Title: Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection
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Primary objective of trial

Two global, double-blind, randomized, placebo-controlled, phase 3 clinical trials were conducted to determine the efficacy of bezlotoxumab and actoxumab monoclonal antibody treatments individually and concurrently on the rates of recurrent *Clostridium difficile* (*C. difficile*) infection, post initial infection.

Methodology

Efficacy

Participants included patients with primary or recurrent *C. difficile* infection, confirmed with a baseline positive stool test and a high level of diarrhea severity. All participants began receiving standard-of-care oral antibiotic (metronidazole, vancomycin, or fidaxomicin) therapy before or within 1 day of receiving the monoclonal antibodies to be studied.

Appropriate randomization of group assignment, blinding of study-group, and stratification of antibiotic assignment and inpatient/outpatient status were conducted for these clinical trials. Using a 1:1:1:1 ratio, patients randomly received one of four single 60 minute intravenous infusions: bezlotoxumab (*B*), actoxumab with bezlotoxumab (*A*-*B*), placebo (*P*), and in one trial an actoxumab alone (*A*) group.

Each of the two trials were designed and powered to determine the efficacy of the treatments, measured with two endpoints of interest. The primary end point was the proportion of patients with no recurrence through the 12 week post-infusion period. The secondary end point was distribution of the time to recurrent infection throughout the 12 week period or the rate of sustained cure. Efficacy was assessed in the modified intent-to-treat population.

Safety

During the 12 week period, safety was assessed in the as-treated population, including a pre-planned interim analysis. Participants were monitored for adverse events, including recurrent infection.

Statistical methods

Findings were analyzed for each trial as well as a planned analysis of pooled data from both trials, facilitating the discovery of treatment effects. To assess the primary end point, the Miettinen and Nurminen method determined differences between treatment groups for their proportions of recurrence. In assessing the secondary end point, the Kaplan Meier rates measured the rate of sustained cure with 95% confidence intervals provided every 4 weeks. The efficacy of infusion group was also examined in special subgroups of interest. The absolute difference and relative difference between subgroups was expressed as percentage points, comparing *B* and *A*-*B* infusion with *P*. Multiplicity adjustments corrected for the multiple analyses performed.

Results

Subject demographics

Within the modified intent-to-treat population, participant's age ranged from 18 to 100 years old with a median of 66 years. Overall, 56% of participants were women and 86% were white, with demographics balanced across groups. A majority of participants were inpatients.

Efficacy

Recurrent *C. difficile* infection was lower in the *B* group than *P* in both trials. The absolute difference in percentage points was -10.1 in trial 1 and -9.9 in trial 2. The difference was also significantly lower within *A-B* than *P* with -11.6 in trial 1 and -10.7 in trial 2. All reached a significance of $p < 0.001$ (Figure 1). There was no difference between *B* and *A-B* groups on rate of recurrent infection.

The rates of recurrent infection across the 12 week period were significantly different between the *P* group and both the *B* and *A-B* groups as early as 2 weeks post-infusion. However, the rate of sustained cure, the secondary end point, did not prove to be different between *B* and *P* groups within one of the trials.

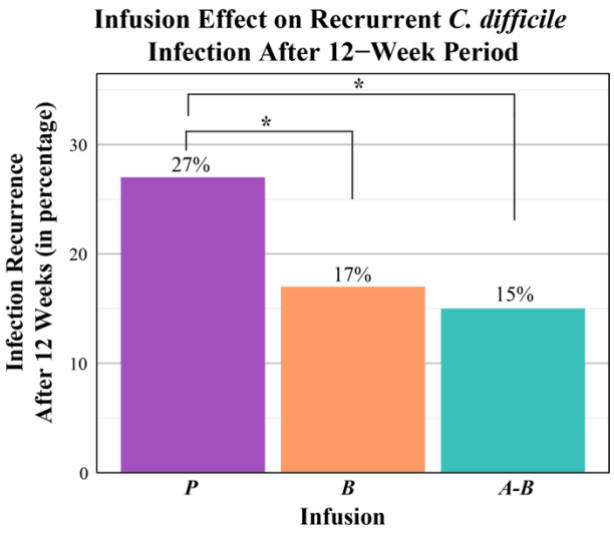

Figure 1: Pooled trial data indicated there was a significant effect of both the B and the A-B group's rates of recurrence compared to the P group (= p <0.001)*

Safety

A pre-planned interim analysis identified that the *A* group had a significantly higher rate of recurrent infection compared to group *A-B* and thus enrollment in group *A* was suspended. Participant death occurred in 7% enrolled, and was more common in the *A* group (11%). The causes behind the serious adverse health events and higher rates of death within the *A* group have not been determined.

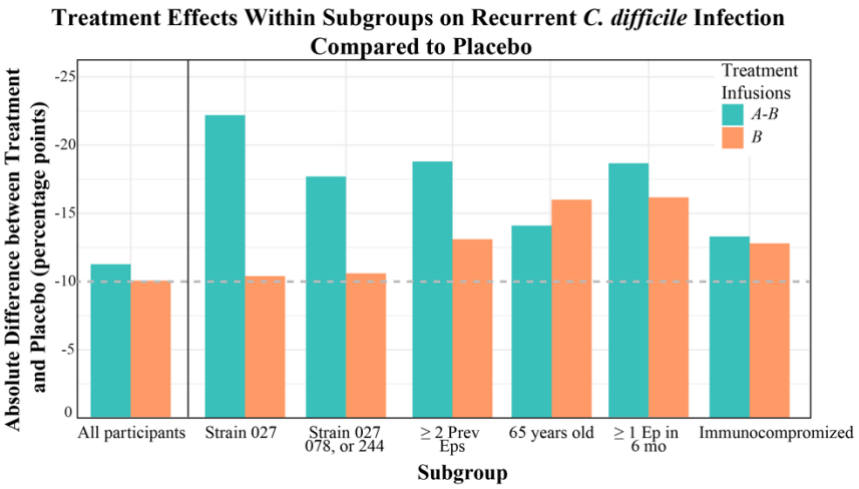

Figure 2: Pooled trial data of the subgroups with the highest absolute difference in treatment effect compared to placebo. (Previous (Prev), Months (mo), Episode of recurrent C. difficile (Ep), Absolute Difference from bezlotoxumab in 'All participants' = dashed line)

Preventative treatment with a single intravenous dose of bezlotoxumab has a positive safety profile when paired with standard of care antibiotic therapy. Various subgroups displayed differing outcomes between the two treatment groups (Figure 2).

Conclusions

A single intravenous treatment of bezlotoxumab, with standard-of-care antibiotics, provided protection against recurrent *C. difficile* infection during the 12 weeks post-infusion period that was significantly better than antibiotics alone.