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

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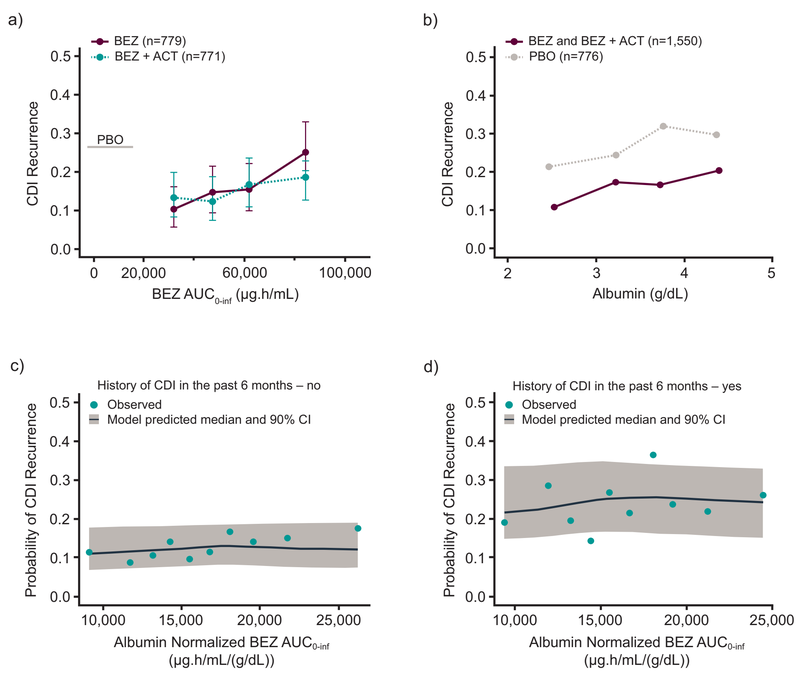
INTRODUCTION

- Bezlotoxumab (BEZ, MK-6072) is a fully human monoclonal antibody targeted against *Clostridium difficile* toxin B, which is indicated to reduce recurrent *C. difficile* infection (rCDI) in adults receiving antibacterial drug treatment for CDI at high risk for rCDI[1]
- The randomized, double-blind Phase 3 trials MODIFY I and MODIFY II evaluated the efficacy and safety of a single infusion of BEZ, actoxumab (ACT, MK-3415, a fully human monoclonal antibody against *C. difficile* toxin A), and ACT plus BEZ, compared with placebo. The primary endpoint was the proportion of participants with rCDI during 12 weeks of follow-up. Compared with placebo-treated participants, those treated with BEZ had a significantly lower rate of rCDI, and the addition of ACT did not improve efficacy.[2] BEZ had a similar safety profile to placebo[2]
- Previous exposure-response (E-R) analyses using logistic regression investigated the relationship between BEZ exposure and rCDI[3]
  - Based on initial graphical exploration, without consideration of covariate effects on pharmacokinetics (PK) or response, an apparent positive E-R trend was observed, with increasing BEZ exposure associated with increasing rCDI rates (**Figure 1a**). A positive trend was also observed between rCDI rates and baseline albumin level (**Figure 1b**)
  - Given the strong association between albumin level and BEZ exposure, the observed trend may have been related to participant covariates. Adjustment for baseline albumin levels and BEZ exposure eliminated the correlation with rCDI rate (**Figure 1c,d**)
  - Logistic regression requires imputation of rCDI for study-discontinued participants, which introduces bias by assuming that none of the discontinued participants would have rCDI. This may have contributed to the positive E-R trend, as participants who prematurely discontinued tended to have lower albumin levels (and therefore exposure levels) due to poor health; these participants may have ultimately experienced a recurrence if they had continued in the study for the full 90 days

Figure 1. Quantile Plot for the Recurrence Rate of *Clostridium difficile* Infection by a) Bezlotoxumab Exposure, b) Baseline Albumin Level and c,d) Albumin-corrected Bezlotoxumab Exposure Deciles



ACT, actoxumab; $AUC_{0\text{-inf}}$, area under the concentration versus time curve from time 0 to infinity; BEZ, bezlotoxumab; CDI, *Clostridium difficile* infection; CI, confidence interval; PBO, placebo.

- Time-to-event (TTE) analysis is an alternative method used in E-R assessment. In addition to occurrence of an event, TTE analysis also utilizes the time to the occurrence of the event. TTE analysis does not make inferences about study-discontinued participants; instead, it can account for both the occurrence of rCDI and for participants discontinuing during the study by censoring these participants by the time of discontinuation.[4] Thus, there is no need for imputation of success or failure for study-discontinued participants
- Here, a TTE analysis was applied to investigate the E-R relationship for BEZ and rCDI, accounting for the time to rCDI and participant discontinuation

METHODS

Data Sources

- The TTE analysis included data from two Phase 3 trials, MODIFY I (NCT01241552) and MODIFY II (NCT01513239)
  - Participants received a single infusion of 10 mg/kg BEZ, 10 mg/kg ACT (MODIFY I only) or 10 mg/kg BEZ + 10 mg/kg ACT, or placebo (0.9% saline) during antibacterial drug treatment for CDI
  - The primary endpoint, rCDI, was defined as the development of a new episode of diarrhea [≥3 or more loose stools in ≤24 hours] associated with a positive stool test for toxigenic *C. difficile* following initial clinical cure of the baseline CDI episode
  - Primary statistical analysis indicated that rCDI rates following ACT treatment alone were similar to placebo, and that combining ACT + BEZ did not improve efficacy compared with BEZ alone. These findings allowed pooling of the placebo and ACT arms, and of the BEZ and BEZ + ACT arms for subsequent analyses
- Individual area under the curve (AUC) estimates were obtained from the previously developed population PK model and observed BEZ concentrations as described in the previous E-R analysis[3]

Time-to-Event Modeling Strategy

- A TTE model was applied, in which the event was defined as rCDI
  - rCDI monitoring started on the third day after antibacterial drug treatment for CDI. All participants were followed until either rCDI occurrence, discontinuation, or until study completion (Day 85) where data were considered censored
  - All participants were aligned so that time=0 for the hazard function coincided with the start of rCDI monitoring

Placebo Model Development

- A placebo model with baseline rCDI hazard was first developed by fitting a hazard function to pooled data from the placebo and ACT arms only
  - Exponential, Weibull, Gompertz, and log-logistic functions were evaluated using change in objective function value (ΔOFV; $p < 0.05$) and goodness-of-fit plots
- The chosen hazard function model was then subjected to stepwise covariate modeling (SCM). This procedure involved stepwise testing of linear and non-linear covariate relationships in a forwards inclusion (ΔOFV of 3.84, $p < 0.05$ for 1 degree of freedom [df]) and backwards exclusion (ΔOFV of 3.84, $p < 0.05$ for 1 df) procedure
- Covariates included age, body weight, gender, hospitalization status, Charlson Comorbidity Index (CCI), severe CDI (Zar score ≥2), baseline albumin level, endogenous immunoglobulin G (IgG) to toxin A (IgG-A; low titer ≤1:1,000; high titer ≥1:5,000), endogenous IgG to toxin B (IgG-B; low titer ≤1:1,000; high titer ≥1:5,000), baseline white blood cell count, compromised immunity, history of CDI in the past 6 months, antibacterial drug treatment for CDI, concomitant use of systemic antibiotics, and concomitant use of proton-pump inhibitors (PPIs)

Exposure-Response for CDI Recurrence

- The relationship between rCDI and BEZ exposure was evaluated by adding data from BEZ and BEZ + ACT groups to the final placebo model with covariates
  - E-R was evaluated by ΔOFV ($p < 0.05$) and goodness-of-fit plots
  - Linear and maximum effect (E_{max}) models were tested for exposure effects
- The final TTE rCDI model was evaluated by means of survival curves as Kaplan-Meier plots overlaying model predictions and observed data for rCDI over time. Numerical and visual predictive checks were also performed, overlaying the observed Day 85 rCDI incidences and the model predicted Day 85 rCDI incidences based on data simulated from the TTE model

RESULTS

Data Sets Analyzed

- The analysis datasets for the TTE model comprised of 2,559 participants from MODIFY I (n=1,396) and MODIFY II (n=1,163)
  - Participants with missing antibacterial drug treatment for CDI end date (n=13) and participants who did not achieve clinical cure and so could not be evaluated for rCDI (n=583) were right censored at Day 1. None of the Day 1 right censored participants had a rCDI event
  - All participants who did not discontinue the study and did not have rCDI were right censored at Day 90, which was the day of the last observed rCDI event

Placebo CDI Recurrence

- The TTE model for rCDI consisted of a Gompertz model, which was parameterized as follows:
  - $h_0(t) = \lambda * \exp(\alpha * T)$

    Where λ = baseline parameter, α = shape parameter and T = time
- Age, endogenous IgG-B, history of CDI in past 6 months, hospitalization, gender, and CCI were identified as significant covariates affecting the baseline parameter (λ), and the concomitant use of systemic antibiotics was a significant covariate on the shape parameter (α), which describes the time-dependence of the hazard (**Table 1**)

Table 1. Significant Covariates on *Clostridium difficile* Infection Recurrence Time-to-Event Placebo Hazard Parameters in Stepwise Covariate Modeling

Covariate	Estimate[a]	Effect on PBO rCDI	p-value
λ	0.0196		
Age – continuous	0.0128	↑1.28%/year	1.60E-03
Endogenous IgG-B – low titer	0.400	↑40.0%	7.67E-03
History of CDI in past 6 months – yes	0.865	↑86.5%	1.20E-07
Hospitalization – outpatients	0.496	↑49.6%	8.62E-03
Gender – male	-0.276	↓27.6%	1.31E-03
Charlson Comorbidity Index – Score ≥3	-0.260	↓26.0%	2.43E-02
α	-0.0609		
Concomitant use of systemic antibiotics – yes	-0.257	↓25.7%	3.04E-02

[a]Parameter estimates and RSE were derived from the NONMEM output.

CDI, *Clostridium difficile* infection; IgG-B, endogenous immunoglobulin G to toxin B; PBO, placebo; rCDI, recurrent *Clostridium difficile* infection; RSE, relative standard error.

Exposure-Response for CDI Recurrence

- Following construction of the placebo-response model, treatment effects were tested on λ and α parameters, which both resulted in significant drops in OFV. However, after inclusion of the treatment effect on λ, addition of a treatment effect on α did not significantly improve fit. Guided by the results of the treatment effect model, exposure effects were only evaluated on λ
- The E-R relationship for BEZ exposure ($AUC_{0\text{-inf}}$) and rCDI rate was characterized with an E_{max} relationship
- The $AUC_{0\text{-inf}}$ associated with 50% maximal response ($EAUC_{50}$) could not be precisely estimated. As $EAUC_{50}$ must fall between exposures corresponding to 0–6 mg/kg (below range of exposures achieved at 10 mg/kg), $EAUC_{50}$ was fixed at 100 µg.h/mL for subsequent model development. Higher $EAUC_{50}$ values (>1,000 µg.h/mL) corresponded to a poorer model fit than lower values
  - This indicated that the exposures achieved at the 10 mg/kg dose in Phase 3 trials were on the maximal response plateau of the E-R curve
- Based on the SCM, only endogenous IgG-B was identified as a significant covariate affecting the E_{max} of the E-R model (ΔOFV -13.6; p = 2.19E-04)
- The final E-R model was parameterized as follows:
  - $h_o(t) = \lambda * \exp(\alpha * T)$

$$\lambda_i = \lambda_{TV} * (1 + cov_{age} * (AGE - 66.0)) * (1 + cov_{endIgGB}) * (1 + cov_{histCDI}) * (1 + cov_{hospitalization}) * (1 + cov_{gender}) * (1 + cov_{Charlson\ index}) * \left(1 + \frac{E_{max} * (1 + COV_{trt,endIgGB}) * AUC_{inf}}{EAUC_{50} + AUC_{inf}}\right)$$

$$\alpha_i = \alpha_{TV} * (1 + cov_{antibiotics\ use})$$

Where λ_i, α_i, λ_{TV} and α_{TV} are the individual and population model parameters of the hazard function. cov_{age}, $cov_{endIgGB}$, $cov_{histCDI}$, $cov_{hospitalization}$, cov_{gender}, $cov_{Charlson\ index}$, and $cov_{antibiotics\ use}$ are covariate effects for age, endogenous IgG-B, history of CDI in the past 6 months, hospitalization, gender, CCI, and concomitant use of systemic antibiotics on the placebo hazard model parameters, respectively. E_{max} is the maximum response, and $EAUC_{50}$ is the AUC_{inf} associated with 50% maximal response. $cov_{trt,endIgGB}$ represents the endogenous IgG-B effect on E_{max}

- Parameter estimates of the final E-R model are summarized in **Table 2**
  - BEZ treatment lowered the hazard for rCDI, reflected by a decrease in the hazard baseline parameter
  - Endogenous IgG-B impacted the extent to which participants benefited from BEZ treatment; BEZ treatment resulted in a decrease of 30.0% in λ for participants with a high endogenous IgG-B titer. For participants with a low endogenous IgG-B titer, the decrease in λ was 65.4% (30.0% * [1+1.18])
- The exposure effect could be described similarly with a constant treatment effect, confirming that exposures achieved at the 10 mg/kg dose are all equally effective (**Table 2**)

Table 2. Parameter Estimates for the Final Bezlotoxumab Treatment and Exposure-Response Model for the Recurrence of *Clostridium difficile* Infection

Parameter	Treatment Model		E-R Model	
	Estimate[a]	%RSE[a]	Estimate[a]	%RSE[a]
λ	0.0175	12%	0.0175	12%
Age – continuous	0.0084	26%	0.0084	26%
Endogenous IgG-B – low titer	0.414	43%	0.414	43%
History of CDI in past 6 months – yes	0.907	20%	0.907	20%
Hospitalization – outpatients	0.374	35%	0.374	35%
Gender – male	-0.156	50%	-0.156	50%
Charlson Comorbidity Index – Score ≥3	-0.209	36%	-0.210	36%
Treatment	-0.299	26%		
Endogenous IgG-B – low titer	1.18	50%		
E_{max}			-3.00	26%
Endogenous IgG-B – low titer			1.18	50%
$EAUC_{50}$ (µg.h/mL)			100 FIX[b]	
α	-0.0567	7%	-0.0567	7%
Concomitant use of systemic antibiotics – yes	-0.220	32%	-0.220	32%

[a]Parameter estimates and RSE were derived from the NONMEM output.

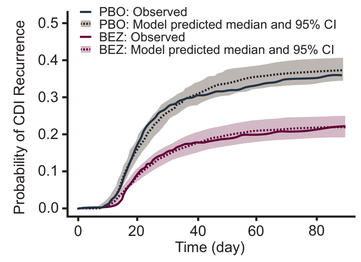
[b]$EAUC_{50}$ was fixed at 100 µg.h/mL for subsequent model development.

CDI, *Clostridium difficile* infection; $EAUC_{50}$, area under the concentration versus time curve at which 50% of effect is obtained; E_{max}, maximum effect; E-R, exposure response; IgG-B, endogenous immunoglobulin G to toxin B; RSE, relative standard error.

Final Model Evaluation

- Model predicted survival curves for pooled BEZ treated and untreated participants were in good agreement with the 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**)

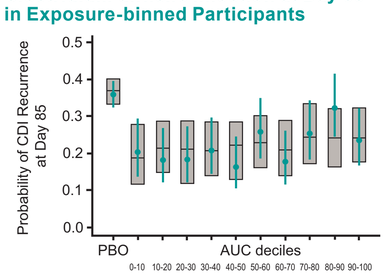
Figure 2. Observed and Model-predicted Survival Curves Based on the Final Exposure-Response Model for the Pooled Placebo and Bezlotoxumab Groups



Solid line: observed survival; dashed line + shaded area: model-based survival (median and 95% prediction interval).

BEZ, bezlotoxumab; CDI, *Clostridium difficile* infection; CI, confidence interval; PBO, placebo.

Figure 3. Visual Predictive Check, Comparing Observed and Model-predicted Incidence of the Recurrence of *Clostridium difficile* Infection at Day 85 in Exposure-binned Participants

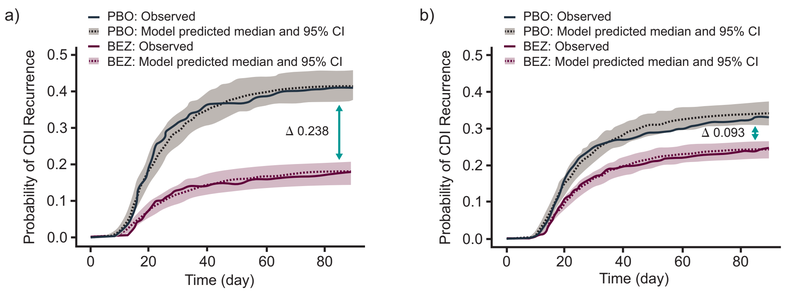


Blue marker: observed CDI recurrence incidence and 95% CI; grey area: model-based CDI recurrence incidence (median and 95% prediction interval).

AUC, area under the concentration versus time curve; CDI, *Clostridium difficile* infection; CI, confidence interval; PBO, placebo.

- Survival curves stratified by treatment and by endogenous IgG-B titer showed that low-titer participants derived greater benefit from BEZ treatment compared with high-titer participants (rCDI reduction of 23.8% and 9.3%, respectively) (**Figure 4**)

Figure 4. Observed and Model-predicted Survival Curves for Pooled Bezlotoxumab and Placebo Groups in the a) Low Endogenous IgG-B Titer Sub-population and b) High Endogenous IgG-B Titer Sub-population



Solid line: observed survival; dashed line + shaded area: model-based survival (median and 95% prediction interval); blue arrow: absolute change in CDI recurrence rate at Day 85.

BEZ, bezlotoxumab; CDI, *Clostridium difficile* infection; CI, confidence interval; IgG-B, endogenous immunoglobulin G to toxin B; PBO, placebo.

CONCLUSIONS

- TTE analysis is a less biased method of analyzing rCDI data than logistic regression, as it does not make inferences about study-discontinued participants; avoiding introduction of confounding effects of albumin and BEZ exposure
- The TTE model for rCDI consisted of a Gompertz placebo hazard model with age, endogenous IgG-B, history of CDI in the previous 6 months, hospitalization, gender, and CCI affecting λ and the concomitant use of systemic antibiotics affecting α
- The E-R relationship for BEZ and rCDI was characterized by an E_{max} model, where high survival rates were associated with the entire range of exposures observed at the 10 mg/kg dose
- Endogenous IgG-B was the only covariate that significantly impacted the E_{max}, suggesting that individuals with low IgG-B titers may derive greater benefit from BEZ treatment compared with individuals with high IgG-B titers
  - Low titers of endogenous neutralizing antitoxin antibodies are a risk factor for rCDI;[5,6] BEZ is hypothesized to reduce rCDI risk by neutralizing *C. difficile* toxin B and bolstering the immune response to CDI
- The E-R effect was equally well described with a fixed treatment effect, confirming that the exposures achieved at the 10 mg/kg dose are all equally effective
- This TTE analysis accounted for time of rCDI and discontinuation without the need for imputation of the endpoint
  - Unlike the previous E-R analysis, the participant covariates that affected the baseline hazard were more causal and easier to interpret clinically. These results suggest that the apparent trend observed between increasing BEZ exposure and rCDI rate in the logistic regression analysis was caused by imputation of study-discontinued participants as having no rCDI, together with the association between BEZ exposure and participant covariates (ie albumin)
- These results support the conclusion of the previous E-R analysis, where exposures achieved at the 10 mg/kg dose are on the plateau of the E-R curve

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