Biologics License Application (BLA) 761046, Bezlotoxumab injection

FDA Introductory Remarks

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Antimicrobial Drugs Advisory Committee Meeting

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Introduction

- BLA 761046, bezlotoxumab injection

- Applicant: Merck Sharp & Dohme Corp.

- Proposed Indication: Prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years of age and older

- Proposed dose: A single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes

- Granted Priority Review: No approved therapies for prevention of *C. difficile* infection recurrence

Background

- Bezlotoxumab is a fully human monoclonal IgG1/kappa antibody that binds to *C. difficile* toxin B

- Development program was initially focused on the combination of anti-toxin A (actoxumab) and anti-toxin B (bezlotoxumab) antibodies

- Two Phase 2 trials (Studies P017 and P018) and two Phase 3 trials (Studies P001 and P002) were conducted

- Bezlotoxumab was administered in addition to the standard of care (SOC) therapy. The duration of SOC therapy prior to bezlotoxumab infusion varied

Clinical Development Program (Phase 2)

- First Phase 2 trial (Study P018) comparing antitoxin A antibody to placebo was terminated early (46 subjects) as emerging nonclinical data suggested that combination of antibodies was more effective

- Second Phase 2 trial (Study P017) compared actoxumab plus bezlotoxumab to placebo
  - 101 subjects randomized to the antibody arm and 99 to the placebo arm
  - Cure rates: 79% in the antibody arm, 76% in the placebo arm
  - Recurrence rates: 7% in the antibody arm, 25% in the placebo arm

- Bezlotoxumab alone was not studied in a Phase 2 trial

Phase 3 Trial P001

- Study P001: 4-arm factorial trial design: actoxumab, bezlotoxumab, actoxumab plus bezlotoxumab, and placebo (0.9% sodium chloride); used to assess the contribution of the individual components to the combination (21 CFR 300.50)

- In December 2010, a Special Protocol Agreement was reached on the design and endpoints for this trial

- Primary Endpoint: CDI recurrence

- Trial conducted from November 2011 to December 2014

Phase 3 Trial P001

- Included an interim analysis that allowed for halting enrollment in one or both of the individual antibody arms if there was sufficient evidence of superiority of the combination over the individual antibody arms

- Enrollment in actoxumab arm was stopped after 235 patients received actoxumab due to safety concerns relative to placebo and low efficacy compared to the combination arm

Phase 3 Trial P002

- Study P002: 3-arm trial: bezlotoxumab, actoxumab plus bezlotoxumab, placebo; protocol was not submitted for a special protocol assessment

- Upon review of the protocol, FDA recommended the primary endpoint be changed to global cure defined as cure and no recurrence; two main concerns with the recurrence endpoint were:
  - In calculating CDI recurrence, subjects who failed initial treatment would be counted as not having a recurrence
  - Any imbalance between treatment groups for clinical cure of the initial episode could confound the assessment of recurrence rate

Phase 3 Trial P002

- The Applicant preferred to retain CDI recurrence as the primary endpoint and global cure as a key secondary endpoint in both trials

- FDA noted that if the monoclonal antibody arm has a lower initial cure rate than placebo, interpretation of the CDI recurrence endpoint may be difficult

- FDA did not agree with the Applicant's proposal to evaluate global cure by analyzing pooled data from the two Phase 3 trials and noted that assessment of the global cure endpoint would be based on the analyses from each trial

- Trial conducted from February 2012 to May 2015

Key Topic Areas

- Efficacy
  - Differences in assessment of primary endpoint between the Applicant and the FDA
  - Differences in clinical outcomes between the two trials
  - Differences in approach to analyses between the Applicant and the FDA
- Safety
  - No major differences in assessment between Applicant and the FDA
  - Discussion about adverse reactions in patients with baseline congestive heart failure

Outline for Today

- Presentations by the Applicant
- Presentations by the FDA
  - Cheryl Dixon, PhD: Efficacy Assessment
  - Hiwot Hiruy MD, PhD: Safety Assessment
- Break
- Open Public Hearing
- Question for Committee

Question

- Has the Applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence in patients aged 18 years and older? Vote Yes/No
  - If yes, please discuss your rationale and provide any recommendations concerning labeling.
  - If no, please discuss your rationale and what additional studies/analyses are needed.

Clinical Efficacy
of Bezlotoxumab for the Prevention of
Clostridium difficile Infection (CDI) Recurrence

Antimicrobial Drugs Advisory Committee Meeting
June 9, 2016

Cheryl Dixon, PhD

Statistical Reviewer

Division of Biometrics IV, Office of Biostatistics

Office of Translational Sciences

Center for Drug Evaluation and Research

Outline

- Regulatory History
- Phase 3 Trials , P001 and P002
    - Design
    - Patient Disposition/Demographics and Characteristics
    - Efficacy Results
- Summary and Conclusions

Regulatory History

- IND submitted November 25, 2005

- Phase 2 trials (conducted between 2005 and 2008)
  - P018 evaluated actoxumab, the anti-toxin A antibody
  - P017 evaluated actoxumab + bezlotoxumab, the combination of anti-toxin A and anti-toxin B antibodies
  - No Phase 2 trial evaluated bezlotoxumab alone

Regulatory History (2)

- End of Phase 2 meeting held October 2009
  - Discussed the design of the Phase 3 trials proposed to evaluate the combination of actoxumab and bezlotoxumab
  - Division concurred with definition of CDI recurrence but stated CDI recurrence rate should be based on all randomized patients and not the subset of clinical cures
  - Advised that a 4-arm factorial design should be conducted in at least 1 of the Phase 3 trials in order to address the combination drug product rule
- Special Protocol Assessment (SPA) agreement reached in December 2010 on the design of the Phase 3 trial P001
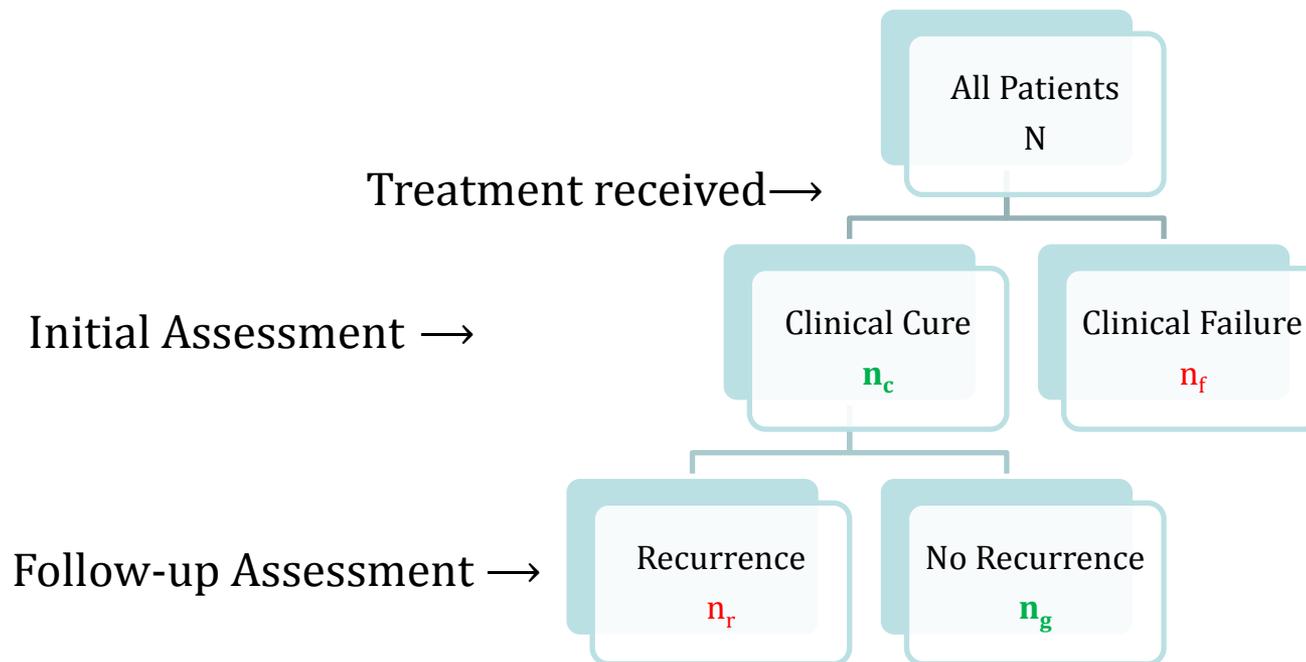
Regulatory History (3)

- Protocol for the Phase 3 trial P002 was reviewed in 2012-13
  - Division requested that the primary endpoint for this trial be revised to global cure (subjects with clinical cure and no CDI recurrence) rather than CDI recurrence due to concerns that
    - The calculation of CDI recurrence rate treats subjects who failed treatment of the initial CDI episode as not having a recurrence
    - Any imbalance between treatment groups in the number of subjects who failed treatment of the initial episode could confound the assessment of CDI recurrence rate
      - Most concerning if the monoclonal antibody arm has a lower initial clinical cure rate than placebo

Regulatory History (4)

- P002 discussions (cont.)
  - Applicant's reasons to preserve primary endpoint
    - No expectation that the monoclonal antibodies would have an impact on initial clinical cure
    - Preference for both trials to have same primary endpoint
    - Power of trial not based on global cure
      - Proposed pooled analyses to address this
  - CDI recurrence retained as primary endpoint
    - Division reiterated its concerns with the endpoint and disagreed with the pooled analyses

Description of Response

All Patients
N

Treatment received→

Initial Assessment →

Clinical Cure
n_c

Clinical Failure
n_f

Follow-up Assessment →

Recurrence
n_r

No Recurrence
n_g
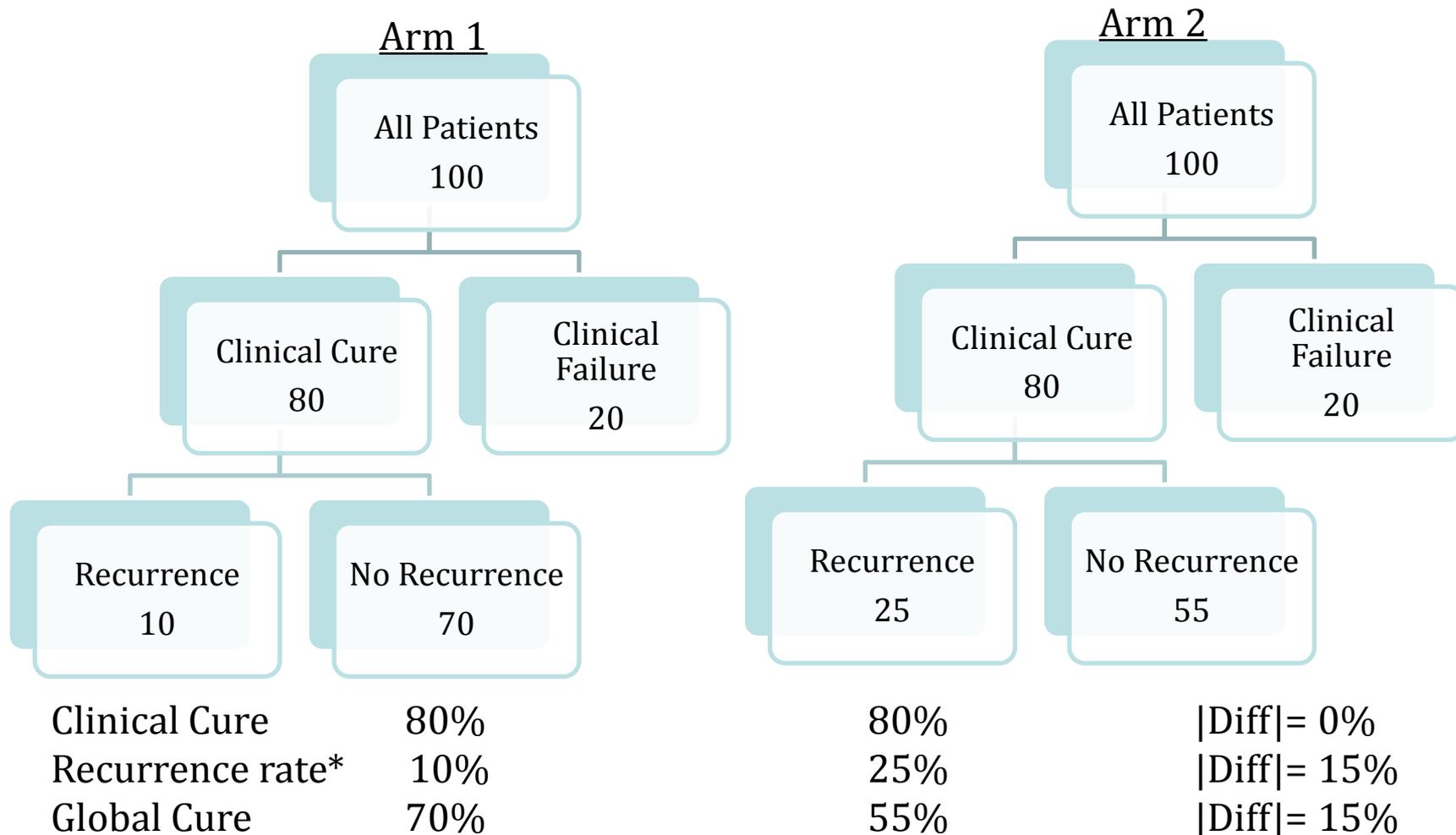
Recurrence rate*= n_r/N

Global cure rate= n_g /N

Complement of recurrence rate= $(n_g + n_f)$/N

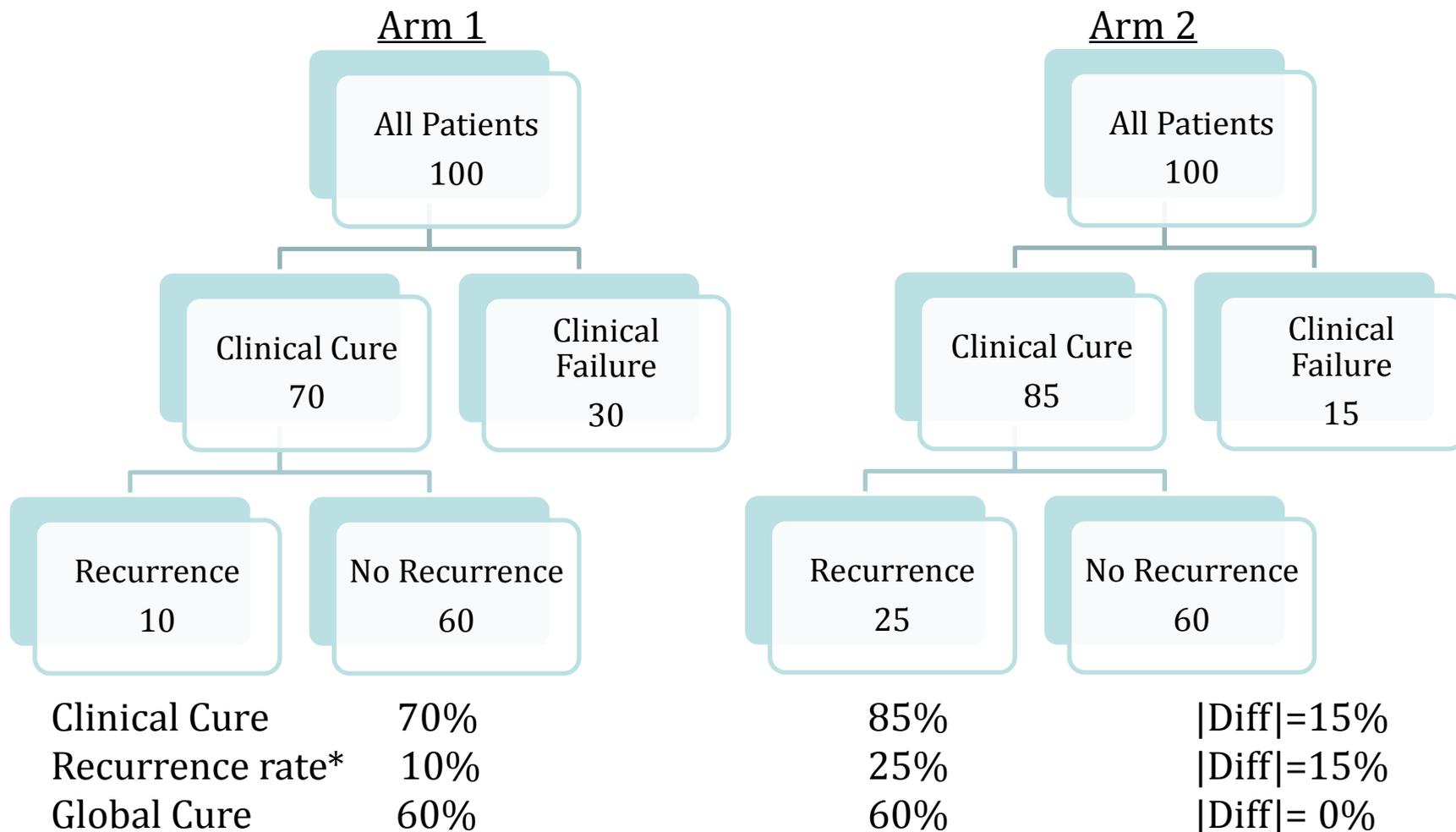Complement of global cure rate= $(n_r + n_f)$/N

*protocol definition
green=positive response   red=negative response

Hypothetical Example 2 (Difference in Clinical Cure)

Arm 1

All Patients
100

Clinical Cure
70

Clinical Failure
30

Recurrence
10

No Recurrence
60

Arm 2

All Patients
100

Clinical Cure
85

Clinical Failure
15

Recurrence
25

No Recurrence
60

	Arm 1	Arm 2	Diff
Clinical Cure	70%	85%	|Diff|=15%
Recurrence rate*	10%	25%	|Diff|=15%
Global Cure	60%	60%	|Diff|= 0%

*protocol definition

Trial P001 and P002 Design

- Both trials randomized, multicenter, double-blind, placebo controlled conducted in subjects ≥ 18 years who were receiving standard of care (SOC) antibiotic treatment for an episode of CDI
  - P001 patients randomized 1:1:1:1 to receive single IV infusion of actoxumab, bezlotoxumab, actoxumab+ bezlotoxumab, or placebo
  - P002 patients randomized 1:1:1 to receive single IV infusion of bezlotoxumab, actoxumab+ bezlotoxumab, or placebo
- Randomization stratified by
  - Oral SOC therapy (metronidazole, vancomycin, or fidaxomicin)
  - Hospitalization status (inpatient or outpatient)
- P001 design included an interim analysis that allowed for the halting of an individual monoclonal antibody arm if sufficient evidence of superiority of the combination was seen

Efficacy Endpoints

- Primary Endpoint: CDI recurrence
  - The development of a new episode of diarrhea (3 or more loose stools in 24 or fewer hours) associated with a positive stool test for toxigenic *C. difficile* following clinical cure of the baseline CDI episode
    - Rate based on the proportion of subjects in the Full Analysis Set (FAS) population with CDI recurrence during the 12-week follow-up period
- Secondary Endpoint: Global cure
  - Clinical cure of the baseline CDI episode and no CDI recurrence
- Exploratory Endpoint: Clinical cure
  - Subject received ≤ 14 day regimen of SOC and had no diarrhea for 2 consecutive days following completion of SOC

Analysis Population

- **Full Analysis Set (FAS)**
  - Subset of all randomized subjects excluding those who
    - did not receive an infusion of study medication ,
    - did not have a positive stool test for toxigenic *C. difficile* at study entry, or
    - did not receive a protocol defined SOC therapy within a 1-day window of the infusion.
  - Additionally in P001, subjects from a single investigative site found by the Applicant to have serious good clinical practice non-compliance issues were excluded

Statistical Methods

- Primary analysis was a comparison of treatment groups in the proportion of subjects with CDI recurrence, global cure, or clinical cure using the FAS population

- Adjusted difference in the rate (monoclonal antibody - placebo) and corresponding 95% confidence intervals stratified by oral SOC therapy and hospitalization status were calculated

- To control type I error rate due to multiple treatment comparisons, a sequential testing approach was used.
  - Combined monoclonal antibody vs placebo, if significant, followed by bezlotoxumab vs placebo comparison
  - P001 also adjusted the alpha level to control for the interim analysis as well as the second primary objective to compare the combined monoclonal antibody arm to each of the individual monoclonal antibody arms.

Patient Disposition

		Actoxumab + Bezlotoxumab	Actoxumab	Bezlotoxumab	Placebo
P001	Randomized	403	242	403	404
	All Treated	388	235	392	397
	FAS	383	232	386	395
P002	Randomized	397		407	399
	All Treated	391		396	381
	FAS	390		395	378

Patient Demographics
and Baseline Characteristics -FAS

- Generally balanced among treatment groups in both trials.

P001	P002	
62 years	64 years	mean age
57%	56%	female
91%	80%	white
49%	48%	metronidazole
48%	48%	vancomycin
3%	3%	fidaxomicin
53%	41%	United States/Canada
35%	43 %	Europe
5%	15%	Asia/Pacific
7%	2%	Other Region

Patient Demographics and Baseline Characteristics- FAS (cont.)

P001	**P002**	
67%	69%	Hospitalized
34%	34%	Prior history of CDI (ever)
12%	14%*	Hypervirulent strain (ribotypes 027, 078 or 244)
3 days	3 days	Median duration of SOC prior to infusion
28%	23%**	Experiencing diarrhea on day of infusion

* 12% actoxumab +bezlotoxumab, 13% bezlotoxumab, 19% placebo
** 26% actoxumab +bezlotoxumab, 18% bezlotoxumab, 26% placebo

P001: Results of Initial Clinical Cure, CDI Recurrence, and Global Cure (FAS)

	Actoxumab + Bezlotoxumab (n=383)	Bezlotoxumab (n=386)	Placebo (n=395)
Initial Clinical Cure	286 (74.7) -8.2 (-13.9, -2.4) p=**0.0057**	299 (77.5) -5.3 (-10.9, 0.3) p=0.0622	327 (82.8)
CDI Recurrence	61 (15.9) -11.6 (-17.3, -5.9) **p<0.0001**	67 (17.4) -10.1 (-15.9, -4.3) **p=0.0006**	109 (27.6)
Global Cure	232 (58.7) 3.5 (-3.4, 10.4) p=0.3165	232 (60.1) 4.8 (-2.1, 11.7) p=0.1647	218 (55.2)

Adjusted difference (95% confidence interval) for monoclonal antibody-placebo stratified by SOC therapy and hospitalization status
Two sided p-value based on chi-square test for comparison of monoclonal antibody arm vs placebo
Bold indicates p-value < 0.025, hierarchical ordering of tests : actoxumab +bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

P002: Results of Initial Clinical Cure, CDI Recurrence, and Global Cure (FAS)

	Actoxumab + Bezlotoxumab (n=390)	Bezlotoxumab (n=395)	Placebo (n=378)
Initial Clinical Cure	282 (72.3)	326 (82.5)	294 (77.8)
	-5.5 (-11.6, 0.6)	4.8 (-0.9, 10.4)	
	p=0.0801	p=0.0973	
CDI Recurrence	58 (14.9)	62 (15.7)	97 (25.7)
	-10.7 (-16.3, -5.1)	-9.9 (-15.5, -4.2)	
	p=0.0002	**p=0.0006**	
Global Cure	224 (57.4)	264 (66.8)	197 (52.1)
	5.2 (-1.7, 12.2)	14.6 (7.8, 21.4)	
	p=0.1386	**p<0.0001**	

Adjusted difference (95% confidence interval) for monoclonal antibody-placebo stratified by SOC therapy and hospitalization status
Two sided p-value based on chi-square test for comparison of monoclonal antibody arm vs placebo
Bold indicates p-value < 0.05, hierarchical ordering of tests : actoxumab +bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

Reasons for Failure to Achieve Clinical Cure (FAS)

		Actoxumab + Bezlotoxumab	Bezlotoxumab	Placebo
P001		N=383	N=386	N=395
	SOC > 14 days	40 (10.4)	36 (9.3)	28 (7.1)
	Continued loose stool	30	23	21
	Resolved diarrhea but continued trt	10	13	7
	Diarrhea during at least 1 of 2 days after SOC completion	44 (11.5)	39 (10.1)	27 (6.8)
	Discontinued prior to end of SOC	9 (2.3)	7 (1.8)	11 (2.8)
	Missing stool info	4 (1.0)	5 (1.3)	2 (0.5)
P002		N=390	N=395	N=378
	SOC > 14 days	46 (11.8)	27 (6.8)	30 (7.9)
	Continued loose stool	37	21	25
	Resolved diarrhea but continued trt	9	6	5
	Diarrhea during at least 1 of 2 days after SOC completion	42 (10.8)	26 (6.6)	34 (9.0)
	Discontinued prior to end of SOC	16 (4.1)	9 (2.3)	14 (3.7)
	Missing stool info	4 (1.0)	7 (1.8)	6 (1.6)

Sensitivity Analyses

- Various sensitivity analyses conducted by Applicant and Division

  - Results of most were fairly consistent

- One sensitivity analysis conducted on CDI recurrence and Global cure imputed as a recurrence/failure, subjects with

  - incomplete stool information (i.e. new episode of diarrhea but stool sample not collected for toxin testing, died prior to Week 12, or whose last stool information collected prior to Day 80) or

  - who received a concomitant medication or procedure potentially useful in the treatment of CDI during the follow-up period

P001: Results of Sensitivity Analysis of CDI Recurrence and Global Cure (FAS)

	Actoxumab + Bezlotoxumab (n=383)	Bezlotoxumab (n=386)	Placebo (n=395)
CDI Recurrence	128 (33.4) -13.4 (-20.1, -6.7) **p=0.0001**	133 (34.5) -12.3 (-19.1, -5.6) **p=0.0004**	185 (46.8)
Global Cure	158 (41.3) 5.2 (-1.5, 12.0) p=0.1286	166 (43.0) 7.1 (0.3, 13.8) p=0.0437	142 (35.9)
Imputed Recurrence/Failure*	67 (17.5)	66 (17.1)	76 (19.2)
NED not tested	25 (6.5)	21 (5.4)	20 (5.1)
Death before Week 12	10 (2.6)	14 (3.6)	13 (3.3)
Alive but last stool info before Day 80	19 (5.0)	18 (4.7)	21 (5.3)
Received CDI treatment	19 (5.0)	23 (6.0)	37 (9.4)

Imputes subjects with new episode of diarrhea (NED) but no stool sample collected for toxin testing, subjects who died prior to Week 12, had their last stool data collected prior to Day 80, or received an active concomitant medication or procedure for CDI during follow-up as recurrence/failure

*Some subjects may have met more than one criterion for imputation as a failure

Adjusted difference (95% confidence interval) for monoclonal antibody-placebo stratified by SOC therapy and hospitalization status

Two sided p-value based on chi-square test for comparison of monoclonal antibody arm vs placebo

Bold indicates p-value < 0.025, hierarchical ordering of tests : actoxumab +bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

P002: Results of Sensitivity Analysis of CDI Recurrence and Global Cure (FAS)

	Actoxumab + Bezlotoxumab	Bezlotoxumab	Placebo
	(n=390)	(n=395)	(n=378)
CDI Recurrence	127 (32.6)	141 (35.7)	150 (39.7)
	-7.1 (-13.9, -0.4)	-4.0 (-10.7, 2.8)	
	p=0.0400	p=0.2528	
Global Cure	155 (39.7)	185 (46.8)	144 (38.1)
	1.6 (-5.2, 8.5)	8.7 (1.8, 15.6)	
	p=0.6395	**p=0.0140**	
Imputed Recurrence/Failure*	69 (17.7)	79 (20.0)	53 (14.0)
NED not tested	22 (5.6)	22 (5.6)	6 (1.6)
Death before Week 12	11 (2.8)	14 (3.5)	13 (3.4)
Alive but last stool info before Day 80	26 (6.7)	24 (6.1)	21 (5.6)
Received CDI treatment	23 (5.9)	30 (7.6)	21 (5.6)

Imputes subjects with new episode of diarrhea (NED) but no stool sample collected for toxin testing, subjects who died prior to Week 12, had their last stool data collected prior to Day 80, or received an active concomitant medication or procedure for CDI during follow-up as recurrence/failure

*Some subjects may have met more than one criterion for imputation as a failure

Adjusted difference (95% confidence interval) for monoclonal antibody-placebo stratified by SOC therapy and hospitalization status

Two sided p-value based on chi-square test for comparison of monoclonal antibody arm vs placebo

Bold indicates p-value < 0.05, hierarchical ordering of tests : actoxumab +bezlotoxumab vs placebo followed by bezlotoxumab vs placebo

Subgroup Analyses

- Numerous subgroup analyses conducted
  - In general, the results of most subgroups were consistent and treatment differences trended in the same direction as the overall population.
  - Exceptions were those of gender and age
    - Treatment differences of CDI recurrence and global cure observed for males were not as large as those observed for females
    - Treatment differences of CDI recurrence and global cure observed for subjects less than 65 years were not as large as those observed for subjects 65 years or older

Efficacy Summary and Conclusions

- **There appears to be a decrease in CDI recurrence with the use of bezlotoxumab**
- However, CDI recurrence endpoint is difficult to interpret
  - Subjects without clinical cure of initial CDI episode treated as not having a recurrence
  - Imbalance in the proportion of subjects with initial clinical cure between treatment groups noted
    - In P001, difference in favor of placebo compared to bezlotoxumab
    - In P002, difference in favor of bezlotoxumab compared to placebo
    - Difference also noted for actoxumab + bezlotoxumab compared to placebo where in both trials difference in favor of placebo
    - **Therefore, a negative effect of bezlotoxumab on clinical cure of the initial CDI episode cannot be ruled out**

Efficacy Summary and Conclusions (cont.)

- Global cure is the more relevant endpoint to assess efficacy
  - Results for global cure are only significant for one of the two trials
  - The significance in this one trial (P002) needs to be interpreted with caution for two reasons
    - The non-significant result of global cure observed for the actoxumab+ bezlotoxumab vs placebo comparison which was to be conducted prior to the bezlotoxumab vs placebo comparison
    - The discordant results observed for clinical cure for bezlotoxumab between the two trials
      - The results for the actoxumab + bezlotoxumab arm were consistent in both trials and the results for bezlotoxumab in P001 are similar to these results.
- **Therefore, there is concern as to whether the efficacy of bezlotoxumab for the prevention of CDI recurrence has been adequately demonstrated**

Bezlotoxumab for Prevention of *Clostridium difficile* Infection Recurrence (BLA 761046)

Presentation of Clinical Safety

Antimicrobial Drugs Advisory Committee Meeting

June 9, 2016

Hiwot Hiruy, MD, PhD
Medical Officer
Division of Anti-infective Products
FDA/CDER

Presentation Outline

- Safety Analysis Methodology
- Overall Exposure to Bezlotoxumab
- Deaths
- Serious Adverse Events
- Treatment Emergent Adverse Events
- Adverse Reactions of Special Interest
  - Infusion related adverse reactions
- Subgroup Analyses
- Summary

Definition of Adverse Event (AE) terms

- **Treatment Emergent Adverse Event (TEAE):** Any AE that occurred during or after infusion of study drug.

- **Serious Adverse Event (SAE):** An adverse event that
  - Results in death
  - Is life-threatening
  - Results in persistent or significant disability/incapacity
  - Results in or prolongs an existing inpatient hospitalization
  - Is a congenital anomaly/birth defect
  - Is another important medical event
  - Is a cancer
 - Is associated with an overdose

Safety Analysis Methodology

- Data from the two Phase 3 trials, Study P001 and P002, were pooled
- Study P001 and P002 had similar adverse event reporting schema
  - All TEAEs reported for the first 4 weeks of the studies
  - Serious AEs reported throughout the 12 weeks

Differences between Study P001 and P002

- Design of Study P001 was adaptive with planned interim analysis

- Study P001 had one additional arm, actoxumab arm, which was dropped after interim analysis and is NOT included in the safety population

- Study P002 had an extension cohort (n=300) that was followed for an additional 9 months

Phase 3 Studies: Data Pooling Schema
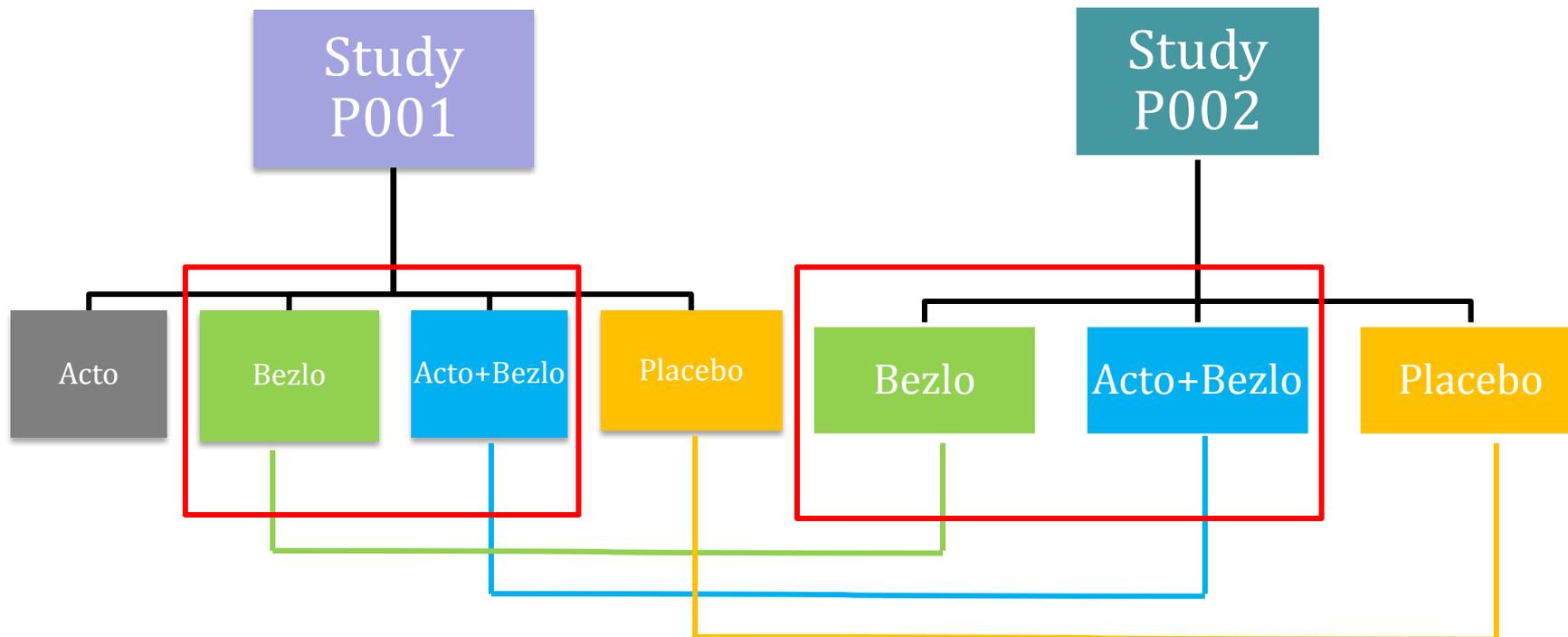
Acto=Actoxumab; Bezlo=Bezlotoxumab

Overall Exposure to Bezlotoxumab
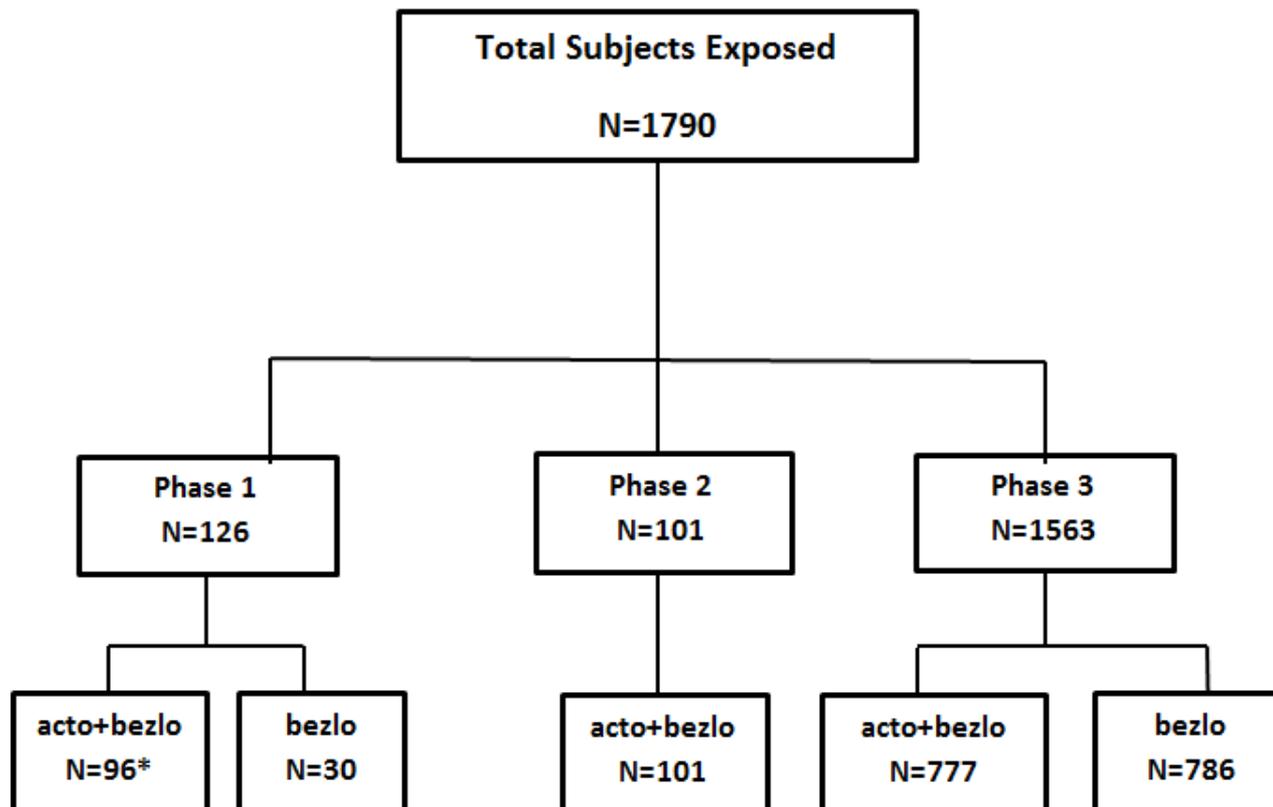
Mortality Rate in Phase 3 Trials (Safety Population)

	Bezlo	Acto+Bezlo	Placebo	Any Bezlo exposure
Over 12 week study period, (%)				
P001	31/390 (8)	20/387 (5.2)	26/400 (6.5)	51/777 (6.6)
P002	25/396 (6.3)	31/390 (8)	33/381 (8.7)	56/786 (7.1)
Total	56/786 **(7.1)**	51/777 **(6.6)**	59/781 **(7.5)**	107/1563 **(6.8)**
During Extension phase, (%)				
Study P002	5/100 (5)	2/112 (1.8)	2/83 (2.4)	3/212 (3.3)

[*]In addition to the above deaths, 28 subjects in the acto arm (11.9%) died in the Phase 3 trial. The mortality rate in the acto arm was significantly higher when compared to the other arms. Of note, the acto arm is not included in the safety population.
Acto=Actoxumab; Bezlo=Bezlotoxumab

Selected Serious Adverse Events in Phase 3 Trials That Occurred During 12 Weeks Following Infusion

MedDRA Preferred Term	Bezlo N=786 n (%)	Acto+Bezlo N=777 n (%)	Placebo N=781 n (%)
Subjects with ≥1 SAE	231 (29.4)	212 (27.3)	255 (32.7)
Cardiac failure*	17 (2.2)	17 (2.2)	7 (1)
Diarrhea	16 (2)	10 (1.3)	12 (1.5)
Abdominal pain	7 (0.9)	4 (0.5)	4 (0.5)
Respiratory failure	5 (0.6)	5 (0.6)	6 (0.8)
Acute kidney injury	6 (0.8)	4 (0.5)	10 (1.3)

*Cardiac failure terms "cardiac failure", "cardiac failure acute", "cardiac failure congestive" and "cardiac failure chronic" were combined.

Acto=Actoxumab; Bezlo=Bezlotoxumab; MedDRA=Medical Dictionary for Regulatory Activities

Selected TEAEs that Occurred in >2% of Subjects during the 4 Weeks Following Infusion

MedDRA Preferred Term	Bezlo N=786 n (%)	Acto+Bezlo N=777 n (%)	Placebo N=781 n (%)
Subjects with ≥ 1 TEAE	485 (61.7)	455 (58.6)	478 (61.2)
Nausea	52 (6.6)	47 (6.0)	39 (5.0)
Diarrhea	47 (6.0)	46 (5.9)	45 (5.8)
Pyrexia	36 (4.6)	31 (4.0)	27 (3.5)
Headache	35 (4.4)	33 (4.2)	24 (3.1)
Vomiting	31 (3.9)	24 (3.1)	21(2.7)
Peripheral edema	19 (2.4)	15 (1.9)	14 (1.8)
Fatigue	18 (2.3)	21 (2.7)	12 (1.5)
Cough	17 (2.2)	7 (0.9)	8 (1.0)
Dyspnea	17 (2.2)	6 (0.8)	13(1.7)

TEAE: Treatment Emergent Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities

Adverse Events of Special Interest

- Infusion-related reactions
  - Evaluation of all TEAEs that occurred within 24 hours of study infusion (days 1 and 2)
  - Subset of TEAEs that fulfilled infusion-related reaction criteria that occurred during days 1 and 2 of the study

Infusion Related Reaction Search Criteria: Sign/Symptoms that developed during days 1 and 2

- Two or more of the following:
  - Muco-cutaneous symptoms (e.g., hives, itch/flushing, swollen lip/tongue/uvula, angioedema, urticaria)
  - Respiratory compromise: Dyspnea, wheeze, stridor, hypoxemia
  - Cardiac:
    - Reduced blood pressure (SBP <90mmHg) or symptoms of reduced BP (hypotonia, collapse, syncope, incontinence)
    - Tachycardia
  - Persistent GI symptoms (e.g., crampy abdominal pain, vomiting)
  - General: Body temperature alteration (pyrexia, diaphoresis, chills), fatigue, and asthenia

- Reduced blood pressure (SBP < 90mmHg) or > 30% decrease from baseline

Modified from Samson et al. J Allergy Clin Immunol 2006; 117: 391

Summary of TEAEs and Infusion-related AEs during Days 1 and 2 After Infusion

	Bezlo N=786 n (%)	Acto+ Bezlo N=777 n (%)	Placebo N=781 n (%)
Subjects with any TEAE	148 (18.8)	120 (15.4)	114 (14.6)
Subjects with serious TEAEs	7 (0.9)	8 (1.03)	9 (1.2)
Subjects with any infusion related AE*	106 (13.5)	77 (9.9)	78(10)

*Infusion related AEs as defined in slide 12

Infusion-related Adverse Reactions

- Four subjects in the bezlotoxumab arm developed adverse reactions potentially attributable to study infusion
  - One subject developed ventricular arrhythmia, chills, and dizziness 36 minutes after the start of infusion; infusion discontinued permanently
  - Two subjects developed hypotension during the infusion
    - Neither of these patients had SBP<90mmHg or >30% drop in SBP from baseline
  - One subject had drop in SBP by 30% from baseline 30 minutes after start of infusion and at the end of infusion

Infusion-related Adverse Reaction Resulting in Permanent Infusion Discontinuation

- 32 year old male with HIV/AIDS, *Pneumocystis* pneumonia, electrolyte abnormalities (hyponatremia and hypokalemia), with no history of arrhythmia
  - Normal baseline ECG with atrial and ventricular rates of 103 beats per minute
- He developed ventricular tachyarrhythmia with heart rate of 200 beats per minute, chills and dizziness approximately 36 minutes after the start of bezlotoxumab infusion
- Vital signs:
  - Pre-infusion: HR 110, BP 110/70, temp 38.3 C, RR 20
  - 30 minutes after start of infusion: HR 200, BP 120/80, temp 38.5 C, RR 20

Infusion-related Adverse Reaction (continued)

- Pre-infusion labs were notable for potassium of 5.3 meq/L, and calcium of 8.2mg/dL

- Concomitant medications included pentamidine 300 mg IV Qday, potassium 40 mmol IV BID, pantoprazole 40 mg IV Qday and prednisone 50 mg BID

- Infusion was discontinued and subject was treated with steroids and histamine blockers intravenously

- Chills and ventricular tachyarrhythmia resolved within 5 minutes, and dizziness resolved within 90 minutes

- ECG performed 30 minutes after discontinuing the infusion showed atrial and ventricular rates of 99

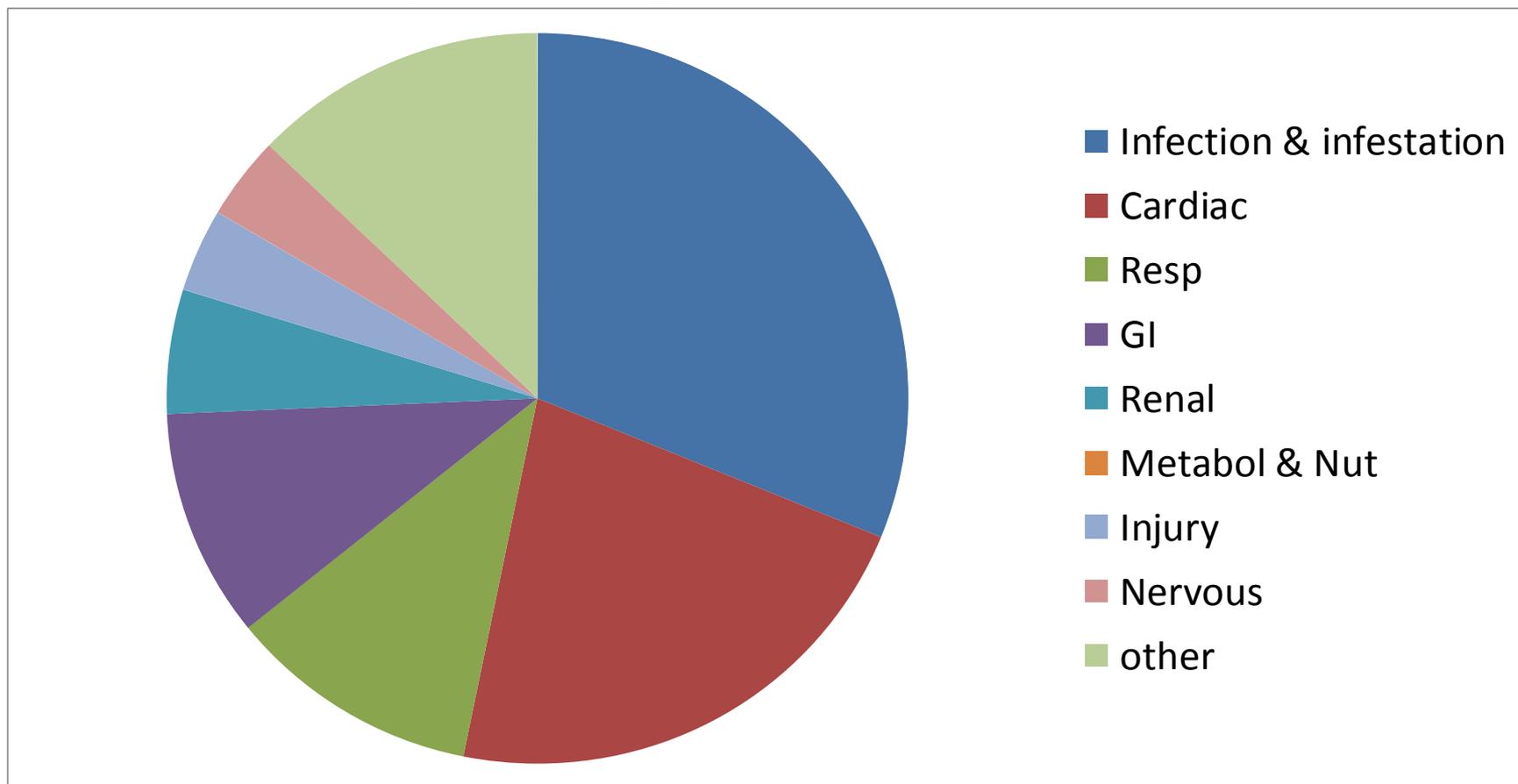- Sponsor considered the event as infusion-related

Subgroup Analysis: Safety Analysis by Baseline Congestive Heart Failure (CHF)

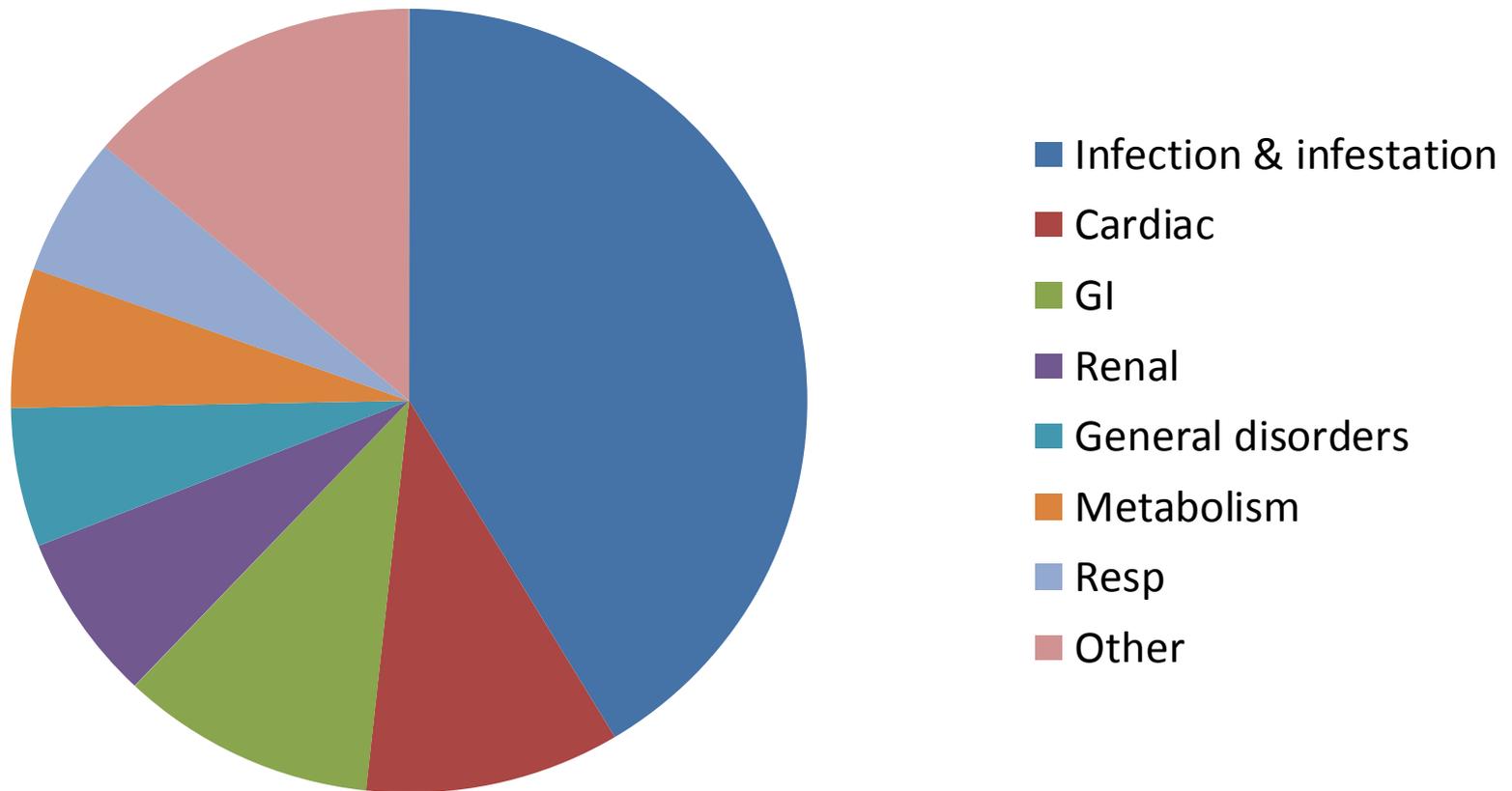|	Baseline CHF N=325 n (%)	No baseline CHF N=2019 n (%)
SAE	159 (48.9)	539 (26.7)
Bezlotoxumab	63 (19.4)	168 (8.3)
Acto+Bezlo	46 (14.2)	166 (8.2)
Placebo	50 (15.4)	205 (10.2)
Death	54 (16.6)	112 (5.5)
Bezlotoxumab	23 (7.1)	33 (1.6)
Acto+Bezlo	18 (5.5)	33 (1.6)
Placebo	13 (4)	46 (2.3)

Adverse Events among the 325 Subjects with Baseline CHF by Treatment Arm

	Bezlo N=118 n (%)	Acto+Bezlo N=103 n (%)	Placebo N=104 n (%)
TEAE	99 (83.9)	78 (75.7)	73 (70.2)
SAE	63 (53.4)	46 (44.7)	50 (48)
Death	23 (19.5)	18 (17.5)	13 (12.5)

SAEs among Bezlo-treated Subjects with Baseline CHF by MedDRA System Organ Class(SOC)

Legend:
- Infection & infestation
- Cardiac
- Resp
- GI
- Renal
- Metabol & Nut
- Injury
- Nervous
- other

SAEs among Placebo-treated Subjects with Baseline CHF by MedDRA System Organ Class(SOC)

Legend:
- Infection & infestation
- Cardiac
- GI
- Renal
- General disorders
- Metabolism
- Resp
- Other

SAEs among Bezlotoxumab-treated Subjects with Baseline CHF by MedDRA Preferred Term

MedDRA Preferred Term	Bezlo N=63 n (%)	Placebo N=50 n (%)
Cardiac failure*	15 (23.8)	5 (10)
Clostridium difficile infection	6 (9.5)	6 (12)
Pneumonia	5 (7.9)	10 (20)
Sepsis	3 (4.8)	5 (10)
Abdominal pain	3 (4.8)	0 (0)
Acute kidney injury	3 (4.8)	3 (6)
Cardiac arrest	3 (4.8)	2 (4)
Chronic kidney disease	3(4.8)	3 (6)
Respiratory failure	3 (4.8)	2 (4)
UTI	3 (4.8)	2 (4)

*Cardiac failure terms "cardiac failure", "cardiac failure acute", "cardiac failure congestive" and "cardiac failure chronic" were combined

Causes of Death in Subjects with Baseline CHF

	Bezlo N=23	Placebo N=13**
Cardiac failure*	5	2
Cardiac arrest	3	2
Respiratory failure	3	1
Cancer	2	0
Sepsis/septic shock	2	1
Cerebrovascular accident /hemorrhage	2	0
Chronic kidney disease	1	1
Pneumonia	1	2
Pneumonia and sepsis	1	0
Cardiopulmonary failure	1	1
Wound infection	1	0
Hyperkalemia	1	0

*One subject with CHF also had endocarditis, chronic kidney disease and aspiration pneumonia listed as causes of death
** Causes of death for 3 subjects in the placebo arm are not listed in the table (n=2 sudden death, n=1 CDI)

Additional Subgroup Analysis

- Subgroup analysis by age (<65 vs ≥65 years), sex, race (white vs non-white) and body weight (≤ 70 kg vs > 70 kg) were carried out.

- There were no significant differences in TEAEs, SAEs and death among the different groups.

Summary

- 1790 subjects have been exposed to bezlotoxumab alone or in combination with actoxumab.

- Overall, the proportions of TEAEs, SAEs and deaths were similar in the bezlotoxumab-containing arms and the placebo arm.

- There was one infusion reaction that led to discontinuation of the bezlotoxumab infusion.

- There were higher numbers of subjects who experienced congestive heart failure in bezlotoxumab-containing arms (17 in bezlo arm, 17 in acto+bezlo arm compared to 7 in the placebo arm).

- There were higher numbers of serious adverse events and death in bezlotoxumab-treated subjects with baseline congestive heart failure as compared to placebo.