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

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Abstract

BACKGROUND AND PURPOSE: Neuromyelitis optica spectrum disorders (NMOSD) is an autoantibody-mediated, B cell-driven disease. Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody that binds to the B cell specific surface antigen CD19, resulting in rapid, profound, and sustained depletion of circulating peripheral B cells in NMOSD subjects (pivotal study). The objective of this study was to conduct population modeling of B cell response following inebilizumab treatment in adult subjects with NMOSD, and to assess the impact of drug exposure to outcome. EXPERIMENTAL APPROACH: A hematopoietic transit model was developed to describe the joint effects of reducing influx from pro-B cells and accelerating CD20+ B cell depletion in the blood by inebilizumab. Furthermore, the relationships between inebilizumab pharmacokinetic (PK) exposure and the primary efficacy endpoint and key secondary efficacy endpoints were evaluated. KEY RESULTS: At the 300 mg dose, there was no apparent relationship between efficacy (reduction in disease attack risk, risk of worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and the number of NMOSD-related in-patient hospitalizations) and PK exposure. Subjects with low, medium, and high PK exposure had a similar hazard ratio of NMOSD attack vs Placebo group. CONCLUSION AND IMPLICATIONS: The pharmacodynamic modeling confirmed effective depletion of B cells is achieved with a 300 mg intravenous dose of inebilizumab administered on Day 1 and Day 15 and every 6 months thereafter. The PK variability between patients had no apparent effect on clinical efficacy.

Running Title: Inebilizumab pharmacodynamic modeling and exposure-response assessment

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ABSTRACT (250 word limit)

BACKGROUND AND PURPOSE : Neuromyelitis optica spectrum disorders (NMOSD) is an autoantibody-mediated, B cell-driven disease. Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody that binds to the B cell specific surface antigen CD19, resulting in rapid, profound, and sustained depletion of circulating peripheral B cells in NMOSD subjects (pivotal study). The objective of this study was to conduct population modeling of B cell response following inebilizumab treatment in adult subjects with NMOSD, and to assess the impact of drug exposure to outcome.

EXPERIMENTAL APPROACH : A hematopoietic transit model was developed to describe the joint effects of reducing influx from pro-B cells and accelerating CD20+ B cell depletion in the blood by inebilizumab. Furthermore, the relationships between inebilizumab pharmacokinetic (PK) exposure and the primary efficacy endpoint and key secondary efficacy endpoints were evaluated.

KEY RESULTS : At the 300 mg dose, there was no apparent relationship between efficacy (reduction in disease attack risk, risk of worsening from baseline in Expanded Disability Status Scale, cumulative total active MRI lesions, and the number of NMOSD-related in-patient hospitalizations) and PK exposure. Subjects with low, medium, and high PK exposure had a similar hazard ratio of NMOSD attack vs Placebo group.

CONCLUSION AND IMPLICATIONS : The pharmacodynamic modeling confirmed effective depletion of B cells is achieved with a 300 mg intravenous dose of inebilizumab administered on Day 1 and Day 15 and every 6 months thereafter. The PK variability between patients had no apparent effect on clinical efficacy.

Bullet point summary: (Each bullet point should have a maximum of 15 words)

What is already known –

Inebilizumab binds to CD19 and depletes peripheral B cells in NMOSD subjects

What this study adds –

300 mg efficacy plateau dose minimizes the impact of PK variability on inebilizumab efficacy

Clinical significance –

300 mg inebilizumab was determined to be the optimal dosage for the treatment of NMOSD

Abbreviations:

AC, Adjudication Committee; ADA, anti-drug antibodies; AUC, area under the concentration-time curve; CI, confidence interval; CL, clearance; CWRES, conditionally weighted residual over time; IPRED, individual

predictions; LLOQ, lower limit of quantitation; NMOSD, neuromyelitis optica spectrum disorder; OLP, open-label period; PK, pharmacokinetic(s); PD, pharmacodynamic(s); PRED, population predictions; RCP, randomized control period

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an autoantibody-mediated, B cell-driven disorder of the central nervous system characterized by attacks of predominantly optic neuritis and longitudinally extensive transverse myelitis. An important feature of NMOSD is the presence of serum autoantibodies against aquaporin-4, such as aquaporin-4-IgG, which is detected in about 80-90% of NMOSD patients (Jarius & Wildemann, 2010). Pathogenic aquaporin-4-IgG can be produced by a subpopulation of CD19-positive ($CD19^+$) CD20-negative ($CD20^-$) B cells showing morphological and phenotypical properties of plasmablasts, which are selectively increased in peripheral blood in NMOSD patients (Chihara et al, 2011). Results of small, uncontrolled studies of the anti-CD20 monoclonal antibodies rituximab have provided some evidence for the therapeutic effect of B cell depletion in NMOSD (Cree et al, 2005; Jacob et al, 2008; Bedi et al, 2011; Kim et al, 2011; Ip et al, 2013). Compared to CD20, CD19 is expressed on a wider lineage of B cells, from pro-B to plasmablasts and some plasma cells. Direct depletion of $CD19^+$ B cells could be more effective in reducing the risk of NMOSD attack by more effectively depleting plasmablasts producing aquaporin-4-IgG.

Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody that binds to the B cell specific surface antigen CD19 resulting in the depletion of B cells, as well as plasmablasts and some plasma cells. Unlike the anti-CD20 monoclonal antibody rituximab, inebilizumab does not mediate complement dependent cytotoxicity (Herbst et al, 2010). The removal of fucose from the monoclonal antibody Fc results in approximately 10-fold increased affinity for the activating Fc gamma receptor IIIA and significantly enhances natural killer cell-mediated depletion of B cells via antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis mechanisms.

In a multicenter, double-blind, randomized, placebo-controlled Phase 2/3 study in adults with NMOSD (NCT02200770, N-MOmentum), inebilizumab treatment significantly reduced the onset of NMOSD attack (hazard ratio 0.272, $p<0.0001$ (Cree BAC et al, 2019). The objectives of this analysis were (1) to develop a population pharmacodynamic (PD) model describing the depletion of the peripheral B cell count by inebilizumab, and (2) to evaluate the relationship between inebilizumab pharmacokinetic (PK) exposure and efficacy endpoints in subjects with NMOSD.

Methods

Patients and trial designs

The peripheral B cell count data were obtained from two randomized, double-blind, placebo-controlled Phase 1 studies (MI-CP200 [Study CP200] and CD-IA-MEDI-551-1102 [Study 1102]) and one multicenter, double-blind, randomized, placebo-controlled Phase 2/3 study (N-MOmentum). Summary of all clinical studies and the descriptive statistics of baseline categorical and continuous covariates are listed in Table 2 and Table 3, respectively.

Each Phase 1 study involved with 28 adult subjects with either Systemic Sclerosis who had at least moderate skin thickening in an area suitable for repeat biopsy (Study CP200) or with relapsing forms of Multiple Sclerosis (Study 1102). Subjects with Systemic Sclerosis were administered with single intravenous dose (0.1, 0.3, 1.0, 3.0, and 10.0 mg kg^{-1}) of inebilizumab or placebo; subjects with relapsing Multiple Sclerosis were either administered with two doses of inebilizumab (30, 100, or 600 mg) or placebo on Day 1 and 15 intravenously or administered a single dose of inebilizumab (60 or 300 mg) or placebo subcutaneously.

In a Phase 2/3 study (N-MOmentum), comprised of a randomized controlled period (RCP) with an open-label extension period (OLP), a total of 230 adult subjects with NMOSD were intravenously administered inebilizumab (300 mg) or placebo on study Day 1 and 15 in the RCP. Subjects who experienced an Adjudication Committee (AC) determined attack in the RCP, or who completed the Day 197 visit without an

attack, exited the RCP and had the option to enroll into the OLP, and initiate or continue treatment with inebilizumab. The trial design schematic is shown in Figure 1.

Pharmacodynamic modeling

The PD effect of inebilizumab on B cells is assayed by measuring $CD20^+$ B cell counts, as inebilizumab interferes with CD19-based detection methods. A hematopoietic transit model was developed to describe the depletion of circulating B cell count data by inebilizumab in adults. The PD effect of inebilizumab was exerted by joint effects of reducing influx from pro-B cells and accelerating $CD20^+$ B cell depletion in the blood, as the following differential equations demonstrate:

$$\frac{dB_0}{\mathrm{dt}} = S_0 - k_{\mathrm{CD19}} \cdot B_0 - k_{\mathrm{inebi}} \cdot B_0 \quad \text{Equation 1}$$

$$\frac{dB_1}{\mathrm{dt}} = k_{\mathrm{CD19}} \cdot B_0 - \frac{n}{\Lambda} \cdot B_1 - k_{\mathrm{inebi}} \cdot B_1 \quad \text{Equation 2}$$

$$\frac{dB_i}{\mathrm{dt}} = \frac{n}{\Lambda} \cdot (B_{i-1} - B_i) - k_{\mathrm{inebi}} \cdot B_i \quad \text{Equation 3}$$

In the above equations, n is the number of transit compartments and Λ represents the longevity (lifespan) of blood $CD20^+$ B cells. S_0 is the influx rate of pro-B cells (B_0), and the total CD20+ B cell count in the blood (B_{CD20}) is calculated as the sum of $CD20^+$ B cells in all aging compartments (B_i, i =1 to n):

$$B_{\mathrm{CD20}} = \sum_{i=1}^{n} B_i \quad \text{Equation 4}$$

The rate constant k_{CD19} represents the maturation of pro-B to $CD20^+$ B cells in the circulation. Initially k_{inebi}, the accelerated removal of $CD19^+$ pro-B and mature B cells by inebilizumab, was described using an asymptotic E_{max} function. However, the estimated EC_{50} (inebilizumab concentration corresponding to half-maximal B cell depletion) was less than the assay LLOQ, due to the high potency of inebilizumab. As such, a log-linear relationship was used to describe the effect of inebilizumab on depletion of pro-B and mature B cells in blood:

$$k_{\mathrm{inebi}} = \mathrm{slope} \bullet \log C \quad \text{Equation 5}$$

Where C represents the serum concentration of inebilizumab. From population modeling, the PD model with dual activity of inebilizumab to deplete pro-B and mature B cells was superior to the transit model where inebilizumab only depleted the circulating $CD20^+$mature B cells. The final PD model structure is shown in Figure 2.

Pooled CD20+ B cell data from adult subjects previously diagnosed with Systemic Sclerosis (Study CP200), Multiple Sclerosis (Study 1102) and NMOSD (RCP of N-MOmentum) were simultaneously modeled. Demographic covariate screening was performed using generalized additive models implemented in an R package XPOSE4.

Exposure-response relationship

As the subjects were randomized in a 3:1 ratio to receive inebilizumab or placebo treatment in the RCP of N-MOmentum, inebilizumab-treated subjects were grouped by tertiles based on the PK exposure (low, medium, and high) to achieve a comparable sample size to the placebo group for time-to-event analysis. Three PK metrics, namely area under the concentration-time curve following the first dose ($AUC_{0\text{-}14d}$), the cumulative AUC to the last observation in the RCP ($AUC_{cumulative}$), and the systemic clearance (CL) of the first-order elimination pathway, were obtained from the population PK modeling. The relationship between PK exposure and the primary efficacy endpoint (AC-determined NMOSD attack) was evaluated by comparing the efficacy outcome of inebilizumab-treated subjects of low, medium and high PK exposure with placebo in RCP. In addition, a statistically significant improvement with inebilizumab compared to placebo as demonstrated by three key secondary endpoints: worsening from baseline to the last visit of the RCP in Expanded Disability Severity Scale, cumulative total active MRI lesions during the RCP, and number of NMOSD-related in-patient hospitalizations during the RCP.

Potential impacts of body weight, a known PK covariate for therapeutic monoclonal antibodies, and the presence of anti-drug antibodies (ADA) were also assessed on the efficacy outcomes of the pivotal study.

Results

Subjects

In a randomized, double-blind, placebo-controlled Phase 2/3 trial (N-MOmentum), 56 subjects with NMOSD received intravenous infusions of placebo and 174 subjects received inebilizumab (300 mg) on study Day 1 and 15 in the randomized controlled period (RCP, Figure 1). To aid the pharmacodynamic evaluation, peripheral CD20+ B cell count data from two dosing-ranging Phase 1 studies in inebilizumab-treated subjects with Systemic Sclerosis (n=24) or Multiple Sclerosis (n=15) were pooled with that in subjects with NMOSD for population PD modeling. Overview of studies and descriptive statistics of baseline demographics of these subjects are summarized in Tables 1 and 2, respectively.

Pharmacodynamic modeling

The pharmacodynamics of inebilizumab were assessed with an assay for peripheral CD20+ B cells, since inebilizumab interferes with the CD19+ B cell assay. A hematopoietic transit model in which inebilizumab reducing influx from pro-B cells and accelerating $CD20^+$ B cell depletion in the blood was developed to describe the PD effect (Figure 2). The parameter estimates from the final model are summarized in Table 3. The estimated typical baseline CD20+ B cell count and lifespan were 135 cells per μL and 391 days, respectively. Only baseline B cell count was identified as a relevant PD covariate: higher baseline count was associated with more prominent B cell depletion by inebilizumab. Other covariates including age had no impact on the PD of inebilizumab.

The basic goodness-of-fit plots of the final PD model are shown in Figure S1. The conditionally weighted residual (CWRES) over the population predictions (PRED) is shown in Figure S1A to evaluate the model fit. The observations (dependent variables, DV) over the PRED and individual predictions (IPRED) are shown in Figure S1B and S1C, respectively, to diagnose any misspecification of the structural model. The spread of the CWRES is relatively consistent across the PRED range, while the regression lines in Figure S1B and S1C are close to the line of identity, indicating appropriate specification of the model structure and good model fit of the data.

The visual predictive check plots by study are presented in Figure 3. The symbol represents the observed $CD20^+$ B cell count; the black solid and dotted lines represent the observed median at 5th and 95th percentiles, the shaded area represents the 90% confidence interval (CI) of predicted median, 5th and 95th percentiles from 200 clinical simulations.

Exposure-response assessment for NMOSD attack

The Kaplan-Meier plot of AC-determined NMOSD attacks during the RCP in placebo and inebilizumab-treated subjects with low (first-tertile), medium (second tertile) and high (third tertile) $AUC_{0\text{-}14d}$ is shown in Figure 4. Subjects with low and medium $AUC_{0\text{-}14d}$ shown higher probability on attack-free period compared to subjects with high $AUC_{0\text{-}14d}$ and placebo. The AUC following the first dose was selected for the exposure-response (E-R) assessment since the steady-state PK data were unavailable. Per protocol, subjects experiencing NMOSD attack exited the RCP and had the option to enroll into the OLP to initiate or continue to receive inebilizumab treatment, resulting in incomplete PK profiles following the 2nd dose in those who discontinued treatment in the RCP. There was no apparent relationship between the hazard ratio for the primary endpoint with $AUC_{0\text{-}14d}$. There was no apparent relationship between the hazard ratio of NMOSD attack for inebilizumab relative to placebo during the RCP with the first dose AUC of inebilizumab.

Although body weight was identified as a PK covariate from the population modeling, with the 300 mg dose residing on the efficacy plateau, there were no clear trends in efficacy across the different quartiles of body weight (Figure 5). Based on the analysis of the primary efficacy endpoint, the adjustment of inebilizumab fixed dose (300 mg) by body weight is not warranted. The presence of ADA was detected in 25 subjects (8

of 56 placebo, 17 of 174 inebilizumab treatment groups) at baseline or during the RCP. From population modeling, the development of ADA had no significant effect on the PK of inebilizumab. No apparent effect of the presence of ADA on B cell depletion by inebilizumab treatment in the RCP or the primary efficacy endpoint was observed.

Exposure-response assessment for key secondary endpoints

Results of the subgroup analysis in each of the three key secondary endpoints, worsening from baseline to the last visit of the RCP in Expanded Disability Severity Scale (Figure S2), cumulative total active MRI lesions during the RCP (Figure S3), and number of NMOSD-related in-patient hospitalizations during the RCP (Figure S4), by PK exposure ($AUC_{0\text{-}14d}$ or CL) were generally consistent with that of the primary endpoint: no apparent relationship between the PK exposure and efficacy outcome in the RCP was observed. In addition, body weight had no apparent effect on key secondary endpoints. The presence of ADA had no observed impact on PK of inebilizumab or the B cell depletion in subjects with NMOSD. Despite the small number of subjects who tested positive for ADA during the RCP, there was no apparent effect of ADA on the key secondary endpoints.

Discussion and Conclusions (1,500 words limit)

Inebilizumab is an affinity-optimized, afucosylated, CD19-directed cytolytic antibody for the treatment of NMOSD, a rare autoimmune disease. Following cell surface binding to B lymphocytes, inebilizumab results in antibody-dependent cellular cytolysis. In a Phase 2/3 study N-MOmentum, 300 mg inebilizumab intravenously administered two weeks apart resulted in profound and persistent peripheral CD20+ B cell depletion and significant reduction in NMOSD attack during the 28-week RCP.

The pharmacokinetics of intravenously administered inebilizumab were adequately described by a 2-compartment model with parallel first-order and time-dependent nonlinear elimination pathways (Yan L et al, submitted). As for other therapeutic monoclonal antibodies, the CL and V_d of inebilizumab increased with body weight: subjects with large body weight tended to have lower PK exposure following fix dose administration. This analysis focused on the evaluation of pharmacodynamics of inebilizumab using a population modeling approach, and exposure-response assessments to evaluate the impact of PK exposure, body weight and the presence of ADA on efficacy endpoints for the treatment of NMOSD.

The pooled $CD20^+$ B cell data from two dose-ranging Phase 1 studies of inebilizumab in subjects with scleroderma and Multiple Sclerosis were initially utilized for exploration of various PD models. Then the B cell data from the pivotal NMOSD study were included for the development of the base model. Further assessments were performed to identify and evaluate demographic covariate effects on B cell response to inebilizumab treatment.

Compared to CD20, CD19 is expressed on a wider lineage of B cells, from pro-B to plasmablasts and some plasma cells. A mechanistic hematopoietic transit model was developed to describe the depletion of peripheral B cell count in adults following inebilizumab treatment. In this model, inebilizumab depletes $CD20^+$ B cells in each aging compartment as well as pro-B in blood. Given the high potency of inebilizumab, EC_{50} (inebilizumab concentration corresponding to half-maximal B cell depletion) could not be reliably estimated. Instead, the pharmacodynamic effect of inebilizumab was described using a log-linear model (Equation 5), which approximates an asymptotic exposure-response relationship when the PK exposure exceeds EC_{50}.

The estimated k_{CD19} was 0.0751 d^{-1}, corresponding to a 13-day residence time of CD19+ pro-B cells before maturation to CD20+ B cells in the circulation. On the other hand, mature CD20+ B cell has a rather long lifespan, with an estimated typical value of 391 days in humans. However, there was a large interindividual variability of CD20+ B cell lifespan across subjects.

Although Systemic Sclerosis subjects in a Phase 1 study (Study CP200) tended to have lower estimate of B cell depletion slope than Multiple Sclerosis and NMOSD subjects, from population analysis the difference was not statistically significant. On the other hand, the effect of inebilizumab on slope increased with baseline

$CD20^+$ B cell count: the effect of inebilizumab was greater in subjects with higher $CD20^+$ B cell count at baseline. ADA, age and other demographic covariates had no impact on PD of inebilizumab.

The goodness-of-fit and visual predictive check plots were used to evaluate the appropriateness of the model structure in predicting the clinical data. Due to the small sample size of each dose group of Phase 1 studies (Studies CP200 and 1102), the prediction bands although captured the depletion and recovering trends of $CD20^+$B cell response, in some regions deviated from the observations (Figure 3). Nevertheless, when the sample size is adequate (N-MOmentum), the B response in adult subjects with NMOSD was well described by the PD model.

There was no apparent relationship of PK exposure ($AUC_{0\text{-}14d}$) to inebilizumab and the outcome of the primary or key secondary efficacy endpoints (Figures 4-5, S2-S4). Results of the exposure-response analyses confirmed that the fixed dose of 300 mg inebilizumab resides at the efficacy plateau for the treatment of NMOSD. In fact, the efficacy was slightly lower in subjects with high $AUC_{0\text{-}14d}$, likely due to random variability across subgroups (Figures 4-5). The relationship of $AUC_{cumulative}$ and time to onset of NMOSD attack during the RCP was skewed since subjects experiencing NMOSD attack exited the RCP and had the option to enter an OLP to receive active inebilizumab treatment per protocol (Figure 5). The early withdrawal from the RCP led to a lower $AUC_{cumulative}$ in subjects that experienced NMOSD attack. In addition, subjects with slow, medium and fast CL of inebilizumab had nearly identical outcomes, confirming that the 300 mg fixed dose of inebilizumab resides at the efficacy plateau (Figure 5).

Although body weight has an impact on PK based on the population PK analysis, it did not affect the inebilizumab efficacy. The 300 mg dose, residing at the efficacy plateau, minimized the impact of PK variability on efficacy outcome. As such, dose-adjustment by body weight is not warranted.

Consistent with the absence of significant impact of ADA on inebilizumab PK, from population modeling and exposure-response assessment, the presence of ADA had no impact on PD (B cell depletion) or efficacy endpoints in subject with NMOSD. However, this conclusion should be taken with caution due to the small number of subjects who tested positive for ADA during the RCP.

The population PD modeling and results of the exposure-response analysis of the primary and key secondary endpoints demonstrate that the 300 mg fixed dose of inebilizumab is an adequate dose to achieve an effective B cell depletion and reduced risk for AC-determined NMOSD attack.

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Data availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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Author contribution statement:

LY, BW and WR wrote the manuscript. EK, DS, WR, DC and LY designed the research. LY, BW, DS, WR, EK and DC interpreted the data. LY, BW, BM, RC and DS analyzed the data.

Conflict of interest statement:

LY, DS, DC, EK and WAR are employees of Horizon Therapeutics and hold Horizon stock. BW, BM and RC are employed by Amador Bioscience. Amador Bioscience reports payment for consultation from Viela Bio (now Horizon Therapeutics).

Ethics approval statement:

The authors declare that this manuscript adheres to the journal's Declaration of Transparency and Scientific Rigor, that the studies from which data was collected and analyzed were approved by the ethics committees of the participating investigational sites, and that the studies conform to Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; MHRA Good Clinical Practice for Clinical Trials; or European Medicines Agency Guidelines for Good Clinical Practice.

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