Pharmacodynamic modeling and exposure-response assessment of inebilizumab in subjects with neuromyelitis optica spectrum disorders

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Disclosures

- **L. Yan, D. She, D. Cimbora, E. Katz** and **W.A. Rees** are employees of Viela Bio
- **B. Wang, B. Mitchel** and **R. Criste** are employees of Amador Bioscience. Amador Bioscience reports payment for consultation from Viela Bio
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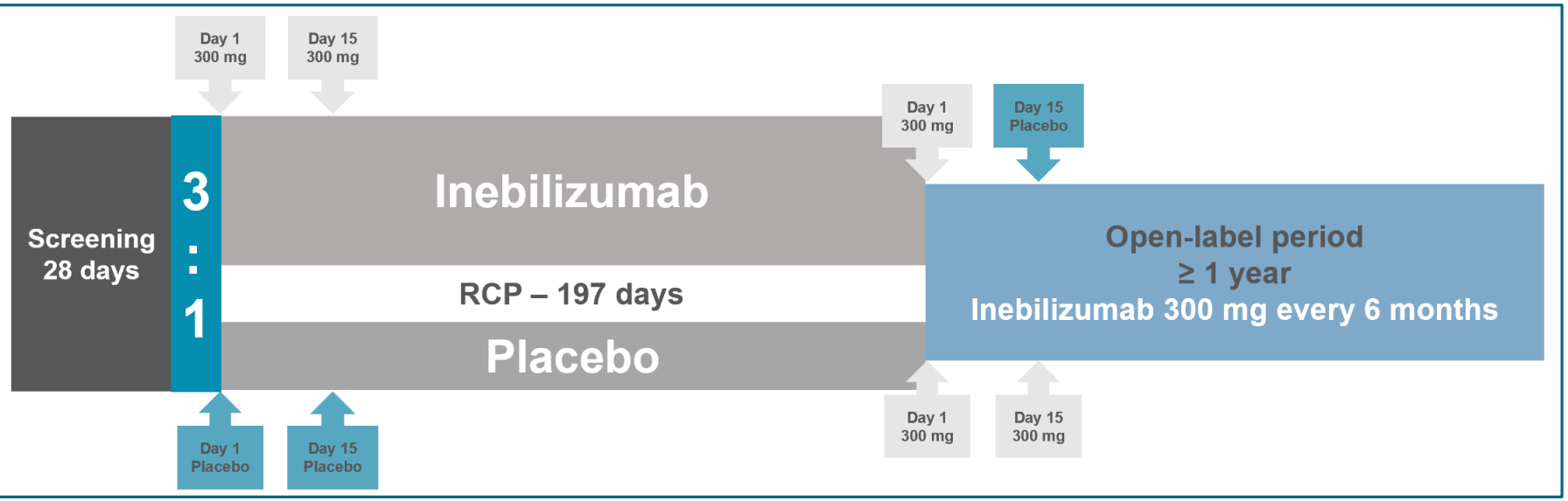
Background and Study Design

- Neuromyelitis optica spectrum disorder (NMOSD) is an autoantibody-mediated, B cell-driven disease
- Compared to CD20, CD19 is expressed on a wider range of the B cell lineage, from pro-B to plasmablasts and some plasma cells
- Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1κ monoclonal antibody that binds to CD19 resulting in effective depletion of B cells

Study NCT02200770 is a multicenter, double-blind, randomized, placebo-controlled, phase 2/3 study assessing the efficacy and safety of inebilizumab in patients with NMOSD[1]



NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period

1. Cree BAC et al. Lancet 2019;394:1352–63;

Objective and Methods

Objectives	• To conduct population modeling of B cell response following inebilizumab treatment in adult subjects with NMOSD • To assess the impact of drug exposure to efficacy outcomes
Methods	• A hematopoietic transit model was developed to describe the depletion of circulating CD20+ B cell by inebilizumab • As the subjects were randomized in a 3:1 ratio to receive inebilizumab or placebo treatment in the RCP, inebilizumab-treated subjects were grouped by tertiles based on the PK exposure (low, medium and high) to achieve comparable sample size as the placebo group for time-to-event analysis • The relationships between inebilizumab pharmacokinetic (PK) exposure and the primary and key secondary efficacy endpoint were evaluated by comparing the efficacy outcome of inebilizumab-treated subjects of low, medium and high PK exposure with placebo in the RCP. Kaplan-Meier plots and forest plots were generated to facilitate the assessments of the E-R relationship

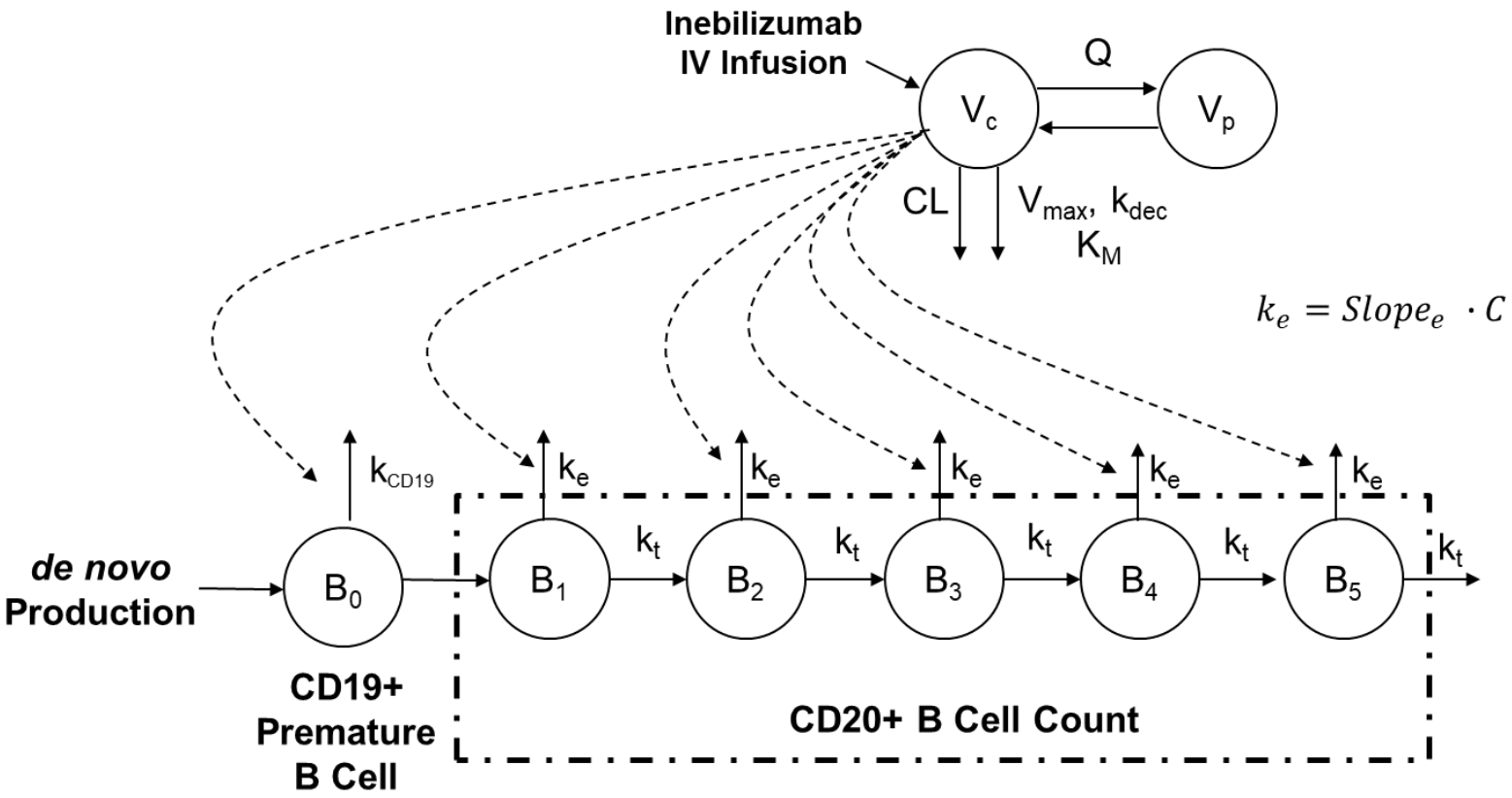
NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period.

Results

- Treatment with inebilizumab led to rapid, profound, and sustained depletion of circulating B cells in NMOSD patients
- Circulating CD20+ B cell count data was best described by a transit model with inebilizumab depleting CD20+ B cells in each aging compartment as well as premature (CD19+/CD20-) B cells
- Baseline CD20 count was a covariate on inebilizumab effect; ADA, demographic covariates and AQP4 status had no impact on PD response to inebilizumab treatment
- At the 300 mg dose, there was no apparent relationship between efficacy (reduction in disease attack risk, worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and number of NMOSD-related in-patient hospitalizations) with PK exposure
- Body weight has no apparent impact on primary and key secondary efficacy endpoints
- Subjects with low, medium and high PK exposure had a similar hazard ratio of AC-determined NMOSD attack for inebilizumab, confirming that the 300 mg fixed dose of inebilizumab resides at the efficacy plateau

ADA: anti-drug antibodies; AQP4: autoantibodies against aquaporin-4; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; PK: pharmacokinetics

Pharmacodynamic Model of Inebilizumab

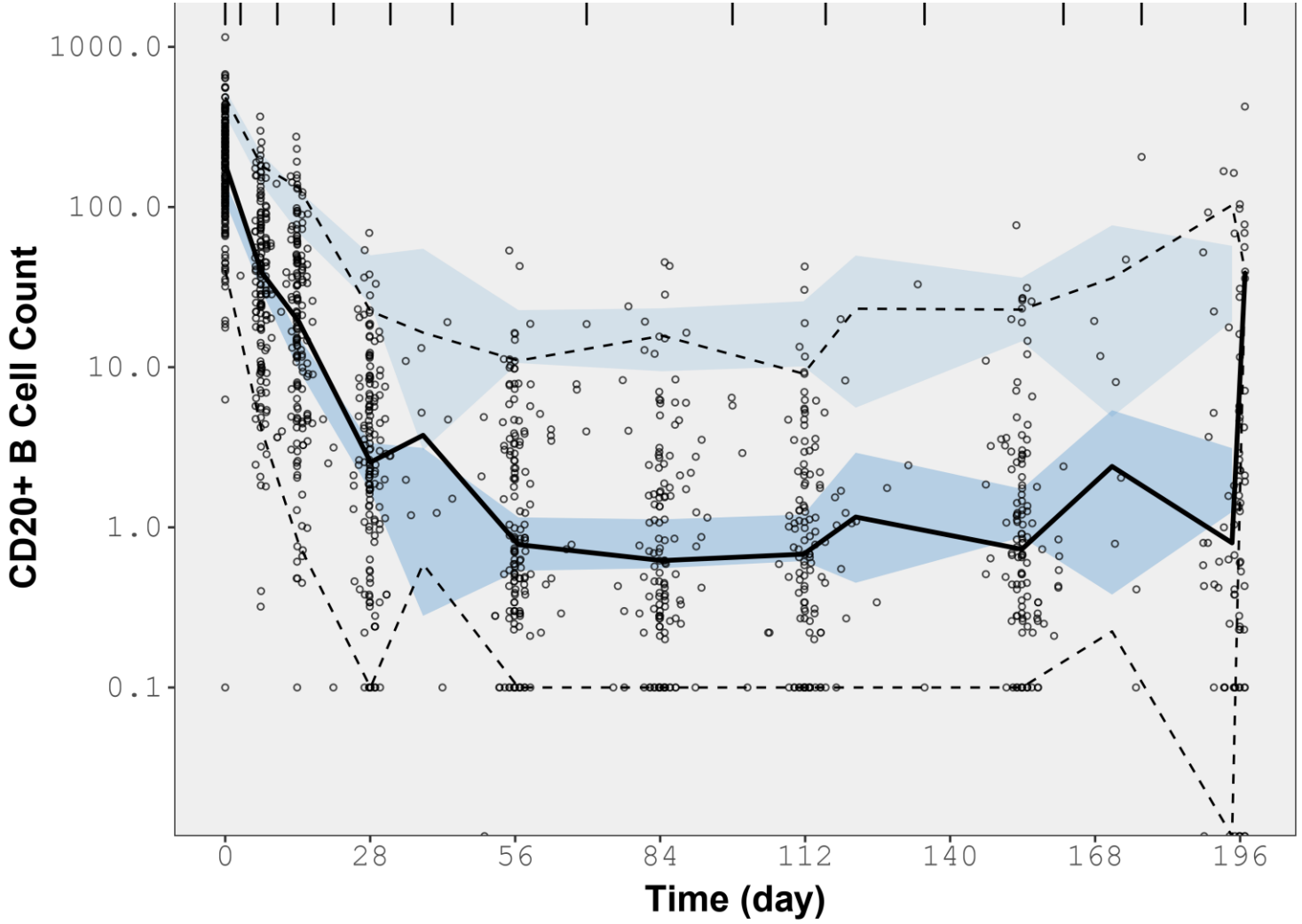


Inebilizumab depletes CD19+ premature B cells and mature CD20+ B cells in peripheral blood

Parameter	Population Estimate	Standard Error
Slope	0.0140	0.0006
Effect of baseline CD20 on slope [a]	0.272	0.051
Lifespan (d)	391	50.2
Baseline CD20	135	6.08
k_{CD19}	0.0751	0.0103
Interindividual variability[b]		
η_{Slopee}	51.8	3.3
$\eta_{Lifespan}$	126	10
$\eta_{Baseline\ CD20}$	59.2	3.9
η_{kcd19}	110	17
Residual variability		
Proportional error [b]	60.8	1.6

[a] Natural exponents
[b] Displayed as %CV

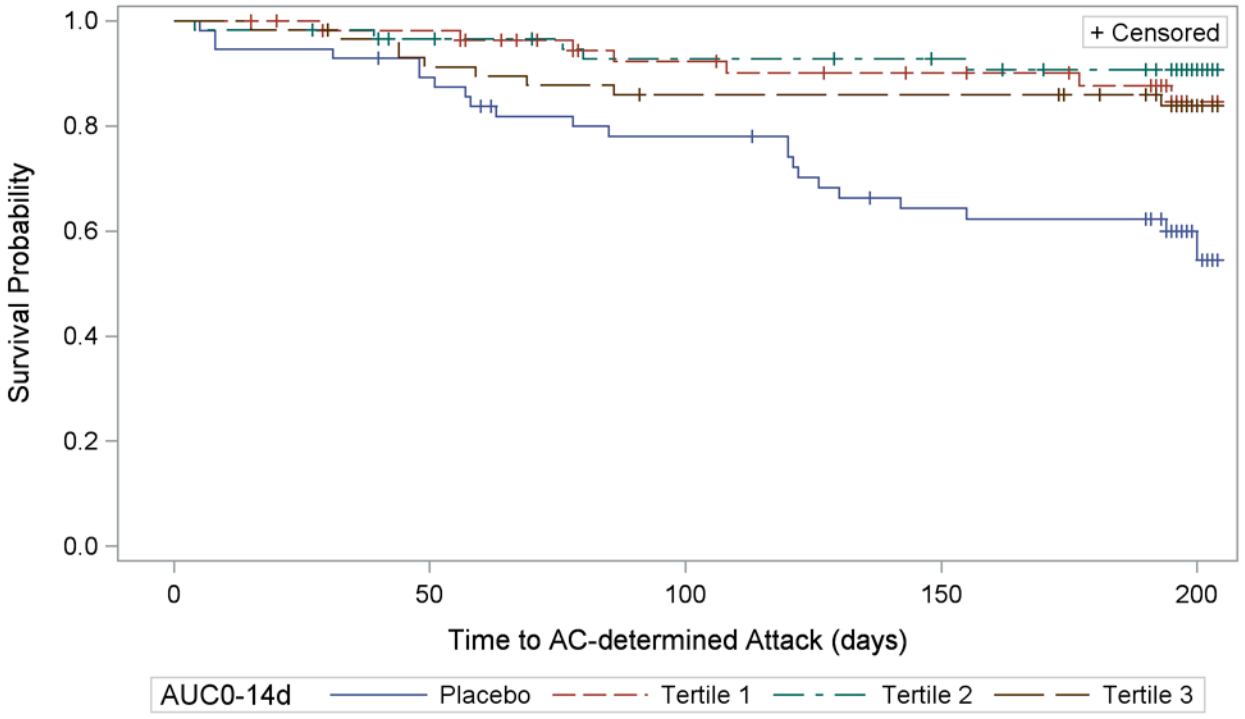
Observed and Model-Predicted CD20 B Cell Counts



Symbol: observed CD20+ B cell count; Black solid and dotted lines: observed median, 5th and 95th percentiles; Shaded area: 90% confidence interval of predicted median, 5th and 95th percentiles from 200 clinical simulations

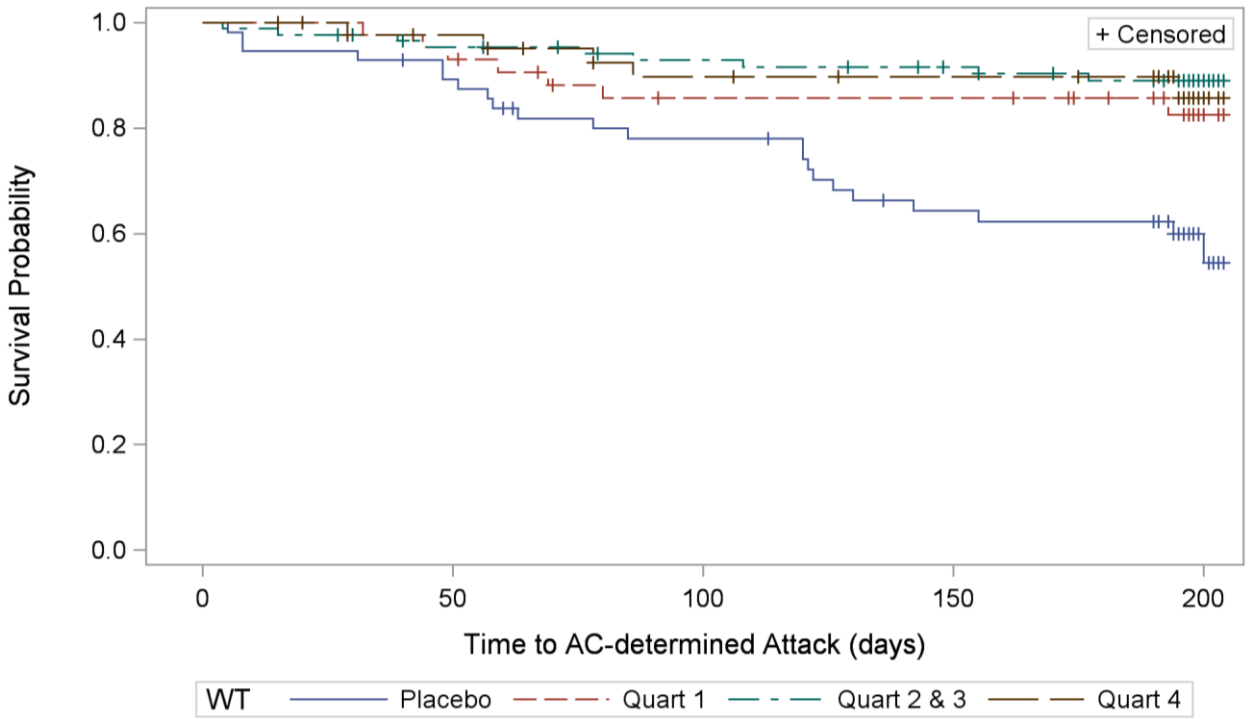
Subjects with different PK exposure and body weight had a similar hazard ratio of AC-determined NMOSD attack for 300 mg inebilizumab vs placebo

Kaplan-Meier (Survival) Plot for Time to AC-Determined NMOSD Attack During the RCP in Placebo and Inebilizumab-Treated Subjects with Low, Medium and High AUC_{0-14d}



Placebo	56	49	41	32	11
Tertile 1	58	54	44	39	9
Tertile 2	58	53	49	47	17
Tertile 3	58	52	48	48	14

Low, Medium and High Body Weight

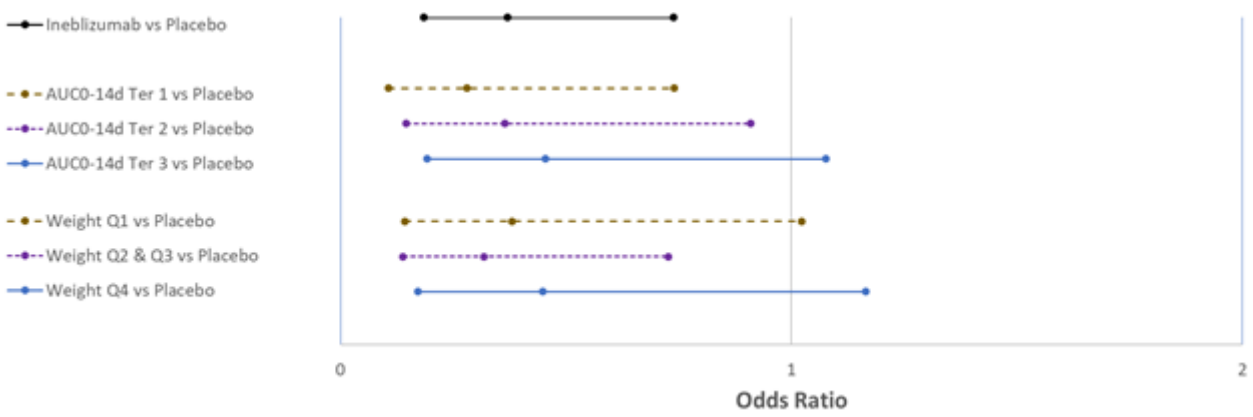


Placebo	56	49	41	32	11
Quart 1	43	40	33	33	8
Quart 2 & 3	87	80	75	71	23
Quart 4	44	39	33	30	9

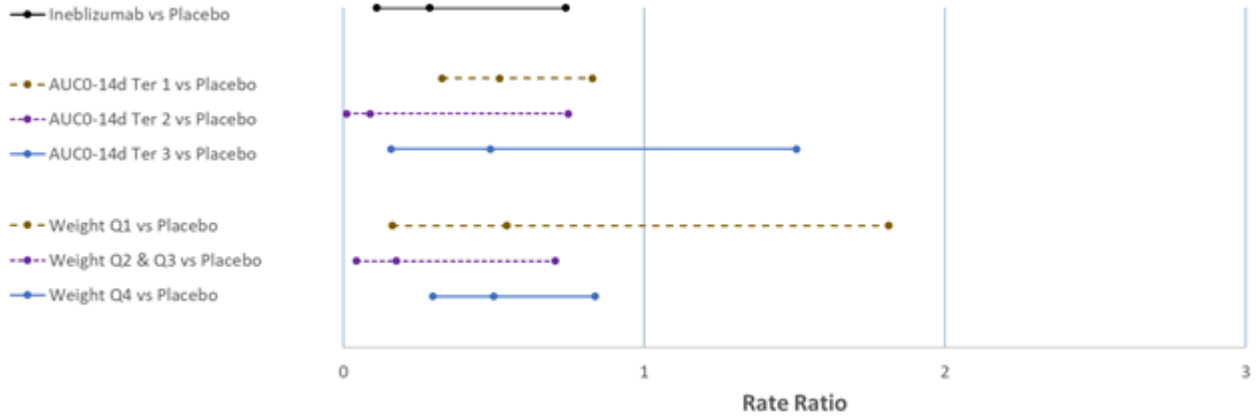
AUC_{0-14d}: area under the concentration-time curve from time 0 to 14 days postdose; NMOSD, neuromyelitis optica spectrum disorder; PK: pharmacokinetics; RCP, randomized controlled period; Quart 1= inebilizumab treated subjects with lowest quartile body weight; Quart 2 & 3 = inebilizumab-treated subjects with interquartile range (2nd and 3rd Quartile) of body weight; Quart 4 = inebilizumab-treated subjects with large quartile of body weight. Tertile 1 = 300mg inebilizumab-treated subjects with low AUC_{0-14d}; Tertile 2 = 300mg inebilizumab-treated subjects with medium AUC_{0-14d}; Tertile 3 = 300mg inebilizumab-treated subjects with high AUC_{0-14d}; The numbers under the legend represent the corresponding number of subjects for placebo

Subjects with different PK exposure and body weight have similar secondary efficacy outcomes: efficacy plateaued at the 300mg dose

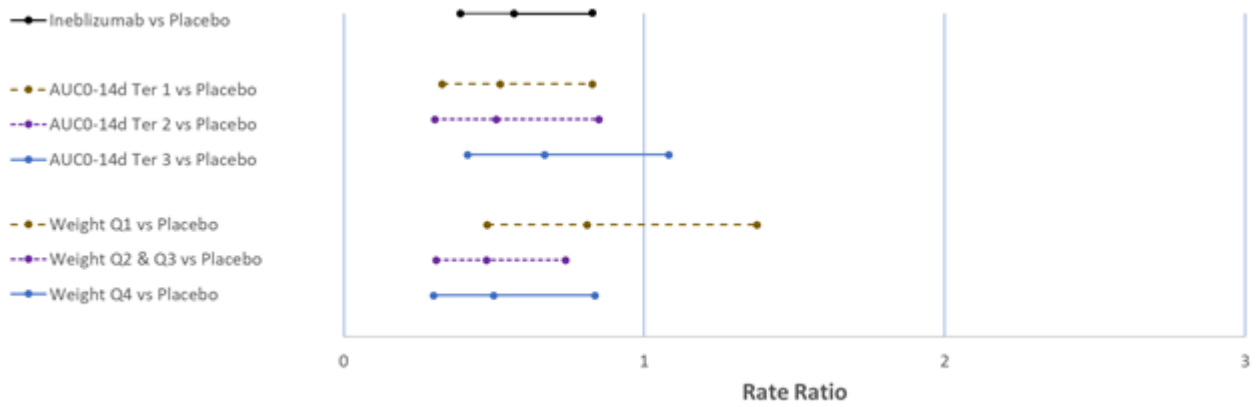
Forest Plot of Worsening from Baseline in EDSS During the RCP



Forest Plot of Number of NMOSD-Related In-Patient Hospitalization During the RCP



Forest Plot of the Cumulative Number of Active MRI Lesions During the RCP



EDSS: Expanded disability Status Scale; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; PK: pharmacokinetics; RCP, randomized controlled period

Conclusions

- **The pharmacodynamic modeling and exposure-response analyses of primary and key secondary endpoints confirmed effective depletion of B cells is achieved with 300 mg dose administered as an IV infusion on Day 1 and Day 15 and every 6 months thereafter**
- **The PK variability between patients had no apparent effect on the hazard ratio for NMOSD attack**
- **At the efficacy plateau, the potential impact of PK variability was reduced, there was no apparent effect of body weight or the presence of ADA on the primary efficacy endpoint**
- **300mg fixed dose of IV inebilizumab is the optimal dosage for the treatment of NMOSD, no dosage adjustment by body weight is warranted**

ADA: anti-drug antibodies; NMOSD, neuromyelitis optica spectrum disorder; PK: pharmacokinetics