A Time-to-Event Analysis of the Exposure-Response Relationship for Bezlotoxumab Concentrations and CDI Recurrence

**INTRODUCTION**

- Bezlotoxumab (BEZ, MK-6772) is a fully human monoclonal antibody targeted against Clostridium difficile toxin B, which is believed to reduce recurrent CDI.
- The randomized, double-blind Phase 3 trials MODIFY I and MODIFY II evaluated the efficacy and safety of a single infusion of BEZ, reoxumab (ACT, MK-3415), a fully human monoclonal antibody against C. difficile toxin A, and ACT plus BEZ, compared with placebo.

**METHODS**

### Data Sources

- The TTE was analyzed using data from two Phase 3 trials: MODIFY I (NCT01491552) and MODIFY II (NCT01513239).
- Participants received a single infusion of 10 mg/kg BEZ, 10 mg/kg ACT (MODIFY I) or 10 mg/kg BEZ + 10 mg/kg ACT, or placebo (0.9% saline) during antimicrobial drug treatment for CDI.

### Time-to-Event Modeling Strategy

1. **TTE Model Application:** A TTE model was applied, in which the event was defined as CDI.
2. **CDI Monitoring:** For the primary endpoint, CDI occurred, discontinued, or was censored at the time of death or loss to follow-up.
3. **Primary Data Analysis:** Inclusion in the TTE analysis was limited to participants who did not have a history of CDI in the previous 6 months, were not on oral anti-diarrheal medications, and were not concurrently treated with systemic antibiotics.

### Placebo Modeling

- A placebo model with baseline CDI hazard was first developed by fitting a hazard function to pooled data from the placebo and ACT arms only.

### Covariates

- Covariates included age, body weight, gender, hospitalization status, Charlson Comorbidity Index (CCI), severe C. difficile infection (CDI), and age at time of diagnosis.

### Exposure-Response for CDI Recurrence

- The relationship between BEZ exposure and rCDI was evaluated by adding data from BEZ and ACT groups to the placebo model with covariates.

### Placebo CDI Recurrence

- The TTE model for CDI consisted of a Gompertz model, which was parameterized as follows:

\[ \log(-\log(1 - \text{rate of CDI recurrence})) = \theta \times (\text{age} - \text{baseline age}) \]

### Results

**Data Sets Analyzed**

- The analysis database for the TTE model comprised of 2,559 participants from MODIFY I and MODIFY II, with the following participants:
  - Participants with missing microbiology results or participants who did not achieve clinical cure and were not evaluated for CDI.
  - Participants who did not complete the study and did not have CDI.

### Final Model Evaluation

- Model predicted survival curves for pooled BEZ treated and untreated participants were in good agreement with observed survival profiles (Figure 2). Furthermore, model predictions for each exposure decile were also in good agreement with observed values, confirming the validity of the E-R model (Figure 3).

**CONCLUSIONS**

- TTE analysis is a less biased method of analyzing CDI data than logistic regression, as it does not make inferences about study-discontinued participants.
- Avoiding introduction of confounding effects of antibody and BEZ exposure.
- The E-R relationship for CDI consisted of a Gompertz placebo hazard model with age, endogenous IgG-B, history of CDI in the previous 6 months, hospitalization status, and the concomitant use of systemic antibiotics affecting \( \alpha \).
- The E-R relationship for BEZ and CDI was characterized by an \( \alpha \) model, where high survival was achieved with the observed range of exposures.
- Low levels of endogenous neutralizing antibodies are a risk factor for CDI.
- BEZ is hypothesized to reduce CDI risk by neutralizing CDI directly and by lowering the intensity to CDI.

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