BLA 761046: Bezlotoxumab Injection
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ADVISORY COMMITTEE BRIEFING MATERIALS
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Antimicrobial Drugs Advisory Committee Meeting Briefing Document

Bezlotoxumab Injection

For the Prevention of *Clostridium difficile* Infection (CDI) Recurrence

BLA 761046

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Kenilworth, New Jersey, U.S.A.

ADVISORY COMMITTEE BRIEFING MATERIALS:
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug Antibody(ies)
AE	Adverse Event
APaT	All Patients As Treated
AUC0-inf	Area Under the Curve from zero to infinity
BLA	Biologics License Application
CDAD	*Clostridium difficile* Associated Diarrhea
CDI	*Clostridium difficile* infection
CI	Confidence Interval
CSR	Clinical Study Report
DTL	Drug Tolerance Limit of ADA assay
eDMC	External Data Monitoring Committee
ECL	Electrochemiluminescence
EIA	Enzyme Immunoassay
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FMT	fecal microbiota for transplantation
GCP	Good Clinical Practice
Ig	Immunoglobulin
ITT	Intent To Treat
IV	Intravenous
kg	Kilogram
MAA	Marketing Authorisation Application
mAb	Monoclonal Antibody
MBL	Massachusetts Biologics Laboratory
mcg	Microgram
mg	Milligram
ml	Milliliter
NAb	Neutralizing Anti-drug Antibody(ies)
NAP	North American Pulsed-field
NHDS	National Hospital Discharge Survey
NIS	Nationwide Inpatient Sample
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PP	Per Protocol
PPI	Proton Pump Inhibitor
SoC	Standard of Care
U.S.	United States

1 SUMMARY

Clostridium difficile (*C. difficile*) is a spore forming, gram-positive bacillus that causes infection in humans. It produces two toxins: toxin A, an enterotoxin, and toxin B, which is primarily a cytotoxin [1] [2]. The current theory of pathogenesis of *C. difficile* infection (CDI), previously known as *C. difficile* associated diarrhea (CDAD), is that toxigenic strains of *C. difficile*, either endogenous to the colon or recently acquired, flourish after disruption of the normal bacterial colonic flora and release toxins that disrupt the intestinal epithelium. Symptoms of CDI can range from mild diarrhea to profuse watery diarrhea, leading to dehydration, life threatening complications, and sometimes death. The morbidity and mortality associated with CDI is high − in 2011 there were an estimated 29,000 deaths associated with CDI in the United States, exceeding the number of deaths associated with multi-drug resistant infection and methicillin-resistant *Staphylococcus aureus* (MRSA) infection combined. *C. difficile* has been declared an urgent public health threat by the Centers for Disease Control and Prevention (CDC).

While standard of care antibiotic therapy for CDI is generally effective at resolving the symptoms of CDI, 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. After initial treatment and resolution of diarrhea, up to 35% of CDI patients experience recurrence, which is defined as a return of CDI within weeks to months after the resolution of the initial episode [3] [4] [5]. 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% [6] [3] [5]. Currently there are no therapies indicated for prevention of CDI recurrence, thereby making prevention of CDI recurrence a critical unmet medical need.

A novel approach to the prevention of recurrent CDI is the use of monoclonal antibodies (mAbs) directed against the toxins produced by *C. difficile* as a form of passive immunity in patients receiving antibiotic therapy for CDI. Bezlotoxumab is a fully human mAb of the IgG1 class that binds with high affinity to *C. difficile* toxin B and neutralizes its activity by preventing it from binding to host cells. In neutralization studies with 81 distinct clinical isolates of *C. difficile* spanning 18 ribotypes and at least 7 toxinotypes, bezlotoxumab fully neutralized toxins of all strains tested.

Bezlotoxumab is not an antibiotic, and, therefore, has no inherent antibacterial activity. Preclinical pharmacology studies showed that bezlotoxumab prevents binding of toxin B to its target cells, blocking the cellular intoxication cascade at its first step, and averting the damage and inflammation that normally lead to the symptoms of CDI. Toxin neutralization translates to effective protection in mouse and hamster models of primary or recurrent CDI (when co-administered with the human anti-toxin A mAb [actoxumab], as both mAbs are needed in this animal model), including increased survival, decreased morbidity, and gross intestinal pathology and prevention of damage/inflammation in the gut wall.

Bezlotoxumab administered alone or in combination with actoxumab was evaluated in repeat-dose toxicity studies in mice, and in tissue cross-reactivity studies with human and Swiss Webster or CD1™ mouse tissues. No findings of toxicological significance were observed in these studies.

Bezlotoxumab has pharmacokinetic properties that are similar to those of other fully human monoclonal antibodies, and it is eliminated by protein catabolism. It is not affected by hepatic drug metabolizing enzymes or transporter proteins. Thus, bezlotoxumab has a low potential for drug-drug interactions. As bezlotoxumab binds specifically to an exogenous toxin, rather than immunological factors such as T-cell signaling components or cytokines, it does not cause immune-mediated adverse reactions, and is unlikely to act as a perpetrator of cytokine-mediated drug-drug interaction. Bezlotoxumab is not renally or hepatically eliminated. It may be administered to a diverse population without dose adjustment, including elderly patients, patients with hepatic impairment, and patients with any degree of renal impairment, including those on dialysis. Consistent with other therapeutic monoclonal antibodies that do not interact with the hERG channel due to their relatively large size, bezlotoxumab does not have a clinically meaningful effect on QTc interval.

Two pivotal Phase 3 trials (P001 and P002, also known as MODIFY I and MODIFY II, respectively) were conducted in over 2600 patients with CDI who were receiving standard of care antibiotic therapy for CDI (i.e., oral metronidazole, oral vancomycin [+/- IV metronidazole], or oral fidaxomicin [+/- IV metronidazole]). These trials demonstrated that the administration of a single IV 10 mg/kg dose of bezlotoxumab is superior to placebo in prevention of CDI recurrence (primary endpoint) over a follow-up period of 12 weeks.

The Phase 3 clinical development program enrolled a large population of subjects at over 300 sites in 30 countries, and overall baseline characteristics were balanced across treatment groups. Subjects with confirmed CDI who were receiving standard of care treatment (metronidazole, vancomycin, or fidaxomicin) for CDI were eligible. The entry criteria for this study were not restrictive, especially with regard to exclusionary criteria. As a result, subjects with all levels of CDI severity, with underlying comorbidities, and with or without multiple prior CDI recurrences were enrolled, thereby making the trial subjects a diverse population of CDI patients at risk for recurrence. Overall, 781 subjects who received bezlotoxumab alone, 773 subjects who received the combination of actoxumab + bezlotoxumab, and 773 subjects who received placebo were included in the efficacy analysis population (the Full Analysis Set [FAS] population) across the 2 pivotal Phase 3 clinical trials (P001 and P002).

CDI recurrence rates were 17.4% in the bezlotoxumab and 27.6% in the placebo arms (one-sided p=0.0003) in P001 (MODIFY I) and 15.7% in the bezlotoxumab and 25.7% in the placebo arms (one-sided p=0.0003) in P002 (MODIFY II). The Phase 3 trial results also showed that the combination of the two mAbs (actoxumab + bezlotoxumab) does not have a safety or efficacy benefit over bezlotoxumab alone. In addition, the CDI recurrence rate in patients who received actoxumab alone (P001) was similar to the rate observed in the patients who received placebo.

The safety profile of bezlotoxumab has been characterized in approximately 800 patients who received bezlotoxumab at the proposed clinical dose for product labeling of 10 mg/kg IV in combination with standard of care CDI antibiotic therapy in the Phase 3 trials. The incidence of adverse events (AEs) in the bezlotoxumab arms was generally similar to that in the placebo arms. The most frequently reported AEs (≥4%) in the bezlotoxumab arms that were observed at a higher incidence in the bezlotoxumab arm than in the placebo arm were nausea (6.6%), diarrhea (6.0%), pyrexia (4.6%), and headache (4.5%). Discontinuation of the infusion was rare (1 [0.1%] event in the bezlotoxumab arms), as was the incidence of drug-related serious AEs (SAEs) (4 [0.5%] in the bezlotoxumab, 6 [0.8%] in the actoxumab + bezlotoxumab, and 2 [0.3%] in the placebo arms). There was no association between changes in hematology and chemistry laboratory values, vital signs, or QTc intervals and treatment arm. Bezlotoxumab administration did not result in the development of treatment emergent anti-drug antibodies in the Phase 2 and 3 trials; these results support the conclusion that bezlotoxumab has a very low potential for immunogenicity.

This briefing document provides an overview of the development of bezlotoxumab, including preclinical and clinical data which support the conclusion that bezlotoxumab:

- Fulfills a significant unmet medical need for therapies to prevent CDI recurrence
- Produces a clinical and statistically significant reduction in the incidence of CDI recurrence in patients 18 years or older receiving antibiotic therapy for CDI.
- Is efficacious in a diverse group of patients, including patients at highest risk for CDI recurrence.
- Is well tolerated and has a safety profile similar to placebo.
- Has a favorable benefit/risk profile.

The proposed indication is:

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

The recommended dose of bezlotoxumab is 10 mg/kg administered as an intravenous (IV) infusion over 60 minutes as a single dose.

Given the potential for bezlotoxumab to address a serious unmet medical need, the FDA has granted the bezlotoxumab Biologics Licensing Application (BLA) a priority review designation.

2 BACKGROUND

This document provides a summary of the results of clinical trials conducted to support the licensure of bezlotoxumab (also known as MK-6072, CDB1, or MDX-1388, also referred to as BEZLO), a monoclonal antibody (mAb) targeted against *C. difficile* toxin B. Results of trials of actoxumab, the mAb targeted against *C. difficile* toxin A (also known as MK-3415,

GS-CDA1, or CDA1, also referred to as ACTO), although not intended for licensure, are also described herein, as bezlotoxumab was evaluated alone or in combination with actoxumab in clinical trials. The combined administration of bezlotoxumab and actoxumab (hereafter referred to as actoxumab + bezlotoxumab) is also known as MK-3415A.

2.1 *Clostridium difficile* Infection (CDI)

C. difficile is an anaerobic, spore-forming gram-positive bacillus that produces two toxins: toxin A, an enterotoxin, and toxin B, which is primarily a cytotoxin [1] [2].

Most, if not all, strains isolated from CDI patients have been toxin B (+) strains, with a majority also expressing toxin A [7] [8]. Disruption of protective colonic microflora results in excessive growth of *C. difficile* and toxin production and development of disease.

The spectrum of symptoms associated with CDI includes abdominal pain, profuse watery diarrhea, pseudomembranous colitis, and death. CDI symptoms can be exacerbated in the elderly and patients with co-morbidities [9]. 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% in Europe and North America [10] [11] [12] [13].

The main risk factors for CDI are: host factors (advanced age, impaired immune status, comorbid conditions), increased exposure to *C. difficile* spores (via the hospital/facility environment, increased length of hospital stay, infected roommates, or hand carriage through healthcare personnel), and factors that disrupt the colonic microflora (antimicrobials, other medications [such as cytotoxic chemotherapy], or procedures) [14] [15].

CDI is diagnosed based on patient symptoms and detection of toxigenic *C. difficile* in stool [9]. The most common approaches for testing in the clinical setting include polymerase chain reaction (PCR) tests which detect the microbial toxin genes, and enzyme immunoassay (EIA) tests which detect the presence of toxins in stool.

Current strategies for treating CDI include use of CDI-active antibiotics, and discontinuation of treatment of concurrent infections with antibiotics that disrupt the gut microbial flora, when possible. Published treatment guidelines consider oral metronidazole, oral vancomycin and oral fidaxomicin guidelines as standard-of-care CDI-active antibiotics [16] [17]; in this document, these agents are collectively termed standard of care antibiotics. For mild cases of primary CDI, oral metronidazole is recommended as the standard of care. For more severe cases of CDI, oral vancomycin or oral fidaxomicin are recommended. The addition of IV metronidazole to oral vancomycin is recommended in severe, complicated cases.

2.2 Health Burden of CDI

CDI is the most commonly recognized cause of diarrhea-associated nosocomial infection in adults in the United States and Europe [18] [19] [9]. Cases of community-associated CDI have been increasing in recent years, suggesting that the disease is spreading outside of the hospital into the broader community [20] [21] [22] [23] [24] [25] [26]. In 2011, approximately one third of CDI cases in the United States were community-associated CDI [4] [27] [21]. The U.S. Centers for Disease Control (CDC) has declared *C. difficile* as one of

three urgent public health threats caused by bacterial infections [28]. According to the CDC estimates, in 2011 *C. difficile* was responsible for 453,000 infections and was associated with approximately 29,000 deaths [4].

Primary CDI results in a substantial economic burden due to increases in the use of health care resources; intensive care unit (ICU) admission, prolonged therapy, or surgery [29] [30] [31] [32] [33] [34] [35]. The estimated cost for CDI in acute care settings in the United States is $4.8 billion (2008 dollars) [36].

CDI recurrence further increases the cost-impact of the disease. Patients with recurrent CDI tend to have longer hospital stays, and are more likely to be readmitted to the hospital compared with patients with primary CDI; consequently, the associated costs are higher [37] [38] [39] [40]. After adjustment for demographics, comorbidities and medications, recurrent CDI was associated with a 2.5 times higher rate of hospital readmissions and nearly 4 times higher rate of readmission days compared with non-recurrent CDI [38]. The 180-day estimated attributable inpatient cost of recurrent CDI in the United States is $11,631 (95% CI, $8,937–$14,588) (2014 costs) [41]. Cost estimates of CDI do not consider the high costs that may be absorbed in the outpatient settings.

2.3 CDI Recurrence – Unmet Medical Need

One of the greatest challenges in managing CDI is preventing its recurrence. After initial treatment and resolution of diarrhea, up to 35% of CDI patients experience recurrence [3] [4] [5]. Of those who have a primary recurrence, 40% will have another CDI episode, and after 2 recurrences, the likelihood of an additional episode increases to 65%. The severity of disease, associated complications, and the rate of hospitalizations increase dramatically for patients who have experienced recurrence at least once [5].

The risk factors for CDI recurrence are associated with inadequate antitoxin antibody response and persistent disruption of the colonic flora, which create an environment where *C. difficile* flourishes and causes disease [3] [42] [43] [44] [45] [5] [46] [6]. These risk factors include: advanced age (>65 years), previous episodes of CDI, a weakened immune system, infection with certain *C. difficile* ribotypes associated with poor outcomes (e.g., BI/NAP1/027, also known as ribotype 027), exposure to antibiotics (particularly clindamycin, cephalosporins, and fluoroquinolones), hospitalization/length of hospital stay, comorbidities (such as inflammatory bowel disease, colorectal cancer, or kidney disease), use of proton pump inhibitors (PPIs), and surgery of the gastrointestinal tract [47] [48] [9] [49] [4] [47] [50].

Published literature on CDI clinical management, as well as treatment guidelines, suggest various approaches for the treatment of recurrent CDI. These include repeat courses of vancomycin or metronidazole, vancomycin in tapered and pulsed doses, vancomycin followed by rifaximin, fidaxomicin, IV immunoglobulin, and therapy with microorganisms including fecal microbiota for transplantation (also referred to as fecal bacteriotherapy or FMT) [51]. Treatment of a first recurrent CDI episode with a repeat course of metronidazole or vancomycin is successful in ~50% of patients [9]. 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 [52]. Fecal microbiota for transplantation remains an investigational treatment option, as it has not been tested in large randomized clinical trials, and its safety and efficacy have not been established. None of the therapies listed above have been tested in adequately powered, randomized, controlled clinical trials in patients with multiple CDI recurrences. There are no treatments that are currently licensed for prevention of CDI recurrence. Accordingly, the availability of safe and efficacious therapies for prevention of CDI recurrence represents a critical unmet medical need.

3 NON-CLINICAL PROGRAM

3.1 Mechanism of Action

Standard of care antibiotics for CDI target the *C. difficile* bacterium. While this approach is generally successful in resolving the primary infection, disruption of the microbiota that normally colonizes the human gut is a collateral effect with any antibiotic, including the antibiotics used to treat CDI [53] [54]. Because the enteric microbiota provides a natural defense against *C. difficile*, through competition for nutrients and the release of metabolites that directly inhibit *C. difficile* germination and growth [55], continued disruption of the enteric microbiota in the days and weeks following treatment with CDI-active antibiotics can allow surviving or newly acquired *C. difficile* spores to germinate, causing recurrence of CDI [53]. The period of continued dysbiosis following cure of the initial episode is considered to be the at-risk window of susceptibility to recurrence. Treatment of recurrent CDI with additional courses of antibiotics causes further disruption of microbiota and can perpetuate a cycle of recurrent disease.

The symptoms of CDI are caused by either or both of the large clostridial toxins produced by *C. difficile*, toxin A and toxin B. In preclinical studies, *C. difficile* toxin A and toxin B have been shown to cause disruption of cellular morphology, depolarization, and death of gut epithelial cells, leading to intestinal wall damage and disruption of the intestinal barrier function that normally regulates transport of water and solutes across the gut wall [8] [54]. Additionally, affected cells release pro-inflammatory mediators such as IL-8, which attract neutrophils and monocytes, further exacerbating damage [56] [57].

Passive or active immunization with antibodies against toxins A and B is protective in rodents challenged with toxigenic strains of *C. difficile*, underscoring the important role of toxins in mediating CDI in animal models [58] [59] [60] [61] [62]. In patients, Kyne et al. [63] [64] and Leav et al. [65] demonstrated that antibody-mediated protection extends to clinical disease by showing a correlation between serum levels of neutralizing antitoxin antibodies and the incidence of both primary and recurrent CDI.

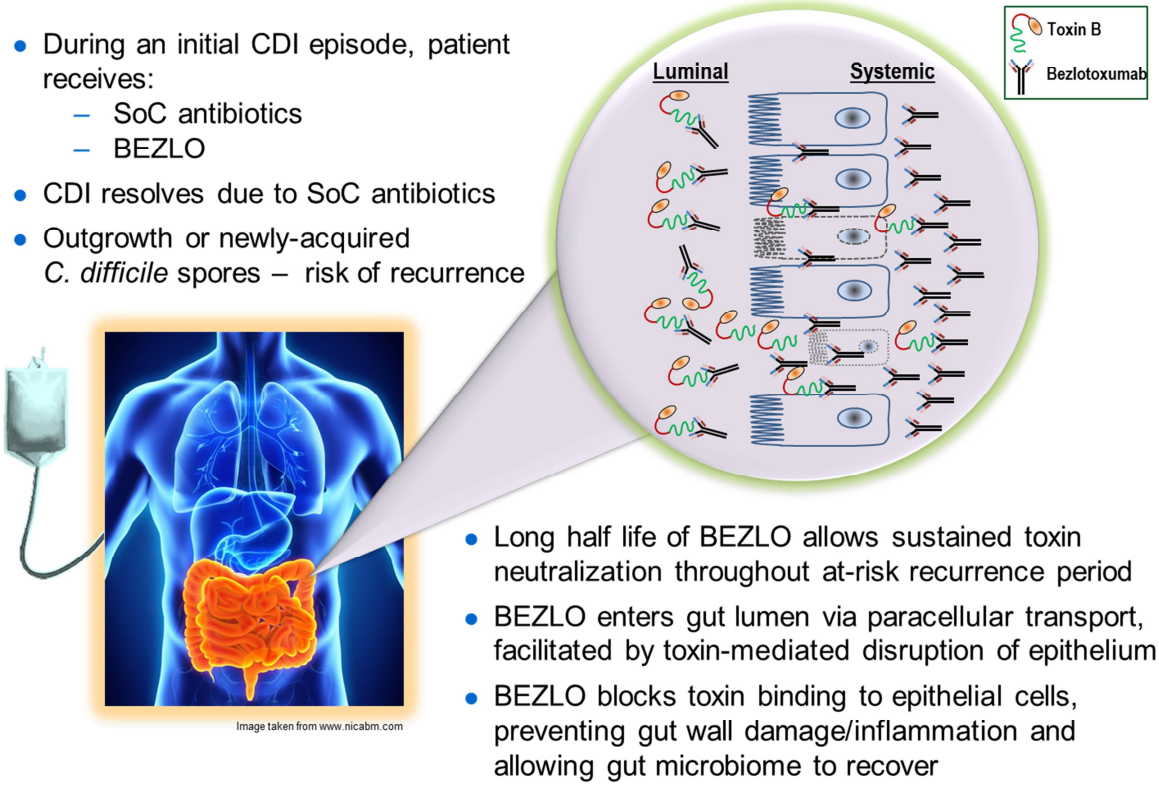
The relative biological importance of *C. difficile* toxins A and B in CDI is complex and appears to be host species-dependent. Neutralization of both toxins appears necessary for maximal protection in hamsters and mice, but neutralization of toxin B alone appears sufficient in piglets [62] and humans, the latter as evidenced by the results of the Phase 3 trials of bezlotoxumab given alone or in combination with actoxumab (described herein [see Section 6.3]).

Bezlotoxumab is a mAb specifically directed against *C. difficile* toxin B. It does not cross-react with toxin A or with human tissues. Bezlotoxumab binds with high affinity to the receptor binding domain of toxin B ($K_d < 1 \times 10^{-9}$ M) and neutralizes its activity by preventing it from binding to host cells. Bezlotoxumab fully neutralizes toxin B of all ribotypes of *C. difficile* tested to-date, as assessed in a comprehensive *in vitro* neutralization study encompassing 81 individual clinical isolates from North America, Europe and Japan and including the following 18 clinically-important ribotypes: 001, 002, 003, 012, 014, 017, 018, 023, 027, 053, 063, 077, 078, 081, 087, 106, 198, and 369.

Bezlotoxumab does not have antimicrobial activity and does not take the place of antibiotic therapy for the baseline episode of CDI. As a mAb, bezlotoxumab has a long half-life with serum concentrations observed for up to 12 weeks post-infusion. Thus, when administered concurrently with SoC antibiotics (metronidazole, vancomycin, or fidaxomicin) during a CDI episode, bezlotoxumab prevents recurrent infections, by providing passive immunity against *C. difficile* toxin B produced by the outgrowth of persistent or newly-acquired spores, throughout the at-risk window of susceptibility to recurrence, when the gut microbiota has not yet fully recovered. Notably, administration of bezlotoxumab is expected to be sparing of the normal gut microbiota, thus allowing the body's natural defense against *C. difficile* the opportunity to re-establish itself once standard of care antibiotics have been discontinued following successful cure of an initial episode of CDI.

While the precise site of action of bezlotoxumab in patients is unknown, the site of infection in CDI - and thus the site of toxin production - is within the lumen of the intestine, whereas bezlotoxumab is administered systemically through intravenous infusion. The preclinical data suggest that bezlotoxumab crosses the gut wall through paracellular transport, facilitated by toxin-induced disruption of the gut epithelium, to reach the site of infection in the lumen of the gut. Consistent with this, bezlotoxumab was detected in intestinal content of hamsters and piglets infected with *C. difficile* (but not in healthy animals). Because toxin can cross the epithelial wall from the luminal to the systemic space through the same mechanism, binding of bezlotoxumab to toxin may also occur on the systemic side of the intestinal wall, thereby preventing potential systemic effects of the infection.

Figure 1
Mechanism of Action of Bezlotoxumab



3.2 Nonclinical Toxicology

The ICH S6(R1) guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals indicates that only short term safety studies in one species are required for antibody products directed at foreign targets such as bezlotoxumab and actoxumab. As such, two-week toxicity studies in mice and in vitro tissue cross-reactivity studies have been conducted. No additional toxicity studies, including reproductive toxicity studies, were required. No findings of toxicological significance were observed in the in vivo repeat-dose toxicity studies in mice performed with bezlotoxumab and/or actoxumab. The no-observed-adverse-effect-level (NOAEL) for bezlotoxumab alone or in combination with actoxumab was ≥125 mg/kg per molecule (the maximum feasible dose and highest dose tested). There were no findings of toxicological significance observed in the in vitro tissue cross-reactivity studies using normal human or SW or CD1™ mouse tissues.

4 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The evaluation of bezlotoxumab (either alone or in combination with actoxumab) was comprehensive. The clinical development program, including the trials involving actoxumab only, consisted of nine clinical trials: five Phase 1 trials, two Phase 2 trials, and two pivotal Phase 3 trials. All clinical trials have been completed, and no trials are ongoing. A summary of the clinical development program is provided in [Table 1].

Table 1
Summary of the Bezlotoxumab Clinical Development Program

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 (MODIFY I)	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 (MODIFY II)	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, placebo=0.9% sodium chloride

5 CLINICAL PHARMACOLOGY

The clinical pharmacology program included five Phase 1 trials in healthy adult subjects evaluating the safety, pharmacokinetics (PK), and immunogenicity of bezlotoxumab and actoxumab, each administered alone or in combination (actoxumab + bezlotoxumab). Four trials studied bezlotoxumab: a dose-ranging PK trial of bezlotoxumab and actoxumab alone and in combination (P020), a trial assessing a 60 minute infusion of actoxumab + bezlotoxumab (P005), a trial of actoxumab + bezlotoxumab in Japanese subjects (P006), and a trial examining the immunogenicity and tolerability of a second dose of actoxumab + bezlotoxumab given 12 weeks after the first dose (P004). Subjects received doses ranging from 0.3 mg/kg to 20 mg/kg of bezlotoxumab alone or in combination with actoxumab. P019 was an additional Phase 1 trial that examined actoxumab alone, and will not be discussed further given the focus on bezlotoxumab as the product for registration. Because therapeutic mAbs have a low potential for drug-drug interactions (DDI), no dedicated DDI studies were performed. A summary of the key findings from the clinical pharmacology program is presented below.

5.1 Pharmacokinetics in Humans

Bezlotoxumab PK was characterized by a population PK analysis based on data obtained from Phase 1 (P004, P005, and P006) and Phase 3 (P001 and P002) trials. This analysis included 72 healthy subjects from the Phase 1 trials, including 29 healthy subjects who received a second dose of actoxumab + bezlotoxumab (P004), as well as 1515 subjects with CDI from the Phase 3 trials who received a 10 mg/kg dose of bezlotoxumab administered alone or as actoxumab + bezlotoxumab. In addition to the population PK analysis, PK data from these subjects with CDI were also used to assess exposure-response relationships for efficacy and safety [see Sections 6.3.8 and 7.3.2].

Key findings related to bezlotoxumab PK:

- The absorption, distribution, metabolism, and excretion (ADME) of bezlotoxumab are similar to other IV administered mAbs [66] [67] [68], with 100% bioavailability, limited extravascular distribution, low clearance, and elimination by degradation through protein catabolism.
- Bezlotoxumab was detected in the stool of subjects with CDI, indicating that it reaches the site of infection in the gut, though the gut is not thought to be a major route of elimination for this mAb.
- There is no PK interaction between actoxumab and bezlotoxumab; hence, the PK of bezlotoxumab can be considered independently of actoxumab in subjects who received both mAbs.
- Based on the population PK analysis, the geometric mean (%CV) clearance (CL) of bezlotoxumab is 0.317 L/day (40%), with a volume of distribution of 7.33 L (16%) and an elimination half-life (t½) of approximately 19 days (28%).

- With a half-life of 19 days, bezlotoxumab is present in serum at measurable concentrations during the first 12 weeks after treatment, when patients are at greatest risk of recurrence.
- In subjects with CDI who received a single 10 mg/kg IV dose of bezlotoxumab, mean bezlotoxumab area-under-the curve concentration (AUC0-inf) and peak concentration (Cmax) are 53,000 µg.h/mL and 185 µg/mL, respectively. Bezlotoxumab has moderate PK variability (40% and 21% CV for AUC0-inf and Cmax).
- The AUC0-inf and Cmax of bezlotoxumab in healthy subjects increases in an approximately dose proportional manner across the 0.3 to 20 mg/kg dose range.

5.2 Effect of Intrinsic and Extrinsic Factors on Bezlotoxumab Exposure

Intrinsic Factors

Therapeutic antibodies such as bezlotoxumab are primarily eliminated by protein catabolism and thus clearance is not dependent on a single organ [68]. Consequently, intrinsic factors such as organ dysfunction or age typically have limited effect on the exposure of therapeutic antibodies [69] and therefore are not anticipated to affect the exposure of bezlotoxumab to a clinically meaningful extent. For this reason, dedicated Phase 1 trials of intrinsic factors and organ dysfunction were not conducted for bezlotoxumab. Instead, the potential effects of intrinsic factors, including demographic variables, organ dysfunction, and relevant laboratory parameters such as albumin, were assessed in a population PK analysis based on pooled Phase 1 healthy subject and Phase 3 patient PK data.

The clearance of bezlotoxumab increased with increasing body weight. The resulting exposure differences were adequately addressed by the administration of a weight-based dose. The effects of age, gender, BMI, race, ethnicity, albumin, clinical comorbidities, renal impairment, and hepatic impairment on the exposure of bezlotoxumab are moderate (i.e. less than 40%) and not clinically meaningful. As such, the dose of 10 mg/kg may be used in patients from a broad demographic background with various disease states without dose adjustment, including elderly patients, patients with hepatic impairment, and patients with any degree of renal impairment, including those on dialysis.

Extrinsic Factors

Concomitant medications are not anticipated to affect the PK of bezlotoxumab, as mAbs are not eliminated by metabolic or transporter pathways that are typically affected by concomitant medications. Standard of care therapies for the treatment of CDI (i.e., metronidazole, vancomycin, and fidaxomicin), as well as concomitant non-standard of care systemic antibiotic use and PPI use, were evaluated in the population PK analysis. Based on this analysis, the effects of standard of care therapies and concomitant use of non-standard of care systemic antibiotics or PPIs on the PK of bezlotoxumab were small (i.e., 20% or less) and not clinically meaningful.

Likewise, bezlotoxumab is not anticipated to affect the PK of concomitantly administered medications, as it is a highly specific mAb that targets a non-endogenous antigen (*C. difficile*

toxin B). No inflammatory-mediated effects on metabolic enzymes are expected, since bezlotoxumab does not react with an endogenous target; consequently, no drug-drug interaction studies in the disease state were performed.

Thus, as bezlotoxumab is eliminated by protein catabolism and is neither hepatically metabolized nor renally eliminated, no dose adjustments for bezlotoxumab or concomitant medications are necessary. Bezlotoxumab has a low potential to be a perpetrator or victim of drug-drug interactions.

Dose Selection

The bezlotoxumab clinical dose of 10 mg/kg was selected for evaluation in Phase 2 based on data from preclinical studies and clinical trials in healthy subjects. The 10 mg/kg dose in healthy subjects produced median serum concentrations that were approximately matched to concentrations that provided protection from CDI in a hamster model.

Data from the Phase 2 trial demonstrated robust efficacy for the prevention of CDI recurrence at the 10 mg/kg dose. Thus, the 10 mg/kg dose was selected for the pivotal Phase 3 trials. As discussed below, administration of this dose led to reduction in CDI recurrence in both Phase 3 trials, and consequently, the dose of 10 mg/kg is proposed for product labeling.

6 CLINICAL DEVELOPMENT PROGRAM

The Phase 2/3 clinical development program included four trials in which bezlotoxumab and actoxumab were studied alone or in combination (actoxumab + bezlotoxumab). The two Phase 2 trials were P018 and P017, and the two Phase 3 trials were P001 and P002 (MODIFY I and MODIFY II). All four of these clinical trials were randomized, double-blind, placebo-controlled, multi-center, safety and efficacy trials conducted in adults 18 years of age or older who were concurrently receiving standard of care antibiotic treatment for a primary or recurrent episode of CDI. The trials were designed to assess whether a single IV infusion of the mAbs (either alone or in combination), given with standard of care antibiotics, decreases the proportion of subjects with CDI recurrence, as compared to treatment with a single infusion of placebo given with standard of care antibiotics. The two pivotal Phase 3 trials followed subjects for efficacy and safety for 12 weeks; they were identical in design, conduct, and statistical analysis with the following exceptions: (1) P002 had 3 treatment groups instead of 4 (the actoxumab alone arm was not included in the trial because in the earlier Phase 2 trial (P018), the CDI recurrence rate among subjects who had received actoxumab alone was similar to the rate observed in the subjects who had received placebo); (2) P002 did not include a planned interim analysis for stopping enrollment in the individual mAb treatment groups; and (3) P002 had an extended follow-up period through Month 12 in a subset of subjects (approximately 300) to assess for CDI recurrence and colonization with toxigenic *C. difficile*. The approach of ensuring consistency in design, conduct, and statistical analysis in the two Phase 3 trials resulted in a robust dataset to confirm the efficacy and safety findings.

This section summarizes the results from the 4 efficacy trials which evaluated bezlotoxumab and actoxumab. Results from the Phase 2 trials informed the design of the Phase 3 program.

Therefore, a brief overview of the efficacy results from the two Phase 2 (P017 and P018) trials is presented in Section 6.1. The design of the Phase 3 clinical development program was rigorous and comprehensive. A detailed description of the design of the two Phase 3 trials (P001 and P002) and a summary of the efficacy results are included in Section 6.2.

6.1 Phase 2 Trials – Protocol 018 and Protocol 017

Actoxumab vs Placebo (Protocol 018)

P018 was a randomized, multicenter, double-blind, placebo-controlled trial planned to be conducted in 150 subjects 18 years of age or older who were receiving standard of care treatment (oral or IV metronidazole or oral vancomycin) for CDI. Subjects were randomized 2:1 to receive a single IV infusion of 10 mg/kg actoxumab (N=100) or 0.9% sodium chloride as placebo (N=50) for no less than 2 hours. Prior to completing enrollment, the trial was stopped due to a Sponsor decision to focus on the clinical development of the combined administration of actoxumab + bezlotoxumab. At that point, 29 and 17 subjects were randomized to the actoxumab and placebo arms, respectively. The results showed virtually no difference in the CDI recurrence rates between the actoxumab and placebo groups; specifically, the proportion of subjects with a CDI recurrence was 17.2% in the actoxumab and 17.7% in the placebo group. The mean days to resolution of diarrhea and mean length of hospital stay were 2.3 and 14 days, respectively, in the actoxumab group compared to 2.4 and 18 days, respectively, in the placebo group [65].

Actoxumab + Bezlotoxumab vs Placebo (Protocol 017)

P017 (CA-GCDX-06-02) was a randomized, multicenter, double-blind, placebo-controlled trial that enrolled 200 subjects 18 years of age or older who were receiving standard of care treatment for primary or recurrent CDI (oral or IV metronidazole or oral vancomycin). Subjects were randomized 1:1 to receive a single IV infusion of actoxumab + bezlotoxumab (10 mg/kg of each mAb) (N=101) or 0.9% sodium chloride as placebo (N=99) for no less than 2 hours. Overall, the trial population was largely female (66.0%) and White (87.5%); approximately half of enrolled subjects were hospitalized at study entry (51%). Subjects ranged in age from 20 to 101 years (mean age = 63.8 years), and the 027 strain was isolated from stool in 29% of subjects. The treatment groups were similar with respect to baseline characteristics.

Data from all 200 subjects who received the infusion of study medication were used in the efficacy analyses (Intent to Treat [ITT] population). Recurrence of CDI was significantly less frequent in the actoxumab + bezlotoxumab treatment group (7%) than in the placebo treatment group (25%) in the ITT population (p=0.0004). The Kaplan-Meier analysis showed that the time to CDI recurrence differed significantly between the two study groups (p=0.0003). Clinical cure rates in the actoxumab + bezlotoxumab and placebo arms were 79% vs. 76%, respectively, indicating actoxumab + bezlotoxumab had no impact on the efficacy of the SoC antibiotics. [70]

In summary, P017 demonstrated that the addition of actoxumab + bezlotoxumab to standard of care antibiotic agents significantly reduced the recurrence of CDI.

6.2 Phase 3 Trials – Protocol 001 and Protocol 002

The Phase 3 clinical program consisted of 2 trials, P001 and P002 (also known as MODIFY I and MODIFY II, respectively). This is the largest clinical development program conducted to date to assess therapies for CDI, randomizing 2655 subjects with primary or recurrent CDI.

6.2.1 Design of the Phase 3 Trials

Two nearly identical randomized, double-blind, placebo-controlled, Phase 3 trials (P001 and P002) were conducted to evaluate the efficacy, safety, and tolerability of the mAbs 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 (Table 2). The adequacy of the P001 protocol design to meet regulatory requirements was agreed upon by the FDA in a Special Protocol Assessment.

Table 2
Phase 3 Clinical Development Program

Protocol	Treatment Arms	Stratification	Planned N	Trial Design
P001 (MODIFY I)	ACTO BEZLO ACTO+BEZLO Placebo	Oral SoC Metronidazole Vancomycin Fidaxomicin	1600	Adaptive: one interim analysis
P002 (MODIFY II)	BEZLO ACTO+BEZLO Placebo	Hospitalization status Inpatient Outpatient	1200	Traditional

P001 was an adaptive-design trial, and subjects were randomized in a 1:1:1:1 ratio into 1 of 4 treatment groups (bezlotoxumab, actoxumab, actoxumab + bezlotoxumab, or placebo). Randomization was stratified according to the following factors at the time of randomization:

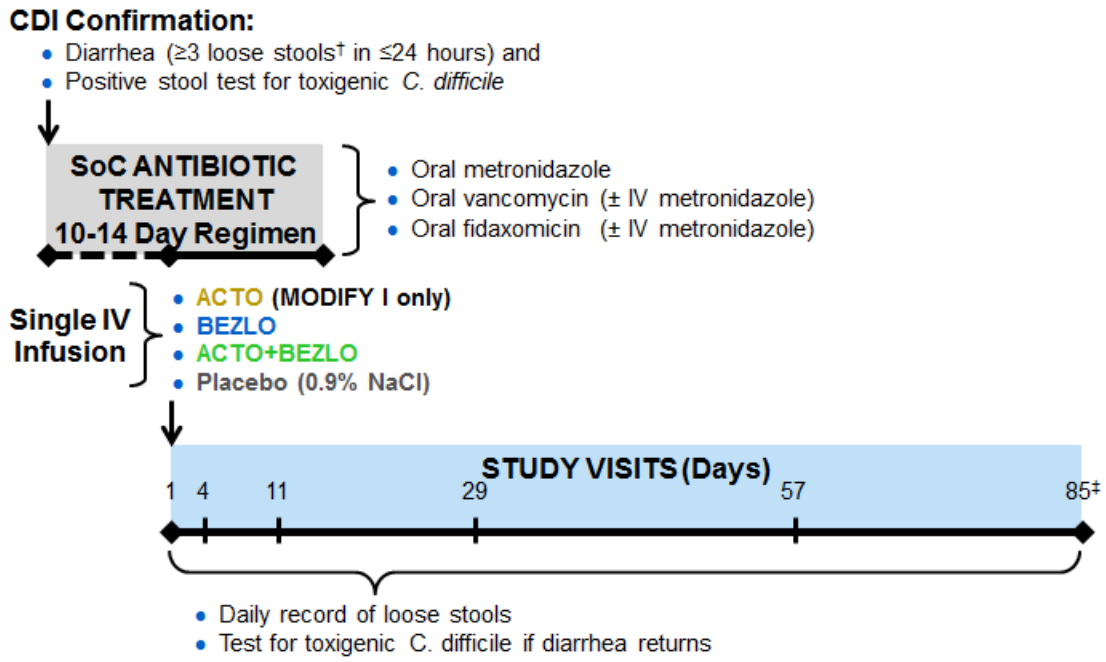
- Standard of care antibiotic therapy: metronidazole, vancomycin, or fidaxomicin
- Hospitalization status: inpatient or outpatient.

Standard of care therapy was selected as a stratification variable to balance the distribution of standard of care therapy over the treatment groups and to enforce a quota of 20% minimum of the trial population within the vancomycin and metronidazole stratum. The enrollment quota was intended to provide sufficient numbers to estimate response rates in each stratum. The choice of hospitalization status as a stratification factor was based upon the review of the Phase 2 data which suggested that this variable was associated with the risk for recurrent CDI.

P001's adaptive design incorporated an interim analysis in which one or both of the individual mAb treatment groups (bezlotoxumab and/or actoxumab) could be dropped if actoxumab + bezlotoxumab was significantly better than the given mAb in reducing CDI recurrence. Use of a factorial design provided an adequate assessment of each antibody's contribution to the overall treatment effect of the combination to address the U.S. FDA Combination Drug Product Rule (21 CFR 300.50).

P002 was identical to P001 in design and conduct, with the following three major exceptions: P002 contained three treatment groups (bezlotoxumab, actoxumab + bezlotoxumab, and placebo), did not incorporate an interim analysis, and had an extended follow-up period of 9 months conducted in a subset of ~300 subjects to assess for CDI recurrence through Month 12. All other design features were identical for P001 and P002 [Figure 2].

Figure 2
Phase 3 Trial Design for Protocols 001 and 002



† Defined by standardized Bristol Stool Chart.
‡ 85 days=12 weeks.

The protocols allowed for the enrollment of subjects with diverse ages, underlying comorbidities (including immunocompromising conditions), ongoing systemic antibiotic use, history of multiple CDI recurrences, severe CDI, and in multiple healthcare settings (including nursing homes and intensive care units).

Confirmation of the diagnosis of the baseline CDI episode required diarrhea (3 or more loose stools of Type 5, 6 and/or 7 on the Bristol Stool Chart in a 24-hour period) associated with a positive stool test for toxigenic *C. difficile*. The Bristol Stool Chart was chosen as the method to identify loose stools as it has been validated in multiple languages and populations and is used by clinicians for its ease of use for stool consistency documentation [71]. In two recent studies, Bristol Stool types 5, 6 or 7 were associated with the identification of *C. difficile* infection [72] [73]. Testing of stool for toxigenic *C. difficile* was performed at a local laboratory prior to randomization from a stool sample collected no more than 7 days prior to infusion of study medication. Methods permitted per protocol included cell cytotoxicity assay, culture with toxin detection or strain typing, or commercial assays. 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). An additional stool sample provided prior to or within 72 hours following administration of the study medication infusion was frozen and shipped to a central laboratory for culture and susceptibility testing. The *C. difficile* strains isolated were sent for toxigenic strain typing by REA and PCR ribotyping.

All subjects were required to be receiving oral standard of care antibiotic therapy for the presenting episode of CDI. The agents (metronidazole, vancomycin, or fidaxomicin), doses, and duration were specified per protocol. Subjects on oral vancomycin or oral fidaxomicin could have also received IV metronidazole. The regimens of standard of care antibiotics used in the Phase 3 trials were administered in accordance with treatment guidelines (metronidazole and vancomycin) or approved labeling (fidaxomicin), and included regimens to treat mild-moderate, severe, and severe-complicated CDI. Choice of standard of care antibiotic therapy was at the discretion of the health care provider. Subjects enrolled in these trials were to be prescribed a standard of care regimen for a minimum of 10 days and a maximum of 14 days.

A single IV infusion of 10 mg/kg of each mAb was diluted in 0.9% sodium chloride to a final volume of 200-250 ml 0.9% sodium chloride and administered over 60 minutes through a 5 micron or smaller in-line or extension filter. The placebo group was given 200-250 ml of 0.9% sodium chloride. Study medication infusion was administered as soon as possible relative to the initiation of the standard of care therapy regimen; it was required that study medication infusion was administered during the standard of care treatment course. The study design required infusion of the study medication during the SoC therapy so that the antibody would be present during the full at-risk period for CDI recurrence, which begins immediately after the end of the SoC therapy.

Efficacy was assessed over an appropriate risk period for CDI recurrence (12 weeks). Prior epidemiological studies and clinical trials showed that the majority of CDI recurrences due to the same strain (based on whole genome sequencing or multilocus variable-number tandem-repeat analysis) occur within the first 8 to 16 weeks following cure of the initial episode, with the rates of recurrence decreasing with each sequential month [74] [43]. A subset of subjects (~100 per group) was followed for 12 months to evaluate if treatment with the mAb delayed onset of CDI recurrence versus prevented CDI recurrence.

All subjects were monitored closely for any diarrhea during the 12-week follow-up period. They were given a diary in which to record loose stool counts each day. Subjects were contacted by phone or in person daily for the first 2 weeks and twice per week during Weeks 3 to 12 to ensure completion of the stool diary and to determine if there was a new episode of diarrhea. If there was a new episode of diarrhea at any time during the 12-week follow-up, a stool sample was to be collected and tested for toxigenic *C. difficile*, regardless of suspected diagnosis. The stool sample was tested at the local laboratory and an aliquot was frozen and sent to the central laboratory for culture, sensitivity, and typing. A subject with diarrhea associated with a positive test at either the local or central laboratory was considered to have CDI recurrence. A broad window (14 days) was used to associate onset of a new episode of diarrhea with a positive stool test so as to minimize the chance that a CDI recurrence would be missed due to timing of stool collection.

6.2.2 Efficacy and Safety Endpoints and Analysis Populations

[Table 3] lists the primary, secondary, and exploratory efficacy endpoints assessed through the 12-week follow-up period in the pivotal Phase 3 trials (P001 and P002). The endpoints are also described below. [Figure 3] displays a diagram of the populations for the Phase 3 efficacy endpoints. The full analysis set (FAS) population was the primary population for the efficacy analyses unless otherwise noted. The FAS population is a subset of all randomized subjects. Subjects were excluded from the FAS for the following reasons: (i) did not receive an infusion of study medication; (ii) did not have a positive local stool test for toxigenic *C. difficile* at study entry; or (iii) did not receive a protocol defined standard of care therapy within a 1 day window prior to the infusion. Analyses were also performed in the per protocol (PP) population which excluded subjects due to important protocol deviations that could substantially affect the primary efficacy results.

Table 3
Primary, Secondary, and Exploratory Efficacy Endpoints in Phase 3 Clinical Trials

Phase 3 Efficacy Endpoint/Population		Definition
Primary	CDI recurrence/FAS	Development of a new episode of diarrhea (3 or more loose stools in 24 hours) associated with a positive local or central laboratory stool test for toxigenic *C. difficile* following clinical cure of the baseline episode
Secondary	CDI recurrence/subset of FAS with clinical cure	
	CDI recurrence in important subgroups/FAS	Development of a new episode of diarrhea associated with a positive local or central laboratory stool test for toxigenic *C. difficile* following clinical cure of the baseline episode in those: ▪ with or without a history of CDI in the 6 months prior to enrollment, ▪ infected with or without the BI/NAP1/027 strain, ▪ infected with or without an epidemic strain[†], ▪ with or without clinically severe CDI at study entry,[§] ▪ <65 years of age and those ≥65 years of age, ▪ with and without compromised immunity[‡]
	Global cure/FAS	Clinical cure of the baseline episode AND no CDI recurrence
Exploratory	Time to CDI recurrence/FAS	Number of days until the start of CDI recurrence (the first date of the new episode of diarrhea)
	Clinical cure/FAS	Receipt of ≤ 14 day regimen of standard of care therapy AND no diarrhea (≤ 2 loose stools per 24 hours) for 2 consecutive days following completion of standard of care therapy for the baseline CDI episode
	Diarrhea recurrence/FAS	Development of a new episode of diarrhea (3 or more loose stools in 24 hours), irrespective of cause

[†] Defined in protocols as including but not limited to BI/NAP1/027, 001, 078, and 106. Due to changing epidemiology of *C. difficile* and after consultation with Scientific Advisory Committee members prior to unblinding of the Phase 3 database, the definition of "epidemic strain" was revised to include 2 groups: (i) epidemic strains: a group of common strains (isolated in ≥4% of subjects enrolled across the Phase 3 program), which includes ribotypes 027, 014, 002, 001, 106, and 020; (ii) hypervirulent strains: a group of strains that have been associated with poor outcomes: ribotypes 027, 078, or 244.
[§] Defined as Zar score ≥ 2
‡ Based on immunosuppressive medications taken at the time of randomization or medical conditions that affect the immune system
CDI = *Clostridium difficile* infection; FAS = Full Analysis Set

Definitions of Efficacy Endpoints

- CDI Recurrence: The primary efficacy endpoint in both pivotal Phase 3 trials was the proportion of subjects with CDI recurrence during the 12 week (Day 85 ± 5 days) follow-up period. CDI recurrence was defined as the development of a new episode of diarrhea (3 or more loose stools in 24 hours) associated with a positive stool test either from the local or central laboratory for toxigenic C. difficile following clinical cure of the baseline

episode. Diarrhea was defined as 3 or more bowel movements with loose stools, defined as Type 5, 6 and/or 7 on the Bristol Stool Chart in a 24 hour period.

- CDI recurrence among the subset of subjects who achieved clinical cure: A **secondary endpoint** in the Phase 3 trials was assessment of the proportion of subjects with CDI recurrence during the follow-up period among the subset of subjects who attained clinical cure of their baseline episode.
- CDI recurrence among important subgroups: As a secondary efficacy objective, CDI recurrence rates were assessed in subgroups at high risk for CDI recurrence or CDI-related adverse outcomes. These groups are: (1) subjects with one or more CDI episodes in the 6 months before enrollment, (2) subjects infected with ribotype 027, or those infected with one of three strains associated with poor outcomes (ribotypes 027, 078 or 244), (3) subjects with clinically severe CDI, (4) subjects $\geq$65 years of age, and (5) subjects with compromised immunity.
- Global Cure: Global cure (also known as sustained clinical response), a key **secondary efficacy endpoint,** was the proportion of subjects with clinical cure of the baseline CDI episode (as defined below) and no CDI recurrence through 12 weeks.
- Clinical Cure: Clinical cure of the initial episode, **an exploratory endpoint**, was defined as the proportion of subjects having received $\leq$14 days of standard of care therapy and having no diarrhea for 2 immediate (consecutive) days after completion of standard of care treatment.

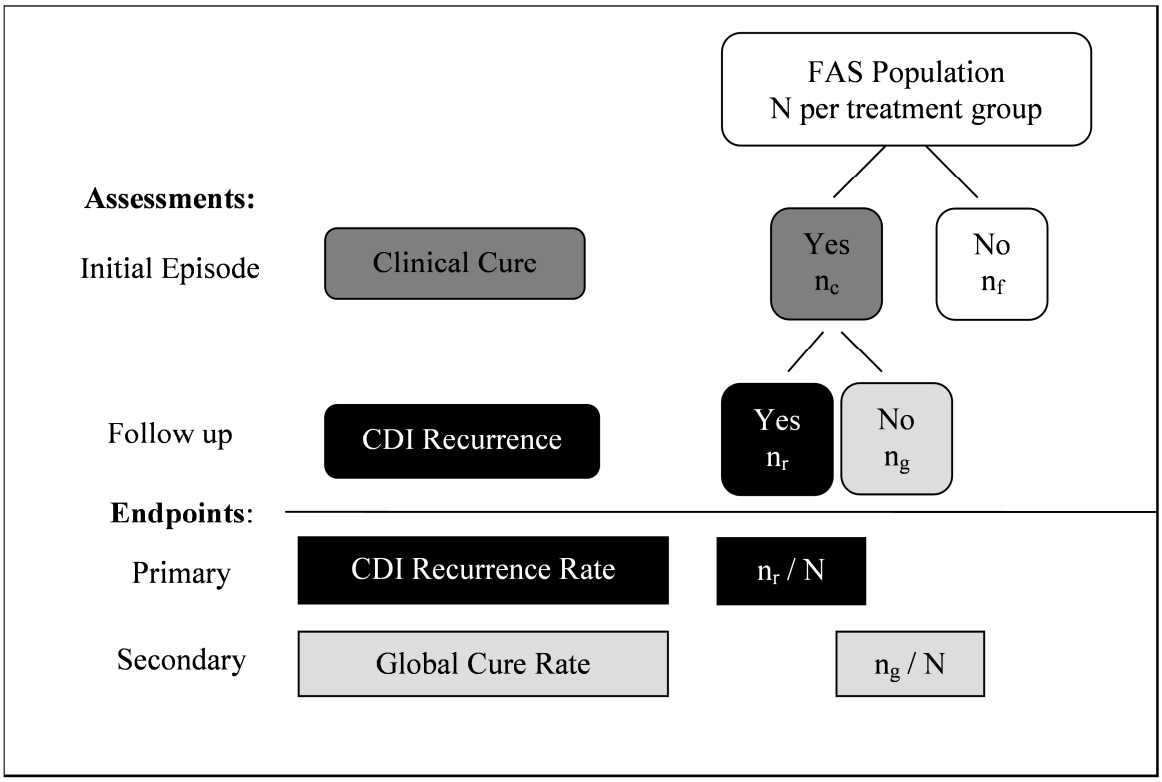
The selection of CDI recurrence as the primary endpoint and design elements related to the evaluation of this endpoint were predicated on multiple considerations, including (1) the underlying mechanism of action for monoclonal antibodies which involves preventing the development of symptoms associated with a new episode of CDI; (2) the results from the proof of concept Phase 2 trial which confirmed that the monoclonal antibodies had an impact on the prevention of CDI recurrence but did not have an impact (beneficial or harmful) on the baseline CDI episode (i.e., did not impact on the clinical cure endpoint for the baseline episode), and (3) consideration of the potential use of this preventative drug in CDI recurrence in the clinical practice setting.

Resolution of the initial episode (which was standardized in the studies via the rigorous clinical cure definition defined above) was required in order for a subject to be included in the assessment for the CDI recurrence response. Thus, evaluation of CDI recurrence was dependent on the response to standard of care antibiotic therapy, which was a post-randomization event. The study design required administration of the study medication during the course of standard of care antibiotic therapy rather than after it had concluded to ensure that the antibody would be present during the full at-risk period for CDI recurrence (which begins immediately after the end of the standard of care therapy). Therefore, it was considered important to enroll patients during the period they were receiving the standard of care antibiotic.

The endpoints described above were developed and included in these protocols to provide a complete perspective and understanding of the effects of bezlotoxumab on CDI recurrences as well as on the baseline episode. Each endpoint offers a different perspective in the evaluation of efficacy.

CDI recurrence, as defined above, is the most specific endpoint for the intended indication of prevention of CDI recurrence. For the primary endpoint, patients who achieved clinical cure of their baseline CDI episode formed the at-risk population for CDI recurrence, and those patients not achieving clinical cure were counted as not having a CDI recurrence. As a pre-specified secondary analysis, patients not achieving clinical cure of the baseline episode were removed from the analysis of CDI recurrence. In another secondary analysis, the global cure endpoint, patients not achieving clinical cure of the baseline episode are treated as failures. Both of these key secondary endpoints provide critical supportive information for the evaluation of efficacy.

Figure 3
Phase 3 Efficacy Endpoints



Safety Objectives:

- Primary safety objective: to evaluate the safety profile in subjects receiving a single infusion of monoclonal antibody therapy with standard of care therapy for CDI as compared to those subjects receiving a single placebo infusion and standard of care therapy for CDI; and

- Secondary safety objective: to assess infusion-specific reactions occurring within 24 hours of the start of the infusion in the treatment group receiving a single infusion of monoclonal antibody therapy (with standard of care therapy), as compared to the treatment group receiving a single placebo infusion with standard of care therapy.

Safety measurements collected to address the safety objectives included clinical adverse events (AEs), vital signs, laboratory assessments, and electrocardiograms (ECGs). Adverse events were identified based on careful assessment or measurement of subject symptoms, vital signs and/or physical examination findings, ECG findings, and laboratory measures. Non-serious AEs were collected from the time of study medication infusion until Week 4 post-infusion. Serious adverse events (SAEs) were collected from the time of study medication infusion until the Week 12 post-infusion visit. Because of the difference in reporting periods for non-serious and serious AEs, safety analyses are summarized separately for the first 4-week follow-up period and for the entire 12-week follow-up period.

Subjects were evaluated for infusion-specific reactions for 24 hours immediately post infusion. If the subject was an outpatient, the study staff was to contact the subject approximately 24-hours post infusion to inquire about post-infusion reactions. Additionally, subjects were instructed to call the site staff if an adverse reaction occurred within the first 24 hours.

Safety was also assessed based on laboratory tests, including hematology, chemistry, and urinalysis collected at each scheduled visit through Week 4. Laboratory tests were performed by the central laboratory. Additional safety measurements include recording of vital signs (blood pressure, pulse, temperature, and respirations) and ECGs. Vital signs were monitored just prior to the infusion, at approximately 30 minutes after the start of the infusion, at the end of the infusion, and at all scheduled and unscheduled visits. Body temperature was also recorded by the subject on Days 1 to 14.

Per ICH guidelines, a clinical study of the effect of monoclonal antibodies on the QT interval is not required, and therefore a formal QTc study was not conducted as part of the clinical development program. Instead, ECG data were collected in the Phase 3 trials. The primary purpose of the ECG analyses was to assess the potential effect of the antibodies on the QT interval. An ECG was conducted just prior to infusion and within 2 hours after the completion of the infusion.

All randomized subjects who received an infusion of study medication, either as a full or partial dose, comprise the All Patients as Treated (APaT) population and were included in the safety analyses. Safety summaries display subjects by actual treatment received as opposed to randomized treatment.

6.2.3 Statistical Considerations

Miettinen and Nurminen's method for stratified data was used to compare the treatment groups with respect to the proportion of subjects with CDI recurrence using the FAS population (primary efficacy objective) [75]. The strata were the same as those used for randomization. This same methodology was employed to compare treatment groups with

respect to CDI recurrence in the predefined subgroups (secondary objective), the proportion of subjects with global cure between the treatment groups (secondary objective), and the proportion of subjects with clinical cure (exploratory objective). The nonparametric Kaplan-Meier method was used to estimate the time to CDI recurrence and the time to resolution of the baseline CDI episode distribution for each treatment group.

Both P001 and P002 had a planned sample size of 400 subjects per group. Comparisons between mAb and placebo groups for the primary endpoint of CDI recurrence were performed at a 1-sided alpha level of 0.0125 (for P001) and 0.025 (for P002) to maintain strong control of the family wise type I error at a one sided 0.025 level. This provided ~95% power to detect the following differences in the incidence of CDI recurrence between mAb therapy, $\pi 1$, and placebo, $\pi 2$, in P001 and P002:

Protocol 001				Protocol 002			
$\pi 1$	**$\pi 2$**	**Difference**	**Power**	**$\pi 1$**	**$\pi 2$**	**Difference**	**Power**
.08	.171	.091	95%	.08	.163	.083	95%
.09	.184	.094	95%	.09	.176	.086	95%
.10	.198	.098	95%	.10	.189	.089	95%

The integrated statistical analysis of efficacy provided:

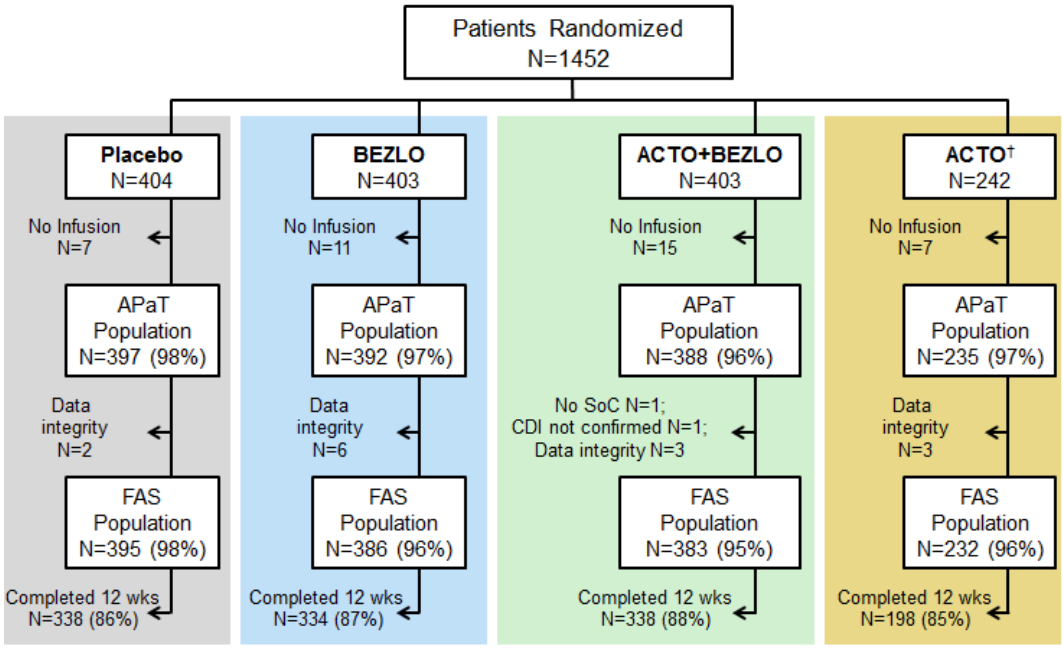
1. Increased precision for estimating the treatment effect for the primary endpoint of CDI recurrence and the key secondary endpoint of global cure. The individual protocol analyses were expected to have sufficient power for the CDI recurrence endpoint; however, the statistical power for achieving success for the global cure endpoint within the individual protocols could have been lower than desired as the studies were not planned with global cure as the primary endpoint. Combining the data from both studies provided a large enough sample size to achieve adequate power to assess differences between the active mAb and the placebo groups for the global cure endpoint.
2. Increased precision for estimating the effect of a single infusion of mAb therapy on CDI recurrence within important subgroups.

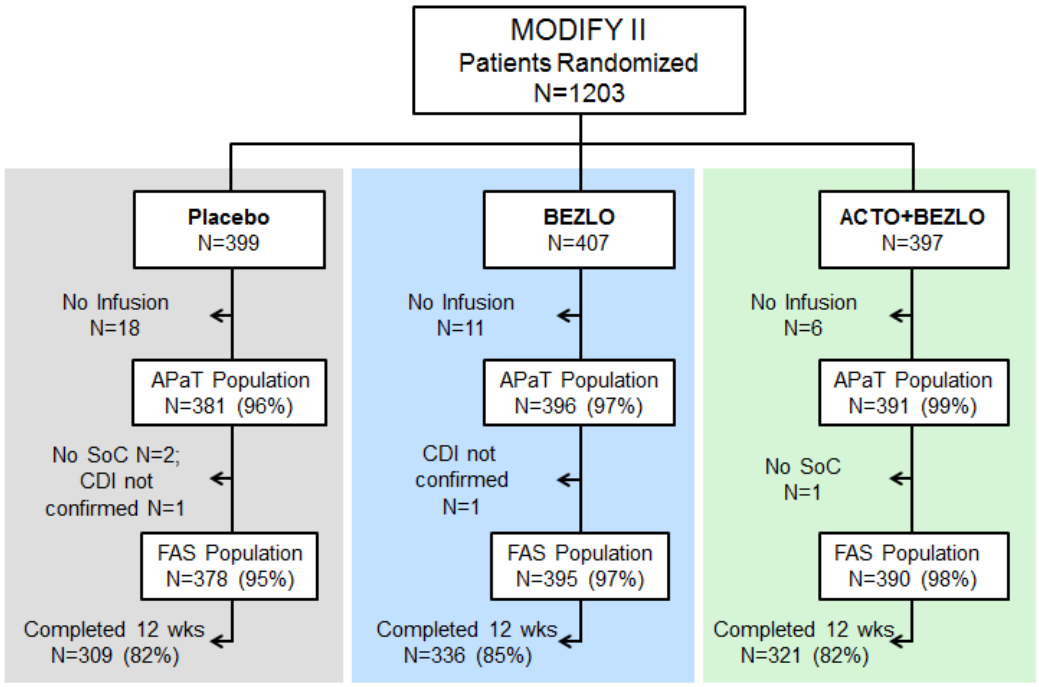
6.2.4 Subject Disposition

P001 was conducted from 01-Nov-2011 to 11-Sep-2014. P002 was conducted from 09-Feb-2012 to 22-May-2015. The number of subjects in each analysis population by treatment group from these trials is summarized in Figure 4. A total of 2655 subjects were randomized into the two Phase 3 trials: 803 subjects were randomized to the placebo group, 810 subjects were randomized to the bezlotoxumab group, 800 subjects were randomized to the actoxumab + bezlotoxumab group, and 242 subjects were randomized to receive actoxumab. A total of 2580 (97%) subjects received the infusion of study medication (actoxumab + bezlotoxumab, actoxumab, bezlotoxumab, or placebo) and were included in the safety analysis population (APaT). Overall, 2559 (96%) randomized subjects were included in the FAS population (primary efficacy population). Reasons for exclusion from the FAS were predefined as follows: (i) did not receive infusion of study medication (75 subjects [2.8%]); (ii) did not have a positive local stool test for toxigenic *C. difficile* (3 subjects [0.1%]); and

(iii) did not receive protocol defined standard of care therapy within a 1 day window prior to or after the infusion (4 subjects [0.2%]). Following study onset, exclusion from the FAS was modified to also include GCP non-compliance; 14 (0.5%) subjects at one site were excluded from the FAS due to this reason.

Figure 4
Number of Subjects in Phase 3 Trial Populations (by Treatment Group and Trial)





APaT=all patients as treated; GCP=good clinical practices; FAS=full analysis set.

Subject disposition for the study and for the infusion of study medication is summarized in Table 4. The majority of subjects (85.0%, 2174/2559) in the FAS population completed the study. Overall, 385 (15.0%) subjects discontinued the study before the Week 12 visit. The most common reasons for premature study discontinuation were death (7.1%), withdrawal by subject (4.1%), and lost to follow-up (2.8%). The proportions of FAS subjects who prematurely discontinued the study were similar in the actoxumab + bezlotoxumab (14.7%), bezlotoxumab (14.2%), and actoxumab (14.7%) treatment groups; premature study discontinuations were slightly more common in the placebo group (16.3%).

Almost all of the subjects in the FAS population (2547 [99.5%]) received a full dose of study medication (i.e., study medication disposition = completed). There were 12 subjects (0.5%) who received a partial dose of study medication (study medication disposition = discontinued): 4 in the actoxumab + bezlotoxumab group (all 4 due to technical problems), 2 in the bezlotoxumab group (1 adverse event, 1 withdrawal by subject), and 6 in the actoxumab group (1 adverse event, 5 technical problems).

Table 4
Disposition of Subjects
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO+BEZLO n (%)	BEZLO n (%)	Placebo n (%)	ACTO n (%)
Subjects in population	773	781	773	232
Main Study Disposition				
Completed	659 (85.3)	670 (85.8)	647 (83.7)	198 (85.3)
Discontinued	114 (14.7)	111 (14.2)	126 (16.3)	34 (14.7)
Adverse Event	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.4)
Death	48 (6.2)	52 (6.7)	56 (7.2)	26 (11.2)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Lost To Follow-Up	26 (3.4)	21 (2.7)	22 (2.8)	2 (0.9)
Physician Decision	5 (0.6)	3 (0.4)	3 (0.4)	1 (0.4)
Progressive Disease	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)
Protocol Violation	3 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
Withdrawal By Subject	30 (3.9)	34 (4.4)	39 (5.0)	3 (1.3)
Study Medication Disposition				
Completed Study Medication	769 (99.5)	779 (99.7)	773 (100.0)	226 (97.4)
Discontinued Study Medication	4 (0.5)	2 (0.3)	0 (0.0)	6 (2.6)
Adverse Event	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.4)
Technical Problems	4 (0.5)	0 (0.0)	0 (0.0)	5 (2.2)
Withdrawal By Subject	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Each subject is counted once for Trial Disposition and once for Subject Study Medication Disposition				

6.2.5 Subject Characteristics

Overall, in both P001 and P002, treatment groups were generally balanced with regard to key baseline characteristics [Table 5] with two exceptions. In P002, there was a higher percentage of subjects ≥65 years of age in the actoxumab + bezlotoxumab group (61.8%) compared with the bezlotoxumab group (51.9%). In P002, there was a lower percentage of subjects with the 027 strain in both the actoxumab + bezlotoxumab (15.5%) and bezlotoxumab (18.1%) groups compared with the placebo group (26.6%).

P001 was conducted in 19 countries at 154 clinical trial sites. Distribution of subjects by region was as follows: North America 53.0% (United States 46.8%, Canada 6.2%), Europe 34.5%, Latin America 6.7%, Asia Pacific 5.0%, and Africa 0.7%. Overall, 56.8% of the trial population was female, and 90.5% of subjects were white. Subjects ranged in age from 18 to 100 years (mean age, 62.5 years). The trial enrolled a diverse patient population, with participation of a substantial number of patients with risk factors for CDI recurrence or CDI-related adverse outcomes. In the FAS population, 51% of subjects were ≥65 years of age, 27% had at least one episode of CDI in the 6 months prior to the baseline CDI episode (14% had 2 or more prior lifetime episodes), 16% had clinically severe CDI, 22% were immunocompromised, 67% were hospitalized at study entry, and 38% received at least one dose of a systemic antibiotic at some point during the follow-up period. Among subjects in the FAS population with a positive *C. difficile* culture of the baseline stool sample, a strain associated with poor outcomes (ribotypes 027, 078, and 244) was isolated from 19% (16% were ribotype 027). Metronidazole was the standard of care antibiotic for 46% of subjects, while 48% received vancomycin, and 4% received fidaxomicin.

P002 was conducted in 17 countries at 165 sites. Distribution of subjects by region was as following: North America 40.8% (United States 40.8%, Canada 6.4%), Europe 42.6%, Asia Pacific 15.1%, and Latin America 1.5%. Overall, 56.0% of subjects were female, and 79.5% were white. Subjects ranged in age from 18 to 98 years (mean age, 64.3 years). Similar to P001, P002 enrolled a substantial number of patients with risk factors for CDI recurrence or CDI-related adverse outcomes. In the FAS population, 56% of subjects were ≥65 years of age, 28% had at least one episode of CDI in the 6 months prior to the baseline episode (14% reported 2 or more lifetime episodes), 17% had clinically severe CDI, 18% were immunocompromised, 69% were hospitalized at study entry, and 40% received at least one dose of a systemic antibiotic at some point during the follow-up period. Among subjects in the FAS population with a positive *C. difficile* culture of the baseline stool sample, a strain associated with poor outcomes (ribotypes 027, 078, and 244) was isolated from 23% (20% were ribotype 027). Metronidazole was the standard of care antibiotic for 47% of subjects, while 47% received vancomycin, and 4% received fidaxomicin.

Table 5
Baseline Characteristics (P001 and P002) (FAS Population)

	P001				P002		
	ACTO + BEZLO n (%)	**ACTO n (%)**	**BEZLO n (%)**	**Placebo n (%)**	**ACTO + BEZLO n (%)**	**BEZLO n (%)**	**Placebo n (%)**
Subjects in population [1]	383	232	386	395	390	395	378
Stratification Variables							
Metronidazole	89 (49.3)	112 (48.3)	190 (49.2)	192 (48.6)	191 (49.0)	189 (47.8)	182 (48.1)
Vancomycin	182 (47.5)	113 (48.7)	182 (47.2)	189 (47.8)	187 (47.9)	190 (48.1)	184 (48.7)
Fidaxomicin	12 (3.1)	7 (3.0)	14 (3.6)	14 (3.5)	12 (3.1)	16 (4.1)	12 (3.2)
Inpatient	254 (66.3)	158 (68.1)	257 (66.6)	261 (66.1)	269 (69.0)	273 (69.1)	259 (68.5)
Outpatient	129 (33.7)	74 (31.9)	129 (33.4)	134 (33.9)	121 (31.0)	122 (30.9)	119 (31.5)
Other Baseline Characteristics							
Female	211 (55.1)	130 (56.0)	229 (59.3)	223 (56.5)	212 (54.4)	213 (53.9)	226 (59.8)
Renal impairment	49 (12.8)	37 (15.9)	55 (14.2)	61 (15.4)	47 (12.1)	68 (17.2)	49 (13.0)
Hepatic impairment	29 (7.6)	14 (6.0)	23 (6.0)	24 (6.1)	27 (6.9)	26 (6.6)	20 (5.3)
Region of enrollment [2]							
North America	204 (53.3)	132 (56.9)	196 (50.8)	208 (52.7)	158 (40.5)	158 (40.0)	158 (41.8)
Europe	131 (34.2)	80 (34.5)	139 (36.0)	132 (33.4)	161 (41.3)	174 (44.1)	161 (42.6)
Asia-Pacific	17 (4.4)	10 (4.3)	20 (5.2)	23 (5.8)	63 (16.2)	59 (14.9)	54 (14.3)
Latin America	29 (7.6)	9 (3.9)	26 (6.7)	30 (7.6)	8 (2.1)	4 (1.0)	5 (1.3)
Africa	2 (0.5)	1 (0.4)	5 (1.3)	2 (0.5)	---	---	---
Protocol-Defined Subgroups of Interest							
≥65 years of age	200 (52.2)	122 (52.6)	185 (47.9)	199 (50.4)	241 (61.8)	205 (51.9)	206 (54.5)
≥1 CDI episode in past 6 months	96 (25.1)	69 (29.7)	103 (26.7)	109 (27.6)	104 (26.7)	113 (28.6)	110 (29.1)
≥2 CDI episodes in past (ever)	48 (12.5)	34 (14.7)	43 (11.1)	73 (18.5)	55 (14.1)	57 (14.4)	53 (14.0)
Immunocompromised	78 (20.4)	55 (23.7)	87 (22.5)	92 (23.3)	75 (19.2)	82 (20.8)	53 (14.0)
Severe CDI	62 (16.2)	31 (13.4)	67 (17.4)	60 (15.2)	80 (20.5)	55 (13.9)	65 (17.2)
PCR Ribotype, Subjects in population [3]	226	144	253	245	251	237	241
027, 078, or 244 strain	44 (19.5)	30 (20.8)	51 (20.2)	44 (18.0)	46 (18.3)	51 (21.5)	71 (29.5)
027 strain [2]	37 (16.4)	24 (16.7)	46 (18.2)	36 (14.7)	39 (15.5)	43 (18.1)	64 (26.6)

[1] FAS population
[2] P001: Africa: South Africa. Asia-Pacific: Australia, New Zealand. Latin America: Brazil, Chile, Colombia, Mexico. Europe: Austria, Belgium, Czech Republic, Denmark, Germany, Israel, Italy, Portugal, Spain, United Kingdom. North America: Canada, United States. P002: Asia Pacific: Japan, Korea, Taiwan. Latin America: Argentina. Europe: Czech Republic, Finland, France, Germany, Israel, Poland, Russian Federation, Spain, Sweden, Switzerland, Turkey. North America: Canada, United States..
[3] FAS population with a positive culture

Characteristics of the Baseline CDI Episode

Key characteristics relating to the baseline CDI episode, including the onset of the episode relative to the day of study medication infusion, the loose stool count that confirmed that subjects met the protocol definition of diarrhea, and the type of test used at the local laboratory to confirm the presence of toxigenic *C. difficile* in stool, are summarized by treatment group for the Integrated FAS population in Table 6. The study design allowed subjects to enroll at any time during treatment with the standard of care antibiotic, provided that a stool test obtained within the 7 days prior to infusion of the study medication was positive for toxigenic *C. difficile*. Overall, 13.9% of subjects in the FAS received the study medication infusion within 2 days following the onset of the baseline CDI episode. An additional 23.0%, 35.4%, and 26.3% of subjects received the infusion 3 to 4 days, 5 to 7 days, and 8 or more days after the onset of the baseline CDI episode.

As part of the diagnosis of CDI, subjects were required to have diarrhea, defined as at least 3 bowel movements with loose stools (Bristol Stool Chart types 5, 6 and/or 7) in a 24-hour period. The subjects did not need to meet the diarrhea criterion on the day of randomization (i.e., diarrhea could have resolved prior to randomization). For a few subjects (0.7%) in the FAS population, the loose stool count at the onset of diarrhea was recorded as unknown, because either the subject could not recall the exact number or a fecal collection device was employed shortly after the first loose bowel movement. For all of these cases, the investigator confirmed that the patient had diarrhea that would meet protocol-defined criteria. Only 2 subjects, 1 in the actoxumab + bezlotoxumab group and 1 in the placebo group, entered the study without meeting the protocol definition of diarrhea. Most subjects had 3-6 or 7-10 loose stools at qualification (68.2% and 21.1%, respectively). The proportions of subjects in each category of loose stools at qualification were similar across treatment arms.

Among all subjects in the integrated FAS population, EIA was the most common test method used (47.3%) followed by PCR (45.6%), anaerobic culture (5.7%), and cell cytotoxicity assay (1.4%). In P001, PCR was the most common test method used (54.5%) followed by EIA (39.5%). However, in P002 the frequency of EIA use was higher (56.7%) and the frequency of PCR was lower (34.8%). Similar to the integrated FAS population, a small proportion used anaerobic culture or cell cytotoxicity assay in both studies.

Table 6
CDI Diagnosis
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO		BEZLO		Placebo		ACTO	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	773		781		773		232	
Days Prior to Infusion of Onset of Presenting CDI Episode								
Day of Infusion	4	(0.5)	1	(0.1)	4	(0.5)	2	(0.9)
1-2 Days Prior	111	(14.4)	114	(14.6)	99	(12.8)	31	(13.4)
3-4 Days Prior	174	(22.5)	180	(23.0)	167	(21.6)	67	(28.9)
5-7 Days Prior	273	(35.3)	274	(35.1)	289	(37.4)	71	(30.6)
8-10 Days Prior	82	(10.6)	83	(10.6)	93	(12.0)	29	(12.5)
11-13 Days Prior	33	(4.3)	36	(4.6)	36	(4.7)	9	(3.9)
14+	81	(10.5)	87	(11.1)	79	(10.2)	20	(8.6)
Unknown	15	(1.9)	6	(0.8)	6	(0.8)	8	(2.1)
Number of Loose Stools at Qualification[‡]								
Unknown[†]	5	(0.6)	5	(0.6)	7	(0.9)	1	(0.4)
<3	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)
3-6	531	(68.7)	532	(68.1)	530	(68.6)	153	(65.9)
7-10	174	(22.5)	156	(20.0)	159	(20.6)	50	(21.6)
10+	62	(8.0)	87	(11.1)	76	(9.8)	28	(12.1)
Missing	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Type of Local Laboratory Test Used for Baseline CDI Diagnosis[§]								
EIA	363	(47.0)	372	(47.6)	385	(49.8)	90	(38.8)
Cell Cytotoxicity Assay	16	(2.1)	10	(1.3)	6	(0.8)	5	(2.2)
Culture	49	(6.3)	42	(5.4)	45	(5.8)	10	(4.3)
PCR	345	(44.6)	357	(45.7)	337	(43.6)	127	(54.7)

[‡]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

Standard of Care Therapy Onset and Duration

The duration of standard of care therapy and the number of days subjects received standard of care therapy prior to receiving the study medication infusion are summarized by treatment group for the Integrated FAS population in Table 7. The total duration of standard of care therapy was calculated as the number of calendar days between the first day the subject received at least one dose of standard of care antibiotic to the last day a dose of standard of care therapy was given (inclusive), with some exceptions for switches in standard of care therapy prior to randomization. All post-infusion standard of care switches were included when calculating the duration of standard of care. The median number of days subjects received standard of care therapy across all treatment groups was 14 days. A small number

of subjects (n=70, 3.0%) received fewer than 10 days of standard of care antibiotic therapy. The proportions of subjects that received fewer than 10 days of standard of care therapy were similar across treatment groups. Approximately one-third of the subjects who received fewer than 10 days of standard of care therapy died, withdrew consent, or were lost to follow-up before they completed standard of care therapy. Approximately 85% of subjects in the FAS population received the per protocol duration of standard of care (i.e., 10 to 16 calendar days): of these, 60.6% of subjects received between 10 and 14 calendar days of standard of care antibiotic, and an additional 25.6% received antibiotic treatment for 15 or 16 calendar days. Exactly 10% received more than 16 calendar days of standard of care treatment. These subjects were counted as clinical failures. The proportion of subjects with duration of standard of care therapy >16 days was 9.0% in the bezlotoxumab group and 8.8% in the placebo groups.

The majority of subjects (91.7%) in the FAS population began standard of care therapy ≥1 day prior to receiving the study medication infusion, 8.1% of subjects began the standard of care antibiotic on the same day as the study medication infusion, and 5 subjects (0.2%) began standard of care antibiotic the day after study medication infusion was initiated (Table 7). The median number of days between the start of the standard of care antibiotic and administration of the study medication infusion was 3 days for all treatment groups; the range was 14 days before infusion to one day after infusion. The day of the start of standard of care treatment relative to the day of the study medication infusion was generally similar across treatment groups.

Table 7
Duration of Standard of Care Therapy and Days on Standard of Care Therapy Prior to Infusion, Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO n (%)	BEZLO n (%)	Placebo n (%)	ACTO n (%)
Subjects in population	773	781	773	232
Total Days on Standard of Care Therapy				
1-7 days	12 (1.6)	13 (1.7)	9 (1.2)	5 (2.2)
8-9 days	12 (1.6)	14 (1.8)	10 (1.3)	11 (4.7)
10-14 days	465 (60.2)	473 (60.6)	482 (62.4)	130 (56.0)
15-16 days	189 (24.5)	207 (26.5)	200 (25.9)	58 (25.0)
> 16 days	92 (11.9)	70 (9.0)	68 (8.8)	26 (11.2)
Unknown	3 (0.4)	4 (0.5)	4 (0.5)	2 (0.9)
N	770	777	769	230
Mean	14.3	14.0	13.9	14.1
SD	6.1	5.9	5.0	5.2
Median	14.0	14.0	14.0	14.0
Quartiles	11 to 15	11 to 15	11 to 15	11 to 15
Range	3 to 79	2 to 87	3 to 67	3 to 46
Days on Standard of Care Therapy Prior to Infusion				
Started 1 Day after Infusion	3 (0.4)	0	1 (0.1)	1 (0.4)
0 days	60 (7.8)	67 (8.6)	61 (7.9)	18 (7.8)
1-2 days	258 (33.4)	251 (32.1)	269 (34.8)	81 (34.9)
3-4 days	233 (30.1)	239 (30.6)	230 (29.8)	77 (33.2)
5-6 days	172 (22.3)	176 (22.5)	172 (22.3)	46 (19.8)
> 6 days	47 (6.1)	48 (6.1)	40 (5.2)	9 (3.9)
N	773	781	773	232
Mean	3.2	3.3	3.2	3.1
SD	2.2	2.2	2.1	2.1
Median	3.0	3.0	3.0	3.0
Quartiles	2 to 5	2 to 5	2 to 5	2 to 4
Range	-1 to 14	0 to 14	-1 to 13	-1 to 14

6.2.6 P001 Interim Analysis Outcome

At the P001 interim analysis, the eDMC recommended that enrollment in the actoxumab group be stopped, a decision driven by both low efficacy compared to the combination mAb group (25.3% CDI recurrence in the actoxumab group versus 14.6% in the actoxumab + bezlotoxumab group, p=0.008) and an observed increase in the number of deaths and SAEs in the actoxumab arm relative to placebo. In the interim analysis cohort, 15% of actoxumab subjects died and 42% experienced a SAE during the 12 week follow up period compared to 6% and 33%, respectively, of placebo subjects.

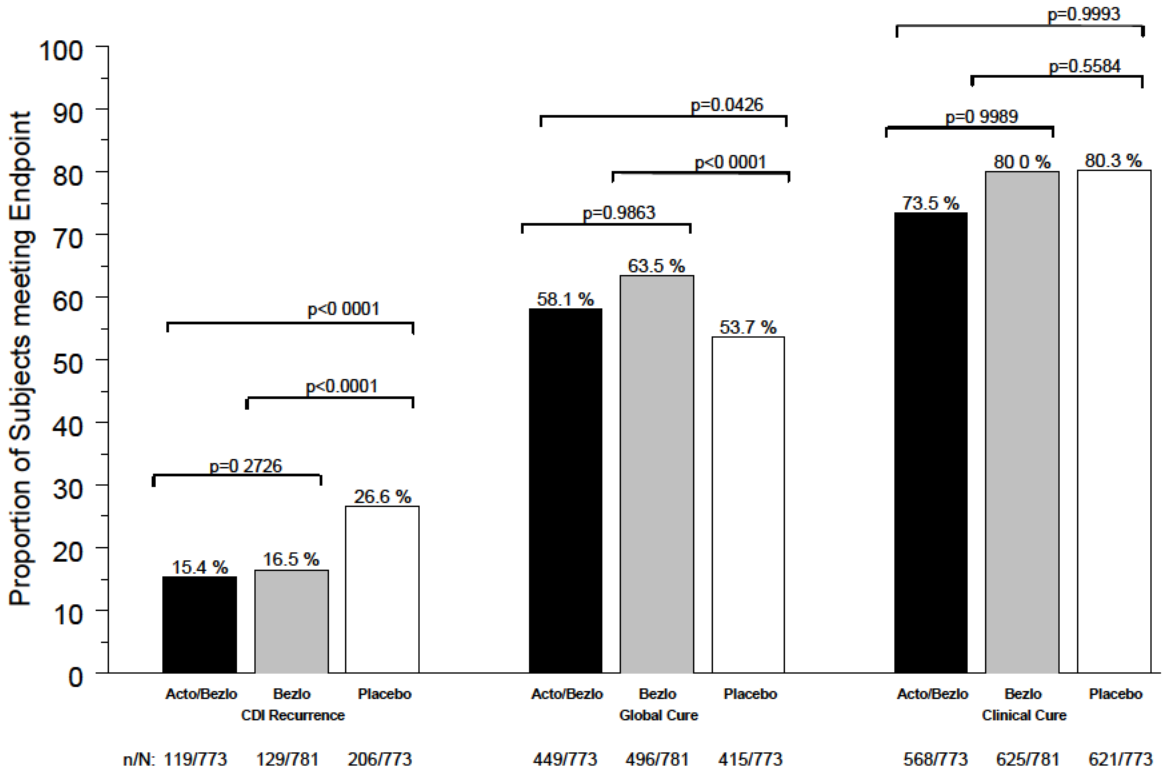
After final database lock and unblinding, a review of the types of adverse events with a fatal outcome reported for the actoxumab group revealed that these adverse events also occurred in other treatment groups, including the placebo group. Furthermore, these events occurred in individuals of advanced age and with underlying medical conditions, therefore a causal association between actoxumab and mortality could not be established.

6.3 Phase 3 Efficacy Results

6.3.1 Overview of the Integrated (P001 + P002) Phase 3 Results

Figure 5 shows the integrated (P001 + P002) Phase 3 efficacy results for the primary, secondary, and exploratory endpoints of CDI recurrence, global cure, and clinical cure in the FAS population, respectively. The pivotal Phase 3 studies demonstrated that bezlotoxumab significantly reduces the CDI recurrence rate through 12 weeks following a single dose. As there is no evidence that the combination of the two mAbs (actoxumab + bezlotoxumab) provides an efficacy benefit over bezlotoxumab alone, bezlotoxumab was selected as the product for registration. The remaining sections of this document focus on the comparison between the bezlotoxumab and placebo groups. Results for the actoxumab + bezlotoxumab group are included as supportive information.

Figure 5
Summary of Efficacy Analyses
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population



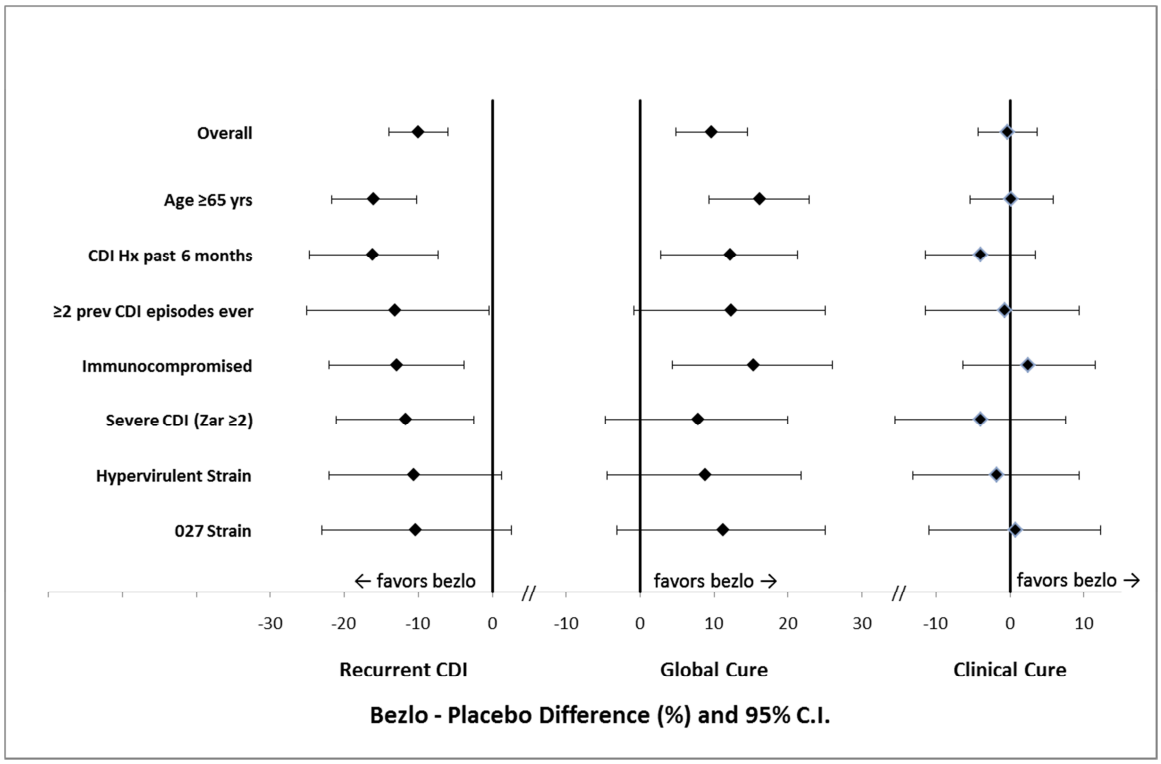
Note: One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs. P002), SoC therapy (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (inpatient vs. outpatient)

A graphical presentation of the differences between bezlotoxumab and placebo for the endpoint of CDI recurrence, the key secondary endpoint of global cure, and the exploratory endpoint of clinical cure is provided for important subgroups in the integrated dataset in Figure 6. These subgroups were predefined in the secondary efficacy objectives of the protocols after careful consideration to select factors that were shown to increase the risk of CDI recurrence, and/or CDI-related adverse outcomes. All factors were identified at the time of study entry. These subgroups included subjects infected with the *C. difficile* 027 strain, as well as those infected with an "epidemic" strain. Given the changing epidemiology, the epidemic category in the final analysis included two subgroups: (1) the most common strains isolated at baseline in the Phase 3 program (ribotypes 027, 014, 002, 001, 106, and 020) and (2) hypervirulent strains (ribotypes 027, 078, or 244).

For both the recurrent CDI and global cure endpoints, the point estimates of the difference (bezlotoxumab minus placebo) favor bezlotoxumab for all subgroups, and the nominal 95% confidence intervals exclude zero for many of the subgroups, indicating a robust and consistent treatment effect. For the clinical cure endpoint, the point estimates of the difference (bezlotoxumab minus placebo) are close to zero, and the nominal 95% confidence

intervals include zero for all subgroups, indicating that bezlotoxumab does not have an impact on this endpoint.

Figure 6
Summary of Efficacy Analyses by Subgroup Full Analysis Set Population



6.3.2 CDI Recurrence (Primary Endpoint)

6.3.2.1 CDI Recurrence in FAS (Primary Endpoint)

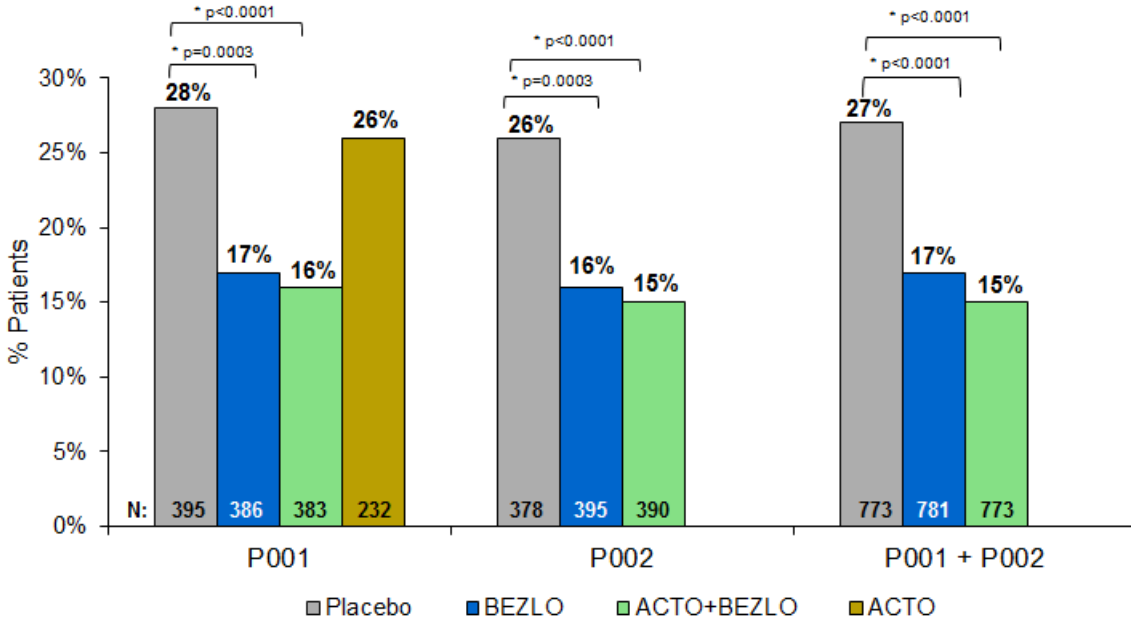
The results for the primary endpoint, CDI recurrence, in the FAS population are presented in Figure 7 and Table 8. The results from each of the individual Phase 3 trials provide strong and consistent evidence that treatment with bezlotoxumab significantly decreases the proportion of subjects with CDI recurrence over a period of 12 weeks as compared to treatment with placebo, and the decrease in the rate of CDI recurrence is clinically significant. The combination of the 2 mAbs (actoxumab + bezlotoxumab) does not have an efficacy benefit over bezlotoxumab alone. The results from the integrated dataset provide increased precision for the estimate of this effect.

Both individual trials demonstrated that bezlotoxumab was superior to placebo in the reduction of CDI recurrence and the efficacy results were highly consistent across the 2 Phase 3 trials. Lower proportions of subjects in the FAS experienced CDI recurrence in the bezlotoxumab treatment group (P001: 17.4%, P002: 15.7%) as compared with the placebo

treatment group (P001: 27.6%, P002: 25.7%). The absolute reduction in CDI recurrence was approximately 10% and the relative reduction was approximately 40% for each trial. These results are clinically significant, as evidenced by the fact that the number needed to treat (NNT) to prevent a case of CDI recurrence is low (NNT = 10).

In reducing CDI recurrence, bezlotoxumab and actoxumab + bezlotoxumab were comparable. The adjusted differences between the bezlotoxumab and placebo group and the actoxumab + bezlotoxumab and placebo group were both statistically significant (both $p \leq 0.0003$). There was no statistically significant difference between these two treatment groups in P001, P002, or the integrated data. That is, the combination of actoxumab + bezlotoxumab did not demonstrate an efficacy benefit over treatment with bezlotoxumab alone.

Figure 7
Proportion of Subjects with CDI Recurrence
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population



* Significantly different from placebo, one-sided p-value.

Table 8
Analysis of the Proportion of Subjects with CDI Recurrence
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	15.9 (61/383)	-11.7	-11.6 (-17.4, -5.9)	<0.0001
BEZLO	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[†]
ACTO + BEZLO vs. BEZLO		-1.4	-1.4 (-6.7, 3.9)	0.2997

	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	14.9 (58/390)	-10.8	-10.7 (-16.4, -5.1)	<0.0001
BEZLO	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[†]
ACTO + BEZLO vs. BEZLO		-0.8	-0.8 (-5.9, 4.2)	0.3718

	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	15.4 (119/773)	-11.3	-11.2 (-15.2, -7.2)	<0.0001
BEZLO	16.5 (129/781)	-10.1	-10.0 (-14.0, -6.0)	<0.0001
Placebo	26.6 (206/773)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO vs. BEZLO		-1.1	-1.1 (-4.8, 2.5)	0.2726

[†] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs. P002), 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

6.3.2.2 Incidence of CDI Recurrence in the Per Protocol Population

Consistency of the superior efficacy of bezlotoxumab relative to the placebo with respect to the primary endpoint of CDI recurrence was also demonstrated for the P001 and P002 trials in the PP population. Lower proportions of subjects in the PP experienced CDI recurrence in the bezlotoxumab treatment group (P001 = 19.0% [63/332]; P002 = 16.6% [55/331]) as compared with the placebo treatment group (P001: 31.4% [96/306], P002: 29.4% (89/303). The adjusted differences between the bezlotoxumab and placebo group were statistically significant for both trials (-12.4%and -13.2% for P001 and P002, respectively, both $p \leq 0.0002$).

6.3.2.3 Incidence of CDI Recurrence in Subset of FAS with Clinical Cure of the Initial Episode

Superior efficacy of bezlotoxumab over placebo was also demonstrated in P001, P002, and the integrated dataset for the secondary endpoint which evaluated CDI recurrence in the subset of FAS subjects with clinical cure of the baseline CDI episode (i.e., denominator for this analysis was limited to clinical cures as opposed to the entire FAS population) [Table 9]. In the integrated dataset, among subjects with clinical cure, the proportion of subjects with CDI recurrence was lower among subjects receiving bezlotoxumab (20.6%) than among subjects receiving placebo (33.2%). The estimated difference between the bezlotoxumab treatment group and the placebo group, adjusted for the stratification factors of hospitalization status and standard of care therapy, was -12.2% (95% CI: -17.1% to -7.4%, $p<0.0001$) among subjects with clinical cure of the baseline episode. Similar results were observed for actoxumab + bezlotoxumab.

There was no difference in the proportion of subjects with CDI recurrence among subjects with clinical cure of the baseline episode when comparing actoxumab + bezlotoxumab treatment to bezlotoxumab treatment (estimated adjusted difference 0.4% (95% CI: -4.2% to 5.0%, $p<0.5623$).

Table 9
Analysis of the Proportion of Subjects with CDI Recurrence
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population with Clinical Cure of the Initial Episode

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	21.3 (61/286)	-12.0	-11.7 (-18.6, -4.7)	0.0006
BEZLO	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[†]
ACTO + BEZLO vs. BEZLO		-1.1	-1.0 (-7.7, 5.8)	0.3906

	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	20.6 (58/282)	-12.4	-11.9 (-19.0, -4.7)	0.0006
BEZLO	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[†]
ACTO + BEZLO vs. BEZLO		1.5	1.6 (-4.6, 8.0)	0.6962

	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	21.0 (119/568)	-12.2	-11.8 (-16.7, -6.8)	<0.0001
BEZLO	20.6 (129/625)	-12.5	-12.2 (-17.1, -7.4)	<0.0001
Placebo	33.2 (206/621)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO vs. BEZLO		0.3	0.4 (-4.2, 5.0)	0.5623

[†] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

6.3.2.4 CDI Recurrence by Stratification Factors

Efficacy was demonstrated in clinically important subgroups, including subgroups based on the stratification variables at study entry (standard of care antibiotic choice and hospitalization status) [Table 10]. Importantly, consistency of the magnitude of the efficacy effect was observed regardless of standard of care therapy with metronidazole or vancomycin and regardless of whether a subject was hospitalized/institutionalized or treated as an outpatient. As the number of subjects enrolled on fidaxomicin was limited (<4% of the entire population), the interpretation of the results from this subgroup is also limited, though a numerical advantage still remained for bezlotoxumab versus placebo for this subgroup.

Table 10
CDI Recurrence by Stratification Variables
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO N=773	BEZLO N=781	Placebo N=773
Standard of Care Therapy			
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			
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%)

6.3.2.5 CDI Recurrence in Subgroups at High Risk for CDI Recurrence (Secondary Objective)

The proportion of subjects with CDI recurrence in important subgroups was assessed as a secondary objective. Results from the integrated dataset (P001+ P002) are presented in Figure 8 and Table 11.

Across important subgroups at high risk for CDI recurrence and/or with factors associated with poor prognoses, bezlotoxumab consistently lowered CDI recurrence rates compared to placebo: subjects ≥65 years of age, with a past history of CDI, with clinically severe CDI, infected with the 027 strain, or with compromised immunity. While the absolute reduction in the CDI recurrence rates relative to placebo in the overall population for bezlotoxumab was -10.0%, the difference often exceeded this value in these important high risk groups. The largest absolute reductions in CDI recurrence in the bezlotoxumab group versus placebo were in subjects who were ≥65 years of age (absolute difference -16.0%, 95% CI: -21.7%, -10.2%) and those who had one or more CDI episode in the 6 months prior to the baseline episode (absolute difference -16.1%, 95% CI -24.7%, -7.3%). For the majority of the subgroups, the 95% CI for the difference between bezlotoxumab and placebo did not include zero indicating the robustness of this finding; the exception was for the 027 ribotype subgroup, which had a relatively smaller size resulting in wide confidence intervals.

In general, the direction and magnitude of the difference in CDI recurrence rates between bezlotoxumab and placebo was similar to the difference observed between actoxumab + bezlotoxumab and placebo for all important subgroups, with the exception of subjects infected with the 027 ribotype. In this subgroup, CDI recurrence rates were 23.6% in bezlotoxumab arm, 11.8% in actoxumab + bezlotoxumab arm, and 34.0% in the placebo arm. Given the small number of subjects in each treatment group, it cannot be fully determined if this difference is due to a true advantage of actoxumab + bezlotoxumab over bezlotoxumab. Nevertheless, the magnitude of the difference between bezlotoxumab and placebo for subjects infected with the 027 strain (-10.4%) is consistent with the efficacy in the overall population (-10.0%).

Figure 8
CDI Recurrence in Subgroups: Risk Factors for CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

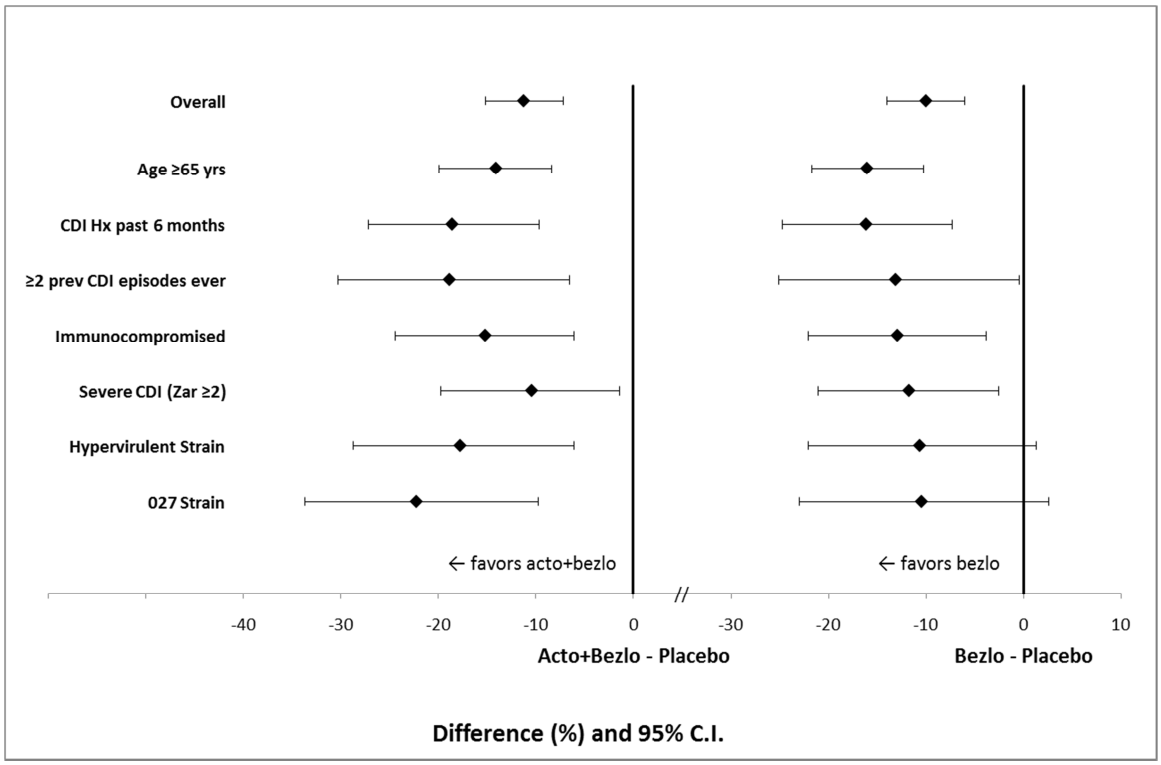


Table 11
CDI Recurrence in Subgroups: Risk Factors for CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO N=773	BEZLO N=781	Placebo N=773
	% (n/m) Difference (95% CI[§]) vs. Placebo	% (n/m) Difference (95% CI[§]) vs. Placebo	% (n/m)
Age ≥ 65 year	17.2 (76/441) -14.1 (-19.9, -8.4)	15.4 (60/390) -16.0 (-21.7, -10.2)	31.4 (127/405)
1 or more CDI episodes in previous 6 months	22.5 (45/200) -18.6 (-27.2, -9.7)	25.0 (54/216) -16.1 (-24.7, -7.3)	41.1 (90/219)
≥ 2 previous CDI episodes in the past	23.3 (24/103) -18.8 (-30.3, -6.6)	29.0 (29/100) -13.1 (-25.1, -0.4)	42.1 (53/126)
Immunocompromised at study entry [‡]	13.1 (20/153) -15.2 (-24.4, -6.1)	15.4 (26/169) -12.9 (-22.1, -3.8)	28.3 (41/145)
Clinically severe CDI at study entry [†]	12.0 (17/142) -10.4 (-19.8, -1.4)	10.7 (13/122) -11.7 (-21.1, -2.5)	22.4 (28/125)
Infected with Hypervirulent Ribotype [¦]	14.4 (13/90) -17.7 (-28.7, -6.1)	21.6 (22/102) -10.6 (-22.1, 1.3)	32.2 (37/115)
Infected with 027 Ribotype	11.8 (9/76) -22.2 (-33.7, -9.8)	23.6 (21/89) -10.4 (-23.0, 2.6)	34.0 (34/100)

Data in cells: % (n/m) where m = Number of subjects within subgroup and n = Number of subjects within subgroup that met the criteria for endpoint.
§ Based on the Miettinen and Nurminen method without stratification.
‡ Based on medical conditions or medications received that may result in immunosuppression.
† Zar score ≥ 2
¦ Hypervirulent ribotype included the following: 027, 078, or 244 ribotypes

6.3.2.6 Time to CDI Recurrence

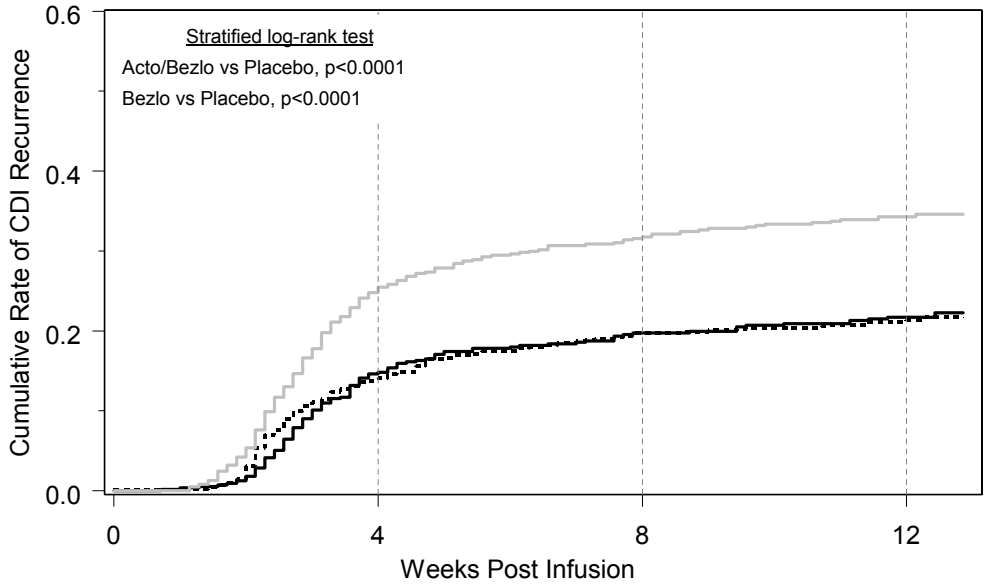
Differences between the treatment groups in the time to CDI recurrence for the integrated dataset are displayed in Figure 9. The Week 12 Kaplan-Meier CDI recurrence event rate in the bezlotoxumab treatment group (21.3%, 95% CI: 18.1% to 24.6%) was lower than the event rate in the placebo group (34.3%, 95% CI: 30.5% to 38.1%). The bezlotoxumab and placebo treatment groups were significantly different with respect to the distribution of time to CDI recurrence ($p<0.0001$). Similarly, the distributions of time to CDI recurrence were significantly different for the actoxumab + bezlotoxumab and placebo groups ($p<0.0001$), but the distribution of time to CDI recurrence was similar for the actoxumab + bezlotoxumab and bezlotoxumab groups.

While the majority (approximately 71%) of all recurrences (across all treatment groups) occurred within the first 4 weeks following the infusion, recurrences occurred thorough out

the 12 week follow-up period. Differences between the bezlotoxumab and placebo groups in the distributions of time to CDI recurrence were apparent as early as 2 weeks post infusion and were maintained throughout the 12-week follow-up period. The absolute differences between bezlotoxumab and placebo in the Kaplan-Meier CDI recurrence rates were 11, 12, and 13 percentage points at Week 4, Week 8, and Week 12, respectively.

The 12-week Kaplan Meier rates for CDI recurrence displayed in Figure 9 are higher than the 12-week incidence of CDI recurrence reported for the primary endpoint (see Section 6.3.2.1). This is because patients who failed to achieve a clinical cure were right censored in this graph at Day 1, the day of infusion. In this regard, the Kaplan Meier rates shown here align more closely with the 12-week incidence of CDI recurrence seen in the clinical cure subset (see Section 6.3.2.3). These results for the time to CDI recurrence were also demonstrated in the individual trial analyses.

Figure 9
Time to CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population



No. at Risk: KM Estimates (95% CI)

Acto/Bezlo	773	465: 0.148 (0.119, 0.178)	416: 0.197 (0.164, 0.231)	301: 0.217 (0.182, 0.252)
Bezlo	781	518: 0.140 (0.113, 0.168)	463: 0.197 (0.165, 0.229)	343: 0.213 (0.181, 0.246)
Placebo	773	443: 0.255 (0.220, 0.289)	386: 0.317 (0.280, 0.355)	272: 0.343 (0.305, 0.381)

Patients who failed to achieve a clinical cure were right censored at Day 1, the day of infusion.

6.3.2.7 Characteristics of CDI Recurrence Episodes

A total of 454 subjects in the integrated FAS population had a CDI recurrence during the 12-week follow-up period. The impact of the study treatment on the CDI recurrent episode was assessed by treatment group using descriptive statistics [Table 12].

In addition to reducing the proportion of subjects with CDI recurrence, treatment with bezlotoxumab was associated with fewer loose stool counts and a shorter duration compared to treatment with placebo when a recurrent episode occurred. While the median number of loose stools on the day of onset of a recurrent CDI episode was the same across groups (4), the median number of loose stool counts on the day of maximum loose stools during the recurrent episode was 4 for the bezlotoxumab versus 6 for the placebo groups. The recurrent CDI episode resolved within 2 days of the start of the episode in 58.9% of bezlotoxumab recipients versus 47.6% of placebo recipients. Recurrent CDI episodes among actoxumab + bezlotoxumab recipients were similar in duration and intensity to those among bezlotoxumab recipients; the median loose stool count was 4 (on the day of maximum loose stool counts), and the recurrent episode resolved within 2 days for 63.0% of actoxumab + bezlotoxumab recipients.

Ribotyping data were available for *C. difficile* isolates obtained at both baseline and at recurrence for 269 (59.3%) of the 454 subjects having recurrent CDI. The majority (75.8%) of these subjects had the same ribotype isolated at both time points, consistent with a presumed relapse of CDI. Reinfection was the likely cause for recurrence in 24.2% of subjects in whom different ribotypes were identified at baseline and recurrence. The proportion of reinfections versus presumed relapses was generally similar across treatment groups.

Table 12
Diagnosis and Severity of New CDI Episode
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population with CDI Recurrence

	ACTO + BEZLO N=119	BEZLO N=129	Placebo N=206
Subjects in population	119	129	206
Diarrhea onset, severity and duration			
Number of loose stools at onset of new episode			
Median	4	4	4
IQR	3-5	3-5	3-6
Min - Max	3-20	3-22	3-20
Maximum number of loose stools during CDI episode			
Median	4	4	6
IQR	3-6	3-6	4-8
Min - Max	3-22	3-22	3-23
Time to resolution of new episode (days)			
≤ 2	63.0 (75/119)	58.9 (76/129)	47.6 (98/206)
3-4	16.8 (20/119)	18.6 (24/129)	28.6 (59/206)
5-7	10.9 (13/119)	14.7 (19/129)	16.0 (33/206)
8-10	3.4 (4/119)	3.1 (4/129)	3.9 (8/206)
≥ 10	5.9 (7/119)	4.7 (6/129)	3.9 (8/206)
Ribotype			
Same as Baseline Ribotype	44.5 (53/119)	47.3 (61/129)	43.7 (90/206)
Different than Baseline Ribotype	15.1 (18/119)	13.2 (17/129)	14.6 (30/206)
Data not available[†]	40.3 (48/119)	39.5 (51/129)	41.7 (86/206)

[†] Ribotype not available for baseline and/or recurrence stool sample as sample not tested/isolated at central laboratory.

6.3.3 Global Cure (Secondary Endpoint)

Global cure, a secondary endpoint, was defined as the proportion of subjects with clinical cure of the baseline CDI episode and no CDI recurrence through Week 12. Results for this endpoint are displayed in [Table 13]. This table contains 1-sided p-values evaluating the superiority of: (1) the active treatments compared to placebo and (2) actoxumab + bezlotoxumab compared to bezlotoxumab.

In P002, bezlotoxumab was superior to placebo in achieving global cure (66.8% versus 52.1%, one-sided p<0.0001). In P001, although there was a numerical difference favoring bezlotoxumab over placebo with respect to achieving global cure, statistical significance was not attained (60.1% versus 55.2%, one-sided p=0.0861). This lack of significance can be attributed to the lower clinical cure rates for subjects in the bezlotoxumab group as discussed

later in this document. The results from the integrated dataset for the secondary endpoint of global cure provide strong supportive evidence that treatment with bezlotoxumab is superior to placebo for the global cure endpoint. A significantly higher proportion of subjects achieved global cure in the bezlotoxumab treatment group (63.5%) as compared to the placebo group (53.7%). The estimated difference between the bezlotoxumab group and the placebo group, adjusted for the stratification factors of hospitalization status and standard of care therapy, was 9.7% (95% CI: 4.8% to 14.5%, one-sided p<0.0001).

The proportion of subjects achieving global cure in the actoxumab + bezlotoxumab treatment group (58.1%) was numerically higher than in the placebo group (53.7%) based on the integrated dataset, and in each study; however, this difference was not significant for either study or for the integrated dataset (one-sided p=0.1646, p=0.0722, p=0.0426, in P001, P002, integrated data, respectively). Based on the integrated results, a lower proportion of subjects achieved global cure in the actoxumab + bezlotoxumab treatment group (58.1%) as compared to the bezlotoxumab group (63.5%). The estimated difference between the groups, adjusted for the stratification factors, was -5.5% (95% CI: -10.3, -0.6, one-sided p=0.9863). Therefore, the combination of both mAbs (actoxumab + bezlotoxumab) provides no benefit over bezlotoxumab alone for global cure.

Consistency of the efficacy of bezlotoxumab relative to the placebo with respect to the global cure endpoint was also demonstrated for the P001 and P002 trials in the PP population. Higher proportions of subjects in the PP experienced global cure in the bezlotoxumab treatment group (P001 = 61.4% [204/332]; P002 = 69.5% [230/331]) as compared with the placebo treatment group (P001: 54.6% [167/306], P002: 53.8% (163/303). The adjusted difference between the bezlotoxumab and placebo group was statistically significant for P002 (difference 16.0%, p < 0.0001), and approached significance for P001 (difference 6.9%, p < 0.0397).

Table 13
Analysis of the Proportion of Subjects with Global Cure
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	58.7 (225/383)	3.6	3.5 (-3.5, 10.4)	0.1646
BEZLO	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[†]
ACTO + BEZLO vs. BEZLO		-1.4	-1.4 (-8.3, 5.5)	0.6532

	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	57.4 (224/390)	5.3	5.2 (-1.8, 12.2)	0.0722
BEZLO	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[†]
ACTO + BEZLO vs. BEZLO		-9.4	-9.4 (-16.1, -2.7)	0.9969

	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO	58.1 (449/773)	4.4	4.3 (-0.6, 9.3)	0.0426
BEZLO	63.5 (496/781)	9.8	9.7 (4.8, 14.5)	<0.0001
Placebo	53.7 (415/773)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
ACTO + BEZLO vs. BEZLO		-5.4	-5.5 (-10.3, -0.6)	0.9863

[†] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

6.3.3.1 Global Cure in Subgroups at Risk for CDI Recurrence

As shown in Figure 10, in the integrated data (P001 + P002), treatment with bezlotoxumab was associated with a higher proportion of subjects with global cure compared to placebo across important subgroups and was consistent with the general conclusions from the primary analysis [Table 14]. For bezlotoxumab, the absolute increase in the global cure rates relative to placebo in the overall population was 9.7%. Similarly, in all important subgroups, global cure rates were higher in the bezlotoxumab group than in the placebo group; the subgroups with the largest absolute increases in global cure were subjects ≥65 years of age (absolute

difference 16.2%, 95% CI 9.3, 22.9) and those who were immunocompromised at study entry (absolute difference 15.3%, 95% CI 4.4, 26.0). The 95% CI for the difference between the bezlotoxumab group and placebo group did not include zero for these 2 subgroups and the subgroup of subjects with 1 or more CDI episodes in the previous 6 months.

The magnitude of the difference between bezlotoxumab and placebo was larger than the magnitude of the difference between actoxumab + bezlotoxumab and placebo for all important subgroups, with the exception of subjects infected with the 027 ribotype. In this subgroup, the global cure rate in the actoxumab + bezlotoxumab group was 63.2% compared to 56.2% for the bezlotoxumab group and 45.0% for the placebo group. The magnitude of the difference in global cure rates between bezlotoxumab and placebo for this important high risk group (11.2%) is consistent with the overall population (9.7%).

Figure 10
Global Cure in Subgroups: Risk Factors for CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

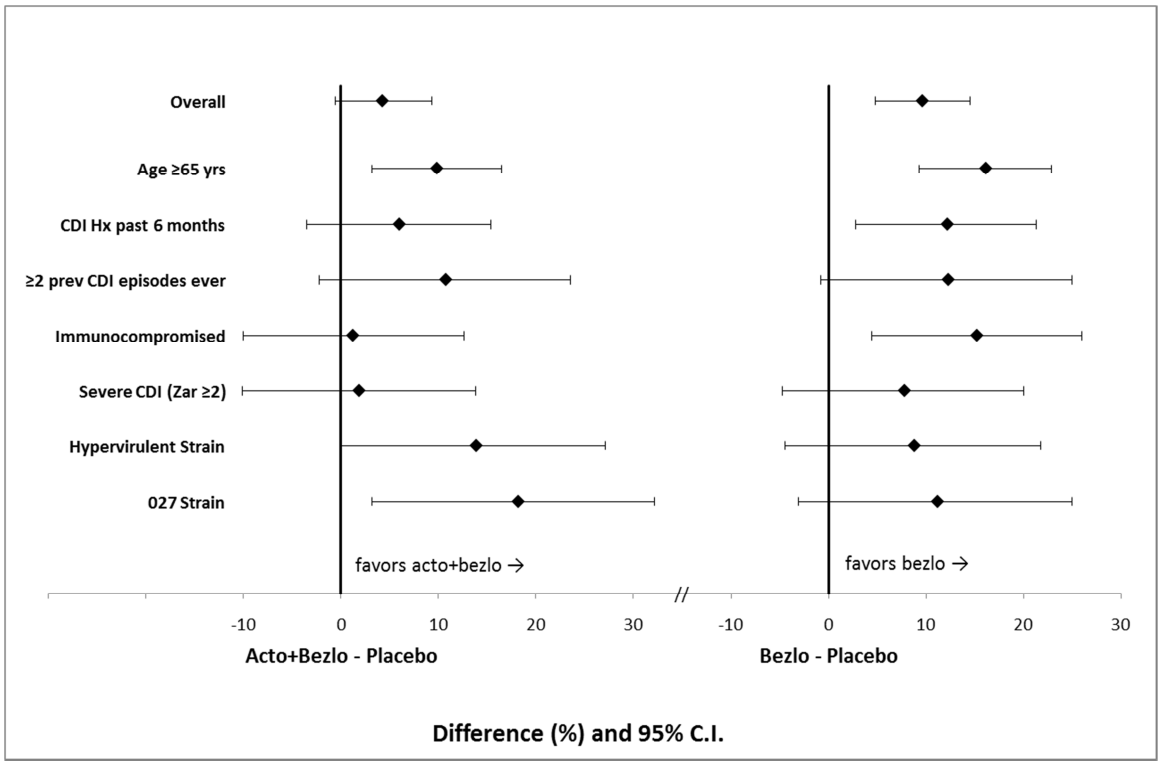


Table 14
Global Cure in Subgroups: Risk Factors for CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO N=773	BEZLO N=781	Placebo N=773
	% (n/m) Difference (95% CI[§]) vs. Placebo	% (n/m) Difference (95% CI[§]) vs. Placebo	% (n/m)
Age ≥ 65 year	58.0 (256/441) 9.9 (3.2, 16.5)	64.4 (251/390) 16.2 (9.3, 22.9)	48.1 (195/405)
1 or more CDI episodes in previous 6 months	48.0 (96/200) 6.0 (-3.5, 15.4)	54.2 (117/216) 12.2 (2.8, 21.3)	42.0 (92/219)
≥ 2 previous CDI episodes in the past	50.5 (52/103) 10.8 (-2.2, 23.5)	52.0 (52/100) 12.3 (-0.8, 25.0)	39.7 (50/126)
Immunocompromised at study entry [‡]	51.6 (79/153) 1.3 (-10.0, 12.6)	65.7 (111/169) 15.3 (4.4, 26.0)	50.3 (73/145)
Clinically severe CDI at study entry [†]	50.7 (72/142) 1.9 (-10.1, 13.8)	56.6 (69/122) 7.8 (-4.7, 20.0)	48.8 (61/125)
Infected with Hypervirulent Ribotype [¦]	60.0 (54/90) 13.9 (0.1, 27.1)	54.9 (56/102) 8.8 (-4.5, 21.8)	46.1 (53/115)
Infected with 027 Ribotype	63.2 (48/76) 18.2 (3.2, 32.2)	56.2 (50/89) 11.2 (-3.1, 25.0)	45.0 (45/100)

Data in cells: % (n/m) where m = Number of subjects within subgroup and n = Number of subjects within subgroup that met the criteria for endpoint.
§ Based on the Miettinen and Nurminen method without stratification.
‡ Based on medical conditions or medications received that may result in immunosuppression.
† Zar score ≥ 2
¦ Hypervirulent ribotype included the following: 027, 078, or 244 ribotypes

6.3.4 Clinical Cure (Exploratory Endpoint)

Bezlotoxumab does not have any activity against the *C. difficile* organism, and, as a result, the Phase 3 studies were designed for bezlotoxumab to be administered concomitantly with standard of care antibiotics for the baseline CDI episode. Hence, it was anticipated to have no impact on the proportions of subjects who achieved clinical cure beyond that already afforded by the standard of care antibiotics. As expected, efficacy of the standard of care antibiotic was not impacted by administration of bezlotoxumab; there was no substantial difference in the rate of clinical cure when comparing the bezlotoxumab and placebo groups for either trial. In P002, the clinical cure rate was higher in the bezlotoxumab vs. placebo arm, where as in P001, the clinical cure rate was higher in the placebo vs. bezlotoxumab arm [Table 15]. This result is not unexpected for an endpoint that is not affected by an intervention. The magnitude of the differences between the arms in each trial were similar (approximately 5%) such that in the integrated analysis clinical cure rates were nearly identical in the bezlotoxumab and placebo groups (80.0% and 80.3%, respectively; one-sided p=0.5584).

Table 15
Analysis of the Proportion of Subjects with Clinical Cure
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO	74.7 (286/383)	-8.1	-8.2 (-13.9, -2.4)	0.9973
BEZLO	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†
ACTO + BEZLO vs. BEZLO		-2.8	-2.8 (-8.8, 3.2)	0.8196

	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO	72.3 (282/390)	-5.5	-5.5 (-11.6, 0.6)	0.9605
BEZLO	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†
ACTO + BEZLO vs. BEZLO		-10.2	-10.3 (-16.1, -4.4)	0.9997

	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO	73.5 (568/773)	-6.9	-6.8 (-11.0, -2.6)	0.9993
BEZLO	80.0 (625/781)	-0.3	-0.3 (-4.3, 3.7)	0.5584
Placebo	80.3 (621/773)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO vs. BEZLO		-6.5	-6.6 (-10.8, -2.4)	0.9989

† One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

An evaluation of the reasons that subjects were not counted as clinical cures for the baseline CDI episode [Table 16] did not identify a clear etiology for the numerical differences in the clinical cure rate seen for bezlotoxumab compared to placebo in the individual studies.

Table 16
Reasons for Failure to Achieve Clinical Cure
Phase 3 Studies (P001, P002)
Full Analysis Set Population

	P001		P002	
	BEZLO n (%)	Placebo n (%)	BEZLO n (%)	Placebo n (%)
Subjects in population	386	395	395	378
Clinical Cure = Yes	299 (77.5)	327 (82.8)	326 (82.5)	294 (77.8)
Clinical Cure = No	87 (22.5)	68 (17.2)	69 (17.5)	84 (22.2)
SoC Therapy Regimen > 14 days	36 (9.3)	28 (7.1)	27 (6.8)	30 (7.9)
Continued loose stools	23 (6.0)	21 (5.3)	21 (5.3)	25 (6.6)
Diarrhea Resolved within first 10 Days of Regimen	13 (3.4)	7 (1.8)	6 (1.5)	5 (1.3)
Diarrhea during at least one of the 2 consecutive days following end of SoC Therapy	39 (10.1)	27 (6.8)	26 (6.6)	34 (9.0)
No information regarding loose stool counts following end of SoC Therapy	12 (3.1)	13 (3.3)	16 (4.1)	20 (5.3)
Discontinued prior to end of SoC therapy	7 (1.8)	11 (2.8)	9 (2.3)	14 (3.7)
Lost-to-follow-up	2 (0.5)	3 (0.8)	2 (0.5)	1 (0.3)
Death	4 (1.0)	4 (1.0)	2 (0.5)	8 (2.1)
Adverse Event	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Physician Decision	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Subject Withdrew Consent	1 (0.3)	3 (0.8)	4 (1.0)	3 (0.8)
Missing stool counts	5 (1.3)	2 (0.5)	7 (1.8)	6 (1.6)

Note: SoC Therapy Regimen of greater than 14 days was defined as more than 16 calendar days of SoC Therapy.
SoC = Standard of Care

6.3.4.1 Clinical Cure in Important Subgroups at Risk for CDI Recurrence

The proportions of subjects achieving clinical cure in important subgroups are displayed in Figure 11 and Table 17. Similar to the results for the entire Phase 3 FAS population, a similar proportion of subjects in the high risk subgroups achieved clinical cure of the baseline episode in the bezlotoxumab group as compared to the placebo group, and a lower proportion of subjects achieved clinical cure of the baseline episode in the actoxumab + bezlotoxumab group as compared to the placebo group.

Figure 11
Clinical Cure in Subgroups: Risk Factors for CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

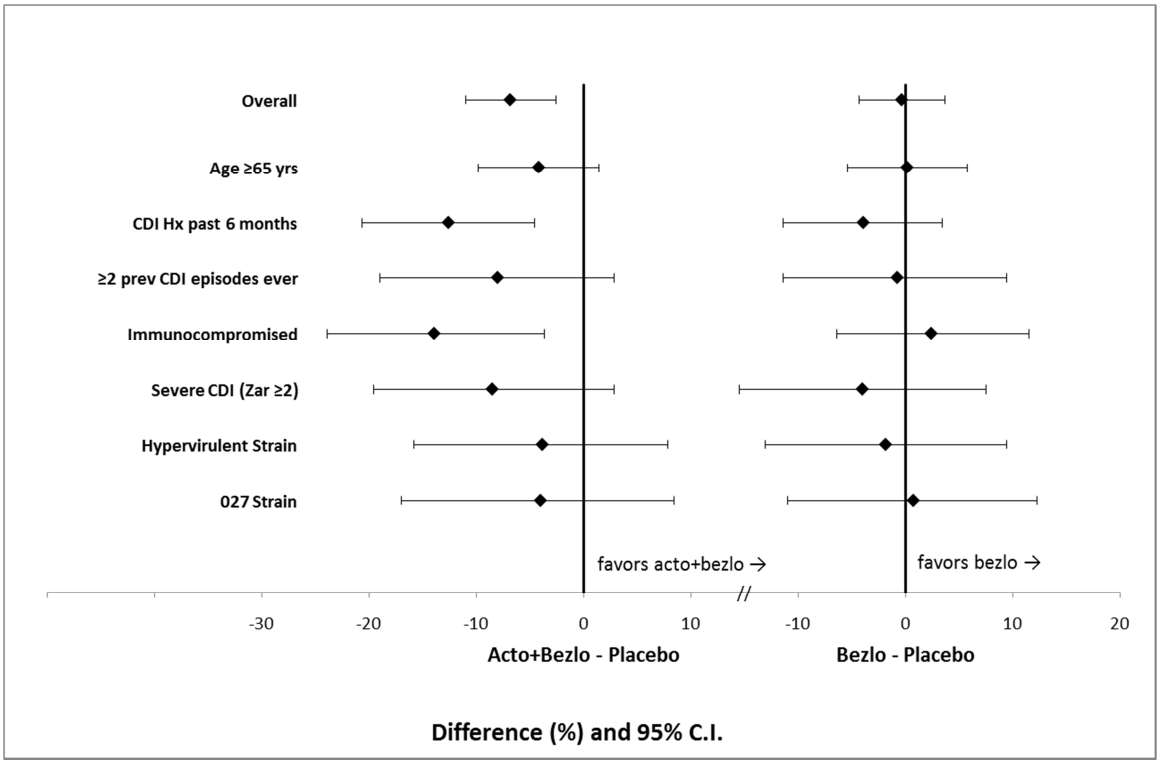


Table 17
Clinical Cure in Subgroups: Risk Factors for CDI Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO N=773	BEZLO N=781	Placebo N=773
	% (n/m) Difference (95% CI[§]) vs. Placebo	% (n/m) Difference (95% CI[§]) vs. Placebo	% (n/m)
Age ≥ 65 year	75.3 (332/441) -4.2 (-9.8, 1.4)	79.7 (311/390) 0.2 (-5.4, 5.8)	79.5 (322/405)
1 or more CDI episodes in previous 6 months	70.5 (141/200) -12.6 (-20.7, -4.6)	79.2 (171/216) -3.9 (-11.4, 3.4)	83.1 (182/219)
≥ 2 previous CDI episodes in the past	73.8 (76/103) -8.0 (-19.0, 2.8)	81.0 (81/100) -0.7 (-11.4, 9.4)	81.7 (103/126)
Immunocompromised at study entry [‡]	64.7 (99/153) -13.9 (-23.9, -3.7)	81.1 (137/169) 2.4 (-6.4, 11.5)	78.6 (114/145)
Clinically severe CDI at study entry [†]	62.7 (89/142) -8.5 (-19.6, 2.8)	67.2 (82/122) -4.0 (-15.5, 7.5)	71.2 (89/125)
Infected with Hypervirulent Ribotype [¦]	74.4 (67/90) -3.8 (-15.8, 7.8)	76.5 (78/102) -1.8 (-13.1, 9.4)	78.3 (90/115)
Infected with 027 Ribotype	75.0 (57/76) -4.0 (-17.0, 8.4)	79.8 (71/89) 0.8 (-11.0, 12.3)	79.0 (79/100)

Data in cells: % (n/m) where m = Number of subjects within subgroup and n = Number of subjects within subgroup that met the criteria for endpoint.
§ Based on the Miettinen and Nurminen method without stratification.
‡ Based on medical conditions or medications received that may result in immunosuppression.
† Zar score ≥ 2
¦ Hypervirulent ribotype included the following: 027, 078, or 244 ribotype

6.3.5 Diarrhea Recurrence (Exploratory Endpoint)

The proportion of subjects with any diarrhea recurrence, irrespective of etiology, was an exploratory endpoint. The evaluation of diarrhea recurrence included subjects who were counted as meeting the primary endpoint of CDI recurrence (development of a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode) plus subjects who had a new episode of diarrhea following clinical cure of the baseline CDI episode but either had a negative test for toxigenic *C. difficile* or who did not have a test performed.

In the integrated dataset, a lower proportion of subjects had diarrhea recurrence in the bezlotoxumab treatment group (27.3%) and the actoxumab + bezlotoxumab treatment group (25.9%) as compared to the placebo group (37.5%) [Table 18]. The estimated difference between the bezlotoxumab treatment group and the placebo group, adjusted for the

stratification factors of hospitalization status and standard of care therapy, was -10.1% (95% CI: -14.7 to -5.5, p< 0.0001) among subjects in the FAS population. The estimated difference between the actoxumab + bezlotoxumab treatment group and the placebo group, adjusted for the stratification factors of hospitalization status and standard of care therapy, was -11.5% (95% CI: -16.0 to -6.9, p<0.0001) among subjects in the FAS population. This same superiority effect for the bezlotoxumab group and the actoxumab + bezlotoxumab group versus placebo was also demonstrated in the datasets for the individual studies (P001, P002).

Table 18
Analysis of the Proportion of Subjects with Diarrhea Recurrence
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO	26.4 (101/383)	-14.9	-14.8 (-21.3, -8.3)	<0.0001
BEZLO	28.2 (109/386)	-13.0	-12.9 (-19.4, -6.3)	<0.0001
Placebo	41.3 (163/395)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO vs. BEZLO		-1.9	-1.8 (-8.1, 4.4)	0.2804

	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO	25.4 (99/390)	-8.2	-8.1 (-14.5, -1.7)	0.0066
BEZLO	26.3 (104/395)	-7.3	-7.2 (-13.6, -0.8)	0.0133
Placebo	33.6 (127/378)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO vs. BEZLO		-0.9	-0.9 (-7.0, 5.3)	0.3919

	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO	25.9 (200/773)	-11.6	-11.5 (-16.0, -6.9)	<0.0001
BEZLO	27.3 (213/781)	-10.2	-10.1 (-14.7, -5.5)	<0.0001
Placebo	37.5 (290/773)	---	---	---
		Pairwise Comparisons		
Comparison of Active Treatment Groups		Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
ACTO + BEZLO vs. BEZLO		-1.4	-1.3 (-5.7, 3.0)	0.2724

† One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

Table 19 demonstrates that the higher proportion of subjects with diarrhea recurrence in the placebo group (37.5%) relative to the proportion of subjects with diarrhea recurrence in the actoxumab + bezlotoxumab (25.9%) and bezlotoxumab (27.3%) treatment groups is due solely to a higher proportion of subjects with confirmed CDI recurrence (26.6% in subjects receiving placebo compared to 15.4% in the actoxumab + bezlotoxumab group and 16.5% in the bezlotoxumab group). As expected, the proportion of subjects with diarrhea recurrence that was not confirmed to be due to CDI was similar across treatment groups (10.5% in the actoxumab + bezlotoxumab group, 10.8% in the bezlotoxumab group, and 10.9% in subjects receiving placebo).

Overall, 30.2% (703/2327) of FAS subjects in the integrated dataset had a return of diarrhea after achieving clinical cure of their baseline episode, and 64.6% (454/703) of these subjects who had a diarrhea recurrence had toxigenic *C. difficile* isolated from an associated stool sample and were counted as having a CDI recurrence. The remaining 35.4% (249) of subjects across the 3 treatment groups who had a recurrence of diarrhea but were not counted as having a CDI recurrence were divided between those whose stool test was negative for toxigenic *C. difficile* (n=133, 18.9% of diarrhea recurrences) and those who did not have a stool sample tested for toxigenic *C. difficile* (n=116, 16.5% of diarrhea recurrences) [Table 19]. Of the 116 subjects not tested, most (n=90, 12.8% of diarrhea recurrences) experienced a diarrhea episode which lasted only 1 or 2 days. Only 2 of the 28 bezlotoxumab-treated untested subjects who had a single day of diarrhea received treatment with a SoC antibiotic. A small proportion of untested subjects (26 subjects overall, 3.7% of diarrhea recurrences) had more than 2 days of diarrhea: 11 subjects receiving actoxumab + bezlotoxumab; 6 subjects receiving bezlotoxumab; and 9 subjects receiving placebo. This small number gives confidence that the impact on the overall findings from the primary analysis of CDI recurrence would be minimal had these laboratory assessments been conducted.

Table 19
Assessment of Diarrhea Recurrence
Phase 3 Studies (P001 + P002 Integrated)
Full Analysis Set Population

	ACTO + BEZLO n (%)	BEZLO n (%)	Placebo n (%)	Total n (%)
Subjects in population	773	781	773	2327
Diarrhea following Clinical Cure (Diarrhea Recurrence)	200 (25.9)	213 (27.3)	290 (37.5)	703 (30.2)
Tested positive for toxigenic *C. difficile* (CDI Recurrence)	119 (15.4)	129 (16.5)	206 (26.6)	454 (19.5)
Did not test positive for toxigenic *C. difficile*	81 (10.5)	84 (10.8)	84 (10.9)	249 (10.7)
Tested Negative for toxigenic *C. difficile*	34 (4.4)	41 (5.2)	58 (7.5)	133 (5.7)
Not tested for toxigenic *C. difficile*	47 (6.1)	43 (5.5)	26 (3.4)	116 (5.0)
1-2 days of diarrhea	36 (4.7)	37 (4.7)	17 (2.2)	90 (3.9)
More than two days of diarrhea	11 (1.4)	6 (0.8)	9 (1.2)	26 (1.1)
No Diarrhea following Clinical Cure	368 (47.6)	412 (52.8)	331 (42.8)	1111 (47.7)
Did not achieve Clinical Cure	205 (26.5)	156 (20.0)	152 (19.7)	513 (22.0)

6.3.6 Efficacy in Special Populations

The efficacy of bezlotoxumab on the primary endpoint of CDI recurrence was also evaluated in subjects with demographic or clinical characteristics that may potentially impact the outcomes (e.g., advanced age, gender, weight, race, and organ function [including renal function/impairment and hepatic function/impairment]). A reduction in CDI recurrence rates in bezlotoxumab treated subjects compared to placebo recipients was seen in all evaluated special populations.

6.3.7 Sensitivity Analyses

A number of supportive and sensitivity analyses have been performed to assess the robustness of the primary analysis for supporting the conclusion that bezlotoxumab is superior to placebo in the prevention of CDI recurrence. These analyses address two key issues that could impact the assessment of the primary endpoint. The first issue is the definition of the primary endpoint incorporates clinical cure of the baseline episode which is a post-randomization event. The second issue concerns missing or incomplete assessments.

Clinical Cure of Baseline Episode –A Post-randomization Event

P001 and P002 required infusion of the study medication during the course of SoC antibiotic therapy for the baseline episode. The study design included this feature to ensure that the antibody would be present during the full at-risk period for CDI recurrence, which begins immediately after the end of the SoC therapy. However, recurrence can only be assessed in the setting of clinical cure of the baseline CDI episode and, due to the study design, clinical cure of the baseline episode was a post-randomization event with the theoretical potential of being influenced by the infusion of randomized study therapy. The expectation prior to starting the Phase 3 program was that infusion of the monoclonal antibodies would have no impact (beneficial or harmful) on clinical cure of the baseline episode based on the mechanism of action of the antibodies and the results of the Phase 2 program. The results from the two trials (P001 and P002) support this expectation as clinical cure rates in the bezlotoxumab and placebo groups were both 80%. Nonetheless, the impact of clinical cure on the interpretation of the CDI recurrence endpoint requires further evaluation to assess the robustness of the primary analysis.

Two questions arise because of post-randomization nature of the clinical cure assessment:

- What is the impact of differences in observed clinical cure rates among the treatment groups?
  and
- What is the impact of imputing a clinical cure failure as a “success” for CDI recurrence?

Several supportive and sensitivity analyses have been performed to address these questions.

Missing or Incomplete Assessments

The robustness of the primary analysis results in the setting of missing data and incomplete assessment of study participants was also explored. In this Phase 3 program, missing data could result from a number of situations. Subjects who failed to complete the 12 week follow period, either due to death or discontinuation from the trial for another reason, had an incomplete assessment of CDI recurrence. Subjects may have had a documented return of diarrhea, but were missing an associated stool toxin test to confirm a recurrent CDI. Finally, subjects may have received a concomitant therapy or have undergone a procedure that is potentially useful in the treatment of CDI without further information to confirm a CDI recurrence. This can be considered as possible evidence of a "missed" CDI recurrence and can therefore be considered as a type of incomplete assessment.

6.3.7.1 Analyses to Assess Impact of Clinical Cure - A Post-Randomization Event

Four sensitivity analyses were conducted to assess the impact of clinical cure on the interpretation of the CDI recurrence endpoint. In addition, two of the protocol-defined endpoints (global cure and CDI recurrence in the subset of subjects achieving clinical cure) provide strong support demonstrating the robustness of the primary analysis with regard to the impact of clinical cure. The four sensitivity analyses are described below.

Propensity Score Analysis

A pre-specified propensity score analysis was conducted to assess the impact on the primary endpoint of subjects in the treatment groups potentially having different probabilities of achieving a clinical cure due to imbalances in baseline predictors for clinical cure. This analysis compares treatment groups with respect to recurrence rates stratified by the propensity of achieving clinical cure by adjusting for imbalances in baseline predictors of clinical cure that might have played a role in the different observed rates of clinical cure. The propensity of clinical cure was calculated from a logistic regression model predicting clinical cure from important baseline factors among all subjects included in the FAS population. Both univariate and multivariate logistic regression models were employed to assess the predictive value of baseline variables for the clinical cure endpoint.

For each protocol, a stepwise selection process was used to enter and remove factors from a multivariate regression model. A significance level of 0.2 was used for entering an effect into the model and for determining if an effect would stay in the model. The following baseline variables were included as candidates for the stepwise selection model: Age (< 65 vs. ≥65), Gender (Male vs. Female), Weight (≤70 kg vs. >70 kg), Region (North America vs. Other), Hospital Status (In-patient vs. Out-patient), Initial Standard of Care (Metronidazole vs. Vancomycin vs. Fidaxomicin), CDI History-Past 6 Months (Yes vs. No), 027 Strain (Yes vs. No), Epidemic Strain (Yes vs. No), Clinically Severe CDI (Yes, Zar Score ≥ 2 vs. No, Zar Score < 2), Compromised Immunity (Yes vs. No), Hepatic Impairment (Yes vs. No), Renal Impairment (Yes, Serum creatinine ≥ 1.5 mg/dL vs. No, Serum creatinine < 1.5 mg/dL), Charlson Score (<3 vs. ≥3), Albumin (≤35 gm/L vs. >35 gm/L), Endogenous B antibody (≤1:1000 vs. 1:5000 vs. ≥1:25000), Endogenous A antibody (≤1:1000 vs. 1:5000 vs. ≥1:25000), and # of Protocol-Defined CDI Risk Factors (None vs. ≥1).

In P001, the following factors were retained in the final model: endogenous B antibody, Clinically Severe CDI, Hepatic Impairment, and Albumin. In P002, the following factors were retained in the final model: Albumin and Clinically Severe CDI (as in P001), Region, Compromised Immunity, and Weight. Using the protocol-specific final regression models, subjects were divided into tertiles of roughly equal size based on propensity score.

Results of the propensity analysis are shown in Table 20 below. The P001 results adjusting for the propensity of achieving clinical cure (low, medium, high) are consistent with the primary analysis for CDI recurrence and demonstrate that the observed difference in clinical cure rates did not overly influence the primary study results for CDI recurrence. The recurrence rates were 17.5% (66/377) for bezlotoxumab and27.3% (105/385) for placebo with an adjusted difference of -9.0 (95% CI, -14.9, -3.1) and p =0.0015. The P002 results adjusting for the propensity of achieving clinical cure (low, medium, high) are also consistent with the primary analysis for CDI recurrence and demonstrate that the observed difference in clinical cure rates did not overly influence the primary study results for CDI recurrence. The recurrence rates were 15.7% (62/395) for bezlotoxumab and 25.7% (97/378) for placebo with an adjusted difference of -9.9 (95% CI, -15.6, -4.2) and p =0.0004.

Table 20
Sensitivity Analysis of the Proportion of Subjects with CDI Recurrence Adjusting for Propensity to Achieve Clinical Cure
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	17.5 (66/377)	-9.8	-9.0 (-14.9, -3.1)	0.0015
Placebo	27.3 (105/385)	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	15.7 (62/395)	-10.0	-9.9 (-15.6, -4.2)	0.0004
Placebo	25.7 (97/378)	---	---	---

[†] One sided p-value based on the Miettinen and Nurminen method stratified by propensity (Low, Medium, High) for achieving clinical cure, 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

The propensity score analyses for P001 and P002 confirm the consistent, robust efficacy effect of bezlotoxumab versus placebo on the primary endpoint of CDI recurrence.

Multiple Imputation Analyses

The primary analysis of CDI recurrence effectively used an imputation approach in which subjects who did not achieve clinical cure were not eligible to be counted as recurrences and thus were counted as "successes" or non-recurrences in the CDI recurrence assessment. Two post-hoc sensitivity analyses were conducted, therefore, to assess the impact on the primary endpoint of allowing such subjects to be counted as recurrences. The two analyses consider

the CDI recurrence assessment as missing in subjects who did not achieve clinical cure and then use multiple imputation methodology to estimate CDI recurrence rates and treatment differences.

The first multiple imputation sensitivity analysis was conducted under the assumption of "missing not at random" (MNAR); the second was conducted under the assumption of "missing at random" (MAR). These analyses address both questions regarding the impact of clinical cure on the interpretation of the CDI recurrence endpoint: 1) different observed clinical cure rates and 2) imputing a clinical cure failure as a "success" for CDI recurrence.

- Under MNAR, it is assumed that achieving an initial clinical cure is related to the treatment received, and therefore, having a "missing" CDI recurrence assessment is also related to the treatment received. If the missingness is related to treatment, it is reasonable to assume that the underlying CDI recurrence rate might be higher for those having a "missing" CDI recurrence assessment. Therefore, applying the treatment-specific CDI recurrence rate observed in those who achieved initial clinical cure to those who did not achieve initial clinical cure (i.e., those with missing CDI recurrence assessment) would result in a biased overall estimate that would potentially underestimate the actual rate. The MNAR analysis uses a more conservative approaching which the CDI recurrence rate for those without clinical cure in both the bezlotoxumab and placebo groups is set equal to the observed rate for those with clinical cure in the placebo group.

- Under MAR, it is assumed that "missing" CDI recurrence assessments occur at random and that the underlying CDI recurrence rate for those having a "missing" CDI recurrence assessment is the same as for those with an observed CDI recurrence assessment. Therefore, applying the treatment-specific CDI recurrence rate observed in those with initial clinical cure to those not achieving initial clinical cure (i.e., those with missing CDI recurrence assessment) produces an unbiased overall estimate of the actual recurrence rate. In the MAR analysis, the CDI recurrence rate for those without clinical cure was set equal to the observed rate for those with clinical cure in each respective treatment group.

Results of the imputation analyses are presented in Table 21 for the MNAR assumption and in Table 22 for the MAR assumption.

For P001, the lower rate of initial clinical cure for the bezlotoxumab group (77.5%, 299/386) compared to the placebo group (82.8%, 327/395) results in more subjects with a "missing" CDI recurrence assessment for the bezlotoxumab group compared to the placebo group. The treatment differences (bezlotoxumab minus placebo) in the sensitivity analyses were -8.2% (p=0.0112) for the MNAR assumption and -10.8% (p=0.0012) for the MAR assumption, as compared to -10.1% (p=0.0003) in the primary analysis. Under the assumption that the "missing" CDI recurrence assessments are related to the treatment received (i.e., MNAR), the CDI recurrence rate for these subjects was conservatively estimated using the observed rate from the placebo group. This analysis likely overestimates the CDI recurrence rate for bezlotoxumab; however, the estimate of the treatment difference is consistent with the

primary analysis and the statistical comparison of bezlotoxumab to placebo remains significant (incorporating both the revised difference and the increased variability introduced by the estimation technique).

For P002, the lower rate of initial clinical cure for the placebo group (77.8%, 294/378) compared to the bezlotoxumab group (82.5%, 326/395) results in more subjects with a "missing" CDI recurrence assessment for the placebo group compared to the bezlotoxumab group. The treatment differences (bezlotoxumab minus placebo) in these sensitivity analyses were -11.4% ($p=0.0006$) for the MNAR assumption and -13.8% ($p<0.0001$) for the MAR assumption, as compared to -9.9% ($p=0.0003$) in the primary analysis. Results in P002 were stronger in these sensitivity analyses due to the lower clinical cure rate in the placebo group. For the integrated dataset (P001+P002), the treatment differences (bezlotoxumab minus placebo) in these sensitivity analyses were -9.8% ($p<0.0001$) for the MNAR assumption and -12.3% ($p<0.0001$) for the MAR assumption, as compared to -10.0% ($p<0.0001$) in the primary analysis.

These results strongly support the primary analysis of CDI recurrence for each trial and provide further evidence for the conclusion that bezlotoxumab is superior to placebo in preventing CDI recurrence.

It is of interest to note that in the analysis of the pre-defined secondary endpoint of global cure, subjects without clinical cure are not eligible to be counted as cured. Thus, in this analysis, these subjects were imputed as a failure for the CDI recurrence assessment. As such, the following four analyses provide a set of results ranging from the least conservative imputation approach to the most conservative imputation approach, and all support the conclusion that bezlotoxumab is superior to placebo in the prevention of CDI recurrence.

- primary endpoint of CDI recurrence
- multiple imputation analysis using MAR
- multiple imputation analysis using MNAR, and
- secondary endpoint of global cure.

Table 21
Sensitivity Analysis of the Proportion of Subjects with CDI recurrence using Multiple Imputation (MNAR)
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	Estimated Rate‡	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	24.9%	-8.4	-8.2 (-15.2, -1.2)	0.0112
Placebo	33.3%	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	Estimated Rate‡	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	21.5%	-11.4	-11.4 (-18.2, -4.5)	0.0006
Placebo	32.9%	---	---	---
	P001+P002			
		Treatment vs. Placebo		
Treatment	Estimated Rate‡	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	23.2%	-10.0	-9.8 (-14.7, -4.9)	< 0.0001
Placebo	33.1%	---	---	---

‡ Estimated rate based on multiple imputation among subjects without clinical cure using CDI recurrence rate among subjects with clinical cure in the placebo group.

† One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), SoC therapy (metronidazole vs. vancomycin +.fidaxomicin) and hospitalization status (inpatient vs. outpatient)

MNAR = missing not at random, SoC = Standard of Care

Table 22
Sensitivity Analysis of the Proportion of Subjects with CDI recurrence using Multiple Imputation (MAR)
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	Estimated Rate‡	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	22.4%	-10.9	-10.8 (-17.6, -4.0)	0.0012
Placebo	33.3%	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	Estimated Rate‡	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	19.0%	-13.9	-13.8 (-20.5, -7.2)	< 0.0001
Placebo	32.9%	---	---	---
	P001+P002			
		Treatment vs. Placebo		
Treatment	Estimated Rate‡	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	20.6%	-12.5	-12.3 (-17.1, -7.5)	< 0.0001
Placebo	33.1%	---	---	---

‡ Estimated rate based on multiple imputation among subjects without clinical cure using CDI recurrence rate among subjects with clinical cure in each respective treatment group.

† One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), SoC therapy (metronidazole vs. vancomycin + fidaxomicin) and hospitalization status (inpatient vs. outpatient)

MAR = missing at random, SoC = Standard of Care

Analysis of Any CDI Recurrence Independent of Clinical Cure Assessment

The final sensitivity analysis expands the risk set for CDI recurrence by including subjects who met a less rigorous definition of clinical cure. This was a post-hoc sensitivity analysis that includes all subjects with CDI recurrence, regardless of whether the subject met the protocol definition of clinical cure. This analysis addresses both questions regarding the impact of clinical cure on the interpretation of the CDI recurrence endpoint: 1) different observed clinical cure rates and 2) imputing a clinical cure failure as a "success" for CDI recurrence.

In the primary analysis, subjects failing to meet the definition of clinical cure, either due to duration of SoC therapy exceeding 16 calendar days or due to the presence of diarrhea on either of the two consecutive days immediately following the end of SoC therapy, were considered as not having had a CDI recurrence. In this sensitivity analysis, subjects were considered as achieving cure of the initial episode following SoC therapy if they had two consecutive diarrhea free days (regardless of the duration of SoC and the timing of the resolution of the initial episode). In this analysis, essentially all subjects achieved clinical cure and thus, were assessed for CDI recurrence.

In an effort to standardize the evaluation of clinical cure as much as possible, the protocol-specified definition of clinical cure was strict: ≤ 14 day regimen (16 calendar days were allowed) of SoC therapy and no diarrhea for 2 consecutive days following completion of SoC therapy. The definition of the primary endpoint of CDI recurrence required that subjects achieve protocol-defined clinical cure to be included in the risk set for developing CDI recurrence. An important component of the study designs was that the monitoring and evaluation of CDI recurrences did not depend on the subject's clinical cure outcome (given that this was a programmatically derived endpoint as opposed to an investigator assessed endpoint). Sites were not aware of Merck's assessment of clinical cure and as such were expected to evaluate each and every return of diarrhea following resolution of the baseline episode. This analysis is especially robust given that the monitoring and evaluation of CDI recurrences did not depend on the subject's clinical cure outcome.

This sensitivity analysis was conducted for P001, P002, and for the P001+P002 integrated dataset. Results are displayed in Table 23. In general, CDI recurrence rates in this sensitivity analysis were about 5% higher than the rates observed for the primary analysis across both treatment groups and across both protocols. Consequently, the results of this sensitivity analysis were consistent with the primary analysis results. For P001, the treatment difference (bezlotoxumab minus placebo) in this sensitivity analysis was -10.9% (p=0.0003) as compared to -10.1% (p=0.0003) in the primary analysis. For P002, the treatment difference in this sensitivity analysis was -10.2% (p=0.0006) as compared to -9.9% (p=0.0003) in the primary analysis. For the integrated dataset (P001 + P002), the treatment difference in this sensitivity analysis was -10.6% (p<0.0001) as compared to -10.0% (p<0.0001) in the primary analysis. These results strongly support the primary analysis of CDI recurrence for each trial and provide further evidence for the conclusion that bezlotoxumab is superior to placebo in preventing CDI recurrence.

Table 23
Sensitivity Analysis of the Proportion of Subjects with CDI Recurrence following Resolution of the Baseline Episode
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

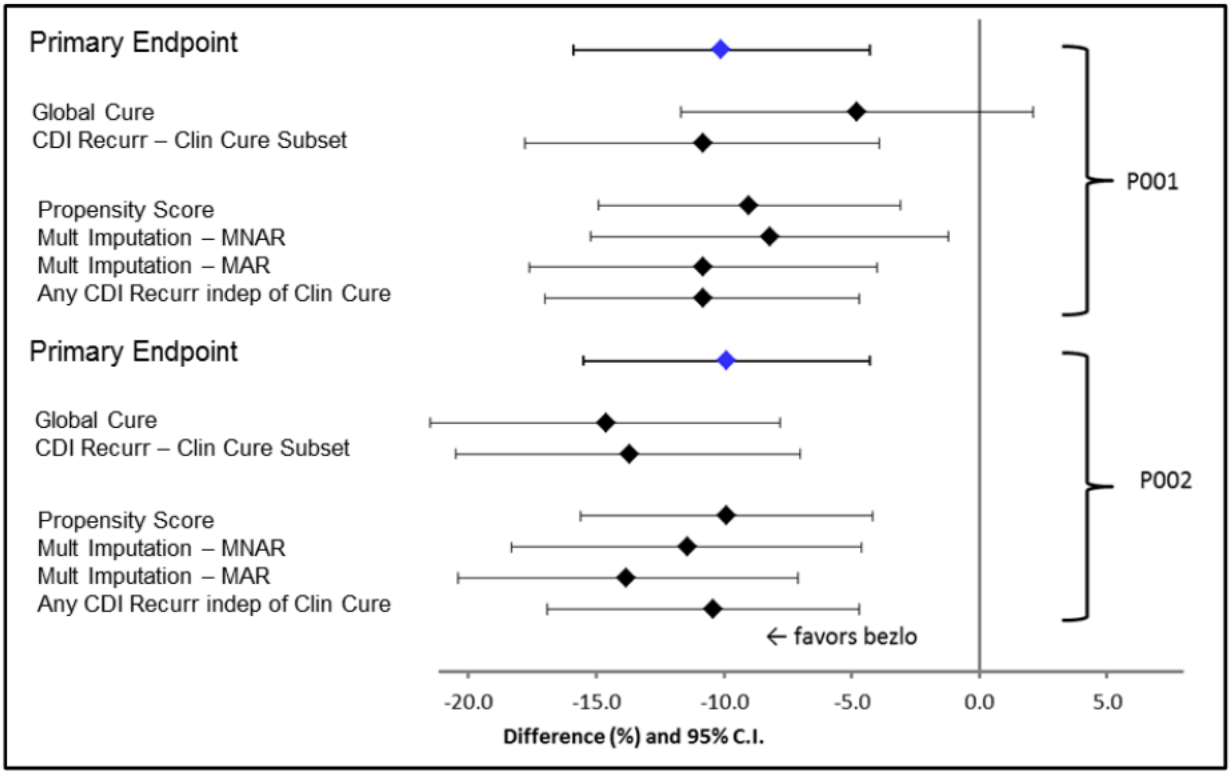
	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	21.4 (83/386)	-10.9	-10.8 (-16.9, -4.6)	0.0003
Placebo	32.4 (128/395)	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	21.3 (84/395)	-10.2	-10.4 (-16.1, -3.9)	0.0006
Placebo	31.5 (119/378)	---	---	---
	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	21.4 (167/781)	-10.6	-10.4 (-14.7, -6.1)	< 0.0001
Placebo	32.0 (247/773)	---	---	---

[†] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

Summary of All Sensitivity Analyses to assess Impact of Clinical Cure

The difference (bezlotoxumab vs. placebo) and 95% confidence interval for the above four sensitivity analyses are summarized in the forest plot displayed in Figure 12 for both P001 and P002. The results of the primary analysis are also displayed for comparison as well as the results for two additional protocol-defined endpoints (global cure and CDI recurrence in the subset of subjects achieving clinical cure). Of the 12 sensitivity/supportive analyses shown (6 analyses for 2 trials), all but one provide a 95% confidence interval for the bezlotoxumab versus placebo comparison that excludes zero. This demonstrates the robustness of primary analysis for supporting the conclusion that bezlotoxumab is superior to placebo in the prevention of CDI recurrence.

Figure 12
Summary of Sensitivity Analyses for the CDI Recurrence Endpoint
Impact of Clinical Cure



6.3.7.2 Analyses to Assess Impact of Missing or Incomplete Assessments

Three sensitivity analyses were conducted to assess the impact of missing or incomplete assessments on the interpretation of the CDI recurrence endpoint. In addition, one of the protocol-defined endpoints (diarrhea recurrence) provides strong support demonstrating the robustness of the primary analysis against the impact of missing or incomplete assessments. The three sensitivity analyses build on each other and are described below.

Subjects Failing to Complete the 12 week follow-up Period

A pre-specified sensitivity analysis was performed that considered any subject who discontinued the study (including deaths) as an imputed failure for the primary endpoint (i.e., having CDI recurrence). In the primary analysis of CDI recurrence, subjects who discontinued the study (including deaths) prior to a CDI recurrence were counted as "successes" or non-recurrences.

Subjects Who have a Return of Diarrhea, but are Missing an Associated Stool Toxin Test

A post-hoc sensitivity analysis was conducted that considered any subject who met the following two criteria as an imputed failure for the primary endpoint (i.e., having CDI recurrence):

- discontinued the study (including deaths)
- had a new episode of diarrhea following clinical cure but did not have a stool sample collected for toxin testing

In the primary analysis of CDI recurrence, subjects who had a new episode of diarrhea following clinical cure but did not have a stool sample collected for toxin testing were counted as "successes" or non-recurrences.

Subjects with Concomitant Therapy or Procedure that is Potentially Useful in the Treatment of CDI

A post-hoc sensitivity analysis was conducted that considered any subject who met the following three criteria as an imputed failure for the primary endpoint (i.e., having CDI recurrence):

- discontinued the study (including deaths)
- had a new episode of diarrhea following clinical cure but did not have a stool sample collected for toxin testing
- received a concomitant medication or procedure potentially useful in the treatment of CDI during the follow-up period

In the primary analysis of CDI recurrence, subjects who received a concomitant medication or procedure potentially useful in the treatment of CDI during the follow-up period, but did not meet the stool count and toxin test criteria were counted as "successes" or non-recurrences.

This third analysis included any subject receiving any of the following concomitant medications at any dose for any duration following the end of SoC therapy (even if for a single day): metronidazole (IV or Oral), vancomycin (Oral and any route not IV), fidaxomicin (Oral), rifaximin (Oral), nitazoxanide (Oral), cholestyramine resin (Oral), teicoplanin (Oral and any route not IV), tigecycline (IV), or *Saccromyces boulardii* (Oral). Additionally, subjects who received immune globulin (IV) at any time after study medication infusion were imputed as failures. Finally, subjects who reported having a fecal transplant after the end of SoC therapy were also imputed as failures.

Results

Table 24, Table 25 and Table 26 summarize the analyses where subjects without complete information are imputed as a "failure" for the CDI recurrence assessment in each of the

protocols separately and for P001 + P002 integrated. As expected for these sensitivity analyses, the proportions of subjects with a CDI recurrence increased across both the placebo and bezlotoxumab treatment groups as compared with the original analysis. The results of these sensitivity analyses confirm the robustness of the treatment effect of bezlotoxumab in prevention of CDI recurrence despite the fact that the number of subjects that were "eligible" for imputation was higher in the bezlotoxumab group as compared with placebo.

In P001, a similar number of subjects discontinued the study in the bezlotoxumab and placebo treatment groups resulting in similar number of subjects who were imputed as failures (12.2% in each arm). As such, the treatment difference in the analysis where subjects discontinuing the study pre-maturely were imputed to be a CDI recurrence (-10.2, p=0.0014) was consistent with that in the original analysis (-10.1, p=0.0003). When additional failures were imputed for subjects who had a return of diarrhea, but were missing an associated stool toxin test, results also remained consistent with those in the original analysis (-10.7, p=0.0008). Due to the fact that a larger number of subjects in the placebo group (n=73, 18.5%) as compared to the bezlotoxumab group (n=58, 15.0%) were imputed as failures in the third version of this analysis (where additional subjects who received CDI treatment were imputed as failures), the adjusted difference in CDI recurrence between bezlotoxumab and placebo was larger in the sensitivity analysis (-13.7, p<0.0001) than in the original analysis (-10.1, p=0.0003).

In P002, a slightly higher percentage of subjects were imputed failures due to discontinuing the study in the placebo arm (15.3%) as compared to the bezlotoxumab treatment group (13.9%). As such, the treatment difference in the analysis where subjects discontinuing the study pre-maturely were imputed to be a CDI recurrence (-11.4, p=0.0005) was larger than that in the original analysis (-9.9, p=0.0003). When additional failures were imputed for subjects who had a return of diarrhea, but were missing an associated stool toxin test and/or received additional CDI treatment, the treatment differences were reduced (-6.0, p=0.0373 and -4.4, p=0.0998, respectively) compared to the original analysis due to a higher number of imputed failures for both criteria in the bezlotoxumab group as compared with placebo. The differences from the original analysis were largely driven by subjects with a "new diarrhea episode not tested" (n=22 in the bezlotoxumab group vs. n=6 in placebo group). Importantly, only 5 of these 22 subjects had more than 2 days of diarrhea (compared with 2 of the 6 subjects in the placebo group) suggesting that most of these subjects likely did not have a recurrent CDI episode.

In the pooled analysis of the two studies (P001 + P002), a similar number of subjects were imputed failures in the bezlotoxumab group compared to the placebo group across all three of the imputed failure analyses. Thus, while there were differences between the two studies in the number of subjects who were imputed failures by treatment group, these differences offset each other and the pooled results for the sensitivity analyses were consistent with the original analysis. The treatment differences (bezlotoxumab minus placebo) were -10.8 (p<0.0001), -8.3 (p=0.0002), and -9.1 (p=0.0001) for the three versions of the sensitivity analyses, respectively, as compared to -10.0 (p<0.0001) in the original analysis.

Table 24
Sensitivity Analysis of the Proportion of Subjects with CDI Recurrence with Imputed Failures‡
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	29.5 (114/386)	-10.2	-10.2 (-16.8, -3.5)	0.0014
Placebo	39.7 (157/395)	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	29.6 (117/395)	-11.4	-11.3 (-17.9, -4.6)	0.0005
Placebo	41.0 (155/378)	---	---	---
	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)†	p-Value†
BEZLO	29.6 (231/781)	-10.8	-10.7 (-15.4, -6.0)	<0.0001
Placebo	40.4 (312/773)	---	---	---

‡Failures were imputed for subjects achieving clinical cure of the initial episode with no documented CDI recurrence who discontinued during the follow up period.

† One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

Table 25
Sensitivity Analysis of the Proportion of Subjects with CDI Recurrence with Imputed Failures[‡]
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	28.5 (110/386)	-10.7	-10.7 (-17.2, -4.1)	0.0008
Placebo	39.2 (155/395)	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	28.6 (113/395)	-6.0	-6.0 (-12.5, 0.6)	0.0373
Placebo	34.7 (131/378)	---	---	---
	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	28.6 (223/781)	-8.4	-8.3 (-13.0, -3.7)	0.0002
Placebo	37.0 (286/773)	---	---	---

[‡]Failures were imputed for subjects achieving clinical cure of the initial episode with no documented CDI recurrence who met one or more of the following conditions: (1) discontinued during the follow up period, and/or (2) had a new episode of diarrhea, but no stool sample was collected for toxin testing.

[†] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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

Table 26
Sensitivity Analysis of the Proportion of Subjects with CDI Recurrence with Imputed Failures[‡]
Phase 3 Studies (P001, P002, and P001 + P002 Integrated)
Full Analysis Set Population

	P001			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	32.4 (125/386)	-13.7	-13.6 (-20.3, -6.8)	<0.0001
Placebo	46.1 (182/395)	---	---	---
	P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	34.2 (135/395)	-4.4	-4.4 (-11.2, 2.3)	0.0998
Placebo	38.6 (146/378)	---	---	---
	P001+P002			
		Treatment vs. Placebo		
Treatment	% (n/N)	Unadjusted Difference	Adjusted Difference (95% CI)[†]	p-Value[†]
BEZLO	33.3 (260/781)	-9.1	-9.1 (-13.8, -4.3)	0.0001
Placebo	42.4 (328/773)	---	---	---

[‡]Failures were imputed for subjects achieving clinical cure of the initial episode with no documented CDI recurrence who met one or more of the following conditions: (1) discontinued during the follow up period (2) had a new episode of diarrhea, but no stool sample was collected for toxin testing, and/or (3) Received an active concomitant medication or procedure for treatment of CDI.

[†] One sided p-value based on the Miettinen and Nurminen method stratified by protocol (P001 vs P002), 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.

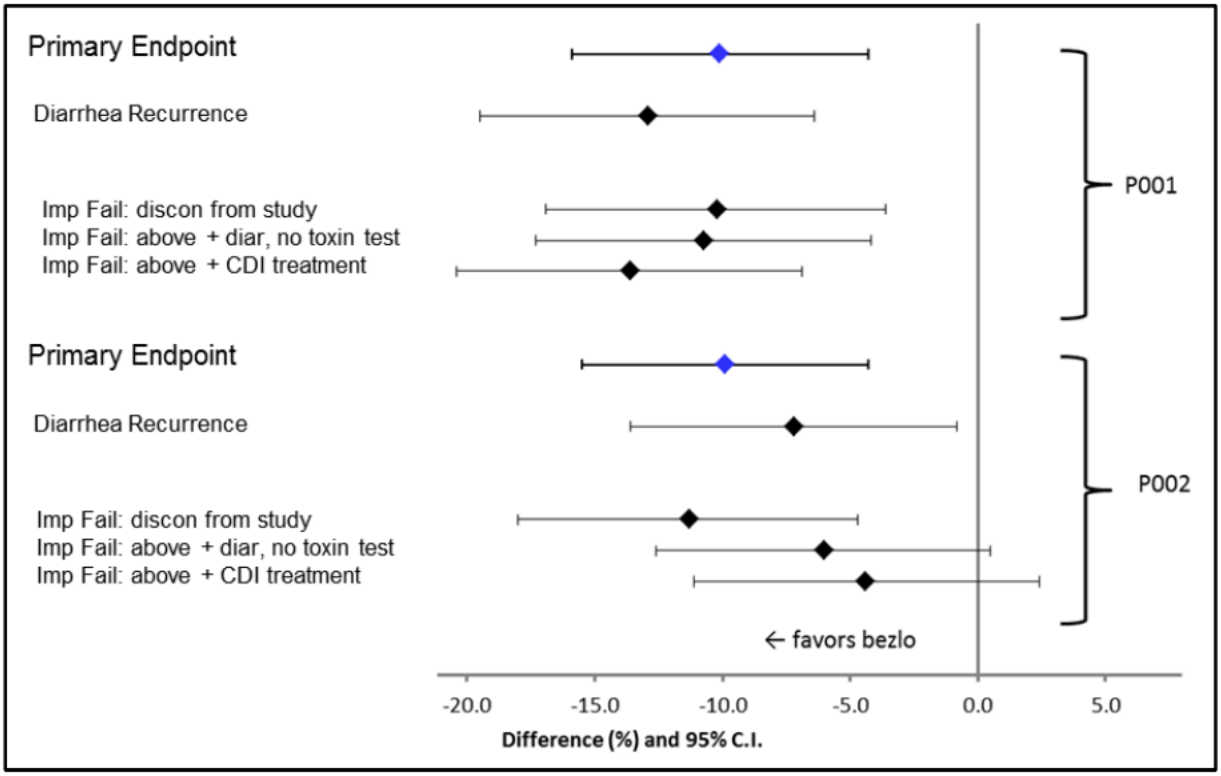
N = Number of subjects included in the analysis population.

SoC = Standard of Care

Summary of Sensitivity Analyses to Assess Impact of Missing or Incomplete Assessments

The difference (bezlotoxumab vs. placebo) and 95% confidence interval for the above three sensitivity analyses are summarized in the forest plot displayed in Figure 13 for both P001 and P002. The results of the primary analysis are also displayed for comparison as well as the results for the protocol-defined endpoint of diarrhea recurrence. Of the 8 sensitivity/supportive analyses shown (4 analyses for 2 trials), all but two provide a 95% confidence interval for the bezlotoxumab versus placebo comparison that excludes zero. This demonstrates the robustness of primary analysis for supporting the conclusion that bezlotoxumab is superior to placebo in the prevention of CDI recurrence in the setting of missing data.

Figure 13
Summary of Sensitivity Analyses for the CDI Recurrence Endpoint
Impact of Missing or Incomplete Assessments



6.3.7.3 Summary of Sensitivity Analyses

A total of 20 sensitivity/supportive analyses have been presented (10 analyses for 2 trials) to address two topics with regard to the primary efficacy analysis: 1) impact of clinical cure of the baseline episode (a post-randomization event) and 2) impact of missing or incomplete assessments. All but three of these analyses provide a 95% confidence interval for the bezlotoxumab versus placebo comparison that excludes zero. This provides compelling evidence of the robustness of primary analysis for supporting the conclusion that bezlotoxumab is superior to placebo in the prevention of CDI recurrence.

6.3.8 Exposure-Response Analyses for Efficacy

An efficacy exposure-response analysis was conducted to investigate the relationship between bezlotoxumab exposure and CDI recurrence based on CDI recurrence and pharmacokinetic data from the Phase 3 trials (P001 and P002). The exposure-response relationship between bezlotoxumab AUC0-inf and CDI recurrence is characterized by an Emax relationship, in which exposures achieved at the 10 mg/kg dose are on the maximal response plateau of the exposure-response curve. Hence, bezlotoxumab exposure following a dose of 10 mg/kg is not an important predictor of CDI recurrence, as higher exposures do not appear to lead to meaningful clinical benefit.

To account for the influence of risk factors (such as clinically severe CDI, a history of CDI, or a high Charlson comorbidity index) for CDI recurrence rates, the effects of these covariates on the rate of CDI recurrence in placebo-treated patients were evaluated. In addition, bezlotoxumab exposure correlates with albumin levels, with lower exposure observed for subjects with low albumin. Moreover, the risk factors of interest correlate with albumin levels, as albumin tends to be lower in patients with poor health. After adjusting for the effect of these covariates and albumin, there were no trends between bezlotoxumab exposure and observed CDI recurrence rates over the range of exposures achieved with 10 mg/kg in Phase 3. This indicates that patient covariates, rather than exposure, are the primary factors influencing CDI recurrence in all subjects.

In summary, exposure-response analyses of pooled data from the Phase 3 trials demonstrate no significant dependence of CDI recurrence on bezlotoxumab exposures over the range of exposures achieved in Phase 3, indicating that the entire range of exposures achieved at the 10 mg/kg dose in Phase 3 are associated with a similar low rate of CDI recurrence.

6.4 Persistence of Efficacy

The efficacy of bezlotoxumab in the prevention of CDI recurrence was consistent through the 12 week follow-up period in both Phase 3 trials. Data from a subset of 293 patients followed for 9 additional months suggest that the efficacy of bezlotoxumab observed in the first 12 weeks is due to prevention of CDI recurrence rather than a delay in onset of a recurrent episode [Table 27]. In this exploratory analysis, no bezlotoxumab-treated subjects who had achieved global cure at the end of the 12-week main study experienced a CDI recurrence in the subsequent 9 months. These findings provide evidence that the efficacy of bezlotoxumab

observed in the main study is due to prevention of CDI recurrence rather than a delay in onset of a recurrent episode after the antibody concentrations are diminished.

Table 27
CDI Recurrence† through 12 Months Following a Single Infusion of Study Medication
(Full Analysis Set Extension Cohort)

	ACTO + BEZLO (N=112) n (%)	BEZLO (N=99) n (%)	Placebo (N=82) n (%)
CDI Recurrence by Week 12	22 (19.6)	16 (16 2)	34 (41 5)
CDI Recurrence by Month 6	22 (19.6)	16 (16 2)	34 (41 5)
CDI Recurrence by Month 9	23 (20 5)	16 (16 2)	34 (41 5)
CDI Recurrence by Month 12	24 (21.4)	16 (16 2)	35 (42.7)

† CDI recurrence rates are cumulative; subjects with recurrence at one time point are also included at subsequent time points.
N = number of subjects who entered the extension study after completion of the primary study (first 12 weeks) and who were included in the FAS population.

6.5 Efficacy Conclusions

A single 10 mg/kg dose of bezlotoxumab is highly efficacious in preventing CDI recurrence, demonstrating a relative reduction of the recurrence rate of ~40% compared to placebo in patients receiving standard of care antibiotic therapy for CDI.

- Bezlotoxumab is superior to placebo in the prevention of CDI recurrence through 12 weeks following administration (primary endpoint).
- The low incidence of CDI recurrence in the bezlotoxumab group, and the clinically meaningful treatment difference in CDI recurrence between the bezlotoxumab and placebo groups were highly consistent across the Phase 3 trials:
  - P001: -10.1 (95% CI -15.9, -4.3), p=0.0003
  - P002: -9.9 (95% CI -15.5, -4.3), p=0.0003
  - P001+P002 (integrated): -10.0 (95% CI -14.0, -6.0), p<0.0001
- Bezlotoxumab is efficacious in key subgroups at high risk for CDI recurrence and/or CDI-related adverse outcomes. These subgroups are:
  - Age ≥65 years
  - Has a history of one or more episodes of CDI in past 6 months
  - Immunocompromised
  - With clinically severe CDI
  - Infected with a hypervirulent strain (027, 078, or 244)
  - Infected with the 027 strain
- Exposures achieved with the clinical dose of 10 mg/kg are associated with a similar low rate of CDI recurrence, indicating that 10 mg/kg is on the plateau of the exposure-response curve for efficacy.

- Bezlotoxumab is highly efficacious with respect to the global cure endpoint (secondary endpoint).
- Efficacy of the SoC antibiotic is not diminished by administration of bezlotoxumab; clinical cure rates were comparable for the bezlotoxumab and placebo groups in the Phase 3 trials.
- The combination of actoxumab and bezlotoxumab does not provide a meaningful efficacy benefit over bezlotoxumab alone.
- The totality of the efficacy data supports the selection of bezlotoxumab as the product for registration.

7 PHASE 3 SAFETY RESULTS

This section discusses the safety data for bezlotoxumab when given alone or in combination with actoxumab, i.e., actoxumab + bezlotoxumab. See Table 1 for a list of the clinical trials conducted. Each trial was designed to assess the safety and tolerability of a single IV infusion of mAb at a dose of 10 mg/kg, when given with standard of care antibiotics, compared to treatment with a single infusion of placebo with standard of care antibiotics.

The primary assessment of the safety profile of bezlotoxumab is based on comparison to that of placebo as demonstrated in the integrated P001 and P002 Phase 3 dataset. The safety profile of actoxumab + bezlotoxumab is included as a protocol-specified analysis for the Phase 3 trials; such data can also provide supporting data to the overall safety profile of bezlotoxumab. Data from subjects who received actoxumab alone are not included in this section, primarily due to the results of the pre-planned interim analysis of P001 and the subsequent termination of the actoxumab only group in P001 (see Section 6.2.6). Safety data from healthy subjects in Phase 1 trials and from the Phase 2 study in subjects with CDI did not indicate any safety concerns.

The integrated Phase 3 APaT population dataset from P001 and P002 comprise the primary safety database in support of the licensing application for bezlotoxumab and are described in detail (including adverse events during first 4 weeks after infusion, serious adverse events during 12 weeks following infusion, infusion-specific adverse events, exposure-response analysis, and immunogenicity) in this section.

7.1 Safety Evaluation Plan

For each Phase 1, Phase 2, and Phase 3 trial in which bezlotoxumab was administered, monitoring of safety was done by the investigator(s) at each study visit. The investigator assessed the severity/intensity of all AEs and assessed whether or not there was a reasonable possibility that the AE was related to study therapy. Drug-related AEs were those that the investigator assessed to be related to study therapy.

In the Phase 3 trials (P001 and P002), non-serious AEs were collected from the time of infusion until Week 4 post-infusion. Serious adverse events (SAEs) were collected from the time of infusion until the Week 12 post-infusion visit. In P002, a subset of subjects (~300)

participated in 9-month extended follow-up period. During this follow-up period, SAEs determined to be related to study medication infusion or with a fatal outcome were reported. The safety analysis in all trials included common AEs, drug-related AEs, SAEs, AEs that were both serious and drug-related, and discontinuations due to AEs. Additionally, the Phase 3 trials evaluated changes in pre- and post-infusion ECGs, changes in vital signs, and changes in laboratory values. To monitor for the potential for acute hypersensitivity reactions, subjects in P001 and P002 were evaluated for infusion-specific reactions for 24 hours immediately post infusion. Subjects in Phase 3 were also monitored for the development of anti-bezlotoxumab antibodies.

All summaries in this section display subjects by actual treatment received instead of the treatment group to which the subjects were randomized. AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) using Versions 18.0 for the analyses.

The Phase 3 safety data were also analyzed to identify potential safety signals in demographic subgroups and in vulnerable subjects, based on key intrinsic or extrinsic factors. These include certain key intrinsic factors, including age (young versus elderly with elderly defined as ≥65 years and ≥75 years), gender (male versus female), race (White versus all others), weight (≤ 70 kg versus > 70 kg, and organ function (renal impairment versus no renal impairment and hepatic impairment versus no hepatic impairment). Extrinsic factors include region, standard of care stratum, and hospitalization stratum. The safety data presented herein demonstrates that bezlotoxumab has a favorable safety and tolerability profile which is similar to placebo.

7.2 Overall Extent of Exposure

A summary of the overall extent of exposure to bezlotoxumab, actoxumab + bezlotoxumab, and placebo in the clinical development program is presented in [Table 28]. These data include Phase 1 trials in healthy subjects and Phase 2 and 3 trials in subjects with CDI. The summary of subject exposure includes data from 1790 subjects exposed to bezlotoxumab, either alone or in combination with actoxumab; of these, 126 were healthy subjects in Phase 1, and 1664 were patients with CDI in Phase 2 and 3.

Table 28
Summary of Subject Exposure with Bezlotoxumab, Actoxumab + Bezlotoxumab, or Placebo

Treatment	Phase 1[†]	Phase 2[‡]	Phase 3[§]	Total Number of Subjects[‖]
BEZLO	30	-	786	816
ACTO + BEZLO	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.
[‡] P017 is included in this safety summary.
[§] P001 and P002 are included in this safety summary.
[‖] Includes healthy volunteers and patients with CDI.

In the Phase 3 trials (P001 and P002), a total of 777 subjects received actoxumab + bezlotoxumab, 786 subjects received bezlotoxumab, and 781 subjects received placebo. The majority of subjects (>96%) in each active treatment group received the intended dose of 10 mg/kg. No subjects received an overdose (>20 mg/kg per antibody, i.e., the highest mg/kg dose of bezlotoxumab that was studied in the Phase 1 P020 trial). The majority of subjects (92.8 %) received the infusion over approximately 60 minutes (i.e., ≥45 to <75 minutes) corresponding to a rate of infusion of 2.7 to 5.6 mL/min. As the dose of bezlotoxumab was diluted in 200 or 250 mL normal saline, the bezlotoxumab concentration in the infusate ranged from 1.2 to 8.0 mg/mL. Because bezlotoxumab dose is calculated as mg/kg based on actual body weight, the range of bezlotoxumab doses administered on a mg basis was large given the corresponding range of subject body weights (range of body weights: 29.8 to 194 kg; range of bezlotoxumab doses: 300 to 2000 mg). The median dose of bezlotoxumab was 700 mg, which was consistent with the median weight of 70 kg among bezlotoxumab-treated subjects. Only one subject discontinued the infusion due to an AE [Section 7.3.1.2].

7.3 Summary of Adverse Events

Table 29 summarizes the AEs experienced by subjects during the first 4 weeks following infusion with study treatment in the integrated Phase 3 dataset (P001 + P002). Bezlotoxumab, when given alone or with actoxumab, was generally well tolerated with a safety profile similar to placebo.

The majority of subjects reported one or more AEs (60.5% across all treatment groups), with similar percentages reported in the bezlotoxumab (61.7%), actoxumab + bezlotoxumab (58.6%), and placebo (61.2%) treatment groups. Overall, drug-related AEs (6.6%), serious drug-related AEs (0.5%), and deaths (3.9%) were infrequent and occurred at similar rates across treatment groups. One subject in the bezlotoxumab group (0.1%) discontinued due to a serious drug-related SAE.

During the 12 weeks post-infusion, 29.8% of subjects experienced an SAE, and 7.1% of subjects died, as compared to 19.0% and 3.9%, respectively, in the first 4 weeks following infusion with study treatment. Almost all of the subjects reporting drug-related AEs and drug-related SAEs were identified during the first 4 weeks post-infusion.

Table 29
Adverse Event Summary
During 4 Weeks Following Infusion
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		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 event	322	(41.4)	301	(38.3)	303	(38.8)	926	(39.5)
with drug-related† adverse events	50	(6.4)	59	(7.5)	46	(5.9)	155	(6.6)
with serious adverse events	123	(15.8)	156	(19.8)	167	(21.4)	446	(19.0)
with serious drug-related adverse events	5	(0.6)	4	(0.5)	2	(0.3)	11	(0.5)
who died	28	(3.6)	32	(4.1)	32	(4.1)	92	(3.9)
discontinued‡ due to an adverse event	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
discontinued due to a serious adverse event	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

7.3.1 Analysis of Overall Adverse Events

Table 30 presents the number and percentage of subjects with specific AEs (incidence ≥2% in one or more treatment groups) by system organ class/preferred term and treatment group in the integrated Phase 3 dataset (P001 + P002). AEs most frequently reported during the 4 weeks post-infusion were: diarrhea (5.9%), nausea (5.9%), abdominal pain (4.3%), CDI (4.2%), pyrexia (4.0%), headache (3.9%), and vomiting (3.2%). In addition, diarrhea, nausea, pyrexia, and headache were the most common AEs in the bezlotoxumab group. A numerically higher proportion of subjects in the placebo group (6.1%) reported an AE of CDI during the first 4 weeks post-infusion compared to 3.5% for subjects receiving actoxumab + bezlotoxumab and 2.9% for subjects receiving bezlotoxumab.

Overall, the reported AEs were generally as expected considering the medical condition under study as well as the age and the baseline comorbidities of the trial population.

Table 30
Subjects With Adverse Events During 4 Weeks Following Infusion
(Incidence ≥ 2% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		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)

Subjects With Adverse Events During 4 Weeks Following Infusion
(Incidence ≥ 2% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		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.

In general, the incidence of AEs was similar across the treatment groups. When compared to the placebo group, the incidence of the following events was different (i.e., the 95% CI of the treatment difference does not include zero): (1) favoring bezlotoxumab over placebo: CDI, dehydration, and mental status changes; (2) favoring actoxumab + bezlotoxumab over placebo: CDI and sepsis; (3) favoring placebo over bezlotoxumab: hypertension; and (4) favoring placebo over actoxumab + bezlotoxumab: musculoskeletal pain, hypertension, and international normalized ratio increased. Each of these events generally occurred in ≤2% of subjects in each of the treatment groups, with the exception of CDI which was reported at a higher rate in the placebo group (6.1%) compared to the bezlotoxumab and actoxumab + bezlotoxumab groups (2.9% and 3.5%, respectively). CDI recurrence is an efficacy endpoint in the trials and the investigators were instructed to record CDI as an AE only if the event met serious AE criteria. As expected from the favorable efficacy result associated with bezlotoxumab, i.e., the decreased CDI recurrence rate, CDI was recorded as an AE at a lower frequency in the bezlotoxumab and actoxumab + bezlotoxumab groups compared to the placebo group.

7.3.1.1 Drug-Related Adverse Events

The number and percentage of subjects who reported specific AEs, assessed by the investigator to be related to infusion of the study medication with an incidence ≥0% in any treatment group or system organ class through Week 4, are presented in Table 31 for the integrated Phase 3 dataset (P001 + P002). Overall drug-related AEs were infrequent and similar across the treatment groups (bezlotoxumab: 7.5%; actoxumab + bezlotoxumab: 6.4%; placebo: 5.9%). The most frequently reported drug-related AEs across the treatment groups were nausea (0.8%), fatigue (0.6%), dizziness (0.6%), and headache (0.6%). The incidences of individual drug-related AEs were comparable between the bezlotoxumab and placebo groups (i.e., the 95% CIs for the treatment differences do not include zero).

Table 31
Subjects With Drug- Related Adverse Events During 4 Weeks Following Infusion
(Incidence ≥ 0.5% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO + BEZLO		BEZLO		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	777		786		781		2,344	
with one or more drug-related adverse events	50	(6.4)	59	(7.5)	46	(5.9)	155	(6.6)
Nausea	6	(0.8)	8	(1.0)	4	(0.5)	18	(0.8)
Fatigue	5	(0.6)	5	(0.6)	4	(0.5)	14	(0.6)
Pyrexia	3	(0.4)	4	(0.5)	1	(0.1)	8	(0.3)
Alanine aminotransferase increased	0	(0.0)	4	(0.5)	2	(0.3)	6	(0.3)
Dizziness	3	(0.4)	6	(0.8)	6	(0.8)	15	(0.6)
Headache	4	(0.5)	6	(0.8)	4	(0.5)	14	(0.6)

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.

7.3.1.2 Serious Adverse Events

SAEs were collected for the full 12-week follow-up period in the two Phase 3 trials. The number and percentage of subjects who reported specific SAEs with an incidence >1% in any treatment group during the 12-week follow-up period are presented in Table 32 for the integrated Phase 3 dataset (P001 + P002). A total of 29.8% of subjects experienced an 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 compared to the bezlotoxumab and actoxumab + bezlotoxumab groups. The incidence for other frequently reported SAEs was similar across groups. SAEs generally reflected the underlying comorbidities and advanced age of the subjects enrolled.

Table 32
Subjects With Serious Adverse Events During 12 Weeks Following Infusion (Incidence ≥ 1% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		BEZLO		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	777		786		781		2,344	
with one or more serious adverse events	212	(27.3)	231	(29.4)	255	(32.7)	698	(29.8)
with no serious adverse events	565	(72.7)	555	(70.6)	526	(67.3)	1,646	(70.2)
Blood and lymphatic system disorders	**10**	**(1.3)**	**11**	**(1.4)**	**8**	**(1.0)**	**29**	**(1.2)**
Cardiac disorders	**24**	**(3.1)**	**36**	**(4.6)**	**27**	**(3.5)**	**87**	**(3.7)**
Cardiac failure congestive	8	(1.0)	6	(0.8)	2	(0.3)	16	(0.7)
Gastrointestinal disorders	**37**	**(4.8)**	**49**	**(6.2)**	**42**	**(5.4)**	**128**	**(5.5)**
Diarrhoea	10	(1.3)	16	(2.0)	12	(1.5)	38	(1.6)
General disorders and administration site conditions	**18**	**(2.3)**	**19**	**(2.4)**	**19**	**(2.4)**	**56**	**(2.4)**
Hepatobiliary disorders	**8**	**(1.0)**	**7**	**(0.9)**	**2**	**(0.3)**	**17**	**(0.7)**
Infections and infestations	**93**	**(12.0)**	**104**	**(13.2)**	**138**	**(17.7)**	**335**	**(14.3)**
Clostridium difficile infection	31	(4.0)	24	(3.1)	54	(6.9)	109	(4.7)
Pneumonia	14	(1.8)	12	(1.5)	20	(2.6)	46	(2.0)
Sepsis	6	(0.8)	13	(1.7)	24	(3.1)	43	(1.8)
Septic shock	7	(0.9)	4	(0.5)	10	(1.3)	21	(0.9)
Urinary tract infection	11	(1.4)	15	(1.9)	9	(1.2)	35	(1.5)

Subjects With Serious Adverse Events During 12 Weeks Following Infusion (Incidence ≥ 1% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		BEZLO		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**7**	**(0.9)**	**10**	**(1.3)**	**9**	**(1.2)**	**26**	**(1.1)**
Metabolism and nutrition disorders	**10**	**(1.3)**	**11**	**(1.4)**	**16**	**(2.0)**	**37**	**(1.6)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**16**	**(2.1)**	**18**	**(2.3)**	**16**	**(2.0)**	**50**	**(2.1)**
Nervous system disorders	**24**	**(3.1)**	**13**	**(1.7)**	**8**	**(1.0)**	**45**	**(1.9)**
Renal and urinary disorders	**6**	**(0.8)**	**16**	**(2.0)**	**18**	**(2.3)**	**40**	**(1.7)**
Acute kidney injury	4	(0.5)	6	(0.8)	10	(1.3)	20	(0.9)
Respiratory, thoracic and mediastinal disorders	**26**	**(3.3)**	**28**	**(3.6)**	**24**	**(3.1)**	**78**	**(3.3)**
Vascular disorders	**10**	**(1.3)**	**5**	**(0.6)**	**13**	**(1.7)**	**28**	**(1.2)**

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.

The number and percentage of subjects who reported specific SAEs assessed by the investigator to be related to study medication infusion and with an incidence >0% in any treatment group through Week 12 are presented in Table 33. 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 2 serious and drug-related AEs were 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. Only sepsis was reported by more than one subject: 1 subject in the actoxumab + bezlotoxumab group and 1 subject in the bezlotoxumab group. Eleven of the 12 serious and drug-related AEs were reported in the first 4 weeks following the infusion of study medication. There was 1 subject in the bezlotoxumab group who experienced a treatment-related SAE (osteoporotic fracture [of the femur]) during the 9 month extension period. There were 3 subjects with serious and drug-related AEs that resulted in fatal outcome.

Table 33
Subjects With Serious and Related Adverse Events During 12 Weeks Following Infusion (Incidence > 0% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		BEZLO		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	777		786		781		2,344	
with one or more serious and related adverse events	6	(0.8)	4	(0.5)	2	(0.3)	12	(0.5)
with no serious and related adverse events	771	(99.2)	782	(99.5)	779	(99.7)	2,332	(99.5)
Cardiac disorders	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.0)**
Ventricular tachyarrhythmia	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Gastrointestinal disorders	**2**	**(0.3)**	**1**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.1)**
Diarrhoea	1	(0.1)	1	(0.1)	0	(0.0)	2	(0.1)
Small intestinal obstruction	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Infections and infestations	**2**	**(0.3)**	**1**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.1)**
Gastroenteritis	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Sepsis	1	(0.1)	1	(0.1)	0	(0.0)	2	(0.1)
Metabolism and nutrition disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Hypoglycaemia	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.0)**
Squamous cell carcinoma	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Nervous system disorders	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.1)**
Cerebral haemorrhage	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Cerebral infarction	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)

Subjects With Serious and Related Adverse Events During 12 Weeks Following Infusion (Incidence > 0% in One or More Treatment Groups)
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

	ACTO+BEZLO		BEZLO		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.0)**
Haematuria	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**	**3**	**(0.1)**
Pulmonary embolism	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.0)
Pulmonary haemorrhage	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Respiratory arrest	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)

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.

One subject discontinued the study infusion of bezlotoxumab due to an AE. This subject was a 32 year old White man with concurrent medical conditions including *Pneumocystis* pneumonia (PCP), human immunodeficiency virus (HIV) infection, depressive adaption disorder, psoriasis, steatosis hepatis, hypokalemia, transient hyponatremia, fever, and sinus tachycardia. This subject was hospitalized due to PCP and diagnosed with CDI during the hospitalization. No prior episode of CDI in the past 12 months was reported. Two days after starting oral metronidazole as treatment for CDI, the subject enrolled in P001 and received a single infusion of bezlotoxumab. Concomitant therapy included pantoprazole sodium, prednisone, pentamidine, and potassium. After receiving 127 mL of a 250 mL study medication infusion, the subject complained of chills and dizziness. The infusion was discontinued immediately. Clinical examination revealed ventricular tachyarrhythmia with frequencies up to 200 beats per minute (bpm); blood pressure was 120/80 mmHg. An electrocardiogram (ECG) showed the condition to be self-limiting. His symptoms ceased within two minutes. Dimethindene maleate, prednisolone, and ranitidine were administered intravenously. A follow-up ECG was conducted 30 minutes later showing normal heart rhythm. The reporting investigator considered the event of ventricular tachyarrhythmia to be related to the study therapy. The subject recovered from this event and completed the study.

7.3.1.3 Deaths

An integrated summary of AEs with an outcome of death across the Phase 3 trials, reported with an incidence >0% in any treatment group during the 12-weeks post-infusion, is presented in Table 34. During the 12 week post-infusion period, 7.1% subjects across all treatment groups reported one or more AEs with a fatal outcome: bezlotoxumab: 7.1%; actoxumab + bezlotoxumab: 6.6%; and placebo: 7.6%. Approximately half of these subjects (3.9% overall), died during the first 4 weeks post-infusion: bezlotoxumab: 4.1%; actoxumab + bezlotoxumab: 3.6%; and placebo 4.1%. The most frequently reported AEs with a fatal outcome were septic shock 0.6% (n=15), sepsis 0.6% (n=14), cardiac failure 0.4% (n=10), and respiratory failure 0.4% (n=9). A numerically higher proportion of subjects in the placebo group died of sepsis or septic shock as compared to the other 2 treatment groups: 2.2% in the placebo group (n=17) compared to 0.9% in the bezlotoxumab group (n=7) and 0.7% in the actoxumab + bezlotoxumab group (n=5).

Table 34
Subjects With Fatal Adverse Events During 12 Weeks Following Infusion by System Organ Class
Phase 3 Studies (P001 + P002 Integrated)
APaT Population

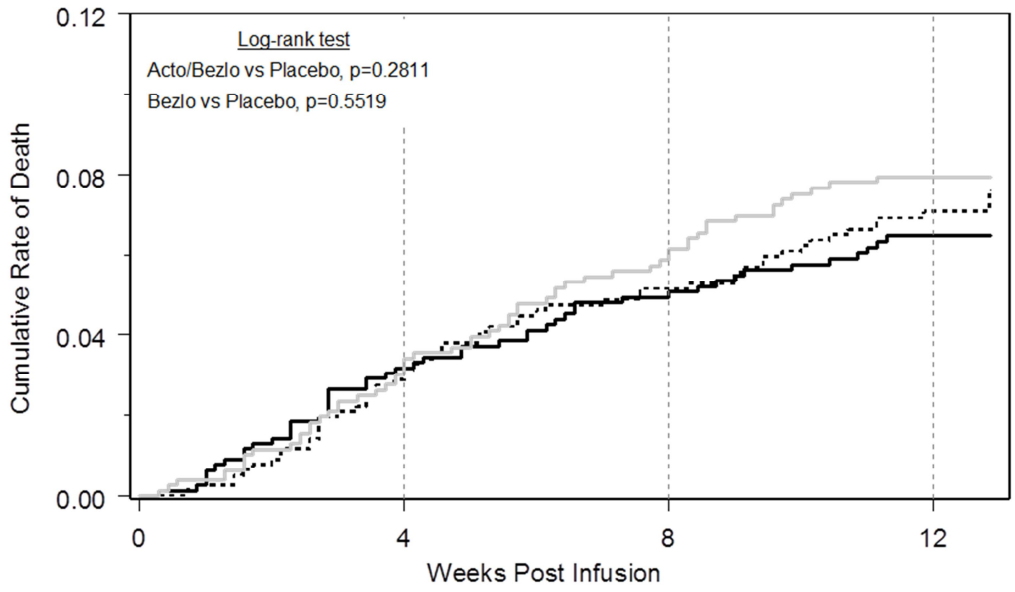
	ACTO+BEZLO		BEZLO		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	777		786		781		2,344	
with one or more fatal adverse events	51	(6.6)	56	(7.1)	59	(7.6)	166	(7.1)
with no fatal adverse events	726	(93.4)	730	(92.9)	722	(92.4)	2,178	(92.9)
Blood and lymphatic system disorders	**1**	**(0.1)**	**2**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.1)**
Cardiac disorders	**8**	**(1.0)**	**14**	**(1.8)**	**12**	**(1.5)**	**34**	**(1.5)**
Gastrointestinal disorders	**4**	**(0.5)**	**2**	**(0.3)**	**0**	**(0.0)**	**6**	**(0.3)**
General disorders and administration site conditions	**4**	**(0.5)**	**5**	**(0.6)**	**8**	**(1.0)**	**17**	**(0.7)**
Hepatobiliary disorders	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.1)**
Infections and infestations	**11**	**(1.4)**	**11**	**(1.4)**	**25**	**(3.2)**	**47**	**(2.0)**
Metabolism and nutrition disorders	**1**	**(0.1)**	**1**	**(0.1)**	**1**	**(0.1)**	**3**	**(0.1)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11**	**(1.4)**	**9**	**(1.1)**	**9**	**(1.2)**	**29**	**(1.2)**
Nervous system disorders	**5**	**(0.6)**	**4**	**(0.5)**	**1**	**(0.1)**	**10**	**(0.4)**
Renal and urinary disorders	**1**	**(0.1)**	**5**	**(0.6)**	**2**	**(0.3)**	**8**	**(0.3)**
Respiratory, thoracic and mediastinal disorders	**9**	**(1.2)**	**11**	**(1.4)**	**9**	**(1.2)**	**29**	**(1.2)**
Vascular disorders	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**

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.

There were 3 subjects who had AEs with a fatal outcome and considered by the investigator to be related to study medication infusion. All 3 subjects were hospitalized 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. In the actoxumab + bezlotoxumab group, one subject from P001 had AEs of sepsis, hypoglycemia, and respiratory arrest, and one subject from P002 had the AE of small intestinal obstruction. In the bezlotoxumab group, one subject from P001 reported AEs of sepsis and cerebral hemorrhage.

Mortality rates for each of the Phase 3 treatment groups were evaluated using Kaplan-Meier plots, and treatment differences were assessed using the log rank test. The results are shown in Figure 14. The Week 12 Kaplan-Meier mortality rates were 7.1% for the bezlotoxumab group, 6.5% for the actoxumab + bezlotoxumab group, and 7.9% for the placebo group. While the placebo group had the highest mortality rate with visual separation of the corresponding Kaplan-Meier mortality plot from the actoxumab + bezlotoxumab and bezlotoxumab groups starting at approximately Week 6 through Week 12, these differences were not statistically significant for the comparison of bezlotoxumab versus placebo (p=0.5519) or the comparison of actoxumab + bezlotoxumab versus placebo (p=0.2811).

Figure 14
Time to Death
All Patients as Treated Population



No. at Risk: KM Estimates (95% CI)

Acto/Bezlo	777	725: 0.032 (0.019, 0.044)	694: 0.051 (0.035, 0.066)	528: 0.065 (0.047, 0.082)
Bezlo	786	739: 0.031 (0.019, 0.044)	703: 0.051 (0.036, 0.067)	539: 0.071 (0.052, 0.089)
Placebo	781	729: 0.034 (0.021, 0.047)	686: 0.061 (0.044, 0.079)	525: 0.079 (0.060, 0.099)

A total of 9 subjects (3.1% of the integrated Phase 3 population) died during the 9-month extension phase: bezlotoxumab: n=5 (5.0% of the treatment group); actoxumab + bezlotoxumab: n=2 (1.8%); and placebo: n=2 (2.4%). None of these fatal AEs was deemed to be related to study medication infusion by the investigator.

7.3.1.4 Infusion-Specific Adverse Events

In both Phase 3 studies, subjects were evaluated for infusion-specific reactions during the infusion and for 24 hours post infusion. These include any of the following: infusion-site adverse experiences, pyrexia, chills, rash, arthralgia, myalgia, joint swelling, obstructive airways disorder, bronchospasm, stridor, dysphonia, headache, fatigue, pruritus, urticaria, hypotension, hypertension, nasal congestion, nausea, vomiting, flushing, angioedema, dyspnea, and dizziness/lightheadedness. Overall, in the integrated dataset across both Phase 3 trials (P001 and P002), 8.6% of subjects reported one or more infusion specific AEs: 10.3% in the bezlotoxumab group, 8.0% in the actoxumab + bezlotoxumab group, and 7.6% in the placebo group. The proportion of subjects in the bezlotoxumab group who reported one or more infusion specific AEs was similar to placebo (difference 2.8%, 95% CI [-0.1, 5.6]). The majority of infusion-specific reactions were rated mild (78%) or moderate (22%) and resolved within 24 hours. There were no reports of anaphylaxis, anaphylactoid, or hypersensitivity AEs.

The proportion of individual infusion-specific AEs was 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 of 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.

7.3.1.5 Laboratory, Vital Signs, and Electrocardiogram (ECG) Evaluations

Laboratory Evaluations

In both Phase 3 trials (P001, P002), blood and urine samples for hematology, chemistry, and urinalysis testing were taken on Day 1 prior to study medication 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 diarrhea. Laboratory results determined by the study investigator to be clinically relevant were recorded as AEs. In the integrated data across the Phase 3 trials (P001 + P002), the proportion of subjects that met predetermined criteria for chemistry and hematology values was generally similar across treatment groups. The laboratory evaluation included elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (BILI), and alkaline phosphatase (ALP) values that met prespecified criteria from Day 1 through the end of the study (Week 12) and subjects meeting all of the criteria for potential drug-induced liver injury as specified in the protocol (ALT or AST ≥3x upper limit of normal range [ULN] and BILI ≥2x ULN and ALP <2x ULN). Overall, there were 8 subjects that were identified with liver function laboratory

values meeting potential drug-induced liver injury criteria at some time point during the trial: 4 received actoxumab + bezlotoxumab, 1 received bezlotoxumab and 3 received placebo. Based upon medical review of each of the 8 cases, none of these events was considered to be suggestive of drug-induced liver injury

Vital Signs Evaluations

In the Phase 3 program (P001, P002), vital sign measurements were taken prior to infusion of study medication, at 30 minutes after the start of the infusion, and at the end of the 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). Vital sign measurements determined by the study investigator to be clinically relevant were recorded as AEs. 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.

ECGs

MAb 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 mAb 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). 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.

During the conduct of the Phase 3 trials (P001 and P002), ECG measurements were taken at 2 time points on Day 1: pre infusion and within 120 minutes post infusion. An evaluation was performed of the potential for actoxumab + bezlotoxumab or bezlotoxumab to prolong the QT interval based on paired QTc measurements corrected for heart rate using the Fridericia correction (QTc-f). Mean baseline QTC-f intervals (in msec) were 421.2, 419.7, and 419.5 for bezlotoxumab, placebo, and actoxumab + bezlotoxumab treatment groups, respectively. Slight increases in the mean QTc-f (in msec) were observed in post-infusion ECGs for all treatment groups (placebo: 2.0 msec, bezlotoxumab: 1.6 msec; and actoxumab + bezlotoxumab: 2.7 msec). The proportion of subjects with baseline QTc-f intervals of ≥501 msec were 1.5%, 2.8%, and 1.7% for placebo, bezlotoxumab, and actoxumab + bezlotoxumab groups, respectively. Post-infusion, the proportion of subjects with values ≥501 msec was similar for all treatment groups (placebo: 2.0 msec; bezlotoxumab: 2.2 msec; and actoxumab + bezlotoxumab: 2.1 msec). The majority of subjects across all treatment groups had no increase in QTc-f or had a clinically insignificant QTc-f increase of ≤30 msec (placebo: 94.1%; bezlotoxumab: 94.1%; and actoxumab + bezlotoxumab: 92.8%). A small proportion of subjects in each of the three treatment groups experienced a QTc-f increase of >30 and ≤60 msec from baseline (placebo: 4.0%; bezlotoxumab: 4.7%; and actoxumab +_bezlotoxumab: 5.3%) or>60 msec from baseline (placebo: 1.9%; bezlotoxumab: 1.2%; and

actoxumab + bezlotoxumab: 1.9%). The percentage of subjects with increases exceeding 30 msec from baseline was generally comparable across all treatment groups.

7.3.2 Exposure Response Analysis for Safety

Exposure-response analyses were conducted for all AEs reported during the four weeks following infusion and for all SAEs reported in the 12 weeks following infusion with one of the 3 treatments in the Phase 3 trials (P001, P002). In those analyses, there was no significant association between the incidence of AEs in the four weeks following infusion and bezlotoxumab AUC0-inf ($p > 0.05$). In comparison, a significant exposure-response trend was observed for SAEs over the range of exposure associated with 10 mg/kg, with this relationship characterized by a decrease in SAE incidence with increasing exposure. Upon subsequent covariate evaluation, it was observed that covariates reflecting patient health (such as albumin, concomitant use of non-standard of care systemic antibiotics or proton pump inhibitors [PPIs], hospitalization, and Charlson Comorbidity Index) were strong predictors of the incidence of SAEs. After adjusting for the effect of albumin and concomitant non-standard of care antibiotic use, the two most influential covariates, the trends between bezlotoxumab exposure and incidence of SAEs over the range of exposures achieved with 10 mg/kg in Phase 3 were markedly reduced. Taken together, these analyses indicate that patient covariates, rather than exposure, are the primary factors influencing incidence of AEs and SAEs and that there is no clinically meaningful relationship between the incidence of AEs in the 4 weeks following infusion or SAEs in the 12 weeks following infusion and bezlotoxumab exposures at the clinically recommended dose of 10 mg/kg. Thus, the 10 mg/kg dose of bezlotoxumab is appropriate, even in subgroups expected to have higher than average bezlotoxumab exposure due to intrinsic or extrinsic factor effects.

7.3.3 Immunogenicity

Treatment of patients with therapeutic protein products can result in immune responses of varying clinical relevance. As most adverse events resulting from eliciting an immune response to a therapeutic protein appear to be mediated by humoral mechanisms, circulating antibody (to the therapeutic protein) has been the primary criterion for defining an immune response. For this purpose, standard methodologies were implemented to measure the incidence of anti-drug antibodies (ADA) and neutralizing ADA (NAb). Analysis of samples from the two pivotal Phase 3 trials (P001 and P002) was conducted with ADA assays that were validated according to current guidance and industry standards [76] [77]. Anti-bezlotoxumab antibodies and anti-actoxumab antibodies were measured in serum using separate electrochemiluminescence immunoassays. All samples that were positive in either ADA assay were subsequently tested in the respective NAb assays (anti-bezlotoxumab NAb assay or anti-actoxumab NAb assay).

In the Phase 3 trials (P001 and P002), following dosing with bezlotoxumab alone or in combination with actoxumab, 1414 subjects were evaluable for the immunogenicity analysis. Evaluable subjects included those with at least one sample assay result following treatment. Following dosing with bezlotoxumab alone, there were 710 subjects evaluable for the immunogenicity analysis.

Following dosing with bezlotoxumab, no treatment-emergent (post-baseline) ADA or neutralizing ADA positive subjects were observed. A combination of factors suggests that bezlotoxumab is unlikely to be immunogenic, including: (1) the absence of treatment-emergent positive subjects in Phase 3 trials; (2) the fact that bezlotoxumab is a fully human mAb; and (3) the proposed single dose (as opposed to multiple-dose chronic) administration.

7.4 Safety in Special Populations

The safety of bezlotoxumab was assessed in potentially vulnerable populations in the integrated Phase 3 dataset. Across treatment groups, the safety profile was consistent regardless of age, gender, race, weight, renal impairment, and hepatic impairment. The safety of bezlotoxumab was not assessed in adolescents or children less than 18 years of age or in pregnant or lactating women.

7.5 Safety Conclusions

- Bezlotoxumab has a favorable safety and tolerability profile
- Bezlotoxumab was generally well tolerated. The types and incidence of AEs and SAEs were similar for the bezlotoxumab and placebo groups.
- The incidence of drug-related AEs or drug-related SAEs in subjects receiving bezlotoxumab was low and similar to that in placebo recipients. Only 1 of 786 subjects discontinued the bezlotoxumab infusion due to an adverse reaction, which subsequently resolved.
- The incidence of infusion-specific AEs in the bezlotoxumab arm occurring on the day of or the day after the infusion was low (10%) and similar to placebo. The majority of infusion-specific reactions were rated mild (78%) or moderate (22%) and resolved within 24 hours. There were no reports of anaphylaxis, anaphylactoid, or hypersensitivity AEs.
- There is no evidence of clinically relevant changes in hematology and chemistry laboratory values, vital signs, or QTc intervals in subjects receiving bezlotoxumab.
- Across the range of exposures achieved at 10 mg/kg, no clinically meaningful trend in incidence of AEs or SAEs and exposure was identified.
- Bezlotoxumab has low potential for immunogenicity. After bezlotoxumab treatment, no subjects with anti-drug antibodies or neutralizing anti-drug antibodies were observed in clinical studies.

8 BENEFITS AND RISKS CONCLUSIONS

Disease Burden and Unmet Medical Need

CDI recurrence is a major public health problem with a high unmet medical need. *C. difficile* has been declared an urgent public health threat by the U.S. Centers for Disease Control and Prevention (CDC). The morbidity and mortality associated with CDI is high − in 2011 there were an estimated 29,000 deaths associated with CDI in the United States, exceeding the

estimated annual number of deaths caused by methicillin-resistant *Staphylococcus aureus* (MRSA) infection and multi-drug resistant Gram-negative infections combined.

Although there are approved antibiotics for the treatment of CDI, recurrence of CDI occurs at a high rate following treatment due to persistent or newly-acquired *C. difficile* spores, whose outgrowth (leading to new toxin expression) is facilitated by the gut dysbiosis caused by antibiotics; there are no therapies approved for the prevention of CDI recurrence. There is a need for new therapies with a favorable safety profile which reduce the incidence of CDI recurrence.

A monoclonal antibody directed against the exotoxins produced by *C. difficile* represent a novel non-antibiotic approach to the prevention of CDI recurrence in patients receiving antibiotic therapy for CDI. Endogenous antibody titers against *C difficile* toxins have been reported to correlate with reduced recurrence of CDI [63] [65]. Bezlotoxumab is an antitoxin antibody that binds with high affinity (K_d<1×10^{-9}M) to *C. difficile* toxin B from the 18 unique ribotypes tested and neutralizes its activity by preventing it from binding to host cells. Bezlotoxumab prevents CDI recurrence by providing enhanced passive immunity against toxin produced by the outgrowth of persistent or newly-acquired *C. difficile* spores.

Benefits of Bezlotoxumab

The overall goal of the bezlotoxumab product development program was to demonstrate that mAb therapy directed against the toxins of *C. difficile* is safe and efficacious in the prevention of CDI recurrence in adult subjects receiving antibiotic therapy for CDI. Prevention of CDI recurrence was selected as the primary endpoint for the Phase 3 trials, as this endpoint reflects the mechanism of action of bezlotoxumab and directly addresses the unmet medical need for new therapies to reduce the incidence of CDI recurrence. Moreover, bezlotoxumab did not have an impact on clinical cure of the baseline episode in Phase 2 and efficacy benefit was expected to be solely based on prevention of recurrence.

The global Phase 3 clinical program was comprehensive and included two large double blind, randomized, placebo controlled trials (P001 and P002). The protocols had broad inclusion and limited exclusion criteria permitting evaluation of subjects with diverse underlying comorbidities, with a wide range of clinical characteristics associated with a high risk for CDI recurrence.

Efficacy data from the Phase 3 trials demonstrate that bezlotoxumab is superior to placebo in prevention of CDI recurrence when each are given in combination with SOC, addressing the unmet medical need. The low incidence of CDI recurrence in the bezlotoxumab group, and the treatment difference in CDI recurrence between the bezlotoxumab and placebo groups were highly consistent in each of the Phase 3 trials. The adjusted difference between the bezlotoxumab and placebo group in CDI recurrence rates was -10.1 (95% CI -15.9, -4.3; p=0.0003) in P001 and -9.9 (95% CI -15.5, -4.3; p=0.0003) in P002.

The reduction in CDI recurrence observed in the trials is clinically meaningful. In the combined dataset (P001 + P002) the difference was -10.0 (95% CI -14.0, -6.0; p<0.0001), corresponding to a NNT of 10 patients and an approximately 40% reduction in relative risk

based on the observed incidence of CDI recurrence of 26.6% in the placebo group. Assuming ~83,000 annual episodes of CDI recurrence in the US, a 40% reduction translates to the potential to prevent up to 33,000 cases per year in the US.

The trials included a substantial number of subjects with one or more risk factors for CDI recurrence. Overall, 76% of subjects had at least 1 risk factor. The percentage of subjects with each risk factor in the integrated dataset (P001 and P002) is as follows:

- ≥ 65 years of age: 53%
- ≥ 1 CDI episodes in prior 6 months: 28% (including 14% with multiple prior episodes)
- Severe CDI (Zar score ≥ 2): 16%
- Immunocompromised: 20%
- Infected with 027 ribotype: 18% of those with pathogen isolated
- Infected with 027, 078 or 244 ribotype: 21% of those with pathogen isolated

Across these subgroups at high risk for CDI recurrence, bezlotoxumab consistently lowered CDI recurrence rates compared to placebo. The absolute reduction in the CDI recurrence rate in bezlotoxumab versus placebo was -10.0% in the overall population; the differences exceeded this value in all of the pre-specified high risk groups. Moreover, the 95% CI for the difference between bezlotoxumab and placebo did not include zero for these key subgroups with the exception of subjects infected with the 027 strain; nevertheless, the absolute difference (-10.4%) between bezlotoxumab and placebo for this subgroup was consistent with the overall results. Overall, the efficacy of bezlotoxumab in preventing CDI was clinically significant in these important subgroups, where relative reduction in CDI recurrence rates reached as high as 51% (age ≥65 years).

Bezlotoxumab was superior to placebo in preventing CDI recurrence through the 12-week at-risk period for recurrence in both Phase 3 trials. The difference between the bezlotoxumab and placebo treatment groups in the time to CDI recurrence analysis was significant ($p<0.0001$).

Superior efficacy of bezlotoxumab compared to placebo was demonstrated for the secondary endpoint of global cure in the integrated data (where the sample size had large enough power to detect superiority) as well as in one of the two trials (P002). The global cure rate in the bezlotoxumab group was numerically higher than that in the placebo group in P001 (one-sided $p=0.0861$). For the integrated results, global cure rates were 63.5% in the bezlotoxumab group and 53.7% in the placebo group (one-sided $p<0.0001$). The benefit observed in achieving global cure was driven solely by a reduction in CDI recurrence (i.e., prevention of CDI recurrence).

Efficacy of the standard of care antibiotic was not diminished by administration of bezlotoxumab; in P001, the clinical cure rate was higher in the bezlotoxumab arm vs. the placebo arm, whereas in P002, the clinical cure rate was higher in the placebo arm vs. the bezlotoxumab arm. This is not an unexpected result for an endpoint that is not expected to be impacted by bezlotoxumab. An evaluation of the reasons for clinical failure of the baseline

CDI episode and a comparison of the time to resolution of the baseline CDI episode did not identify a clear etiology for the numerical differences in the clinical cure rates seen for bezlotoxumab compared to placebo in P001 and P002.

Bezlotoxumab exposures across the range achieved at a dose of 10 mg/kg were associated with a similar, low rate of CDI recurrence, indicating that that the exposures associated with the clinical dose are on the plateau of the exposure-response curve for efficacy.

Multiple sensitivity analyses consistently demonstrated that bezlotoxumab's efficacy in the prevention of CDI recurrence is robust across missing data assumptions and definitions of the risk set.

In summary, the benefits of bezlotoxumab in the prevention of CDI recurrence in patients with a primary or recurrent episode CDI have been demonstrated in this large Phase 3 program. The NNT to prevent 1 CDI recurrence is low at 10, and is as low as 6 in patients at high risk for CDI recurrence. Bezlotoxumab has the potential to prevent up to 33,000 cases of CDI cases in US annually. Moreover, bezlotoxumab has the potential to provide a broader benefit in health care and community settings through the prevention of recurrent episodes.

Risks of Bezlotoxumab

The safety database for bezlotoxumab is large and included an assessment of both bezlotoxumab alone and in combination with actoxumab, accounting for approximately 1,700 subjects with CDI in the clinical development program. In the Phase 3 program, in which safety analysis was conducted using integrated data (P001 + P002), 786 subjects received bezlotoxumab, 777 subjects received actoxumab + bezlotoxumab, and 781 subjects received placebo.

Overall, bezlotoxumab was generally well tolerated. The incidence of AEs in the bezlotoxumab and actoxumab + bezlotoxumab groups was comparable to the placebo group and consistent across the subgroups evaluated in Phase 3, based on intrinsic or extrinsic factors of interest (i.e., age, gender, race, weight, renal impairment, hepatic impairment, region, and choice of standard of care antibiotic treatment). Exposure-response analyses of adverse events (AEs) based on pooled data from the Phase 3 trials show no clinically meaningful relationship between the incidence of AEs in the 4 weeks following infusion or serious adverse events (SAEs) in the 12 weeks following infusion and bezlotoxumab exposures.

The incidence of AEs most frequently reported (≥4%) in the bezlotoxumab arm and with a higher frequency in the bezlotoxumab arm than in the placebo arm were nausea (6.6%), diarrhea (6.0%), pyrexia (4.6%), and headache (4.5%). The incidence of these events was generally similar to that in the placebo group. Discontinuation of the infusion due to an adverse event was rare (1 event in the bezlotoxumab group), as was the incidence of drug-related SAEs (4 in the bezlotoxumab, 6 in the actoxumab + bezlotoxumab, and 2 in the placebo groups) during 12-weeks following the infusion.

The types and incidence of SAEs and AEs with a fatal outcome were similar for the bezlotoxumab, actoxumab + bezlotoxumab, and placebo groups. The incidence of drug-

related AEs or drug-related SAEs in subjects receiving bezlotoxumab and actoxumab + bezlotoxumab was low and similar to placebo.

The incidence of infusion-specific AEs in the bezlotoxumab arm occurring on the day of or the day after the infusion was low (10%) and similar to placebo. The majority of infusion-specific reactions were rated mild (78%) or moderate (22%) and resolved within 24 hours. There were no reports of anaphylaxis or anaphylactoid specific AEs.

There were no clinically relevant changes in hematology and chemistry laboratory values, vital signs or QTc intervals in subjects receiving bezlotoxumab or actoxumab + bezlotoxumab.

A potential risk is that treatment with the mAbs might delay the onset of CDI recurrence versus preventing CDI recurrence. In an exploratory analysis of a subset of subjects evaluated for up to 12 months following infusion of the study medication as part of the extension phase of P002, no bezlotoxumab-treated subjects who had achieved global cure at the end of the 12-week main study experienced a CDI recurrence in the subsequent 9 months. These findings provide evidence that the efficacy of bezlotoxumab observed in the main study is due to prevention of CDI recurrence rather than a delay in onset of a recurrent episode.

Bezlotoxumab has a very low potential for immunogenicity, so it unlikely that anti-drug antibodies would compromise the efficacy of the product. Bezlotoxumab administration did not result in the development of treatment emergent anti-drug antibodies in the Phase 2 and 3 trials.

The totality of the safety data show that bezlotoxumab when given with standard of care antibiotics does not increase the risks of giving standard of care alone.

Conclusions

- Bezlotoxumab fulfils a significant unmet medical need for therapies to prevent CDI recurrence.
- Bezlotoxumab is a novel, non-antibiotic approach to the prevention of CDI recurrence which is highly efficacious, demonstrating a relative reduction of the recurrence rate of ~40% compared to placebo.
- Bezlotoxumab is efficacious in a diverse group of patients, including patients at highest risk for CDI recurrence and reduces the recurrence rate by ~50% in patients with risk factors for CDI recurrence.
- Bezlotoxumab is well tolerated with a safety profile similar to placebo.
- Overall, bezlotoxumab has a positive benefit/risk profile for the prevention of CDI recurrence in adult patients receiving antibiotic therapy for CDI.
- The data support the proposed indication for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.

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