alone

Data Source: [Ref. 5.3.5.1: P001, P002]

An integrated Phase 3 dataset (Study P001 + Study P002) was provided. The majority of subjects reported one or more AEs (60.5% across all treatment groups) with similar percentages reported in the actoxumab + bezlotoxumab (58.6%), bezlotoxumab (61.7%), and placebo (61.2%) treatment groups. Overall, 6.6% of subjects reported at least 1 drug-related AE during the first 4 weeks of the follow-up period with similar percentages reported in the actoxumab + bezlotoxumab (6.4%), bezlotoxumab (7.5%), and placebo (5.9%) treatment groups. Across all treatment groups, drug-related AEs were reported most frequently for the SOCs of General Disorders and Administration Site Conditions (1.8%), Gastrointestinal Disorders (1.6%) and Nervous System Disorders (1.6%). The most frequently reported drug-related AEs across all treatment groups were nausea (0.8%), fatigue (0.6%), headache (0.6%), and dizziness (0.6%).

An individual analysis of the two pivotal studies further supports the evidence that the differences the incidence of AEs between the treatment groups were due to chance. In Study P001, the proportions of subjects who experienced at least one AE during the 4- week period following infusion in each treatment group were 59.7%, 67.2%, 65.4%, and 62.0% in the actoxumab + bezlotoxumab, actoxumab, bezlotoxumab, and placebo treatment groups, respectively. In Study P002, the proportions of subjects who experienced at least one AE during the 4- week period following infusion in each treatment group were 57.4%, 58.1%, and 60.4% in the actoxumab + bezlotoxumab, bezlotoxumab, and placebo treatment groups, respectively.

In the phase 1 Study, the most common AEs in the patients receiving bezlotoxumab were headache [11 (36.7%)], fatigue [7 (23.3%)], nausea [2 (6.7%)], vomiting [2 (6.7%)], pain [2 (6.7%)], and seasonal allergy [2 (6.7%)].

In the integrated Phase 1 database, all AEs in the bezlotoxumab or actoxumab + bezlotoxumab treatment groups were non-serious and mild to moderate in intensity, and the majority (89.9%) were assessed by study investigators to be unrelated to infusion.

Serious adverse event / deaths / other significant events

Serious AEs (SAEs), including all deaths, were collected from the time of study medication infusion until the Week 12 post-infusion visit.

In the integrated data across the 2 Phase 3 trials, a total of 29.8% of subjects experienced a SAE during the 12-week follow-up period. The proportion of subjects with a SAE was lower in the active treatment groups compared to placebo (bezlotoxumab: 29.4%; actoxumab + bezlotoxumab: 27.3%; placebo: 32.7%). The most frequently reported SAEs across all treatment groups were CDI (4.7%), pneumonia (2.0%), sepsis (1.8%), diarrhea (1.6%), and urinary tract infection (1.5%). A numerically higher percentage of subjects reported SAEs of CDI, pneumonia, and sepsis in the placebo group as compared to the actoxumab + bezlotoxumab and bezlotoxumab groups.

In the integrated data across the 2 Phase 3 trials, there were a total of 12 (0.5%) subjects reporting one or more serious and drug-related AEs through Week 12 and at least one serious and drug-related AE was reported in each treatment group: 6 (0.8%) in the actoxumab + bezlotoxumab group, 4 (0.5%) in the bezlotoxumab group, and 2 (0.3%) in the placebo group. One in the bezlotoxumab group reported diarrhoea at Day 34. Only sepsis was reported by more than one subject: one subject each in the actoxumab + bezlotoxumab and bezlotoxumab groups.

During the 12 week post-infusion period, 166 (7.1%) subjects in the integrated Phase 3 dataset across the 3 treatment groups reported one or more AEs with a fatal outcome: 51 (6.6%) in the actoxumab + bezlotoxumab group, 56 (7.1%) in the bezlotoxumab group, and 59 (7.6%) in the placebo group. Approximately half of these subjects (92, 3.9%) died during the first 4 weeks post-infusion 28 (3.6%) in the actoxumab +bezlotoxumab group, 32 (4.1%) in the bezlotoxumab group, and 32 (4.1%) in the placebo group. The most frequently reported AEs with a fatal outcome were septic shock (15, 0.6%), sepsis (14, 0.6%), pneumonia (11, 0.5%), cardiac failure (10, 0.4%), and respiratory failure (9, 0.4%). A higher proportion of subjects in the placebo group died of sepsis or septic shock compared to the other 2 treatment groups: 17 (2.2%) in the placebo group compared to 5 (0.7%) in the actoxumab + bezlotoxumab group and 7 (0.9%) in the bezlotoxumab group.

There were 3 subjects who had AEs with a fatal outcome considered by the investigator to be related to study medication. All 3 subjects were hospitalised for serious medical conditions at the time of CDI diagnosis and study entry. All of these events had an onset of < 19 days from day of infusion with study medication. Two of the 3 subjects were in the actoxumab + bezlotoxumab group: One subject (Study P001) with AEs of sepsis, hypoglycemia, and respiratory arrest and one subject (Study P002) with the AE of small intestinal obstruction. In the bezlotoxumab group, one subject reported AEs of sepsis and cerebral haemorrhage. All 3 of these events were associated with bacteraemia, sepsis, or septic shock. The events are consistent with comorbidity.

Study P001

There was one planned interim efficacy analysis to be performed when approximately 640 enrolled subjects (40% of planned total). After a detailed review of the unblinded safety and efficacy data from all four treatment arms and a careful assessment of the benefit/risk ratio, the DMC recommended that enrolment in the MK-3415 arm (i.e., treatment group containing the monoclonal antibody against Toxin A only) be stopped since an increase in SAEs and death were observed in this treatment arm.

Long-term extension Study P002

A subgroup of 295 subjects (112 in the actoxumab + bezlotoxumab group, 100 in the bezlotoxumab group, and 83 in the placebo group) were followed up to 12 months after receiving study medication infusion (referred to as the extension cohort). The demographic characteristics and prognostic risk factors of subjects who participated in the extension phase of the trial were similar across the three treatment groups.

A total of 9 subjects (3.1%) died during the 9-month extension phase. The 9 subjects who died had a total of 15 adverse events with a fatal outcome. None of these AEs were deemed to be treatment-related by the investigator.

Additionally, during the extension phase, one subject (0.3%) in the bezlotoxumab group had an SAE (osteoporotic fracture of the femur) that was considered by the investigator to be drug-related.

Study P020 (Phase 1)

In the integrated Phase 1 database, there were no SAEs, deaths, or discontinuations in any of the treatment groups.

Laboratory findings

In the 2 Phase 3 trials (P001, P002), blood and urine samples for haematology, chemistry, and urinalysis testing were taken on Day 1 prior to study infusion and on post-infusion Day 4 (±1 day), Day 11 (±2 days), and Day 29 (±3 days). A panel of laboratory measurements was also taken at the time of a new episode of diarrhoea. Laboratory results determined by the study investigator to be clinically relevant were recorded as AEs.

The mean change from baseline at the Day 4, Day 11, and Week 4 visits for each of the chemistry and haematology values listed in the individual protocols (Study P001 and Study P002) indicates that the mean changes from baseline were consistent across treatment groups.

Vital signs

In the Phase 3 program (Study P001 and Study P002), vital sign measurements were taken prior to study infusion, at 30 minutes after the start of the study infusion, and at the end of the study infusion on Day 1. Additionally, vital sign measurements were taken at post infusion study visits Day 4 (±1 day), Day 11 (±2days), Day 29 (±3 days), Day 57 (±7 days), and Day 85 (±5 days).

There were no clinically meaningful changes in diastolic or systolic blood pressure, heart rate, or respiratory rate between subjects who received active treatment and those who received placebo.

Safety in special populations

A substantial number of elderly subjects (65 years of age and older) were enrolled in the Phase 3 trials.

In general, the proportion of subjects reporting one or more AEs was slightly higher in the older age group across all treatment groups compared to the younger age group. The overall proportion of SAEs and deaths was also higher in the older age group. The proportions of subjects reporting at least one AE, at least one drug-related AE, or deaths were generally comparable across treatment groups within each age subcategory. Similar to the overall population, the proportion of subjects reporting SAEs was

lower in the actoxumab + bezlotoxumab treatment group compared to the placebo group in both younger and older age subcategories.

Interestingly, for the SOC cardiac disorder, there was a clear trend to increasing frequencies with older age, but however, very similar to the observations in the placebo group. An FDA meeting of the Antimicrobial Drugs Advisory Committee (AMIDAC) discussed the biologic license application for bezlotoxumab injection from MSD and a safety analysis by baseline Congestive Heart Failure (CHF) was performed by FDA. Analysis showed a numerical difference in the occurrence of AEs, SAEs, and death among the bezlotoxumab-treated subjects with baseline CHF as compared to placebo-treated patients. The applicant further satisfactorily discussed these imbalances in responses to CHMP.

The safety of bezlotoxumab was not assessed in adolescents or children less than 18 years of age or in pregnant or lactating women.

Immunological events

Subjects were evaluated during the infusion and for 24 hours post infusion for infusion specific reactions.

Overall, in both Phase 3 trials, 8.6% of subjects reported one or more infusion specific reactions. The proportion of subjects in the bezlotoxumab group (10.3%) who reported one or more infusion specific AEs was similar to placebo (7.6%) (difference = 2.8%, 95% CI [-0.1, 5.6]).

Infusion-related AEs reported in ≥ 0.5% of subjects receiving bezlotoxumab and at a frequency greater than placebo were nausea (2.8%), fatigue (1.1%), pyrexia (1.0%), dizziness (1.3%), headache (1.9%), dyspnoea (0.8%) and hypertension (0.6%).

The proportions of individual infusion specific AEs were similar for the bezlotoxumab and placebo groups, with the exception of hypertension: 5 (0.6%) subjects in the bezlotoxumab versus 0 subjects in the placebo groups reported hypertension (estimated difference = 0.6% [95% CI: 0.1, 1.5]). Hypertension occurred more frequently in the bezlotoxumab group (n=5, 0.6%) compared to placebo (n=0, difference 0.6%, 95% CI [0.1, 1.5]). Hypertension was generally mild to moderate and did not lead to treatment interruption in any subject. All episodes of hypertension resolved within 2 days (range of duration of event 36 minutes to 2 days). None of these subjects required a new or revised dosage of an antihypertensive medication, and no complications from the hypertension were noted.

Safety related to drug-drug interactions and other interactions

As bezlotoxumab is eliminated by protein catabolism and is not metabolized, nor is it renally eliminated, an effect on safety due to drug-drug interactions would not be expected for bezlotoxumab or on concomitantly administered medications based on the low potential of bezlotoxumab to be a perpetrator or victim of such interactions.

Discontinuation due to adverse events

Across the two Phase 3 trials, only 1 subject reported AEs resulting in study medication discontinuation. This subject, randomised to the bezlotoxumab group, experienced ventricular tachyarrhythmia, chills, and dizziness with an onset approximately 36 minutes after the start of the infusion with bezlotoxumab. The subject was given fenistil, prednisolone, and ranitidine intravenously. The chills and ventricular tachyarrhythmia resolved within 2 to 5 minutes, and the dizziness resolved within 90 minutes. The subject went on to complete the study through the 12-week follow-up period.

These events were considered to be related to study medication by the investigator; the ventricular tachyarrhythmia event was reported as an SAE.

Adverse events of special interest

Study P001 and Study P002

Overdose and hepatic safety were defined in the individual Phase 3 trials as events of special interest.

Overdose

Doses higher than the intended dose of 10 mg/kg met the original protocol definition of an overdose. During the conduct of the study the dose level for an overdose was revised in an amendment to the protocol to be >20 mg/kg because doses as high as 20 mg/kg had been shown to be well tolerated in healthy volunteers.

A total of 17 subjects randomized to an active treatment group received more than the intended dose, i.e. $\geq$ 10.5 mg/kg. Of those, 12 experienced an AE: 5 subjects in the actoxumab + bezlotoxumab group and 7 subjects in the bezlotoxumab group. Dose overages ranged from 0.5 to 4.8 mg/kg with the exception of 2 subjects who received 20 mg/kg of bezlotoxumab.

No subjects received a dose >20 mg/kg.

Hepatic Safety

The subjects' laboratory values were monitored during the Phase 3 trials for hepatic safety. To meet the hepatic event of clinical interest (ECI) criteria, all of the following conditions were required: 1) an elevated AST or ALT laboratory value that was greater than or equal to 3X the upper limit of normal; 2) an elevated total bilirubin (BILI) laboratory value that was greater than or equal to 2X the upper limit of normal; 3) an alkaline phosphatase (ALP) laboratory value that was less than 2X the upper limit of normal; and 4) a clinically significant increase in values if baseline values were elevated. Eight subjects were identified in the Phase 3 clinical trials with liver function laboratory values meeting one or more of the potential drug-induced liver injury (DILI) criteria at some point during the trial, including at the time of enrolment in the trial (bezlotoxumab: 1, actoxumab + bezlotoxumab: 4, placebo: 3). Based upon medical review of each of the 8 cases, none of these events was considered to be suggestive of DILI. The laboratory results for these subjects were confounded by pre-existing medical conditions, including HCV infection with recent radiotherapy to the liver, colitis, left kidney mass, and sickle cell anaemia; hence, these pre-existing medical conditions may have contributed to the abnormal laboratory values.

2.6.1. Discussion on clinical safety

The Applicant presented an integrated safety data analysis for the Phase 3 trials. Since these trials were nearly identical trials, this approach is acceptable. Of note, the data from the actoxumab (MK34-15) arm (in Study P001) are excluded from the integrated analyses. This arm was dropped after the interim analysis due to safety concerns. The safety data base for bezlotoxomab includes 786 patients included in the phase 3 trials and 30 healthy subjects included in a phase 1 trial. In addition 777 subjects were treated with the combination therapy actoxumab + bezolotuxumab in the phase 3 studies. This enlarges, to some extent, the data base for subjects exposed to bezolotoxumab.

In the pivotal studies P001 and P002, adverse events experienced by subjects during the first 4 weeks following infusion with study treatment were collected. The majority of subjects (60.5% across all treatment groups) reported one or more AE. However, similar percentages were reported in the 4

treatment groups. An individual analysis of the two pivotal studies further supports the evidence that the differences in the incidence of AEs between the treatment groups were obtained by chance. In general, the incidence of AEs was similar across the treatment groups.

Serious AEs (SAEs), including all deaths, were collected from the time of study medication infusion until the Week 12 post-infusion visit. The proportion of subjects with a SAE was lower in the active treatment groups compared to placebo. The proportion of AEs with fatal outcome was comparable in all treatment groups and consistent with age and comorbidity. A higher proportion of subjects in the placebo group died of sepsis or septic shock compared to the bezlotoxumab treatment groups. In Study P001, the actuxumab arm was discontinued after the planned interim analysis due to safety reasons i.e. increase in SAEs and death. In addition, in the phase 2 study P017 (actuxumab+ bezlotoxumab vs. Placebo), there were 2 drug-related SAEs leading to death, both in the combination arm.

The proportion of subjects reporting one or more AEs was slightly higher in the older age group (65 years of age and older) across all treatment groups compared to the younger age group. The overall proportion of SAEs and deaths was also higher in the older age group. Interestingly, for the SOC cardiac disorder, there was a clear trend to increasing frequencies with older age, but however, very similar to the observations in the placebo group. There are some apparent imbalances in AEs/SAEs in patients with CHF at baseline between the bezlotoxumab and placebo arms. However, the numbers are small and hence it is not possible to draw conclusions on any increased risks of AE/SAEs in CHF patients treated with bezlotoxumab.

No specific safety signals with regard to clinical laboratory evaluations, vital signs and physical findings are detected with the intravenous single-dose treatment with bezlotoxumab 10 mg/kg. Across treatment groups, no remarkable findings with regard to age, gender, race, weight, renal impairment, and hepatic impairment were observed. In particular, no events occurred which would be suggestive of drug-induced liver injury.

In both Phase 3 studies, subjects were evaluated for infusion-specific reactions during the infusion and for 24 hours post infusion. The proportion of subjects in the bezlotoxumab group who reported one or more infusion specific AEs was similar to placebo.

Based on the reassuring ECG data obtained from the phase 3 trials, with no signals of QT prolongation above placebo level, no thorough QT study is deemed necessary.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In the clinical study program, a single IV administration of 10 mg/kg of bezlotoxmab in subjects 18 years or older was well tolerated. There were some noted imbalances in AEs/SAEs in patients with CHF at baseline between the bezlotoxumab and placebo arms. However the totality of the safety data at present suggests that there is no clear evidence that bezlotoxumab is associated with a negative effect on cardiac function.

Overall, robust conclusion on safety is however hampered by the small sample patient population; and the underlying morbidity and co-morbidity of the patients.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• None
Important potential risks	• Infusion - related Reactions including Hypersensitivity and Anaphylactic reactions • Potential for Immunogenicity • Potential Lack of Efficacy if Bezlotoxumab is Administered Off-label as Monotherapy
Missing information	• Exposure in Patients < 18 years of age • Exposure in Pregnancy/Lactation • Long term Safety • Repeated Administration of Bezlotoxumab

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
(MK-6072-PN001): Trial in Paediatric Patients Aged 24 months to <18 years (Category 3)	Randomised, double blind, single dose, placebo-controlled trial to evaluate efficacy, safety, and pharmacokinetics of *Clostridium difficile* toxin B human monoclonal antibody (MK-6072, bezlotoxumab) as add on to standard of care antibiotic treatment in children from 2 to less than 18 years of age with *Clostridium difficile* infection (CDI).	To provide information on safety and efficacy in patients with CDI who are 24 month to < 18 years of age. In addition, anti-drug antibody (ADA) assessments will be conducted to assess the potential for immunogenicity.	Planned	Anticipated Final Report: **31 March 2019**

(MK-6072-PN002): Trial in Paediatric Patients Aged <24 Months (Category 3)	Open label, single dose trial to evaluate safety, tolerability, and pharmacokinetics of *Clostridium difficile* toxin B human monoclonal antibody (MK-6072, bezlotoxumab) in children from birth to less than 2 years of age with suspected or documented *Clostridium difficile* Infection (CDI), or at risk for developing CDI.	To provide information on safety and efficacy in patients with CDI who are <24 months of age. In addition, anti-drug antibody (ADA) assessments will be conducted to assess the potential for immunogenicity.	Planned	Anticipated Final Report: **30 November 2020**

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risk: Infusion-related Reactions Including Hypersensitivity and Anaphylactic Reactions	**SmPC:** **Section 4.8 Undesirable effects** *Section for Tabulated list of adverse reaction within Table 1: Adverse Reactions with ZINPLAVA includes infusion related reactions occurring on the day of, or the day after infusion.* *Section for Description of selected adverse reactions under Infusion Related Reactions states that overall, 10 % of subjects in the ZINPLAVA group experienced one or more infusion specific adverse reactions on the day of, or the day after, the infusion compared to 8 % in the placebo group. Infusion specific adverse reactions reported in ≥ 0.5 % of subjects receiving ZINPLAVA and at a frequency greater than placebo were nausea (3 %), fatigue (1 %), pyrexia (1 %), dizziness (1 %), headache (2 %), dyspnoea (1 %) and hypertension (1 %). Of the patients who experienced an infusion specific adverse reaction, the majority reported a reaction with a maximum intensity of mild (78 %) or moderate (20 %), and the majority of reactions resolved within 24 hours following onset.* **Package Leaflet:** **Section 4 Possible side effects** *Includes side effects reported in clinical trials as Common (may affect up to 1 in 10 people): diarrhoea, dizziness, feeling sick (nausea), fever, headache, high blood pressure, shortness of breath, tiredness.* *Tell your doctor or health care professional if you notice any of the side effects above.*	None
Important Potential Risk: Potential for Immunogenicity	**SmPC: Section 4.2 Posology and method of administration** *The experience with ZINPLAVA in patients is limited to a single CDI episode and single administration.* **4.4 Special Warnings and precautions for use** *There is no experience with repeat administration of ZINPLAVA in patients with CDI. In clinical trials, patients with CDI were only administered a single dose of ZINPLAVA.* **Section 4.8 Undesirable effects** *Section for Description of selected adverse reactions under Immune-related Adverse Reactions states that in a Phase 1 clinical trial, healthy subjects received two consecutive doses of 10 mg/kg of bezlotoxumab separated by 12 weeks. The adverse reactions after the second dose were not markedly different from those observed after the first dose, and are consistent with adverse reactions observed in MODIFY I and MODIFY II during which all patients received a single dose.*	None

	Section 5.1 Pharmacodynamic properties *Section 5.1 under Immunogenicity states that Immunogenicity of ZINPLAVA was evaluated using an electrochemiluminescence (ECL) assay in MODIFY I and MODIFY II.* *Following treatment with ZINPLAVA in MODIFY I and MODIFY II, none of the 710 evaluable patients tested positive for treatment-emergent anti-bezlotoxumab antibodies. Although ZINPLAVA is intended for single dose administration, the immunogenicity of bezlotoxumab following a second administration of 10 mg/kg, 12 weeks after the first dose, was assessed in 29 healthy subjects. No anti-bezlotoxumab antibodies were detected after the second dose.* *There is no available data on repeated administration of bezlotoxumab in CDI patients.* **Package Leaflet:** Not applicable	
Important Potential Risk: Potential Lack of Efficacy if Bezlotoxumab is Administered Off-label as Monotherapy	**SmPC:** **Section 4. Clinical Particulars** *Section 4.1 under Therapeutic indications states that ZINPLAVA is indicated for the prevention of recurrence of Clostridium difficile infection (CDI) in adult patients at high risk for recurrence of CDI.* *Section 4.2 under Posology and method of administration states that ZINPLAVA should be administered during the course of antibiotic therapy for CDI.* *Section 4.4 under Special warnings and precautions for use states that ZINPLAVA is not a treatment for CDI and has no effect on the current CDI episode. ZINPLAVA should be administered during the course of antibacterial therapy for CDI. There is no data regarding the efficacy of ZINPLAVA if given after the initial 10- to 14- days of antibacterial therapy for CDI.*	None

	Package Leaflet: **Section 1 What ZINPLAVA is and what is it used for?** *ZINPLAVA is a medicine that is given together with an antibiotic to prevent Clostridium difficile infection (CDI) from coming back in patients 18 years of age or older who have a high risk of CDI coming back.* **How ZINPLAVA works** • *When people get CDI, they are usually given an antibiotic to get rid of the infection but CDI can often come back within weeks or months.* • *The bacteria responsible for CDI produce a toxin that can inflame and damage your colon, causing stomach pain and severe diarrhoea. ZINPLAVA acts by attaching to the toxin and blocking it, thereby preventing the symptoms of CDI from coming back.* **Section 2 What you need to know before you are give ZINPLAVA under Warnings and precautions** *ZINPLAVA is not a treatment for CDI. ZINPLAVA has no effect on the CDI you have now.* *ZINPLAVA is given with the antibiotic therapy you are taking for CDI.*	
Missing Information: Exposure in Patients < 18 years of age	**SmPC:** **Section 4.2 Posology and method of administration** *Section for Posology under Special Populations states that safety and efficacy of bezlotoxumab in patients below 18 years of age have not been established. No data are available.* **Package Leaflet:** **Section 2, What you need to know before you are given ZINPLAVA?** **Children and adolescents** *ZINPLAVA should not be used in children and adolescents below 18 years of age.*	None

Missing Information: Exposure During Pregnancy/ Lactation	**SmPC:** **Section 4.6 Fertility, pregnancy and lactation** *Section under Pregnancy states that there are limited data from the use of bezlotoxumab in pregnant women. Animal studies do not indicate reproductive toxicity. ZINPLAVA should not be used during pregnancy unless the clinical condition of the woman requires treatment with bezlotoxumab.* *Section under Breast Feeding states that it is unknown whether bezlotoxumab is secreted in human milk. Because monoclonal antibodies may be excreted in human milk, a decision should be made whether to discontinue breastfeeeding or to not administer ZINPLAVA, taking into account the importance of ZINPLAVA to the mother.* **Package Leaflet:** **Section 2, What you need to know before you are given ZINPLAVA?** **Pregnancy and breast-feeding** • *If you are pregnant or trying to get pregnant, tell your doctor.* • *We don't know if ZINPLAVA will harm your baby while you are pregnant.* • *If you are breastfeeding or are planning to breastfeed, check with your doctor first.* • *We don't know if ZINPLAVA gets in your breast milk and is passed to your baby.* • *You and your doctor should decide together if you will use ZINPLAVA.*	None
Missing Information: Long Term Safety	**SmPC:** Not applicable **Patient leaflet:** Not applicable	None

Missing Information: Repeated Administration of Bezlotoxumab	**SmPC:** **Section 4.2 Posology and method of administration and** *The experience with ZINPLAVA in patients is limited to a single CDI episode and single administration.* **Section 4.4 Special warnings and precautions for use** *There is no experience with repeat administration of ZINPLAVA in patients with CDI. In clinical trials, patients with CDI were only administered a single dose of ZINPLAVA* **Section 4.8 Undesirable effects** *Section Description of selected adverse reactions under Immune-related Adverse Reactions states that in a Phase 1 clinical trial, healthy subjects received two consecutive doses of 10 mg/kg of bezlotoxumab separated by 12 weeks. The adverse reactions after the second dose were not markedly different from those observed after the first dose, and are consistent with adverse reactions observed in MODIFY I and MODIFY II during which all patients received a single dose.* **Section 5.1 Pharmacodynamic properties** *Section 5.1 under Immunogenicity states that Immunogenicity of ZINPLAVA was evaluated using an electrochemiluminescence (ECL) assay in MODIFY I and MODIFY II.* *Following treatment with ZINPLAVA in MODIFY I and MODIFY II, none of the 710 evaluable patients tested positive for treatment-emergent anti bezlotoxumab antibodies. Although ZINPLAVA is intended for single dose administration, the immunogenicity of bezlotoxumab following a second administration of 10 mg/kg, 12 weeks after the first dose, was assessed in 29 healthy subjects. No anti bezlotoxumab antibodies were detected after the second dose.* *There are no data on repeated administration of bezlotoxumab in patients with CDI.* **Patient leaflet:** Not applicable	None

There are no additional risk minimisation measures.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant declared that Bezlotoxumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers bezlotoxumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Due to space limitations on the vial label (50 ml), the QRD Group accepted to only include the minimum particulars.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zinplava (bezlotoxumab) is included in the additional monitoring list as i*t* contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Clostridium difficile is a spore forming, gram-positive bacillus that causes infection (CDI) in humans. It produces toxins that lead to epithelial damage and inflammation in the gut. Symptoms of CDI can range from mild diarrhea to profuse watery diarrhea, leading to dehydration, life threatening complications, and sometimes death. In vulnerable populations, the incidence of CDI-related morbidity and mortality increases significantly. While antibiotic therapy is generally effective at resolving the symptoms, recurrences are common due to persistent or newly-acquired *C. difficile* spores, whose outgrowth and toxin expression are facilitated by the gut dysbiosis caused by antibiotics.

One of the greatest challenges in managing CDI is preventing its recurrence, a critical unmet medical need. After initial treatment and resolution of diarrhea, 15% to 35% of CDI patients experience recurrence. Of those who have a primary recurrence, 40% will have another CDI episode and after 2 recurrences, the likelihood of an additional episode increases further to as high as 65%. The majority of these recurrences occur within 60 days of the initial treatment, but additional cases can be seen beyond 60 days (Bouza E., 2012; McFarland LV., 2009). Recurrent CDI is more difficult to treat and is associated with more hospitalizations, severe outcomes, and higher costs than initial episodes of CDI.

3.1.2. Available therapies and unmet medical need

Current strategies for treating CDI include using CDI-active antibiotics, halting the use of antibiotics that disrupt the gut microbial flora and promote the conditions that allow *C. difficile* outgrowth (if possible), and providing supportive care, as needed. Oral metronidazole, oral vancomycin and oral fidaxomicin are recommended in treatment guidelines, but only vancomycin and fidaxomicin have a regulatory-approved indication for the treatment of CDI. Treatment strategies are based on treatment guidelines from medical associations (Cohen SH *et al.*, 2010, Debast SB *et al*., 2014, Surawicz CM *et al*., 2013). For mild cases of CDI, oral metronidazole is recommended in treatment guidelines as the standard of care. For more severe cases of CDI, oral vancomycin or oral fidaxomicin are recommended. IV metronidazole in combination with vancomycin may also be used in severe cases.

As noted above, 15% to 35% of patients will experience recurrence of CDI after therapy of the first episode with metronidazole or vancomycin, the most commonly used antibiotics for CDI. Based on treatment guidelines, the approaches to the treatment of recurrent CDI include repeat courses of vancomycin or metronidazole, vancomycin in tapered and pulsed doses, vancomycin followed by rifaximin, fidaxomicin, IV immunoglobulin, and therapy with other microorganisms including fecal microbiota for transplantation (FMT) (Kelly CP *et al*., 2008). Treatment of a first recurrent CDI episode with a repeat course of metronidazole or vancomycin is successful in only ~50% of patients (Leffler DA, Lamont JT., 2015). Treatment of multiple recurrences is particularly difficult, mainly due to persistence of spores in the gut and the inability of the patient to mount an effective immune response to *C. difficile* toxins (Maroo S, LaMont JT., 2006). FMT, although used in increasing numbers, remains an investigational treatment option. Currently, there are no treatments that are licensed for

prevention of CDI recurrence, thereby making availability of safe and efficacious therapies for prevention of CDI recurrence an unmet medical need.

3.2 Main clinical studies

3.2.1 Favourable effects

The Applicant submitted a MA for bezlotoxumab, intended for the prevention of a recurrence of *Clostridium difficile* infection (CDI) in patients 18 years or older receiving antibiotic therapy for CDI. The CDI recurrence was defined as the development of a new episode of diarrhea associated with a positive local or central stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode. The endpoint recurrence of CDI was investigated in both pivotal trials in comparison to placebo treatment. The number of patients completing the studies and included in the full analysis set (FAS) was 781 in the bezlotoxumab group versus 773 in the placebo group. In each of these trials, a lower proportion of subjects had CDI recurrence in the bezlotoxumab group as compared to the placebo group in both pivotal trials (adjusted difference P001: -10.2%, 95%CI -15.9; -4.3%; P002: -9.9%, 95% CI -15.5; -4.3). In pooled analysis (MODIFY I and MODIFY II integrated analysis) CDI Recurrence Rate through 12 Weeks after infusion, showed an observed difference in prevention of CDI recurrence between bezlotoxumab and placebo of about 10% ($p<0.0001$).

The secondary endpoint, global cure, was defined as clinical cure of the baseline CDI episode and no CDI recurrence through Week 12. A higher proportion of subjects had global cure in the bezlotoxumab group as compared to the placebo group in both pivotal trials (adjusted difference P001: 4.8%, 95%CI -2.1; 11.7%; P002: 14.7%, 95% CI 7.7; 21.4). Only the results from P002 were statistically significant with regard to this secondary endpoint.

Excluding patients that did not achieve clinical cure of the initial episode was a secondary analysis of the recurrence endpoint and shows a lower rate of CDI recurrence in bezlotoxumab treated patients in trial P001 (adjusted difference -10.8%, 95%CI -17.7;-3.8, one-sided $p= 0.0013$) and trial P002 (adjusted difference -13.7, 95%CI -20.4;-6.9, one-sided $p <0.0001$).

A prospectively planned combined analysis of the CDI recurrence rates in pre-specified subgroups of patients across the two Phase 3 trials (FAS), showed that overall, 51 % were ≥ 65 years of age, 29% were ≥ 75 years and 39 % received one or more systemic antibacterial agents during the 12 week follow-up period. Of the total, 28 % had one or more episodes of CDI within the six months prior to the episode under treatment (18 % of the patients had one, 7 % had two and a few patients had 3 or more prior episodes). Twenty (20) percent of the patients were immunocompromised and 16 % presented with clinically severe CDI. Among the 976/1554 (62%) patients who had a positive baseline stool culture for *C. difficile* a hypervirulent strain (ribotypes 027, 078 or 244) was isolated in 22 % (217 of 976 patients), of which the majority (87 %, 189 of 217 strains) were ribotype 027. These patients presented risk factors primarily but not exclusively associated with higher risk of CDI recurrence. The results were in favour of bezlotoxumab in patients belonging to the following subgroups characterising a severe CDI and/or representing a prognostic risk factor of having CDI recurrence: with history of CDI in the 6 months prior to enrolment, with clinically severe CDI at study entry, ≥ 65 years, and with compromised immunity.

3.2.2 Uncertainties and limitations about favourable effects

No formal clinical dose-finding study has been performed; the selected dose of 10 mg/kg is mainly based on non-clinical studies, PK-studies and the results achieved in the Phase 2 studies.

CDI recurrence was defined as the development of a new episode of diarrhoea following resolution of the initial episode ("clinical cure"). However, subjects not having clinical cure of the initial episode were considered as not having CDI recurrence and were therefore evaluated as treatment success and not as "non-responders". Even if pre-specified in the analysis plan, this approach is questionable. A more appropriate approach would have been randomisation after achieving clinical cure after the initial episode. If the objective of the treatment is the prevention of recurrence, initial clinical cure must be achieved. This approach is reflected in the secondary endpoint "global cure" which combines initial clinical cure and freedom from recurrence through week 12. Results were statistically significant in only one of the two trials.

The majority of the patients in the two pivotal studies did not have severe CDI and/or prognostic risk factors for developing severe CDI or increasing the possibility for recurrence of CDI. Low numbers of patients with a history of CDI in the past 6 months or ever, compromised immunity, elevated temperature and/or WBC count, impaired renal and/or hepatic function or other serious conditions like pseudomembranous colitis, toxic megacolon, bowel perforation, ileus, or requiring a colectomy or other surgery due to complications of CDI were included. The majority of the patients having a history of CDI had only experienced one prior episode. Most patients were > 65 years old; however, the proportion of patients > 75 years was limited. Around 80% of the patients had Zar score < 2, indicating a less severe CDI. Most patients were not diagnosed with a CDI caused by a hypervirulent strain (including ribotype 027); however, the ribotyping analyses were hampered by a large proportion of unknown strains. Overall, these factors indicate that the enrolled patients might have suffered from mild to moderate CDI, questioning the applicability/generalisability of study results. It is also noted that the results are not in favour of bezlotoxumab for the larger subgroups age < 65 years and men. The efficacy results for the primary endpoint, i.e. the overall observed difference in prevention of CDI recurrence between bezlotoxumab and placebo, was about 10%, but lower in patients with no identified risk factors.

Mechanistically, bezlotoxumab can only act on the toxin prior to binding to the cellular receptors. Given that a normal immunoglobulin will access the enteric lumen to a very limited amount (if at all) some degree of injury to the gut lining must happen in order for the product to show efficacy. It is therefore questionable as to why the more relevant secondary endpoint, global cure (which included cure of the initial episode), did not achieve more convincing results. Furthermore, in one of the trials, the placebo performed numerically better as regards the clinical cure of the initial episode. It is well understood that the Applicant did not claim the indication "clinical cure"; nevertheless an effect on the baseline episodes is deemed clinical relevant and determines the place of bezlotoxumab in the therapeutic armamentarium. In order to benefit from the bezlotoxumab therapy which is initiated during the baseline episode the patient has to recover from the first episode. Furthermore the benefit is limited to the prevention of CDI episode(s) in close timely relation to the baseline episode due to nature of the product (i.e. half-life of 19 days).

Further on, the presence of endogenous antibodies to toxin B at baseline seems to have an influence on clinical cure. This remains an issue of uncertainty which cannot be well explained.

3.2.3 Unfavourable effects

In the two Phase 3 trials, the most common adverse reactions following treatment with bezlotoxumab (reported in ≥ 4 % of patients within the first 4 weeks of infusion) were nausea, diarrhoea, pyrexia and headache. These adverse reactions were reported at a similar frequency in placebo treated patients compared with bezlotoxumab treated patients.

Numerical differences in the occurrence of AEs, SAEs, and death were observed among the bezlotoxumab treated subjects with baseline CHF, as compared to placebo-treated patients. Numbers are, however, small.

In clinical studies, serious adverse reactions occurring within 12 weeks following infusion were reported in 29 % of Zinplava-treated patients and 33 % in patients receiving placebo.

Overall, 10 % of subjects in the bezlotoxumab group experienced one or more infusion specific adverse reactions on the day of, or the day after, the infusion compared to 8 % in the placebo group. Infusion specific adverse reactions reported in ≥ 0.5 % of subjects receiving bezlotoxumab and at a frequency greater than placebo were nausea (3 %), fatigue (1 %), pyrexia (1 %), dizziness (1 %), headache (2 %), dyspnoea (1 %) and hypertension (1 %). Of the patients who experienced an infusion specific adverse reaction, the majority reported a reaction with a maximum intensity of mild (78 %) or moderate (20 %), and the majority of reactions resolved within 24 hours following onset.

3.2.4 Uncertainties and limitations about unfavourable effects

Small sample size, underlying disease and co-morbidity as well as observed numerical difference in the occurrence of AEs, SAEs, and death among the bezlotoxumab-treated subjects with baseline congestive heart failure (CHF) as compared to placebo-treated patients, constitute the major uncertainties and limitations about unfavourable effects.

3.2.5 Effects Table

Table 43. Effects Table for bezlotoxumab (Zinplava) indicated for prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI

Effect	Short Description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Prevention of CDI recurrence	No CDI recurrence through Week 12	Proportion of subjects in the FAS Set	P001: 17.4% P002: 15.7%	27.6% 25.7%	CDI recurrence is defined as the development of a new episode of diarrhoea following clinical cure of the baseline. Subjects not meeting the clinical cure endpoint were considered as not having CDI recurrence. This approach underestimates CDI recurrence and might	Clinical efficacy 3.1

Effect	Short Description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence	References
					overestimate the true efficacy	
Global cure	Clinical cure of the baseline CDI episode and no CDI recurrence through Week 12	Proportion of subjects in the FAS Set	P001: 60.1% P002: 66.8 %	55.2 % 52.1%	Global cure was achieved in both pivotal studies without reaching statistical significance	Clinical efficacy 3.1
Unfavourable Effects						
SAE / Death	Integrated analysis of both phase III trials				The most frequently reported SAEs across all treatment groups were CDI (4.7%), pneumonia (2.0%), sepsis (1.8%), diarrhea (1.6%), and urinary tract infection (1.5%). A numerically higher percentage of subjects reported SAEs of CDI, pneumonia, and sepsis in the placebo group. The interpretation is hampered by ill population and high background incidence of AEs. Most frequently reported reasons for death were septic shock, sepsis, pneumonia, cardiac failure; generally balance between arms; numerically lower number of sepsis in bezlotoxumab arms	

3.3 Benefit-risk assessment and discussion

3.3.1 Importance of favourable and unfavourable effects

Symptoms of CDI can range from mild diarrhoea to profuse watery diarrhoea, leading to dehydration, life threatening complications, and sometimes death. In general antibiotic therapy is effective at resolving the symptoms. However, among patients treated for CDI, 15% to 35% experience a recurrence of CDI. Of note, in vulnerable populations, the incidence of CDI-related morbidity and mortality increases significantly. Therefore the prevention of recurrence is of clinical relevance. The obtained results for the primary endpoint taken at face value are considered of sufficiently high magnitude to be considered important. However, due to the chosen design and the analysis, there is concern that the treatment effect is uncertain and possibly overestimated as can be deduced from the secondary endpoints.

The relevance of the observed difference between bezlotoxumab and placebo was questioned, taken into account that the representativeness of the patient population, in terms of the severity of the CDI and the risk of experiencing recurrence, was considered doubtful. The efficacy outcome seems to be dependent on the severity of the manifested CD infection or the number of risk factors, which include, but are not limited to age > 65 years, previous CDI episodes, compromised immune system, infection with 027 ribotype or other hypervirulent strains.

There appears however to be low to no effect of bezlotoxumab compared to placebo in patients with less severe CDI or with few/no risk factors for developing severe CDI.

Bezlotoxumab given as a single IV 10 mg/kg dose in subjects 18 years or older, was generally well tolerated. The observed safety profile is in general similar to placebo; however there are some apparent imbalances in AEs/SAEs in patients with CHF at baseline between the bezlotoxumab and placebo arms. The numbers are, however, small and it is therefore not possible to draw definitive conclusions on any increased risks of AE/SAEs in CHF patients treated with bezlotoxumab. Totality of the safety data at present, suggests that there is no clear evidence that bezlotoxumab is associated with a negative effect on heart function.

Overall, robust conclusion on safety is hampered by the small sample patient population; and the underlying morbidity and co-morbidity of the patients. However, the safety profile is considered sufficiently reassuring.

3.3.2 Balance of benefits and risks

Based on the totality of the data on efficacy and safety, and taking account of the conclusions reached by the consulted experts, the patients at high risk for CDI recurrence are considered as the appropriate target population to receive bezlotoxumab, aiming to prevent CDI recurrence. This takes account of the favourable results obtained in both Phase 3 trials, particularly pertaining to patients who presented risk factors primarily (but not exclusively) associated with higher risk of CDI recurrence. The aimed high risk groups for preventing CDI recurrence generally conform to the European guidance (ESCMID) on “high risk” categories for CDI recurrence.

3.4 Conclusions

The overall benefit-risk of Zinplava is positive for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zinplava is favourable in the following indication:

ZINPLAVA is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI (see sections 4.2, 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that bezlotoxumab is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.