EU RISK MANAGEMENT PLAN (RMP) FOR

Bezlotoxumab

Intravenous

RMP version to be assessed as part of this application:

RMP Version number: 3.0

Data lock point for this RMP: 31-MAY-2022

Date of finalization: 27-SEP-2023

Rationale for submitting an updated RMP:

This RMP is being updated with the submission of the extension of indication to include paediatric patients 1 year of age and older. The final study data from MK-6072 Protocol 001 are included in section S.III.2 Clinical Trial Exposure. There are no new safety concerns.

This RMP also is being updated per EMA GVP Module V (Rev.2) RMP template guidance to remove immunogenicity as an important potential risk.

Summary of significant changes in this RMP:

The missing information 'exposure in patients <18 years of age' has been removed to reflect the results of the paediatric study MK-6072 P001.

The RMP risks for bezlotoxumab were evaluated based upon EMA GVP Module V (Rev 2) guidance and significant changes are reflected in Module SVII.2. The MAH proposes the removal of the important potential risk of 'immunogenicity' from the list of safety concerns.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 2.2

Approved with procedure: EMEA/H/C/004136/IB/0026

Date of approval (opinion date): 07-JAN-2021

QPPV name*:* Guy Demol, MD

QPPV signature: see signature page

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Experience
ALT	Alanine Liver Transferase
APaT	All Patient as Treated
ATC	Anatomical Therapeutic Chemical classification system
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* Infection (also known as *Clostridioides difficile* infection)
CRF	Clinical Report Form
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FMT	Fecal Microbiota Transplant
GCP	Good Clinical Practice
HCAI	Healthcare Acquired Infection
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorisation Application
mAb	Monoclonal Antibody
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study
PIP	Paediatric Investigation Plan
PPI	Proton Pump Inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
rCDI	Recurrent CDI
RMP	Risk Management Plan

SAE	Serious Adverse Event
SoC	Standard of Care
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or Generic name)**	Bezlotoxumab
Pharmacotherapeutic group(s) (ATC Code)	J06BB21
Marketing Authorisation Holder	Merck, Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Number of medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ZINPLAVA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Bezlotoxumab is a fully human monoclonal antibody (mAb) targeted against *Clostridioides difficile* (previously known as *Clostridium difficile*) toxin B. Bezlotoxumab belongs to the IgG1/kappa isotype subclass.
	Summary of mode of action: Bezlotoxumab binds with high affinity to *C. difficile* toxin B (Kds = 19 and 370 pM in a two-site binding model). Bezlotoxumab prevents the binding of toxin B to its target host cells, blocking the cellular intoxication cascade at its first step, and averting the damage and inflammation that normally lead to the symptoms of *C. difficile* infection.
	Important information about its composition: Method of manufacture: recombinant Biological source: The Chinese hamster ovary (CHO) host cell line CHOK1SV was used for expression of bezlotoxumab. Bezlotoxumab drug product is a clear to moderately opalescent, colorless to pale yellow liquid at a target concentration of 25 mg/mL bezlotoxumab mAb in 150 mM NaCl, 20 mM sodium citrate, 20 µM diethylenetriaminepentaacetic acid (DTPA), 0.025% (w/v) polysorbate 80 (PS-80), pH 6.0.
Hyperlink to the Prescribing Information	See latest approved Prescribing information in Module 1.3 from submission sequence 0059.

Table I.1: Product Overview

Indication(s) in the EEA	Current: ZINPLAVA (bezlotoxumab) is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI.
	Proposed: ZINPLAVA (bezlotoxumab) is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in adult and paediatric patients 1 year of age and older at high risk for recurrence of CDI.
Dosage in the EEA	Current: ZINPLAVA (bezlotoxumab) should be administered during the course of antibacterial therapy for CDI. ZINPLAVA (bezlotoxumab) should be administered as a single intravenous infusion of 10 mg/kg. The experience with ZINPLAVA in patients is limited to a single CDI episode and single administration.
Pharmaceutical form(s) and strengths	Current: 25 mg/mL concentrate for solution for infusion
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

Indication: Prevention of recurrence of *Clostridioides difficile* infection (CDI) in adult and paediatric patients 1 year of age and older at high risk for recurrence of CDI

CDI epidemiology among adults

CDI is a significant health problem that is associated with morbidity and mortality, relatively high recurrences [Ref. 5.4: 044763]. CDI is the most common HCAI in Europe and the United States and one of the most common HCAI elsewhere where the rate of such infections is not routinely tracked [Ref. 5.4: 044763, 046KS0, 046PJK, 046PJM, 03R67D].

Incidence of CDI:

From the 1970s to approximately 2010, the incidence of CDI in Europe, the United States, and other countries increased [Ref. 5.4: 046KR2, 046PJM]. In the US, a decline in healthcare-associated infections led to a 24% reduction in CDI cases from 2011 to 2017 [Ref. 5.4: 0829W8]. Similarly, in the UK, the rate of all CDI cases per 100,000 population, per year has fallen from 107.6 in 2007-2008 to 22.1 in 2018-2019 [Ref. 5.4: 05KCK0]. In a representative study of the U.S. population, the Centers for Disease Control and Prevention (CDC) reported the estimated incidence of CDI in 2011 was 147.2 per 100,000 people and the estimated number of cases was approximately 450,000. The majority (57%) of all estimated U.S. CDI cases were in patients 65 years old and older: 66% of healthcare-associated CDI and 72% of CDI recurrences were in those 65 years old and older [Ref. 5.4: 046PJM]. In many other countries, the incidence of CDI is reported based on an inpatient population. In Canada, the incidence in 2007 was 5.35 per 1,000 admissions with an estimated 38,000 cases of CDI [Ref. 5.4: 0479W6]. In 2011 in Italy, the incidence of CDI was 2.3 per 10,000 patient-days [Ref. 5.4: 046KRK]. In Australia, the incidence of CDI in 2012 was 4.03 per 10,000 patient-days [Ref. 5.4: 046MSW]. Outbreaks and other reports of CDI have been reported in numerous countries including Austria [Ref. 5.4: 0479VL], Belgium [Ref. 5.4: 0479V3], Chile [Ref. 5.4: 046Q9R], Denmark [Ref. 5.4: 047BJQ], Germany [Ref. 5.4: 03RPZB], Japan [Ref. 5.4: 046VLV], Korea [Ref. 5.4: 03R3RM], Norway [Ref. 5.4: 03RPZB] and Turkey [Ref. 5.4: 046MYJ].

During the COVID-19 pandemic, changes in infection prevention and control practices, health-seeking behaviors, and antibiotic prescribing practices may have affected CDI incidence. Incidence of CDI during the first wave of the pandemic was lower than incidence during the same time period in the 1-2 years preceding the pandemic in Spain [Ref. 5.4: 0872S0] and Ireland [Ref. 5.4: 0872S7] and stable in the US [Ref. 5.4: 0872RY]. In an analysis that accounted for a longer period of follow-up (through June 2021), both hospital- and community-acquired CDI incidence increased in Canada [Ref. 5.4: 086K50].

Incidence of Recurrent CDI:

In the United States, the estimated annual incidence of recurrent community-associated CDI was 7.0 per 100,000 persons in the total population with a corresponding estimated 21,600 cases of recurrent community-associated CDI. The estimated annual incidence of recurrent healthcare-associated CDI in the U.S. was 19.9 per 100,000 persons with an estimated 61,400 cases annually [Ref. 5.4: 046PJM]. Estimates of community-associated CDI and healthcare-associated CDI recurrence were higher for patients 65 years and older. In hospital-based surveillance in 14 countries in Europe, estimated incidence of recurrent healthcare-associated CDI was 5.9 per 100,000 patient-days [Ref. 5.4: 0872S5]. A study conducted in France reported that among the 14,739 survivors of the index CDI hospital stay, 2135 (14.5%) required at least one readmission with rCDI within 12 weeks following discharge (mean interval between discharge and readmission, 18 ± 20 days). More than 80% of readmission with rCDI occurred within 8 weeks [Ref. 5.4: 05KPBC].

Prevalence of CDI:

In the United States, an estimated 453,000 cases occur each year, and approximately 83,000 recurrences and 29,300 deaths are associated with *C. difficile* annually. A total of 12,275 cases of *Clostridium difficile* infection were reported by NHS trusts in England between 1 April 2018 and 31 March 2019 [Ref. 5.4: 05KCK0]. The economic burden of *C. difficile* infection (CDI) is estimated to be $4.8 billion in excess medical costs [Ref. 5.4: 05KC52]. CDI also occurs outside of health care settings, but community-associated disease is not routinely reported on a national level and incidence rates are often not well established.

Prevalence of recurrent CDI:

One of the greatest challenges in managing CDI is preventing the recurrence of CDI. Between 15-35% of patients with CDI who are successfully treated for CDI with the most commonly prescribed antibiotics, oral metronidazole and oral vancomycin, experience a recurrence of CDI [Ref. 5.4: 046Q9T, 046PJM, 046JFB]. Of those who have a first recurrence of CDI, 40% will have another recurrence of CDI and after 2 recurrences, 60% or more will have another recurrence of CDI [Ref. 5.4: 046Q9T, 046JFB]. The majority of these recurrences occur within 60 days of successful treatment [Ref. 5.4: 046Q9T, 046JFB]. Oral fidaxomicin is also indicated for the treatment of CDI; in fidaxomicin clinical trials, the CDI recurrence rate has been observed to be lower among patients treated with fidaxomicin than patients treated with vancomycin (14% vs. 26%) [Ref. 5.4: 03RHFQ].

Of the total 453,000 estimated annual U.S. CDI cases, 18% (83,000) were recurrent cases [Ref. 5.4: 046PJM]. European studies report estimates of recurrence that are consistent with the U.S. data; Bauer et al reported the recurrence rate in Europe was 18% [Ref. 5.4: 03RPZB]. Dependent upon the underlying population and the definition of recurrence, other European studies yield recurrence results within the 10-35% range [Ref. 5.4: 0872S5, 03RPZC, 046QCS, 047BJQ, 046SG3, 046K80, 03QXMP, 046KRB].

Recurrent CDI is more difficult to treat and is associated with more hospitalizations, severe outcomes, and higher costs than initial CDI episodes. Patients with recurrent CDI were more likely than their counterparts who did not have a recurrence to have at least one more hospitalization and have more hospital days in the 180 days after discharge or treatment for the index CDI episode [Ref. 5.4: 047T4D]. In a U.S. hospital-based study, among patients with CDI, those with recurrent CDI had 33% higher hazard of death after 180 days of discharge or treatment for index CDI episode compared with patients without recurrent CDI when adjusting for patient demographics, comorbidities, and medications received during their index CDI hospitalization [Ref. 5.4: 048Q4Q]. In a publication from the CDC, 83% of CDI deaths were inpatients 65 years and older and 9% of CDI cases in those 65 years and older resulted in death [Ref. 5.4: 046PJM].

Demographics of the population in the authorized indication:

The target population is adults with an acute episode of primary or recurrent CDI and who are at high risk for recurrence of CDI.

Risk factors for CDI:

C. difficile spores can persist outside the human body on hard surfaces for up to five months [Ref. 5.4: 049C2D] and may be found on commonplace items in the healthcare environment such as bed linens, bed rails, floors, bathroom fixtures, and medical equipment [Ref. 5.4: 03YFJ5]. *C. difficile* contamination has been found on 49% of sites in hospital rooms occupied by patients with CDI and on 29% of sites sampled in rooms occupied by asymptomatic *C. difficile* carriers [Ref. 5.4: 049C2D]. CDI can spread from person-to-person on contaminated equipment and on the hands of healthcare providers and visitors [Ref. 5.4: 047BJV]. The median incubation period for CDI after acquisition of *C. difficile* spores is approximately 3 days [Ref. 5.4: 046PJN, 046JJ7]. Because of the hardiness of the *C. difficile* spores and their ability to persist in and around hospital equipment, hospitalized patients are at an increased likelihood of being exposed to *C. difficile* spores that can then infect them.

Host related risk factors for CDI include advanced age (>65 years), exposure to antibiotics (particularly clindamycin, cephalosporins and fluoroquinolones), especially prolonged exposure and exposure to more than one antibiotic, a weakened immune system, comorbidities such as IBD or colorectal cancer, kidney disease, use of PPIs which reduce stomach acid, and surgery of the GI tract. Another critical host related risk factor is previous *C. difficile* infection [Ref. 5.4: 0479VN, 047BJV, 046KS0, 046PJK, 03RNPX, 046PJM]. Although gender has not been specifically identified as a risk factor for CDI, Lessa et al, reported that community-acquired CDI was more common in women than men after adjustment for age and other potential confounders (incidence per 100,000 among women 61.0 (51.2, 70.8) vs. men 42.5 (34.8, 49.8)) [Ref. 5.4: 046PJM].

Risk Factors for CDI Recurrence:

Several studies have examined the risk factors for recurrent CDI [Ref. 5.4: 046Q9T, 046KQN, 0408NJ, 0408NH, 03QYCM, 046JFB, 0408NK, 03RT8S]. The main conditions for recurrence include an inadequate antitoxin antibody response and persistent disruption of the colonic flora due to antibiotics received before or to treat the primary CDI episode. Mechanistically these conditions create an environment that permits *C. difficile* to flourish and cause recurrent disease. The host-related risk factors contributing to this mechanism include age, with older patients at greater risk, comorbidities and compromised immune response. The use of certain antibiotics before and after diagnosis of *C. difficile*, especially clindamycin, cephalosporins and fluoroquinolones, are important risk factors for CDI recurrence. More recently, PPIs have been identified as a risk factor for recurrent CDI [Ref. 5.4: 03R2CV]. The environmental risk factors for CDI include hospitalization and length of stay, as this increases risk of exposure to *C. difficile* spores that may be present in the hospital environment or may be transmitted from caretakers in the hospital. Recurrence is more common among patients with healthcare-associated CDI compared to community-associated CDI. The organism-related risk factors associated with recurrent CDI include specific *C. difficile* strains. In the U.S., infection with Ribotype 027 (also known as BI or NAP1 when different typing methods are used) has been associated with an increased risk for recurrent CDI [Ref. 5.4: 046Q9W, 03R2CV, 046PJM].

The main existing treatment options:

Current strategies for treating CDI include discontinuing therapy with the inciting antibiotic agents that disrupt the gut flora and stimulate conditions that allow *C. difficile* to flourish, and starting antibiotic therapy for CDI. Fidaxomicin is recommended for treatment of an initial episode of CDI, with vancomycin as an acceptable alternative; metronidazole is an alternative agent for use for non-severe cases if access to vancomycin and fidaxomicin is limited[Ref. 5.4: 0833J4]. Only vancomycin and fidaxomicin have regulatory approval for the treatment of CDI. Treatment strategies are based on treatment guidelines from medical associations Guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recommend treatment with fidaxomicin for treatment of a recurrence of CDI; a standard course or a pulsed and tapered regimen of vancomycin are acceptable alternatives for a first CDI recurrence. A 2013 update of the treatment guidance of the European Society of Clinical Microbiology and Infectious Diseases [Ref. 5.4: 04VYHP] includes the following points: except for very mild CDI that is clearly induced by antibiotic usage antibiotic treatment is advised;the main antibiotics that are recommended are metronidazole, vancomycin and fidaxomicin; fecal transplantation is strongly recommended for multiple recurrent CDI; in case of perforation of the colon and/or systemic inflammation and deteriorating clinical condition despite antibiotic therapy, total abdominal colectomy or diverting loop ileostomy combined with colonic lavage is recommended. However, a recent narrative review [Ref. 5.4: 055SPF] states that: Oral vancomycin will become the first choice when antibiotic treatment for CDI is necessary; fidaxomicin is a good alternative, especially in patients at risk of relapse; vancomycin combined with faecal microbiota transplantation remains the primary therapy for multiple recurrent CDI.

Various approaches to the treatment and prevention of further CDI recurrence include repeat courses of vancomycin or fidaxomicin, vancomycin in tapered and pulsed doses, vancomycin followed by rifaximin, IV immunoglobulin, and therapy with other microorganisms including fecal microbiota for transplantation (also referred to as fecal bacteriotherapy or FMT) [Ref. 5.4: 05KC4L, 03QVFH, 0872S2].

ZINPLAVA is an effective and well-tolerated adjunctive treatment that is indicated for prevention of recurrent CDI when given during a course of antibiotic therapy. A recent real-world multicenter study demonstrated successful prevention of rCDI with bezlotoxumab, with observed recurrence rates that were comparable to Phase 3 clinical trial results [Ref. 5.4: 05HF3B]. Multiple prior CDI recurrences were associated with a higher risk of subsequent rCDI, supporting the use of bezlotoxumab earlier in the disease course.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The severity of CDI ranges from colonization with *C. difficile* to severe diarrhea and dehydration, kidney failure, toxic megacolon, and death. More severe cases of CDI result in increased length of hospitalization and health care resource utilization. While the severity of CDI may be confounded by overall health status or other factors, the mortality rate attributable to CDI ranges between 5 and 10% [Ref. 5.4: 03QVFJ, 03RPWZ, 03RT92, 046KRT]. In a report from the CDC, the mortality rate associated with CDI was approximately 6%. The death rate was higher in hospital or healthcare-acquired CDI compared to community-acquired CDI (8.9 vs. 0.7 per 100,000) and the death rate significantly increased with age [Ref. 5.4: 046PJM]. Patients with recurrent CDI, compared to those with primary CDI, are at greater risk for death and subsequent hospitalization [Ref. 5.4: 048Q4Q, 047T4D].

Important co-morbidities:

Patients with CDI can have multiple comorbidities that make them susceptible to the disease via exposure to the *C. difficile* spores, disruption of gut microbiome and reduced immune response to CDI. The important comorbidities in patients with *C. difficile* include those that affect the microbiome and integrity of the gut; these include infections for which wide-spectrum antibiotics are used. Another comorbidity of interest includes compromised immunity, whether by underlying disease or by exposure to medications that induces suppressed immunity. Examples of subjects with compromised immunity include: transplant patients, oncology patients or patients on chemotherapy. All comorbidities that lead to exposure to health care settings increase risk of exposure to *C. difficile* spores. Additional comorbidities include patients with infections requiring prolonged treatment with high-risk antibiotics such as clindamycin, cephalosporins and fluoroquinolones, renal impairment, hepatic impairment, inflammatory bowel disease, autoimmune diseases, including rheumatoid arthritis and patients receiving PPIs or other gastric acid suppression treatment.

CDI epidemiology among paediatric populations

Incidence of CDI:

Incidence of CDI among paediatric patients increased in the US from 1991 to 2009, rising from 2.6 to 32.6 infections per 100,000 person-years [Ref. 5.4: 03RT8T]. In the US hospital setting specifically, incidence increased from 4.4 per 10,000 patient-days in 2001 to 6.5 per 10,000 patient-days in 2006 [Ref. 5.4: 03QVDL], with a similar incidence rate in 2013 (7.1 cases per 10,000 patient-days) as in 2006 [Ref. 5.4: 086K5J]. CDI incidence among paediatric inpatients in the Netherlands was also stable over approximately the same time period of 2009-2015 [Ref. 5.4: 04MPF8]. Incidence among paediatric inpatients in the US declined to 4.9 cases per 10,000 patient-days by 2019 [Ref. 5.4: 086K5J].

Prevalence of CDI and CDI recurrence:

In the US, there are approximately 16,900 paediatric CDI cases annually [Ref. 5.4: 046PJM]. Approximately 10-30% of paediatric patients with a case of CDI are expected to have a recurrent episode [Ref. 5.4: 03RT8T, 080ZG4, 082XYP, 046PJM, 05CYZL]. Among all paediatric CDI cases, approximately three-quarters are community-acquired, while the remainder are acquired in a healthcare setting [Ref. 5.4: 03RT8T, 046PJM]. Globally, asymptomatic colonization of *C. difficile* is common among infants, occurring in 41% of those aged 6 months to 1 year, compared with 12% in those aged 5-18 years [Ref. 5.4: 0826SG]. Despite relatively high prevalence of *C. difficile* colonization, clinically relevant CDI is rare in infants aged <1 year.

Severe outcomes of CDI are uncommon among paediatric cases and include toxic megacolon (0.1%), colectomy (0.3%), gastrointestinal perforation (0.4%) [Ref. 5.4: 086K5J], and pseudomembranous colitis (1.1%) [Ref. 5.4: 086KD4]. Global estimates of all-cause mortality among paediatric patients with CDI range from 2-5% [Ref. 5.4: 086KD4, 086K5J, 03QVDL].

Risk factors for CDI and CDI recurrence:

Paediatric patients are at higher risk of CDI if they have prior antibiotic exposure, prolonged hospitalization, a history of hospitalization, current use of gastric acid suppressants, or have comorbidities, including neoplastic disease, immunodeficiency, solid organ transplantation, and enteral feeding [Ref. 5.4: 086K55]. Among paediatric patients with CDI, 67%-91% are estimated to have comorbidities [Ref. 5.4: 086KD4, 086K5J, 03QVDL, 080ZG4].

Risk factors for CDI recurrence include malignancy, tracheostomy tube dependence, recent surgery, and antibiotic use in the 30 days before symptom onset [Ref. 5.4: 082XYM, 058630]. As with initial cases of CDI, comorbidities are common among paediatric patients with recurrent CDI. Among paediatric patients with recurrent CDI in a Swedish hospital, 97% had an underlying comorbidity [Ref. 5.4: 080ZG4].

Demographics of the population in the authorized indication:

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

Main existing treatment options:

Vancomycin and metronidazole are commonly used for treatment of paediatric CDI. Limited observational data suggest that vancomycin may result in higher rates of clinical improvement than metronidazole and that recurrence is more likely following metronidazole than vancomycin treatment [Ref. 5.4: 080Z6N]. Fidaxomicin is an oral, narrow-spectrum antibiotic that has activity against both *C. difficile* and its spores, thereby treating both initial episodes of CDI and reducing recurrence [Ref. 5.4: 080Z6N]. In a randomized controlled clinical trial among paediatric patients aged <18 years with CDI, fidaxomicin was non-inferior to vancomycin for treatment of CDI and also resulted in higher rates of global cure (68% vs. 50%) and longer time to recurrence [Ref. 5.4: 086KDH].

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

Phase 3 clinical studies were conducted with both bezlotoxumab (a fully human mAb to *C. difficile* toxin B) and actoxumab (a fully human mAb to *C. difficile* toxin A), alone and in combination. However, these studies indicated that the combination of bezlotoxumab and actoxumab did not have a meaningful efficacy benefit over bezlotoxumab alone. Therefore, the final product selected for registration was bezlotoxumab (see Sec SIII.1). As the nonclinical toxicology program was intended to support all clinical studies, both bezlotoxumab and actoxumab, alone and in combination, were studied.

The nonclinical toxicology program was designed in accordance with current regulatory guidelines for biotechnology-derived pharmaceuticals (ICH Topic S6(R1)). The guideline indicates that if there are no relevant species in which to study mAbs directed against exogenous targets (i.e., bacterial toxins) such as bezlotoxumab and actoxumab, the toxicology evaluation may be limited to a repeated dose toxicity study of ≤14 days duration in a single species. No additional toxicity studies, including reproductive toxicity studies, are appropriate. Based on this guidance, the nonclinical toxicology program for bezlotoxumab and actoxumab was limited to (1) an exploratory single-dose toxicokinetic study, (2) Good Laboratory Practices (GLP) -compliant repeat-dose toxicity studies in which mice were exposed to bezlotoxumab and actoxumab, alone and in combination over a period of approximately 2 weeks, and (3) in vitro tissue cross-reactivity studies. Safety pharmacology, genetic, chronic, and reproductive toxicity and carcinogenicity studies are not generally required for mAbs directed at foreign targets and were therefore not conducted. No findings of toxicological significance were observed in in vivo repeat-dose toxicity studies in mice at doses up to 125 mg/kg/dose (the maximum feasible dose) or in vitro tissue cross-reactivity studies.

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

Bezlotoxumab is not anticipated to impact the PK of concomitantly administered medications, as it is a highly specific mAb that targets a non-endogenous antigen (*C. difficile* toxin B). No effect on inflammatory mediated changes of metabolic enzymes is expected, since bezlotoxumab does not react with an endogenous target; thus, no drug-drug interaction studies in the disease state were performed.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
None	N/A
N/A = Not applicable	

No special populations have been identified that require any additional non-clinical data.

Conclusions on Non-clinical Data

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

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief Overview of Development

Phase 3 clinical trials in adults were conducted with both bezlotoxumab (a fully human mAb to *C. difficile* toxin B) and actoxumab (a fully human mAb to C. *difficile* toxin A), alone and in combination. These trials indicated that the combination of bezlotoxumab and actoxumab did not have a meaningful efficacy benefit over bezlotoxumab alone. In addition, actoxumab alone failed to show efficacy. Therefore, the final product selected for registration was bezlotoxumab. Safety data from participants who received actoxumab alone are not discussed in this document. For completeness, all trials in the clinical development program are listed in Table SIII.1.

The pivotal Phase 3 clinical trials in adults (Protocol 001 (P001) and Protocol 002 (P002)) have demonstrated that in participants with CDI and receiving SoC antibiotic therapy for CDI, IV administration of a single 10 mg/kg dose of bezlotoxumab is superior to placebo in preventing CDI recurrence over a period of 12 weeks, and that bezlotoxumab is well-tolerated and has a safety profile similar to placebo. Given these findings, bezlotoxumab has a favorable benefit/risk profile.

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

The overall clinical development program was comprehensive and included evaluation of bezlotoxumab (MK-6072), actoxumab (MK-3415), and the combination of actoxumab and bezlotoxumab (hereafter referred to as actoxumab + bezlotoxumab, also known as MK-3415A) in both healthy participants and in participants receiving a 10- to 14-day course of oral SoC antibiotic for CDI (metronidazole, vancomycin or fidaxomicin) for a primary or recurrent episode CDI. The clinical development program consisted of 9 clinical trials: five (5) Phase 1 trials; two (2) Phase 2 trials; two (2) pivotal Phase 3 trials; and one (1) Phase 3 paediatric trial (Table SIII.1)

Table SIII.1.1: Summary of the Clinical Development Program

Protocol Number	Phase	Trial Objective	Trial Population	Number of Subjects Treated
CA-CDA1-04-01 (Protocol 019)	1	Open-Label, Dose Escalation Study to Evaluate the Safety and PK of *C. difficile* Toxin A Human Monoclonal Antibody (CDA1)	Healthy subjects	Actoxumab: 30
CA-GCDX-05-01 (Protocol 020)	1	Open-Label, Dose Escalation Study to Evaluate the Safety and PK of *C. difficile* Toxin A Human Monoclonal Antibody (GS CDA1) and *C. difficile* Toxin B Human Monoclonal Antibody (MDX-1388)	Healthy subjects	Actoxumab: 6 Bezlotoxumab: 30 Actoxumab + bezlotoxumab: 24
Protocol 005	1	Single Dose Study to Evaluate the Safety, Tolerability, and PK of a 1 hour IV Infusion of MK 3415A	Healthy subjects	Actoxumab + bezlotoxumab: 29 Placebo: 6
Protocol 006	1	Single Dose Study to Evaluate the Safety, Tolerability, and PK of MK-3415A in Healthy Japanese Male Subjects	Healthy male Japanese subjects	Actoxumab + bezlotoxumab: 13 Placebo: 6
Protocol 004	1	Study to Evaluate the Immunogenicity of MK-3415A when given as 2 doses 3 months apart	Healthy subjects	Actoxumab + bezlotoxumab: 30
CA-CDA1-05-02 (Protocol 018)[†]	2	Randomized, Double-Blind, Placebo-Controlled Study of the Clinical Effectiveness of a Human Monoclonal Antibody to Toxin A (CDA1) in Patients being Treated for CDI	CDI patients receiving SoC antibiotics	Actoxumab: 29 Placebo: 17
CA-GCDX-06-02 (Protocol 017)	2	Randomized, Double-Blind, Placebo-Controlled Study of the Clinical Effectiveness of a Human Monoclonal Antibody to *C. difficile* Toxin A (GS-CDA1) and a Human Monoclonal Antibody to *C. difficile* Toxin B (MDX-1388) in Patients being Treated for CDI	CDI patients receiving SoC antibiotics	Actoxumab + bezlotoxumab: 101 Placebo: 99
Protocol 001	3	Randomized, Double-Blind, Placebo Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415, MK-6072, and MK-3415A in Patients Receiving Antibiotic therapy for CDI.	CDI patients receiving SoC antibiotics	Actoxumab: 235 Bezlotoxumab: 390 Actoxumab + bezlotoxumab: 387 Placebo: 400
Protocol 002	3	Randomized, Double-Blind, Placebo Controlled Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-6072 and MK-3415A in Patients Receiving Antibiotic therapy for CDI.	CDI patients receiving SoC antibiotics	Bezlotoxumab: 396 Actoxumab + bezlotoxumab: 390 Placebo: 381
Protocol MK-6072 P001	3	Phase 3, randomized, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the PK, safety, tolerability, and efficacy of a single infusion of bezlotoxumab in paediatric subjects from 1 to <18 years of age receiving antibacterial drug treatment for CDI.	CDI paediatric patients 1 year and older receiving SoC antibiotics	143 participants Bezlotoxumab: 107 Placebo: 36

[†]The trial was stopped early to pursue development of MK-3415A (actoxumab + bezlotoxumab).

SoC – Standard of Care; CDI – *Clostridium difficile* infection; CDA1 and GS-CDA1 = MK-3415 (actoxumab); MDX-1388 = MK-6072 (bezlotoxumab)

The Phase 3 trial design and efficacy data are summarized below:

MK-3415A P001 was an adaptive-design Phase 3 trial in which adult subjects with confirmed CDI and receiving SoC antibiotic treatment for CDI (metronidazole, vancomycin, or fidaxomicin) were randomized in a 1:1:1:1 ratio into 1 of 4 treatment groups (bezlotoxumab, actoxumab, actoxumab + bezlotoxumab, or placebo). At the pre-specified interim analysis, enrollment into the actoxumab arm was stopped, a decision driven by both low efficacy and observed increase in the number of deaths and SAEs relative to placebo. At the final analysis, a total of 1,396 subjects with confirmed CDI were randomized, received study medication and were included in efficacy analyses: 386 in bezlotoxumab, 232 in actoxumab, 383 in actoxumab + bezlotoxumab, and 395 in placebo groups. P001 met the primary efficacy objective demonstrating that treatment with bezlotoxumab significantly decreases the proportion of subjects with CDI recurrence over 12 weeks as compared to treatment with placebo (one-sided p=0.0003). CDI recurrence rates were 17.4% in the bezlotoxumab group and 27.6% in the placebo group [-10.1 (95% CI: -15.9, -4.3)]. For actoxumab + bezlotoxumab group, the CDI recurrence rate was 15.9% and was significantly (one sided p<0.0001) better than placebo but was not significantly better than bezlotoxumab (p=0.2997). Hence, the addition of actoxumab to therapy (i.e., actoxumab + bezlotoxumab) did not have efficacy benefit over bezlotoxumab. The reduction in CDI recurrence rate for the bezlotoxumab group versus placebo was also observed in pre-specified subgroups of subjects at high risk for recurrence and/or CDI-related adverse outcomes (i.e., patients ≥65 years of age, patients with a history of CDI in past 6 months before the baseline episode, patients with clinically severe CDI, patients infected with the 027 ribotype or epidemic strain, or patients with compromised immunity).

MK-3415A P002 was identical to P001 in design and conduct, with the following 3 major exceptions: (1) P002 contained 3 treatment groups (bezlotoxumab, actoxumab + bezlotoxumab, and placebo), (2) was a traditional clinical trial of fixed design, and (3) had an extended 9 month follow-up of a subset of subjects (~300) to assess CDI recurrence and colonization with toxigenic *C. difficile*. All other design features were identical between P001 and P002. A total of 1,163 patients with confirmed CDI were randomized, received study medication and were included in efficacy analyses: 395 in bezlotoxumab, 390 in actoxumab + bezlotoxumab, and 378 in placebo groups. P002 also met the primary efficacy objective and confirmed that treatment with bezlotoxumab significantly decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with placebo (one-sided p=0.0003). CDI recurrence rates were 15.7% and 25.7% in the bezlotoxumab and placebo groups, respectively [-9.9 (95% CI: -15.5, -4.3)]. CDI recurrence rate in the actoxumab + bezlotoxumab group was 14.9% and was significantly (one sided p<0.0001) better than placebo but was not significantly better than bezlotoxumab (p=0.3718). Consistent with P001, reduction in CDI recurrence rate for the bezlotoxumab group versus placebo was observed in all pre-specified subgroups of subjects.

Therefore, given these findings, bezlotoxumab was the final product proposed for adult registration. In support of this decision, the clinical trial exposure and safety data for bezlotoxumab in the Phase 3 (P001 + P002) integrated data are presented in this document. Overall, 786 subjects with a confirmed diagnosis of CDI received a 10 mg/kg dose of bezlotoxumab and 781 received placebo (0.9% NaCl.) Clinical trial exposure and safety data

from the actoxumab alone and the combination actoxumab + bezlotoxumab groups are not included in this document, as bezlotoxumab is the approved product.

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

SIII.2 Clinical Trial Exposure

Adult population: Two Phase 3 trials (MK-3415A P001 + P002) have been completed in adult subjects with CDI who were receiving SoC antibiotic therapy for a primary or recurrent episode of CDI. In the clinical trials, the age range of subjects who received bezlotoxumab was 18-100 years. The protocols had broad inclusion and limited exclusion criteria, permitting a comprehensive evaluation of adult subjects with diverse underlying comorbidities, a wide range of clinical characteristics associated with a high risk for additional CDI episodes, and more than 130 different strains of *C. difficile*.

Table SIII.2.1 displays exposure by dose, in mg/kg and mg, for the 786 subjects who received bezlotoxumab in the integrated P001 and P002 APaT population. Doses are summarized relative to the intended 10 mg/kg dose; no subjects received a dose >20 mg/kg, the highest single dose evaluated in Phase 1 trials.

Of the 14 subjects who received <9.5 mg/kg, one subject, discontinued the infusion before the full volume was administered due to an AE of ventricular tachyarrhythmia, chills, and dizziness.

Of the 9 subjects who received more than the intended dose (defined as ≥10.5 mg/kg), four subjects received the higher than intended dose due to incorrect recording of their weight; two were due to pharmacist error; and three due to presumed incorrect weight assessment (though this could not be verified). Dose overages ranged from 0.5 to 4.8 mg/kg, except for two subjects who received 20 mg/kg of bezlotoxumab. Of the 9 subjects who received a dose ≥10.5 mg/kg, an AE with temporal association to study medication administration was reported for 3 subjects.

Table SIII.2.1: Clinical Trial Exposure to Bezlotoxumab by Dose Adult Phase 3 Studies (PN001 + PN002 Integrated) APaT Population

	MK-6072 (bezlotoxumab) n (%)
Subjects in population	786
MK-6072 (mg/kg)	
< 10 mg/kg	14 (1.8)
10 mg/kg†	763 (97.1)
> 10 mg/kg	9 (1.1)
MK-6072 (mg)	
< 625 mg	282 (35.9)
>= 625 mg to < 1000 mg	428 (54.5)
>= 1000 mg	76 (9.7)
MK-6072 (mg)	
N	786
Mean	730
SD	216
Median	700
Range	50 to 2012

† 10 mg/kg category includes subjects with mg/kg dose that is ≥ 9.5 mg/kg and < 10.5 mg/kg.
MK-6072 = bezlotoxumab alone

Clinical Trial Exposure by Age and Gender in Adults

Clinical trial exposure to bezlotoxumab by age and gender for all adult subjects is summarized in Table SIII.2.2.

Table SIII.2.2: Clinical Trial Exposure to Bezlotoxumab in Adults by Age Category and Gender Phase 3 Studies (PN001 + PN002 Integrated) APaT Population

		MK-6072 (bezlotoxumab)		
		Female n (%)	Male n (%)	Total n (%)
Subjects in population		443	343	786
MK-6072				
< 65 Years	< 10 mg/kg	5 (1.1)	4 (1.2)	9 (1.1)
	10 mg/kg†	216 (48.8)	167 (48.7)	383 (48.7)
	> 10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 65 Years	< 10 mg/kg	2 (0.5)	3 (0.9)	5 (0.6)
	10 mg/kg†	216 (48.8)	164 (47.8)	380 (48.3)
	> 10 mg/kg	4 (0.9)	5 (1.5)	9 (1.1)
< 75 Years	< 10 mg/kg	6 (1.4)	5 (1.5)	11 (1.4)
	10 mg/kg†	303 (68.4)	252 (73.5)	555 (70.6)
	> 10 mg/kg	3 (0.7)	2 (0.6)	5 (0.6)
≥ 75 Years	< 10 mg/kg	1 (0.2)	2 (0.6)	3 (0.4)
	10 mg/kg†	129 (29.1)	79 (23.0)	208 (26.5)
	> 10 mg/kg	1 (0.2)	3 (0.9)	4 (0.5)

† 10 mg/kg category includes subjects with mg/kg dose that is ≥ 9.5 mg/kg and < 10.5 mg/kg.
MK-6072 = bezlotoxumab alone

Clinical Trial Exposure by Racial/Origin in Adults

Clinical trial exposure to bezlotoxumab by race for all adult subjects is summarized in Table SIII.2.4. The majority of bezlotoxumab-treated subjects were White (652/82.9%) followed by Asian (68/8.7%) and Black or African American (46/5.9%).

Table SIII.2.3: Clinical Trial Exposure to Bezlotoxumab in Adults by Race Phase 3 Studies (PN001 + PN002 Integrated) APaT Population

		MK-6072 (bezlotoxumab) n (%)
Subjects in population		786
MK-6072		
American Indian or Alaska Native	< 10 mg/kg	0 (0.0)
	10 mg/kg†	5 (0.6)
	> 10 mg/kg	0 (0.0)
Asian	< 10 mg/kg	2 (0.3)
	10 mg/kg†	66 (8.4)
	> 10 mg/kg	0 (0.0)
Black or African American	< 10 mg/kg	0 (0.0)
	10 mg/kg†	46 (5.9)
	> 10 mg/kg	0 (0.0)
Multiple	< 10 mg/kg	0 (0.0)
	10 mg/kg†	15 (1.9)
	> 10 mg/kg	0 (0.0)
White	< 10 mg/kg	12 (1.5)
	10 mg/kg†	631 (80.3)
	> 10 mg/kg	9 (1.1)

† 10 mg/kg category includes subjects with mg/kg dose that is ≥ 9.5 mg/kg and < 10.5 mg/kg.
MK-6072 = bezlotoxumab alone

Clinical Trial Exposure in Special Populations in Adults

The eligibility criteria for the Phase 3 adult trials (MK-3415A P001 + P002) were unrestrictive and a diverse population was enrolled. Safety was evaluated in subgroups based on intrinsic factors of interest (including age, gender, and race). An exception was that children (<18 years of age) and females who were pregnant and/or lactating were excluded. None of the females who were enrolled and exposed to bezlotoxumab alone were reported to have become pregnant or to have breastfed during the study follow-up period. One subject in P002 receiving actoxumab + bezlotoxumab became pregnant during the course of the trial. On Day 258, the subject had a spontaneous, live, vaginal birth of a healthy, female baby.

Clinical trial exposure to bezlotoxumab in adult special populations is summarized in Table SIII.2.4. Renal impairment was defined as serum creatinine ≥ 1.5 mg/dL. Hepatic impairment was defined by having two or more of the following at baseline: (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 Comorbidity Index).

Table SIII.2.4: Clinical Trial Exposure to Bezlotoxumab in Adults by Special Population
Phase 3 Studies (PN001 + PN002 Integrated)
APaT Population

		MK-6072 (bezlotoxumab)		
		Female n (%)	Male n (%)	Total n (%)
Subjects in population		443	343	786
Renal Impairment				
Yes (Serum creatinine ≥ 1.5 mg/dL)	< 10 mg/kg	1 (0.2)	3 (0.9)	4 (0.5)
	10 mg/kg†	42 (9.5)	78 (22.7)	120 (15.3)
	> 10 mg/kg	0 (0.0)	2 (0.6)	2 (0.3)
No (Serum creatinine < 1.5 mg/dL)	< 10 mg/kg	6 (1.4)	4 (1.2)	10 (1.3)
	10 mg/kg†	382 (86.2)	249 (72.6)	631 (80.3)
	> 10 mg/kg	4 (0.9)	3 (0.9)	7 (0.9)
Unknown	< 10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)
	10 mg/kg†	8 (1.8)	4 (1.2)	12 (1.5)
	> 10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic Impairment				
Yes	< 10 mg/kg	0 (0.0)	1 (0.3)	1 (0.1)
	10 mg/kg†	24 (5.4)	24 (7.0)	48 (6.1)
	> 10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)
No	< 10 mg/kg	7 (1.6)	6 (1.7)	13 (1.7)
	10 mg/kg†	399 (90.1)	299 (87.2)	698 (88.8)
	> 10 mg/kg	4 (0.9)	5 (1.5)	9 (1.1)
Unknown	< 10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)
	10 mg/kg†	9 (2.0)	8 (2.3)	17 (2.2)
	> 10 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)

† 10 mg/kg category includes subjects with mg/kg dose that is = 9.5 mg/kg and < 10.5 mg/kg.
MK-6072 = bezlotoxumab alone

Paediatric population

MK-6072 P001 was conducted in paediatric participants aged 1 to <18 years of age with CDI who were receiving SoC antibiotic therapy for a primary or recurrent episode of CDI. Similar to the adult Phase 3 studies, the protocol had broad inclusion and limited exclusion criteria, permitting an evaluation of participants with diverse underlying comorbidities and a wide range of clinical characteristics associated with a high risk for additional CDI episodes.

Clinical trial exposure by dose in paediatric population

All 107 participants that received bezlotoxumab completed a 10 mg/kg infusion of bezlotoxumab.

Clinical trial exposure by age, gender and race in paediatric population

Clinical trial exposure to bezlotoxumab by age, gender and race for all treated subjects is summarized in table Table SIII. 2.5

Table SIII.2.5: Clinical Trial Exposure to Bezlotoxumab in Pediatric Patients 1 to <18 years of Age
Phase 3 Study (MK-6072 001)
Participants Characteristics APaT

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

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

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

The reason for excluding subpopulations from bezlotoxumab clinical trials were the following: 1) need to exclude subjects with an uncontrolled chronic diarrheal illness that could confound interpretation of safety and/or efficacy results, and 2) need to exclude special populations such as pregnant women. Reasons for excluding subpopulations are summarized in **Table SIV.1.1.**

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Pregnant, breastfeeding, or expecting to conceive or father children within the projected treatment duration.	Avoid potential harm to the unborn fetus or breastfeeding newborn. Adequate and well controlled studies with bezlotoxumab have not been conducted in pregnant women. There are no safety studies in newborns.	**No**	Adequately reflected in the CCDS and SmPC
Lactating women were excluded from the clinical trials.	It is not known whether bezlotoxumab is secreted in human milk.	**No**	Adequately reflected in the CCDS and SmPC
Plans to donate blood and/or blood products within 6 months following the infusion	This exclusion criterion was due to GCP reasons. Monoclonal antibodies, including bezlotoxumab, can be detected in serum for several months after infusion. Therefore, a patient receiving a blood product donated by a subject in the clinical trials would likely receive the experimental antibodies without having consented to receive this experimental product.	**No**	This is not a safety concern for bezlotoxumab
Patient is not expected to survive for 72 hours	This exclusion criterion was included in order to facilitate patient completion of the trial.	**No**	This is not a safety concern for bezlotoxumab.
Patient with a planned surgery for CDI within 24 hours	This exclusion criterion was included in order to facilitate subject completion of the trial.	**No**	This is not a safety concern for bezlotoxumab.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patient 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, and/or 7. Patients with a history of inflammatory bowel disease who are controlled (i.e, had no recent active diarrhea prior to current *C. difficile* episode) may be enrolled if in the opinion of the investigator the symptoms are more likely due to CDI than a f lare of the inflammatory bowel disease.	These subjects were excluded because ulcerative colitis and Crohn's disease are alternative causes of diarrhea. Therefore, the presence of diarrhea due to these chronic conditions in a patient who is colonized with *C. difficile* would have confounded evaluation of the efficacy of bezlotoxumab.	**No**	This is not a safety concern for bezlotoxumab.
Patient has previously participated in this trial, has previously received MK-3415 (actoxumab) or MK-6072 (bezlotoxumab), either alone or in combination, has received a *C. difficile* vaccine, or has received any other experimental monoclonal antibody against *C. difficile* toxin A or B.	This exclusion criterion was included in order to avoid prior medications that may confound the efficacy assessments since these therapies may decrease the incidence of CDI recurrence. Also, efficacy and safety of experimental antibodies and vaccines has not been established.	**No**	There is no evidence to suggest a safety concern for subjects concurrently using these agents with bezlotoxumab.
Patient has received immune globulin within 6 months prior to receipt of the infusion or is planning to receive immune globulin prior to the completion of the 12-Week study period	This exclusion criterion was included in order to avoid concomitant medications that may confound the efficacy assessments since these therapies have been shown to decrease the incidence of CDI recurrence.	**No**	There is no evidence to suggest a safety concern for subjects concurrently using these agents with bezlotoxumab.
Patient for whom treatment with SoC is planned for longer than 14 days (e.g., planned tapered or pulsed regimen of vancomycin).	This exclusion criterion was included because the definition of clinical cure required no more than a 14-day regimen of SoC antibiotics. Therefore, subjects receiving tapered or pulsed regimens for treatment of CDI (which are traditionally longer than 14 days) would have automatically been considered a failure for this endpoint.	**No**	There is no evidence to suggest a safety concern for subjects concurrently using these agents with bezlotoxumab.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patient has received more than 24-hour regimen of cholestyramine, cholestimide, rifaximin, or nitazoxanide within 14 days prior to receipt of the infusion or is planning to receive these medications prior to the completion of the 12-Week study period.	This exclusion criterion was included in order to avoid concomitant medications that may confound the efficacy assessments since these therapies have been shown to decrease the incidence of CDI recurrence.	**No**	There is no evidence to suggest a safety concern for subjects concurrently using these agents with bezlotoxumab.
Patient 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. Patients receiving opioid medications at the onset of diarrhea 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.	In line with guidelines for CDI treatment, these subjects were excluded, since use of these medications can lead to serious complications in patients with CDI.	**No**	There is no evidence to suggest a safety concern for subjects concurrently using these agents with bezlotoxumab.
Patient plans to take the probiotic *Saccharomyces boulardii* or receive FMT, or any other therapies that have been demonstrated to decrease CDI recurrences at any time following infusion (Day 1) and through the completion of the 12-Week study period.	This exclusion criterion was included in order to avoid concomitant medications that may confound the efficacy assessments since these therapies have been shown to decrease the incidence of CDI recurrence.	**No**	There is no evidence to suggest a safety concern for subjects concurrently using these agents with bezlotoxumab.
Patient has any other condition that, in the opinion of the investigator, would jeopardize the safety or rights of the patient participating in the trial, would make it unlikely for the patient to complete the trial, or would confound the results of the trial.	This was to ensure subject safety in the trial or completion of the trial.	**No**	This is not relevant to future use of bezlotoxumab.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. The limitations of the clinical trial program are summarized in **Table SIV.2.1.**

Table SIV.2.1: Limitations of Clinical Trial Program

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	The safety profile is based on data from 786 adult subjects with CDI treated with bezlotoxumab in Phase 3 trials.	Using the "Rule of 3", ADRs with a frequency >1/262 could be detected if there were no background incidence. ADRs with a rare or very rare frequency might not be detected.
Due to prolonged exposure	The half-life of bezlotoxumab is approximately 19 days. Adult subjects in Phase 3 were followed for AEs for 12 weeks (~4.5 half-lives). There were a total of 295 subjects who completed the main study and subsequently entered the extension phase of the study with 100 bezlotoxumab-treated and 83 placebo-treated subjects monitored for a total of 9 months.	There are limited data on factors in adult patients that may affect the half-life of mAbs. While some subjects treated with bezlotoxumab were followed for an extended period, the number of these subjects was limited.
Due to cumulative effects	Phase 3 trials were conducted with a single dose administration. Data on cumulative effects (repeated administration) are limited to a Phase 1 trial in which two doses were administered separated by 12 weeks (P004). No data are available on repeated administration after a shorter interval, and no data are available in adult patients.	P004 demonstrated that administration of 2 doses of actoxumab + bezlotoxumab 12 weeks apart is generally well-tolerated, and no treatment-emergent ADA were detected during the 24 weeks follow-up after the 2nd dose. Phase 3 trials were conducted with a single dose administration, i.e., the intended dose.
Which have a long latency	Nonserious adverse events were reported for 28 days following study medication. Serious adverse events and deaths were reported for all adult subjects in the Phase 3 studies through 85±5 days after infusion with study medication. A limitation is that only a subset of subjects was monitored longer than 85 days. Long term follow-up was limited to 100 subjects who were monitored for SAEs related to study medication and SAEs with a fatal outcome through 12 months post-infusion.	ADRs with a long latency might not be detected in the clinical dataset.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Paediatric population	In Phase 3 trial (MK-6072 P001), 107 paediatric patients 1 year of age and older were exposed to one dose of bezlotoxumab.
Elderly population	A substantial number of elderly subjects (65 years of age and older) were enrolled in the Phase 3 trials, as is expected for subjects with CDI.
Patients with relevant comorbidities: • Patients with hepatic impairment	• In the Phase 3 Studies (MK-3415A PN001 + PN002), 49 patients with hepatic impairment (defined by having two or more of the following at baseline: (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 Comorbidity Index)) were exposed to one dose of bezlotoxumab.
• Patients with renal impairment	• In the Phase 3 Studies (MK-3415A PN001 + PN002), 126 patients with renal impairment (defined as serum creatinine ≥ 1.5 mg/dL) were exposed to one dose of bezlotoxumab.
• Patients with cardiovascular impairment	• In the Phase 3 Studies (MK-3415A PN001 + PN002), 604 patients with a history of a cardiovascular impairment (defined as conditions under the cardiac disorders system order class (MedDRA version 17.1)) were exposed to one dose of bezlotoxumab.
• Immunocompromised patients	• In the Phase 3 Studies (MK-3415A PN001 + PN002), 341 immunocompromised patients (defined as an active hematological malignancy, an active malignancy requiring recent cytotoxic chemotherapy, prior hematopoietic stem cell transplant, prior solid organ transplant, asplenia, or neutropenia/pancytopenia due to other conditions) were exposed to one dose of bezlotoxumab.
• Patients with a disease severity different from inclusion criteria in clinical trials	• The clinical development program included subjects with CDI of any severity; therefore, there were no patients with disease severity different from inclusion criteria
Population with relevant different ethnic origin	In the Phase 3 Studies (MK-3415A PN001 + PN002), 786 patients, which included 5 American Indian or Alaska Native, 68 Asian, 46 Black of African American, 15 multiple ethnicities and 652 White, were exposed to one dose of bezlotoxumab.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure estimates from product market introduction (international birth date: 21-OCT-2016) to 31-MAY-2022 were calculated from our Company's internal product distribution data from Worldwide Financial Reporting System (WFRS) and the Financial Sharing Area (FSA) databases.

A summary of the worldwide distribution of bezlotoxumab from product launch to 31-MAY-2022 presented in Table S V.1.2.1 based on the available data. Given bezlotoxumab is available as a single-use, 1000 mg vial, the assumption was made that each vial distributed represents 1 patient treated. The 625 mg vial is approved and marketed only in Japan, therefore the post marketing exposure data is represented separately in Table S V.1.2.1.

SV.1.2 Exposure

The estimated number of doses of bezlotoxumab distributed worldwide from product launch through 31-MAY-2022 is 20,506. This corresponds to 20,506 estimated patients treated.

Table SV.1.2.1: Summary of Post-authorization Exposure

Strength	Distribution (total number of vials) Cumulative to 31-MAY-2022	Estimated Number of Patients Treated Cumulative to 31-MAY-2022
1000 mg IV	19,886	19,886
625 mg IV	620	620
Total	**20,506**	**20,506**

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Bezlotoxumab is available only through prescribing physicians and other health care providers with prescriptive authority. Neither bezlotoxumab nor its components are known to possess addictive properties.

The MAH has not been made aware of any reports for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Important Identified Risks that are being reclassified

There are no Important Identified Risks for bezlotoxumab.

Important Potential Risks that are being reclassified

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

Revision and Reclassification of concerns identified as Missing Information

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

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no identified or potential risks for bezlotoxumab.

SVII.3.2 Presentation of the Missing Information

There is no missing information for bezlotoxumab.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

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

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

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not applicable

Specific Adverse Reaction Follow-Up Questionnaires:

Not applicable

Other Forms of Routine Pharmacovigilance Activities:

Not applicable

III.2 Additional Pharmacovigilance Activities

Not applicable

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for bezlotoxumab.

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

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Not applicable

V.2 Additional Risk Minimization Measures

Not applicable

V.3 Summary of Risk Minimization Measures

Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for bezlotoxumab

This is a summary of the risk management plan (RMP) for bezlotoxumab. The RMP details important risks of bezlotoxumab, how these risks can be minimised, and how more information will be obtained about bezlotoxumab's risks and uncertainties (missing information).

Bezlotoxumab's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how bezlotoxumab should be used.

This summary of the RMP for bezlotoxumab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of bezlotoxumab's RMP.

I. The Medicine and What It Is Used For

Bezlotoxumab is authorised for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in adult and paediatric patients 1 year of age and older at high risk for recurrence of CDI (see SmPC for the full indication). It contains bezlotoxumab as the active substance and it is given as a single intravenous infusion of 10 mg/kg.

Further information about the evaluation of bezlotoxumab’s benefits can be found in bezlotoxumab’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/zinplava

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of bezlotoxumab, together with measures to minimise such risks and the proposed studies for learning more about bezotoxumab's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine’s packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of bezlotoxumab is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of bezlotoxumab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of bezlotoxumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None
*The important identified or potential risks included in prior versions of the RMP have been updated based on the review of accumulating clinical data and the guidance in GVP module 5 (Rev 2), as per routine updates of the RMP during the life cycle of the product.	

II.B Summary of Important Risks

Not applicable

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of bezlotoxumab.

II.C.2 Other Studies in Post-Authorisation Development Plan

Not applicable

REFERENCES

[Ref. 5.4: 03QVDL] Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at Children's Hospitals in the United States, 2001-2006. Pediatrics 2008;122(6):1266-70.

[Ref. 5.4: 03QVFH] Kelly CP, LaMont JT. Clostridium difficile -- More difficult than ever. N Engl J Med 2008;359(18):1932-40.

[Ref. 5.4: 03QVFJ] Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353(23):2442-9.

[Ref. 5.4: 03QXMP] Goorhuis A, Van der Kooi T, Vaessen N, Dekker FW, van den Berg R, Harmanus C, et al. Spread and epidemiology of Clostridium difficile polymerase chain reaction ribotype 027/toxinotype III in The Netherlands. Clin Infect Dis 2007;45(6):695-703.

[Ref. 5.4: 03QYCM] Hu MY, Katchar K, Kyne L, Maroo S, Tummala S, Dreisbach V, et al. Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection. Gastroenterology 2009;136(4):1206-14.

[Ref. 5.4: 03R2CV] Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. J Hosp Infect 2008;70:298-304.

[Ref. 5.4: 03R3RM] Shin BM, Kuak EY, Yoo SJ, Shin WC, Yoo HM. Emerging toxin A-B+ variant strain of Clostridium difficile responsible for pseudomembranous colitis at a tertiary care hospital in Korea. Diagn Microbiol Infect Dis 2008;60(4):333-7.

[Ref. 5.4: 03R67D] Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010;31(5):431-55.

[Ref. 5.4: 03RHFQ] Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for clostridium difficile infection. N Engl J Med 2011;364(5):422-31.

[Ref. 5.4: 03RNPX] Lessa FC, Gould CV, McDonald LC. A current status of clostridium difficile infection epidemiology. Clin Infect Dis 2012;55(S2):S65-S70.

[Ref. 5.4: 03RPWZ] Miller M, Gravel D, Mulvey M, Taylor G, Boyd D, Simor A, et al. Health care-associated Clostridium difficile infection in Canada: Patient age and infecting strain type are highly predictive of severe outcome and mortality. Clin Infect Dis 2010;50:194-201.

[Ref. 5.4: 03RPZB] Bauer MP, Notermans DW, van Benthem BHB, Brazier JS, Wilcox MH, Rupnik M, et al. Clostridium difficile infection in Europe: a hospital-based survey. Lancet 2011;377:63-73.

[Ref. 5.4: 03RPZC] Wiegand PN, Nathwani D, Wilcox MH, Stephens J, Shelbaya A, Haider S. Clinical and economic burden of clostridium difficile infection in Europe: a systematic review of healthcare-facility-acquired infection. J Hosp Infect 2012;81:1-14.

[Ref. 5.4: 03RT8S] Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? Clinical Microbiology and Infection 2012;18:21-7.

[Ref. 5.4: 03RT8T] Khanna S, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, et al. The Epidemiology of Clostridium difficile Infection in Children: A Population-Based Study. Clin Infect Dis 2013;56(10):1401-6.

[Ref. 5.4: 03RT92] Walker AS, Eyre DW, Wyllie DH, Dingle KE, Griffiths D, Shine B, et al. Relationship Between Bacterial Strain Type, Host Biomarkers, and Mortality in Clostridium difficile Infection. Clin Infect Dis 2013;56(11):1589-600.

[Ref. 5.4: 03YFJ5] McDonald LC, Lessa F, Sievert D, Wise M, Herrera R, Gould C, et al. Vital signs: preventing Clostridium difficile infections. MMWR Morb Mortal Wkly Rep 2012;61(9):157-62.

[Ref. 5.4: 0408NH] Hebert C, Du H, Peterson LR, Robicsek A. Electronic health record-based detection of risk factors for Clostridium difficile infection relapse. Infect Control Hosp Epidemiol. 2013 Apr;34(4):407-14.

[Ref. 5.4: 0408NJ] Eyre DW, Walker AS, Wyllie D, Dingle KE, Griffiths D, Finney J, et al. Predictors of first recurrence of Clostridium difficile infection: implications for initial management. Clin Infect Dis. 2012 Aug;55 Suppl 2:S77-87.

[Ref. 5.4: 0408NK] Zilberberg MD, Reske K, Olsen M, Yan Y, Dubberke ER. Development and validation of a recurrent Clostridium difficile risk-prediction model. J Hosp Med. 2014 Jul;9(7):418-23.

[Ref. 5.4: 044763] Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014 Mar 27;370(13):1198-208.

[Ref. 5.4: 046JFB] McFarland LV. Renewed interest in a difficult disease: Clostridium difficile infections-epidemiology and current treatment strategies. Curr Opin Gastroenterol. 2009 Jan;25(1):24-35.

[Ref. 5.4: 046JJ7] Samore MH, DeGirolami PC, Tlucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. Clostridium difficile colonization and diarrhea at a tertiary care hospital. Clin Infect Dis. 1994 Feb;18(2):181-7.

[Ref. 5.4: 046K80] Schalk E, Bohr UR, Konig B, Scheinpflug K, Mohren M. Clostridium difficile-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia. Ann Hematol. 2010 Jan;89(1):9-14.

[Ref. 5.4: 046KQN] D'Agostino RB Sr, Collins SH, Pencina KM, Kean Y, Gorbach S. Risk estimation for recurrent Clostridium difficile infection based on clinical factors. Clin Infect Dis. 2014 May;58(10):1386-93.

[Ref. 5.4: 046KR2] Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID). Lancet Infect Dis. 2014 Dec;14(12):1208-19.

[Ref. 5.4: 046KRB] Debast SB, Vaessen N, Choudry A, Wiegers-Ligtvoet EA, van den Berg RJ, Kuijper EJ. Successful combat of an outbreak due to Clostridium difficile PCR ribotype 027 and recognition of specific risk factors. Clin Microbiol Infect. 2009 May;15(5):427-34.

[Ref. 5.4: 046KRK] Di Bella S, Musso M, Cataldo MA, Meledandri M, Bordi E, Capozzi D, et al. Clostridium difficile infection in Italian urban hospitals: data from 2006 through 2011. BMC Infect Dis. 2013 Mar 22;13:146.

[Ref. 5.4: 046KRT] Dubberke ER, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, et el. Attributable outcomes of endemic Clostridium difficile-associated disease in nonsurgical patients. Emerg Infect Dis. 2008 Jul;14(7):1031-8.

[Ref. 5.4: 046KS0] Gerding DN, Muto CA, Owens RC Jr. Treatment of Clostridium difficile infection. Clin Infect Dis. 2008 Jan 15;46 Suppl 1:S32-42.

[Ref. 5.4: 046MSW] Slimings C, Armstrong P, Beckingham WD, Bull AL, Hall L, Kennedy KJ, et al. Increasing incidence of Clostridium difficile infection, Australia, 2011-2012. Med J Aust. 2014 Mar 17;200(5):272-6.

[Ref. 5.4: 046MYJ] Soyletir G, Eskiturk A, Kilic G, Korten V, Tozun N. Clostridium difficile acquisition rate and its role in nosocomial diarrhoea at a university hospital in Turkey. Eur J Epidemiol. 1996 Aug;12(4):391-4.

[Ref. 5.4: 046PJK] Leffler DA, Lamont JT. Clostridium difficile infection. N Engl J Med. 2015 Apr 16;372(16):1539-48.

[Ref. 5.4: 046PJM] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015 Feb 26;372(9):825-34.

[Ref. 5.4: 046PJN] McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. N Engl J Med. 1989 Jan 26;320(4):204-10.

[Ref. 5.4: 046Q9R] Aguayo C, Flores R, Levesque S, Araya P, Ulloa S, Lagos J, et al. Rapid spread of Clostridium difficile NAP1/027/ST1 in Chile confirms the emergence of the epidemic strain in Latin America. Epidemiol Infect. 2015 Feb 17:1-5. [Epub ahead of print].

[Ref. 5.4: 046Q9T] Bouza E. Consequences of Clostridium difficile infection: understanding the healthcare burden. Clin Microbiol Infect. 2012 Dec;18 Suppl 6:5-12.

[Ref. 5.4: 046Q9W] Abou Chakra CN, Pepin J, Valiquette L. Prediction tools for unfavourable outcomes in Clostridium difficile infection: a systematic review. PLoS One. 2012;7(1):e30258.

[Ref. 5.4: 046QCS] Cherifi S, Delmee M, Van Broeck J, Beyer I, Byl B, Mascart G. Management of an outbreak of Clostridium difficile-associated disease among geriatric patients. Infect Control Hosp Epidemiol. 2006 Nov;27(11):1200-5.

[Ref. 5.4: 046SG3] Kipper I, Drame M, Maestraggi Q, Ben Rabah M, Novella JL, Mahmoudi R. Clostridium difficile infection in elderly patients: prognostic factors of recurrence [abstract]. Eur Geriatr Med. 2011;2S:S98-S9. Abstract no. PC-220.

[Ref. 5.4: 046VLV] Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S, Fushimi K. The burden of Clostridium difficile-associated disease following digestive tract surgery in Japan. J Hosp Infect. 2012 Nov;82(3):175-80.

[Ref. 5.4: 0479V3] Viseur N, Lambert M, Delmee M, Van Broeck J, Catry B. Nosocomial and non-nosocomial Clostridium difficile infections in hospitalised patients in Belgium: compulsory surveillance data from 2008 to 2010. Euro Surveill. 2011 Oct 27;16(43).

[Ref. 5.4: 0479VL] Indra A, Huhulescu S, Fiedler A, Kernbichler S, Blaschitz M, Allerberger F. Outbreak of Clostridium difficile 027 infection in Vienna, Austria 2008-2009. Euro Surveill. 2009 Apr 30;14(17).

[Ref. 5.4: 0479VN] Jin J. JAMA patient page. Clostridium difficile infection. JAMA. 2014 Nov 5;312(17):1818.

[Ref. 5.4: 0479W6] Levy A, Szabo S, Lozano-Ortega G, Lloyd-Smith E, Leung V, Romney MG. The economic burden of Clostridium difficile infection in Canada [abstract]. Abstracts of the ID Week 2013: Advancing Science, Improving Care; 2013 Oct 2-6; San Francisco, CA. ID Week; 2013. p. 1.

[Ref. 5.4: 047BJQ] Bacci S, St-Martin G, Olesen B, Bruun B, Olsen KE, Nielsen EM, et al. Outbreak of Clostridium difficile 027 in North Zealand, Denmark, 2008-2009. Euro Surveill. 2009 Apr 23;14(16).

[Ref. 5.4: 047BJV] Centers for Disease Control and Prevention (CDC). Frequently asked questions about Clostridium difficile for healthcare providers. Atlanta, GA: CDC; 2012. 6 p.

[Ref. 5.4: 047T4D] Olsen MA, Yan Y, Reske KA, Zilberberg M, Dubberke ER. Impact of Clostridium difficile recurrence on hospital readmissions. Am J Infect Control. 2015 Apr 1;43(4):318-22.

[Ref. 5.4: 048Q4Q] Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent Clostridium difficile infection is associated with increased mortality. Clin Microbiol Infect. 2015 Feb;21(2):164-70.

[Ref. 5.4: 049C2D] Gerding DN, Muto CA, Owens RC Jr. Measures to control and prevent Clostridium difficile infection. Clin Infect Dis. 2008 Jan 15;46 Suppl 1:S43-9.

[Ref. 5.4: 04MPF8] van Dorp SM, Smajlovic E, Knetsch CW, Notermans DW, de Greeff SC, Kuijper EJ. Clinical and Microbiological Characteristics of Clostridium difficile Infection Among Hospitalized Children in the Netherlands. Clin Infect Dis. 2017 Jan15;64(2):192-198.

[Ref. 5.4: 04VYHP] Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014 Mar;20(suppl 2):1-26.

[Ref. 5.4: 055SPF] Ooijevaar RE, van Beurden YH, Terveer EM, Goorhuis A, Bauer MP, Keller JJ, et al. Update of treatment algorithms for Clostridium difficile infection. Clin Microbiol Infect. 2018;24:452-62.

[Ref. 5.4: 058630] Nicholson MR, Thomsen IP, Slaughter JC, Creech CB, Edwards KM. Novel risk factors for recurrent Clostridium difficile infection in children. J Pediatr Gastroenterol Nutr 2015 Jan;60(1):18-22.

[Ref. 5.4: 05CYZL] Aldrich AM, Argo T, Koehler TJ, Olivero R. Analysis of treatment outcomes for recurrent Clostridium difficile infections and fecal microbiota transplantation in a pediatric hospital. Pediatr Infect Dis J. 2019 Jan;38(1):32-6.

[Ref. 5.4: 05HF3B] Hengel RL, Ritter TE, Nathan RV, Van Anglen LJ, Schroeder CP, Dillon RJ, et al. Real-world experience of bezlotoxumab for prevention of Clostridioides difficile infection: a retrospective multicenter cohort study. Open Forum Infect Dis. 2020:ofaa097.

[Ref. 5.4: 05KC4L] Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clin Infect Dis. 2012;55(suppl 2):S154-61.

[Ref. 5.4: 05KC52] Cho JM, Pardi DS, Khanna S. Update on treatment of Clostridioides difficile infection. Mayo Clin Proc. 2020 Apr;95(4):758-69.

[Ref. 5.4: 05KCK0] Chudasama D, Thelwall S, Nsonwu O, Rooney G, Wasti S, Hope R. Annual epidemiological commentary: gram-negative bacteraemia, MRSA bacteraemia, MSSA bacteraemia and C. difficile infections, up to and including financial year April 2018 to March 2019. London (United Kingdom): Public Health England (PHE); 2019 Jul 11. 88 p.

[Ref. 5.4: 05KPBC] Dinh A, Le Monnier A, Emery C, Alami S, Torreton E, Duburcq A, et al. Predictors and burden of hospital readmission with recurrent Clostridioides difficile infection: a French nation-wide inception cohort study. Eur J Clin Microbiol Infect Dis. 2019;38:1297-305.

[Ref. 5.4: 080Z6N] Gonzales-Luna AJ, Carlson TJ, Garey KW. Antibiotic therapies for Clostridioides difficile infection in children. J Pediatric Infect Dis Soc. 2021;10(suppl 3):S52-7.

[Ref. 5.4: 080ZG4] Malmqvist L, Ullberg M, Hed Myrberg I, Nilsson A. Clostridium difficile infection in children: epidemiology and trend in a Swedish tertiary care hospital. Pediatr Infect Dis J. 2019 Dec;38(12):1208-13.

[Ref. 5.4: 0826SG] Tougas SR, Lodha N, Vandermeer B, Lorenzetti DL, Tarr PI, Tarr GAM, et al. Prevalence of detection of Clostridioides difficile among asymptomatic children: a systematic review and meta-analysis. JAMA Pediatr. 2021 Oct;175(10):e212328.

[Ref. 5.4: 0829W8] Guh AY, Mu Y, Winston LG, Johnston H, Olson D, Farley MM, et al. Trends in U.S. burden of Clostridioides difficile infection and outcomes. N Engl J Med. 2020 Apr 2;382(14):1320-30.

[Ref. 5.4: 082XYM] Kociolek LK, Palac HL, Patel SJ, Shulman ST, Gerding DN. Risk factors for recurrent Clostridium difficile infection in children: a nested case-control study. J Pediatr. 2015 Aug;167(2):384-9.

[Ref. 5.4: 082XYP] Nicholson MR, Crews JD, Starke JR, Jiang ZD, DuPont H, Edwards K. Recurrent Clostridium difficile infection in children: patient risk factors and markers of intestinal inflammation. Pediatr Infect Dis J. 2017 Apr;36(4):379-83.

[Ref. 5.4: 0833J4] Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clin Infect Dis. 2021 Sep 1;73(5):e1029-44.

[Ref. 5.4: 086K50] Choi KB, Du T, Silva A, Golding GR, Pelude L, Mitchell R, et al. Trends in Clostridioides difficile infection rates in Canadian hospitals during the coronavirus disease 2019 (COVID-19) pandemic. Infect Control Hosp Epidemiol. In press 2022.

[Ref. 5.4: 086K55] Dong N, Li ZR, Qin P, Qiang CX, Yang J, Niu YN, et al. Risk factors for Clostridioides difficile infection in children: a systematic review and meta-analysis. J Hosp Infect. 2022;130:112-21.

[Ref. 5.4: 086K5J] Edwards PT, Thurm CW, Hall M, Busing JD, Kahn SA, Kellermayer R, et al. Clostridioides difficile infection in hospitalized pediatric patients: comparisons of epidemiology, testing, and treatment from 2013 to 2019. J Pediatr. In press 2022.

[Ref. 5.4: 086KD4] Pai S, Aliyu SH, Enoch DA, Karas JA. Five years experience of Clostridium difficile infection in children at a UK tertiary hospital: proposed criteria for diagnosis and management. PLoS One. 2012 Dec 26;7(12):e51728.

[Ref. 5.4: 086KDH] Wolf J, Kalocsai K, Fortuny C, Lazar S, Bosis S, Korczowski B, et al. Safety and efficacy of fidaxomicin and vancomycin in children and adolescents with clostridioides (clostridium) difficile infection: a phase 3, multicenter, randomized, single-blind clinical trial (SUNSHINE). Clin Infect Dis. 2020 Nov 15;71(10):2581-8.

[Ref. 5.4: 0872RY] Luo Y, Grinspan LT, Fu Y, Adams-Sommer V, Willey DK, Patel G, et al. Hospital-onset Clostridioides difficile infections during the COVID-19 pandemic. Infect Control Hosp Epidemiol. 2021;42:1165-6.

[Ref. 5.4: 0872S0] Ponce-Alonso M, Saez de la Fuente J, Rincon-Carlavilla A, Moreno-Nunez P, Martinez-Garcia L, Escudero-Sanchez R, et al. Impact of the coronavirus disease 2019 (COVID-19) pandemic on nosocomial Clostridioides difficile infection. Infect Control Hosp Epidemiol. 2021;42:406-10.

[Ref. 5.4: 0872S2] Food and Drug Administration [Internet]. Washington (DC): Department of Health and Human Services (HHS). FDA approval of REBYOTA; 2022 Dec 19 [cited 2023 Jan 6]; [about 2 screens]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota.

[Ref. 5.4: 0872S5] Kola A, Wiuff C, Akerlund T, van Benthem BH, Coignard B, Lyytikainen O, et al. Survey of Clostridium difficile infection surveillance systems in Europe, 2011. Euro Surveill. 2016;21(29):pii=30291.

[Ref. 5.4: 0872S7] Hazel K, Skally M, Glynn E, Foley M, Burns K, O'Toole A, et al. The other 'C': hospital-acquired Clostridioides difficile infection during the coronavirus disease 2019 (COVID-19) pandemic. Infect Control Hosp Epidemiol. 2022;43:540-1.

ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable