Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for *Clostridium difficile* infection

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**Background:** The fully human monoclonal antibody bezlotoxumab binds *Clostridioides* (*Clostridium*) *difficile* toxin B and reduces recurrence rates in patients with *C. difficile* infection (CDI) receiving antibacterial treatment for a primary or recurrent episode.

**Objectives:** To investigate whether the timing of bezlotoxumab administration relative to the onset of antibacterial treatment affected clinical outcome in the Phase 3 trials MODIFY I (NCT01241552) and MODIFY II (NCT01513239).

**Methods:** Initial clinical cure and CDI recurrence rates of participants who received bezlotoxumab or placebo were summarized by timing of infusion relative to the start of antibacterial drug treatment for CDI: 0–2, 3–4 and ≥5 days after onset.

**Results:** Of 1554 total participants, 649 (41.8%), 469 (30.1%) and 436 (28.1%) received an infusion 0–2, 3–4 and ≥5 days after onset of antibacterial treatment for CDI, respectively. Regardless of timing of administration, there were no differences in initial clinical cure rates between participants receiving bezlotoxumab (range 77.8% to 81.4%) or placebo (77.8% to 81.7%). Bezlotoxumab efficacy was unaffected by timing of administration; rates of CDI recurrence were lower versus placebo in all subgroups (range 19.3% to 22.8% for bezlotoxumab and 31.7% to 35.8% for placebo). Timing of administration also had no effect on time to resolution of diarrhoea, which was achieved by the end of antibacterial treatment in ~95% of participants in both bezlotoxumab and placebo groups.

**Conclusions:** Bezlotoxumab is effective in preventing CDI recurrence and can be administered at any time before ending antibacterial drug treatment.

**Introduction**

*Clostridioides* (*Clostridium*) *difficile* infection (CDI) is the most frequent cause of healthcare-associated gastrointestinal (GI) infection in the USA and is also increasingly associated with community-acquired GI infections.¹,² Although clinical treatment of CDI with metronidazole, vancomycin or fidaxomicin is often successful, ~25% of individuals experience a recurrence of CDI (rCDI) following treatment of a primary episode³–⁶ and ~40% experience further recurrences following the first rCDI.⁷

Bezlotoxumab (MK-6072) is a fully human monoclonal antibody that binds to *C. difficile* toxin B and is indicated for prevention of rCDI in adults receiving antibacterial drug treatment for CDI who are at high risk for rCDI.⁷,⁸ In the Phase 3 MODIFY I/II trials, a single intravenous dose of bezlotoxumab resulted in a significantly lower rate of rCDI versus placebo during the 12 week follow-up period in participants receiving antibacterial drug treatment for primary or rCDI.⁹ Bezlotoxumab had no effect on initial clinical cure (ICC). Most participants received bezlotoxumab ≥3 days after antibiotic treatment for CDI began.⁹ It is not known if the timing of administration relative to onset of antibiotic treatment affects clinical outcome. The aim of this post hoc analysis of the MODIFY I/II trials was to evaluate the efficacy of bezlotoxumab summarized by timing of infusion relative to the start of antibacterial drug treatment for CDI.

**Methods**

**Study design**

MODIFY I (NCT01241552; P001) and MODIFY II (NCT01513239; P002) were randomized, double-blind, placebo-controlled, multicentre, Phase 3 trials that were conducted from November 2011 to May 2015 at 322 sites in
Risk factors for recurrence, n (%)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bezlotoxumab timing of infusion (N=318)</th>
<th>Placebo timing of infusion (N=331)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–2 days</td>
<td>3–4 days</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>176 (55.3)</td>
<td>136 (55.9)</td>
</tr>
<tr>
<td>inpatient</td>
<td>229 (72.0)</td>
<td>164 (68.6)</td>
</tr>
<tr>
<td>Antibacterial treatment for CDI, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metronidazole</td>
<td>138 (43.4)</td>
<td>126 (52.7)</td>
</tr>
<tr>
<td>vancomycin</td>
<td>163 (51.3)</td>
<td>108 (45.2)</td>
</tr>
<tr>
<td>fidaxomicin</td>
<td>17 (5.3)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Risk factors for recurrence, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 of 5 pre-specified risk factorsa</td>
<td>244 (76.7)</td>
<td>181 (75.7)</td>
</tr>
<tr>
<td>≥1 CDI episodes in past 6 months</td>
<td>92 (28.9)</td>
<td>66 (27.6)</td>
</tr>
<tr>
<td>≥2 previous CDI episodes ever</td>
<td>104 (32.7)</td>
<td>73 (30.5)</td>
</tr>
<tr>
<td>≥65 years of age</td>
<td>145 (45.6)</td>
<td>124 (51.9)</td>
</tr>
<tr>
<td>compromised immunityb</td>
<td>72 (22.6)</td>
<td>56 (23.4)</td>
</tr>
<tr>
<td>severe CDI (Zar score ≥ 2)C</td>
<td>55 (17.3)</td>
<td>37 (15.5)</td>
</tr>
<tr>
<td>C. difficile straina, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>participants with a positive culture</td>
<td>233 (73.3)</td>
<td>141 (59.0)</td>
</tr>
<tr>
<td>ribotype 027, 078 or 244D</td>
<td>48 (20.6)</td>
<td>32 (22.7)</td>
</tr>
<tr>
<td>ribotype 027E</td>
<td>42 (18.0)</td>
<td>30 (21.3)</td>
</tr>
</tbody>
</table>

aPre-specified risk factors include: ≥1 CDI episodes in the past 6 months; severe CDI at baseline; age ≥65 years; ribotype 027, 078 or 244 at baseline; and/or immuno compromised.

bDefined on the basis of medical history or use of immunosuppressive therapy.

cBased on the following at time of randomization: (i) age ≥60 years (1 point); (ii) body temperature >38.3°C (>100°F) (1 point); (iii) body weight); (iv) peripheral white blood cell count >15,000 cells/mm³ within 48 h (1 point); (v) albumin level <2.5 g/dL (1 point); (vi) endoscopic evidence of pseudomembranous colitis (2 points); and (vii) treatment in an ICU (2 points).

dThe denominators used to calculate percentages are the numbers of participants who had a positive culture.

Endpoints

ICC was defined as no diarrhea during the two consecutive days following completion of ≤16 calendar days of antibacterial drug treatment for CDI. rCDI was defined as a new episode of diarrhea associated with a positive stool test for toxigenic C. difficile in participants who had achieved ICC of the baseline CDI episode.

Data and statistical analysis

The analysis population for ICC was the modified ITT (mITT) population, which included all randomized participants in the overall population of the MODIFY I/II trials who received study infusion, had a positive baseline stool test for toxigenic C. difficile and received antibacterial drug treatment for CDI at the time of randomization. Estimation of rCDI was assessed in participants who achieved ICC (clinical cure population). Baseline demographics and clinical characteristics were summarized descriptively.

ICC rates and observed rCDI rates are presented along with adjusted rate differences between the bezlotoxumab and placebo groups and their 95% CIs. Adjusted rate difference was based on the Miettinen and Nurminen method and stratified by trial (MODIFY I versus MODIFY II), antibacterial drug treatment for CDI (metronidazole versus vancomycin versus fidaxomicin) and hospitalization status at time of randomization (inpatient versus outpatient). The non-parametric Kaplan–Meier method was used to estimate the distribution of time to resolution of baseline CDI episode for each treatment group and timing of infusion group.

Results

Participants

This post hoc analysis included 1554 participants, of which 781 received bezlotoxumab and 773 received placebo. In total, 649 (41.8%), 469 (30.1%) and 436 (28.1%) participants received an infusion 0–2, 3–4 and ≥5 days after onset of antibacterial treatment for CDI, respectively (Table 1). The number of participants completing...
the trial through to the end of the 12 week follow-up period was similar in all groups (82.6% to 88.8%), and the baseline characteristics were generally similar between the bezlotoxumab and placebo treatment groups, according to time of infusion initiation (Table 1).

**Efficacy**

ICC rates were similar in all groups, irrespective of treatment administered or timing of administration (range 77.8% to 81.4% for bezlotoxumab and 77.8% to 81.7% for placebo) (Figure 1a). Rates of rCDI were lower with bezlotoxumab compared with placebo across all infusion timing groups (range 19.3% to 22.8% for bezlotoxumab and 33.0% to 35.8% for placebo) (Figure 1b), and the adjusted difference between the bezlotoxumab and placebo groups was similar, regardless of the timing of study medication infusion (~13.1% to ~13.1%).

Time to resolution of diarrhoea was similar for both bezlotoxumab and placebo in each subgroup (Figure S1, available as Supplementary data at JAC Online). In both the bezlotoxumab and placebo treatment groups, ~70% of participants who had been receiving antibacterial treatment for three or more days before infusion of the study medication no longer had diarrhoea at the time of infusion (Study Day 1). By the end of antibacterial treatment, ~95% of participants had resolved their diarrhoea in both treatment groups, regardless of the timing of infusion.

**Discussion**

This post hoc analysis was conducted to evaluate the impact of infusion timing on bezlotoxumab efficacy endpoints. The analysis demonstrated a substantial reduction in the incidence of rCDI with...
bezlotoxumab compared with placebo, regardless of timing of infusion. Bezlotoxumab did not appear to improve ICC rates when given early during the course of antibacterial treatment and irrespective of timing of infusion relative to the onset of antibacterial treatment, as indicated by the similar point estimates and difference between bezlotoxumab and placebo groups. Moreover, early administration of bezlotoxumab did not appear to improve the time to resolution of the primary symptom of CDI, diarrhea. While we did not see an effect of bezlotoxumab on ICC or time to resolution of diarrhea, it is thought that administration early after onset of symptoms could improve outcomes in patients with severe CDI. However, only 17% of participants who were administered study medication within the first two days of onset of antibiotic therapy were classified as having severe CDI; therefore, the sample size was too small to evaluate this hypothesis.

These findings suggest that there can be flexibility in the timing of bezlotoxumab administration, facilitating its use in an outpatient setting. This may improve post-hospitalization follow-up and increase the likelihood of reimbursement from third-party payers. The MODIFY trial design required that the study medication be administered before the end of antibiotic therapy. The rationale for this design was to ensure that the antibodies were in the systemic circulation before onset of the at-risk period for rCDI. A previous study demonstrated that fidaxomicin and vancomycin treatment reduced C. difficile toxin B levels as early as 3–5 days after onset of treatment and this effect was sustained until the end of treatment (10–13 days). Toxin B levels began to rise 9–25 days after the end of therapy (the first follow-up visit) following completion of therapy for both antimicrobial agents. 12 This illustrates the time course of toxin B levels during antibiotic drug treatment for CDI and highlights that toxin levels begin to rise shortly after finishing a course of antibiotic treatment, representing the start of the rCDI risk period. There was a significant correlation between the presence of vegetative cells and spores and high toxin levels. 12 These findings support the theory that it is optimal to administer bezlotoxumab before antibacterial treatment for CDI ends, so that it is in the systemic circulation and available to protect against the damaging effects of new toxin production when the patient is most at risk for relapse or re-infection. Further support for administering bezlotoxumab prior to the end of antibiotic drug treatment is provided by preclinical evidence, which showed that by preventing rCDI during the critical high-risk period, bezlotoxumab treatment allowed the intestinal microbiota time to fully recover its role as a natural defence against C. difficile. 13

This post hoc analysis of the effect of bezlotoxumab infusion timing on clinical outcomes supports the proposal that administration of bezlotoxumab anytime before ending antibacterial treatment is effective in the prevention of rCDI.

In conclusion, the results of this post hoc analysis suggest that bezlotoxumab can be administered any time before ending antibacterial drug treatment for CDI in order to prevent rCDI.

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Supplementary data
Figure S1 is available as Supplementary data at JAC Online.

References


