ECCMID
27th European Congress of Clinical Microbiology and Infectious Diseases
Vienna, Austria

22 – 25 April 2017

Efficacy of Bezlotoxumab in Patients With Recurrent *Clostridium difficile* infection (CDI): Pooled Analysis of Data From the MODIFY Trials

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Background

- *C. difficile* infection (CDI) is one of the most common causes of infectious diarrhea, resulting in a spectrum of disease, ranging from self-limiting diarrhea to pseudomembranous colitis, life-threatening toxic megacolon, and death[1,2]
- After resolution of CDI-related diarrhea and completing initial antibacterial therapy with vancomycin or metronidazole, approximately 25% of patients experience CDI recurrence (rCDI)[3,4]
- Of those who have a primary recurrence, approximately 40% will have another CDI episode; and after 2 recurrences, the likelihood of additional episodes increases to 60%[5,6]
- There have been no drugs approved for prevention of rCDI. The few available therapies have limited efficacy
  - While fidaxomicin has been associated with a lower likelihood of rCDI vs vancomycin after a first recurrence,[7,8] there are no prospective randomized controlled trials investigating the efficacy of fidaxomicin in patients with multiple recurrences of CDI
  - Therefore, although the strength of evidence is limited, some guidelines recommend administration of vancomycin using a tapered or pulsed regimen[9,10] or fecal microbiota transplantation (FMT) in patients with multiple recurrences[9]
- A single 10 mg/kg IV dose of bezlotoxumab (bezlo, a human monoclonal antibody directed against *C. difficile* toxin B) was superior to placebo at preventing rCDI among participants with primary or recurrent CDI given antibacterial drug treatment for CDI in two independent global trials (MODIFY I and MODIFY II)[11]

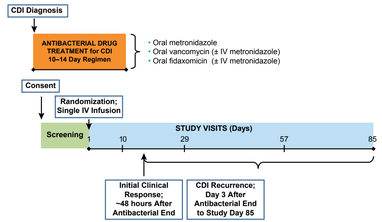
Objectives

- To estimate initial clinical cure and rCDI through 12 weeks in subgroups of participants with primary or recurrent CDI
- To compare initial clinical cure and rCDI between bezlo and placebo in subgroups of participants with primary or recurrent CDI

Methods

- MODIFY I (NCT01241552) and MODIFY II (NCT01513239) were randomized, double-blind, placebo-controlled, multicenter, Phase 3 trials that were conducted from November 1, 2011 through May 22, 2015 at 322 sites in 30 countries (**Figure 1**)

Figure 1. Study Design



Methods (continued)

Endpoints and populations

- Initial clinical cure was defined as receipt of a ≤14-day regimen of antibacterial drug treatment for CDI AND no diarrhea during the 2 consecutive days following completion of antibacterial drug treatment for CDI in the modified intent to treat (mITT) population
- The mITT population included all randomized participants who received study infusion, had a positive baseline stool test for toxigenic *C. difficile*, and were receiving antibacterial drug treatment for CDI at the time of randomization
- rCDI was defined as a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* in mITT participants who achieved initial clinical cure of the baseline CDI episode

Statistical analysis

- All participants in the mITT population who were enrolled in the MODIFY I and MODIFY II studies and who were randomized to bezlo or placebo groups were included in the subgroup analyses
  - Participants were categorized by number of prior CDI episodes (0 CDI episodes, 1 CDI episode and ≥2 CDI episodes)
- Observed initial clinical cure rates, rCDI rates, and rate differences between bezlo and placebo groups and their 95% confidence intervals (CIs) were computed based on Miettinen and Nurminen's method[12]
- The nonparametric Kaplan-Meier (KM) method was used to estimate the distribution of time to rCDI for each subgroup within each treatment group

Results

Participant disposition

- There were 770 participants who received bezlo and 756 participants who received placebo from the mITT population that were included in the present analyses. Participants with unknown prior CDI episodes [28 out 1554 (1.8%)] were not included
- Overall, 66.7% of subjects had primary CDI, 18.5% were experiencing their first recurrence, and 14.8% had 2 or more episodes of CDI prior to the episode under treatment at the time of randomization. The distribution of prior episodes was similar between the two treatment groups
- There were 42 (2.8%) subjects across both treatment groups who had ≥4 prior episodes of CDI. The highest number of prior CDI episodes reported by a single participant was 19 in the bezlo group and 25 in the placebo group
- Demographic and clinical characteristics were generally similar between treatment groups
- Differences in some characteristics were noted between participants with recurrent CDI compared with those with primary CDI (**Table 1**)
  - A higher proportion of participants with recurrent CDI at study entry were ≥65 years of age (59.4%; 302/508) compared with those with primary CDI (46.7%; 475/1018)
  - The most common antibacterial treatment taken by participants with a primary episode was metronidazole (60.2% of participants). Use of metronidazole declined while vancomycin and fidaxomicin use increased as the number of prior episodes increased from 1 prior episode to ≥2 prior episodes
  - A higher proportion of participants with a primary episode were inpatients at the time of randomization (72.3%; 736/1018) compared with participants with recurrent CDI (57.3%; 291/508)
  - A higher proportion of participants with a primary episode had severe CDI at the time of randomization (17.7%; 180/1018) compared with participants with recurrent CDI (11.4%; 58/508)
  - Ribotype 027 was isolated from a stool sample in a lower proportion of participants with a primary episode (16.0%; 103/644) compared with participants with recurrent CDI (25.9%; 81/313)

Results (continued)

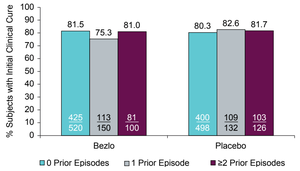
Table 1. Baseline Demographics and Clinical Characteristics by Number of Prior CDI Episodes

Characteristics n (%)	All Participants Prior CDI Episodes		
	0	1	≥2
Subjects in Population	1018	282	226
Female	589 (57.9)	156 (55.3)	131 (57.5)
Age (Years)			
<65	543 (53.3)	110 (39.0)	96 (42.5)
≥65	475 (46.7)	172 (61.0)	130 (57.5)
Antibacterial Drug Treatment for CDI			
Metronidazole	613 (60.2)	93 (33.0)	44 (19.5)
Vancomycin	388 (38.1)	178 (63.1)	164 (72.6)
Fidaxomicin	17 (1.7)	11 (3.9)	28 (12.4)
Hospitalization Status			
Inpatient	736 (72.3)	167 (59.2)	124 (54.9)
Outpatient	282 (27.7)	115 (40.8)	102 (45.1)
Number of Past CDI Episodes (Ever)			
0	1018 (100.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	282 (100.0)	0 (0.0)
2	0 (0.0)	0 (0.0)	129 (57.1)
3	0 (0.0)	0 (0.0)	55 (24.3)
≥4	0 (0.0)	0 (0.0)	42 (18.6)
Compromised Immunity*	215 (21.1)	60 (21.3)	51 (22.6)
Clinically Severe CDI			
(Zar Score ≥2)	180 (17.7)	37 (13.1)	21 (9.3)
027 Ribotype†	103/644 (16.0)	47/177 (26.6)	34/136 (25.0)
CDI Diagnosis Method‡			
EIA or Cell Cytotoxicity Assay	525 (51.6)	136 (48.2)	102 (45.1)
PCR or Culture	493 (48.4)	146 (51.8)	124 (54.9)

*Defined on the basis of a subject's medical history or use of immunosuppressive therapy.
†Denominator is patients in the mITT with a positive culture.
‡Subjects are counted only once in the summary of diagnosis method. Overall, 5.6% of patients were diagnosed via culture and 1.1% were diagnosed with cell cytotoxicity assay.
EIA = enzyme immune assay, PCR = polymerase chain reaction assay, Culture = culture with toxin detection or with strain typing

- The proportion of participants with initial clinical cure was similar* between treatment groups across subgroups defined by number of prior CDI episodes (**Figure 2**).

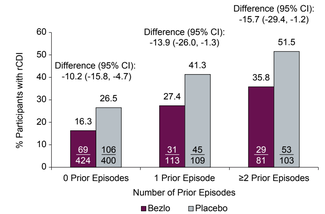
Figure 2. Proportion of Participants with Initial Clinical Cure by Number of Prior CDI Episodes (mITT Population)



*All of the 95% CIs for the differences between treatment groups included 0.

- In both treatment groups, the rCDI rate was higher in participants with 1 or more prior CDI episodes compared with participants with primary CDI (**Figure 3**)
- Treatment with bezlo reduced the rCDI rate compared with placebo in participants with recurrent CDI, including those with multiple prior recurrences (**Figure 3**). The 95% CIs for all the differences between treatment groups excluded zero

Figure 3. Proportion of Participants with rCDI by Number of Prior CDI Episodes (mITT Population with Initial Clinical Cure)



- Only 63% of participants who had a recurrent episode during the follow-up period were treated with an antibacterial (metronidazole, vancomycin, or fidaxomicin bezlo 58%; placebo 66%). As a sensitivity analysis, the outcome for participants who were not treated was changed to no recurrence (**Figure 4**). Participants who received bezlo were less likely to be treated with an antibacterial for the recurrence compared with participants who received placebo, regardless of number of prior episodes
- Among participants who were treated with an antibacterial for an on-study rCDI (**Table 2**):
  - A higher proportion of participants in both treatment groups who had no prior CDI episodes experienced a severe CDI recurrent episode compared with participants with 1 or ≥2 prior CDI episodes
  - A higher proportion of patients who received bezlo were diagnosed at baseline with a test that is not specific for *C. difficile* toxin (i.e., PCR or culture) in each CDI history subgroup

Figure 4. Proportion of Participants Who had a rCDI and Received Antibacterial Drug Treatment by History of Previous CDI Episodes (mITT Population with Initial Clinical Cure)

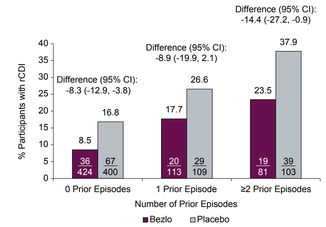


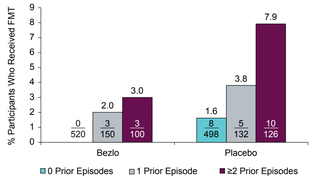
Table 2. Characteristics of Participants who were Treated with An Antibacterial for an On-study rCDI

	Bezlo Prior CDI Episodes			Placebo Prior CDI Episodes		
	0	1	≥2	0	1	≥2
Participants in Population	36	20	19	67	29	39
Clinically Severe CDI (Zar Score ≥2) n (%)	4 (11.1)	1 (5.0)	1 (5.3)	11 (16.4)	2 (6.9)	2 (5.1)
Baseline CDI Diagnosis Method PCR or Culture*	20 (55.6)	13 (65.0)	12 (63.2)	32 (47.8)	13 (44.8)	19 (48.7)

*Overall, 5.6% of participants were diagnosed with culture and 44.7% of participants were diagnosed with PCR.

- The proportion of participants who received an FMT was higher in the subgroups with 1 or ≥2 prior CDI episodes compared with those with no prior CDI episodes (**Figure 5**)
- A total of 6 participants in the bezlo group and 23 participants in the placebo group received FMT

Figure 5. Proportion of Participants who Received an FMT at Any Time During the 12-Week Follow-up Period by Number of Prior CDI Episodes (mITT Population)



FMT = fecal microbiota transplant

- During the 12-Week follow-up period, the total number of deaths was similar between the 2 treatment groups (placebo = 56 vs bezlo = 51; **Table 3**)

Table 3. 30-day and 90-day Mortality Rate by Number of Prior CDI Episodes (APaT Population)

	Bezlo Prior CDI Episodes			Placebo Prior CDI Episode		
	0	1	≥2	0	1	≥2
Participants in Population	520	150	102	504	132	127
Death						
30-Day Mortality	19 (3.7)	4 (2.7)	2 (2.0)	20 (4.0)	3 (2.3)	1 (0.8)
90-Day Mortality	38 (7.3)	9 (6.0)	4 (3.9)	40 (7.9)	10 (7.6)	6 (4.7)

APaT = all patients as treated, Bezlo = bezlotoxumab

Summary and Conclusions

- In participants with recurrent CDI, bezlo was associated with a marked decrease in the proportion of participants with rCDI over a 12-Week follow-up period compared with placebo (~14% absolute difference). The number needed to treat (NNT) was 9.8 in participants with a primary episode, 7.2 in participants with 1 prior episode, and 6.4 in participants with ≥2 prior episodes
- In both treatment groups, the rCDI rate was higher in participants with 1 or more prior CDI episodes compared with participants with primary CDI
- Participants treated with bezlo were less likely to be treated with an antibacterial for rCDI regardless of number of prior episodes
- Only 6 subjects in the bezlo group received an FMT compared with 23 subjects in the placebo group. The proportion of subjects receiving an FMT increased with number of prior episodes, consistent with recommendations for the patient population who typically receives FMTs[13]
- Although not powered to detect a difference, there was a tendency for higher 30-day and 90-day mortality in participants with primary CDI compared with those with recurrent CDI. This is likely related to the age of the participants in these subgroups (participants with primary CDI tended to be older and had severe CDI compared with those with recurrent CDI, **Table 2**)
- Limitations of the analyses in this series are that these results could have been influenced by interventions given after the first recurrence. There were no protocol restrictions on choice of treatment or duration of treatment for participants who experienced a recurrence on study. The efficacy of bezlo is likely underestimated due to the high use of PCR as the diagnostic method overall and the higher proportion of participants receiving bezlo who were diagnosed with this method compared with placebo participants
- This antitoxin antibody shows promise as an adjunct to antibacterial drug treatment for CDI in the prevention of rCDI in patients with primary or recurrent disease

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http://tinyurl.com/j87t3mn