11 December 2025
EMADOC-1700519818-2662399
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Uplizna

International non-proprietary name: Inebilizumab

Procedure No. EMA/VR/0000257358

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AChR	acetylcholine receptor
ADA	Anti-drug antibodies
ADR(s)	adverse drug reaction(s)
(TE)(S)AE	(treatment emergent) (serious) adverse events
AESI	adverse event of special interest
Anti-AChR-Ab+	anti-acetylcholine receptor antibody positive
Anti-MuSK-Ab+	anti-muscle-specific kinase antibody positive
ARDS	acute respiratory distress syndrome
AUC0-14d	area under the curve from time 0 to 14 days postdose
CD	cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum concentration
CSR	clinical study report
ECG	electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
gMG	generalized myasthenia gravis
Ig	immunoglobulin
IP	investigational product
IRR	infusion-related reactions
IST	immunosuppressant therapy
IV	intravenous
IVIg	Intravenous Ig
LLOQ	lower limit of quantitation
LRP4	lipoprotein-receptor-related protein 4
MAH	Marketing authorisation Holder
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MGQOL-15r	Myasthenia Gravis Quality of Life-15, revised
MMRM	mixed-effects model for repeated measures
MTPC	Mitsubishi Tanabe Pharma Corporation
MuSk	muscle-specific kinase
NMOSD	neuromyelitis optica spectrum disorders
NM(J)	Neuromuscular (junction)
OLP	open-label period
PD	pharmacodynamic
(P)DRMI	(Partial) Dropout Reason-based Multiple Imputation
PK	pharmacokinetic
PLEX	plasma exchange
PML	progressive multifocal leukoencephalopathy
pop PK	Population PK
PRO	patient-reported outcome

PSUR	Periodic Safety Update Report
QMG	Quantitative Myasthenia Gravis
RCP	randomized-controlled period
RMP	Risk Management Plan
SAP	statistical analysis plan
ULOQ	upper limit of quantitation

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 04 March 2025 an application for a group of variations.

The following variations were requested in the group:

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
A.6	A.6 Change in ATC Code / ATC Vet Code	Variation type IA

A grouped application consisting of:

C.I.6 (Extension of indication): Extension of indication to include add-on to standard therapy for the treatment of adult patients with generalised myasthenia gravis (gMG) for Uplizna, based on primary analysis results from Study MINT (VIB0551.P3.S1); this is a pivotal phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab in adults subjects with myasthenia gravis. As a consequence, sections 4.1, 4.2, 4.4 ,4.5, 4.6, 4.8, 5.1, 5.2, and 7 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

A.6: Update of the ATC code of inebilizumab to L04AG10 in line with the 2024 ATC INDEX.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labeling, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0206/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0206/2024 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH received Scientific Advice from the CHMP on 26 March 2020 (EMEA/H/SA/2664/3/2020/II). The Scientific Advice pertained to clinical aspects of the dossier.

Design of a single pivotal randomized, placebo-controlled study to evaluate efficacy and safety of inebilizumab added to standard of care treatment in approximately 252 patients with MG (172 anti-acetylcholine receptor antibody positive (AChR-Ab+) and 80 MuSK-Ab+ (anti-muscle-specific kinase antibody positive)). Issues specifically addressed include add-on placebo as comparator; a fixed steroid taper; choice of primary endpoint (change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) at Week 52 for AChR-Ab+ population and Week 26 for the MuSK-Ab+ population) and key secondary endpoints; study population (defined as a baseline MG-ADL score of ≥6, Myasthenia Gravis Foundation of America (MGFA) class II-IV and Quantitative Myasthenia gravis (QMG) ≥ 12 and receiving selected and stable standard of care therapies, including subjects not currently receiving any immunosuppressive therapy); dosing regimen (one infusion Day 1 and Day 15 followed by re-treatment approximately every 6 months); the safety management plan; the 12-months open-label extension phase with 6 months further follow-up off treatment; and statistical analyses (including handling of missing data, rescue therapy), stratification criteria and sample size calculation.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Thalia Marie Estrup Blicher

Timetable	Actual dates
Submission date	4 March 2025
Start of procedure:	22 March 2025
CHMP Rapporteur's preliminary assessment report circulated on:	16 May 2025
PRAC Rapporteur AR	23 May 2025
PRAC outcome	5 June 2025
CHMP comments	10 June 2025
Updated CHMP Rapporteur AR	12 June 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 June 2025
MAH's responses submitted to the CHMP on:	14 Aug 2025
Re-start of procedure:	18 Aug 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 Sep 2025
PRAC Rapporteur AR	18 Sep 2025
Updated PRAC Rapporteur AR	25 Sep 2025
PRAC RMP advice and assessment overview adopted by PRAC	02 Oct 2025

Timetable	Actual dates
Updated CHMP Rapporteur AR	08 Oct 2025
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	11 November 2025
Re-start of procedure:	12 November 2025
PRAC Rapporteur AR	17 November 2025
Updated PRAC Rapporteur AR	20 November 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	25 November 2025
PRAC RMP advice and assessment overview adopted by PRAC	27 November 2025
Updated CHMP Rapporteur AR	04 December 2025
An Oral explanation took place on:	10 December 2025
CHMP opinion:	11 December 2025
The CHMP adopted a report on similarity of Uplizna with Soliris, Vyvgart and Rystiggo on date (Appendix 1)	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Generalized myasthenia gravis (gMG) is a rare chronic autoimmune neuromuscular condition that causes fluctuating weakness of muscles of varying severity, ranging from difficulties in performing daily tasks to life-threatening respiratory insufficiency (Lehnerer et al, 2022; Finnis and Jayawant, 2011).

State the claimed the therapeutic indication

Generalized myasthenia gravis (gMG)

Uplizna is indicated as an add-on to standard therapy for the treatment of adult patients with gMG (see section 5.1).

Epidemiology and risk factors

Myasthenia gravis most commonly affects young adult women (aged under 40 years) and older men (aged over 60 years), but it can occur at any age. Epidemiological studies reveal an increasing prevalence over the past 50 years, due in part to an increase in the frequency of diagnosis in the

elderly (Sanders et al, 2016). As the population has aged, the average age at onset has increased correspondingly.

Information from Orphanet (accessed: 2025-05-08) suggests that the prevalence of MG in the EU is estimated to be 1 per 5,000 population.

Aetiology and pathogenesis

Myasthenia gravis is an organ-specific, antibody-mediated autoimmune disease. The pathogenic autoantibodies against the AChR are primarily of the immunoglobulin G (IgG)1 or IgG3 isotype and induce a complement-dependent, T-cell mediated immunological attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (NMJ) resulting in a decrease in the number of available AChR. In addition, the postsynaptic folds are flattened, or "simplified." Although acetylcholine is released normally, this leads to a decreased efficiency of neuromuscular transmission, ending in reduced endplate potentials which results in the clinical phenotype of skeletal muscle weakness and fatigability.

MuSK is an NMJ protein that is specifically expressed at the postsynaptic membrane, where it colocalises with AChR, and plays a critical role in the maintenance of the normal functional integrity of the NMJ by mediating clustering of AChR (Zong et al, 2012). The inhibition of MuSK synthesis has been found to cause AChR dispersion and endplate disruption (Lazaridis and Tzartos, 2020). The autoantibodies against MuSK are primarily IgG4s and do not induce complement activation; rather they are hypothesised to prevent the assembly of functional protein complexes at the NMJ, thereby inhibiting AChR clustering (Shiraishi et al, 2005).

Low-density lipoprotein receptor-related protein 4 (LRP4) is another NMJ protein expressed at the postsynaptic membrane in close relationship with MuSK. The inhibition of LRP4 has been found to block the agrin-LRP4 interaction disturbing the AChR clustering in the membrane (Li Y, 2019).Approximately 80 to 85% of all MG patients are positive for anti-AChR antibodies, approximately 5 to 8% (Rodolico et al, 2020; Rodriguez et al, 2015; Meriggioli and Sanders, 2012) are positive for anti-MuSK antibodies and approximately 1-2% are anti-LRP4-positive. Antibodies against various other extracellular or intracellular targets are found in several MG patients (e.g., agrin, collagen Q, anti-voltage-gated potassium channel, titin). MG pathogenesis, its clinical presentation and the response of patients to therapy vary depending on the pattern of autoantibodies detected.

While the precise mechanism of initiation and maintenance of auto-sensitisation to the AChR is not clear, abnormalities of the thymus gland (hyperplasia and neoplasia) almost certainly play a role in the majority of MG patients (Meriggioli and Sanders, 2012). As a primary site for the establishment of immune regulation, derangements in the thymus gland may lead to a defect in the immune system's suppression of autoreactive lymphocytes, allowing for the development of anti-AChR immune responses.

Clinical presentation, diagnosis

Myasthenia gravis is a long-term debilitating condition often associated with thymic follicular hyperplasia or thymoma. In about two-thirds of patients, the first symptom is weakness of extrinsic ocular muscles. In 1 of 10 MG patients, symptoms remain limited to extrinsic ocular muscles (ocular myasthenia gravis). However, in more than 80% of patients, the symptoms progress within 2 years to affect other bulbar muscles as well as limb muscles (gMG). The generalised muscle weakness leads to difficulties in mobility, speech, swallowing, and vision, as well as impaired respiratory function and extreme fatigue. Up to 20% of patients experience

potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation. The MGFA Clinical Classification categorises patients according to clinical evaluation, which in increasing severity can be, ocular MG; mild, moderate, severe generalised symptoms of MG; MG that requires intubation.

Validated symptom scales including the MG-ADL, QMG, and Myasthenia Gravis Composite (MGC) scores are used to assess and track the clinical and functional burden of MG, whereas the 15-item Quality of Life scale for Myasthenia Gravis (MG-QoL15r) measures the impact of MG on the patient's quality of life (QoL).

Management

Anticholinesterase inhibitors and immunosuppressant therapies (ISTs) are standard of care for gMG and have reduced mortality and improved quality of life (Evoli et al, 2023). Approximately 85% to 90% of gMG patients respond to these therapies; however, efficacy has limited durability and there are side effects associated with long term use that lead to reduced quality of life (Urban et al, 2018). Additionally, compared to anti AChR Ab+ patients, anti-MuSK-Ab+ patients often have a poorer response to standard therapies such as anticholinesterase inhibitors, and are more likely to remain steroid dependent, despite the addition of other ISTs (Gilhus et al, 2019).

More recently, several therapeutics targeting the complement pathway (eculizumab/Soliris, ravulizumab/Ultomiris, and zilucoplan/Zilbrysq) have been approved for the treatment of anti-AChR-Ab+ gMG, however, these therapies have not been studied in anti-MuSK-Ab+ gMG, considering that IgG4 antibodies do not activate complement (Evoli et al, 2023). Other therapies targeting the neonatal fragment crystallizable receptors have also been approved for use in the treatment of either anti-AChR-Ab+ gMG (efgartigimod alfa/Vyvgart) or both anti AChR Ab+ and anti-MuSK-Ab+ gMG subgroups (rozanolixizumab/Rystiggo, and nipocalimab/Imaavy) (Evoli et al, 2023). Neonatal fragment crystallizable receptors blockers reduce the overall levels of circulating pathogenic autoantibodies by inhibiting the IgG salvage mechanism, but do not directly target the B cells responsible for producing the pathogenic autoantibodies.

2.1.2. About the product

Inebilizumab is a CD19-directed B cell-depleting antibody that binds to the B cell-specific cell surface antigen CD19, resulting in antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis of CD19+ B cells.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

On 26 March 2020, the Committee for Medicinal Products for Human Use (CHMP) provided scientific advice on the development of inebilizumab for treatment of adult patients with gMG as follows:

- The original protocol was proposed as a randomized, parallel-group, double blind, placebo-controlled study in patients with moderate to severe MuSK Ab+ and AChR-Ab+ with gMG. This protocol was endorsed by CHMP during this scientific advice.
- CHMP expressed concern with including patients on no immunosuppressive treatment, since this would increase the heterogeneity of the patient population. The protocol was amended accordingly, to include patients with either immunosuppressive treatment, or under corticosteroids, or both at randomization.

- CHMP stated that whether corticosteroids can be reduced when treating patients with inebilizumab is an important question, but expressed concern with a forced steroid taper, since this may result in sub-optimal management of patients, potentially an overestimation of treatment effect, and may increase the rate of withdrawal from the study. While the concerns of CHMP are acknowledged, the corticosteroid taper aspect of the study design was retained.
- CHMP endorsed the primary and secondary endpoints and the evaluation of efficacy at 6 months.
- CHMP also supported monitoring CD20 and CD19 B cell counts as a pharmacodynamic (PD) endpoint and measurement of anti-AChR and anti-MuSK antibodies. Results for B cell counts, total IgG levels and IgG subclass levels (which include anti-AChR and anti-MuSK-specific IgGs) as PD data are provided with this application.
- CHMP recommended an exploratory study to support dose selection. A separate study to support dose selection was not performed.
- The Committee supported the safety management plan.
- Finally, CHMP advised that a very clear phase 3 study with convincing results in the clinically relevant endpoints could be sufficient to grant an indication considering the rarity of the condition.

There is no guidance for MG.

2.1.4. General comments on compliance with GCP

The Applicant claims that this study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the European Union (EU) Clinical Trials Regulation No 536/2014, and applicable local and regional regulations/guidelines.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Inebilizumab is a humanized IgG1-based anti-CD19 monoclonal antibody and due to the nature of the product is not expected to pose any risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

Considering the above, inebilizumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Listing of Clinical Studies

Study Identifier	Objective(s) of the Study	Study Design/ Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects	Subject Population	Maximum Treatment Duration	Study Status; Report Type
5.3.5.1, Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication							
VIB0551.P3.S1 MINT (20230049)	Primary: Efficacy Secondary: Safety and tolerability, efficacy, PK, immuno-genicity	Phase 3, randomized, double-blind, placebo-controlled	RCP: inebilizumab 300 mg or placebo administered as an IV infusion: Anti-AChR-Ab+ gMG subjects received inebilizumab or placebo on day 1, day 15, and day 183 (week 26) of the 52-week RCP. Anti-MuSK-Ab+ gMG subjects received inebilizumab or placebo on day 1 and day 15 of the 26-week RCP. OLP: inebilizumab 300mg IV administered as an IV infusion: Subjects assigned to placebo during RCP received inebilizumab IV infusions on OLP days 1, 15, 183 (week 26), 365 (week 52), 547 (week 78), 729 (week 104), and 911 (week 130). Subjects assigned to inebilizumab during RCP received IV inebilizumab on OLP day 1 and placebo infusion on OLP day 15 (to avoid potential unblinding), and inebilizumab infusion on OLP days 183 (week 26), 365 (week 52), 547 (week 78), 729 (week 104), and 911 (week 130).	238 randomized: 190 with anti-AChR-Ab+ gMG 95 to inebilizumab 95 to placebo 48 with anti-MuSK-Ab+ gMG 24 to inebilizumab 24 to placebo	Adults with anti-AChR-Ab+ or anti-MuSK-Ab+ gMG	RCP: 52 weeks for anti-AChR-Ab+ gMG population 26 weeks for anti-MuSK-Ab+ gMG population OLP: 3 years for all subjects	Ongoing; Full, Primary analysis

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Anti-AChR-Ab+ = anti-acetylcholine receptor antibody positive; anti-MuSK-Ab+ = anti-muscle-specific kinase antibody positive; gMG = generalized myasthenia gravis; IV = intravenous; OLP = open-label period; PK = pharmacokinetic; RCP = randomized-controlled period.

2.3.2. Bioanalytical methods

2.3.2.1. Pharmacokinetics

Quantification of inebilizumab in human serum was performed primarily with a validated sandwich type ELISA assay . A minor number of samples were analysed with a slightly modified validated sandwich type ELISA assay .

2.3.2.2. PD Biomarker

Bioanalytical methods for quantification of immunoglobulins

IgA, IgG, IgM in serum were quantified with an immunoturbidimetric assay. Immunoglobulin G Subclasses (IgG1-IgG4) were quantified with a nephelometric assay.

Bioanalytical Method for Assessment of Peripheral Blood CD20+ B cell Counts:

CD20 positive (CD20+) B cells were enumerated in peripheral blood as an exploratory objective in study MINT using a validated flow cytometric, fluorescence-activated cell sorting method. Results. CD20+ B cells counts (cell/µL), are considered quasi-quantitative.

2.3.2.3. Immunogenicity

Anti-Inebilizumab Antibodies (ADA's) in Human Serum was detected with a validated bridging assay measured on the Meso Scale Discovery electrochemiluminescence technology platform. A minor number of samples were analysed using a similar separately validated assay at another

Laboratory. Drug tolerance and sensitivity of the ADA assay were evaluated using a rabbit polyclonal anti-inebilizumab antibody. .

2.3.3. Pharmacokinetics

2.3.3.1. Pharmacokinetic data analyses

Software and methods

Noncompartmental analysis was performed for inebilizumab PK parameter estimation using Phoenixâ WinNonlin(R) v.8.3.4 software (Certara [(TM]), Princeton, NJ).

Population pharmacokinetics (pop PK) and PK/PD model parameter estimations and evaluations were implemented with NONMEM 7, Perl Speaks NONMEM (PsN) and R 4.2.3 or above. Pop PK and PK/PD estimations were performed using the first-order conditional estimation with interaction method in NONMEM. Assembly of the PK or exposure-response dataset was performed using SAS® or R software.

Pop PK modelling

A pop PK model for inebilizumab was previously developed by the Applicant based on data from 3 studies: MI-CP200, CD-IA-MEDI-551-1102, and CD-IA-MEDI-551-1155. The PK of inebilizumab could be described by a two-compartment model with parallel linear and time dependent nonlinear elimination pathways. Effect of body weight was included on disposition parameters. Interindividual variability was estimated for clearance, volume of the central compartment, volume of the peripheral compartment and maximum velocity of the saturable clearance process, while the residuals were described by a proportional error model. An effect of Study CP200 was included on maximum velocity of the saturable clearance process.

Study MINT is a Phase 3, randomized, double-blind, multicenter, placebo-controlled study of inebilizumab efficacy and safety in adults with AChRAb+ or MuSK-Ab+ generalized MG. Of the 238 randomized subjects, 190 subjects were anti-AChR-Ab+ and 48 subjects were anti-MuSK-Ab+. Overall, 112 subjects (94.1%) in the inebilizumab group and 110 subjects (92.4%) in the placebo group completed treatment during the randomized controlled period per protocol which was 52 weeks for the anti-AChR-Ab+ subpopulation and 26 weeks for the anti-MuSK-Ab+ subpopulation.

The MINT study contributed 932 measurable inebilizumab concentrations from 121 subjects. A total of 30 sample results were excluded for various reasons. Two subjects were from the open label period (OLP), the others from the randomised treatment arm (300 mg treatment on Day 1, Day 15, and Day 183 for the AChR cohort and Day 1, Day 15 for the MuSK cohort) with at least one measurable inebilizumab PK sample post-dose. The original dataset with placebo treated subjects included 2443 sample results from 238 subjects. Of note 2177 samples were quantified by a method with an established LLOQ.

The PK data in the MINT study was evaluated using the previous final inebilizumab pop PK model via an external validation approach (Table 1).

Table 1: Baseline population characteristics in the external model validation dataset

Characteristics	Previous Model Development [1]	External Model Validation
No. of subjects	213	121*
No. of PK samples	1617	932
Continuous Covariates (unit)	**Median [min, max]**	**Median [min, max]**
Age (years)	44.0 (18.0, 73.0)	46.0 (18.0, 82.0)
Baseline body weight (kg)	66.2 (38.0, 148)	72.0 (36.0, 154)
Baseline height (m)	1.65 (1.43, 1.89)	1.66 (1.47, 1.91)
Body mass index (kg/m^2)	24.7 (15.6, 52.8)	26.1 (15.4, 47.7)
Body surface area (m^2)	1.73 (1.24, 3.16)	1.84 (1.24, 2.78)
Aspartate aminotransferase (U/L)	19.0 (7.00, 164)	16.0 (7.00, 49.0)
Alkaline phosphatase (U/L)	66.0 (26.0, 188)	56.0 (9.00, 125)
Total bilirubin (µmol/L)	7.00 (1.71, 40.0)	8.00 (1.50, 36.0)
Creatinine clearance (mL/min)	110 (50.9, 282)	112 (49.3, 247)
Estimate glomerular filtration rate (mL/min/1.73m^2)	96.6 (42.8, 292)	93.8 (52.0, 203)
Categorical Covariates (group)	**N**	**N**
Sex (Male/Female)	28/185	41/80
Race (White/Asian/Other/NA)	125/39/49/0	69/48/3/1
ADA (Negative/Positive)	192/21	117/4
Region (US/non-US)	—	17/104
Hepatic function (Normal/Mild/Moderate)	191/20/2	116/4/1

*Of these subjects, 119 were from the randomized treatment arm and 2 were from the OLP.

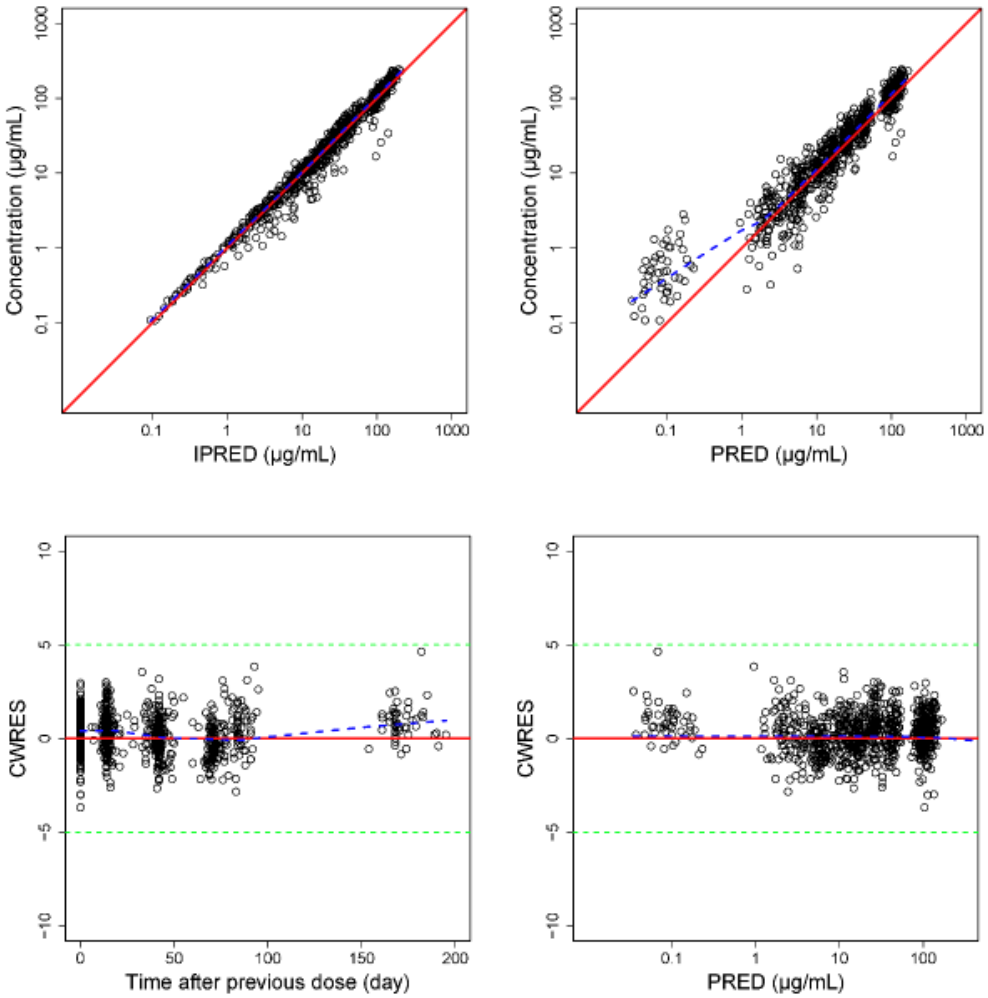
Predicted inebilizumab concentrations for validation subjects were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the final pop PK model using *post hoc* Bayesian forecasting with NONMEM 7. Bias and precision were computed for each subject, then a t-test was used to check whether the mean prediction error value across subjects was significantly different from zero at $p<0.05$ level.

Table 2: Summary of post hoc PK parameters

Descriptions	Geometric mean values of post hoc PK parameters	PK parameters estimate from the previous Model	% Change
Clearance, CL (mL/day)	181.10	188.22	-3.78
Central volume, V_c (mL)	2858.30	2946.39	-2.99
Inter-compartmental clearance, Q (mL/day)	394.17	363.23	8.52
Peripheral volume, V_p (mL)	2586.91	2569.43	0.68
Maximum velocity of the saturable clearance process, V_{max} (µg/day)	818.69	832.50	-1.66
Concentration to achieve half of V_{max}, K_m (µg/mL)	5.89	5.89	0
First-order rate constant for the decrease in V_{max}, K_{dec} (1/day)	0.00294	0.00294	0

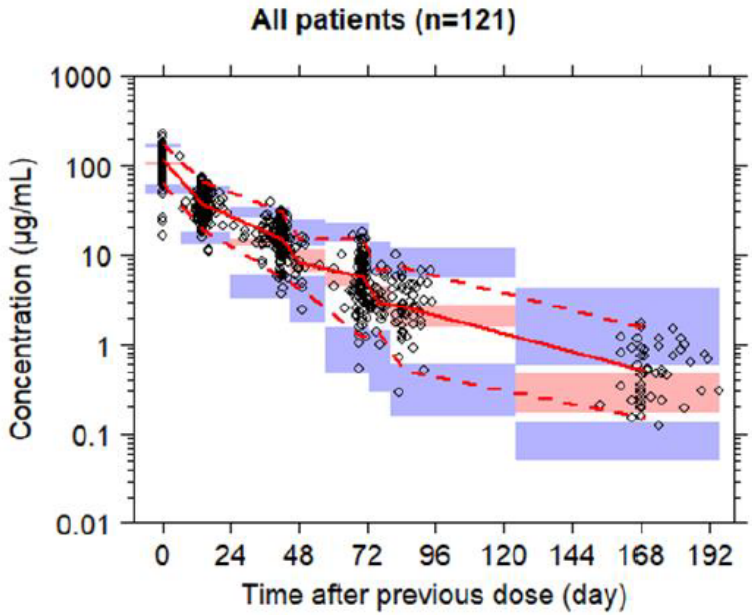
% change = (geometric mean of post hoc value – previous model estimate)/ previous model estimate*100%

Figure 1: General goodness-of-fit plots for all inebilizumab validation subjects.



Top: individual predicted serum inebilizumab concentrations (IPRED) versus observed inebilizumab concentrations (left) and population predicted serum inebilizumab concentrations (PRED) versus observed serum inebilizumab concentrations (right). Bottom: conditional weighted residuals (CWRES) versus time after the previous dose (left) and PRED (right). Points are individual data. Red solid lines represent the unit diagonal (top) or line at zero (bottom). Green dashed lines represent |CWRES| of 5. Blue dashed lines represent the lowess smooth curves.

Figure 2: prediction-corrected visual predictive check (pcVPC) of inebilizumab concentration-time profiles for inebilizumab validation subjects



Circles are observed inebilizumab serum concentrations, a solid red line represents the median observed value, and dashed red lines represent the 2.5 percentile and 97.5 percentile of the observed values. Pink-shaded areas represent the 95% CI of the predicted median concentrations, and the blue-shaded areas represent the 95% CI of the 2.5 percentile and 97.5 percentile of the predicted concentrations.

Table 3: Summary of numerical predictive check in inebilizumab validation subjects.

Range	Observation (%)	
	Expected	All Subjects
Above 95th percentile	5.00	10.8
Above 75th percentile	25.0	41.1
Above 50th percentile	50.0	68.5
Below 50th percentile	50.0	31.5
Below 25th percentile	25.0	10.2
Below 5th percentile	5.00	1.61

The previous Pop PK model was refitted with PK data from study MINT only and the MG subtype was tested as a covariate and found not significant.

PKPD modelling

The purpose was to evaluate the population PK/PD relationships between inebilizumab concentration and CD20+ B-cell counts based on the data from the study MINT and estimate typical values and inter-subject variability of PD parameters and estimate covariate effects of various demographics in adults with gMG. The evaluable patients were defined as patients with PK parameters who have at least one adequately documented inebilizumab administration and a corresponding non-BLQ CD20+ B-cell sample collection after the dose (Table 4). PD observations <LLOQ was implemented as LLOQ/2.

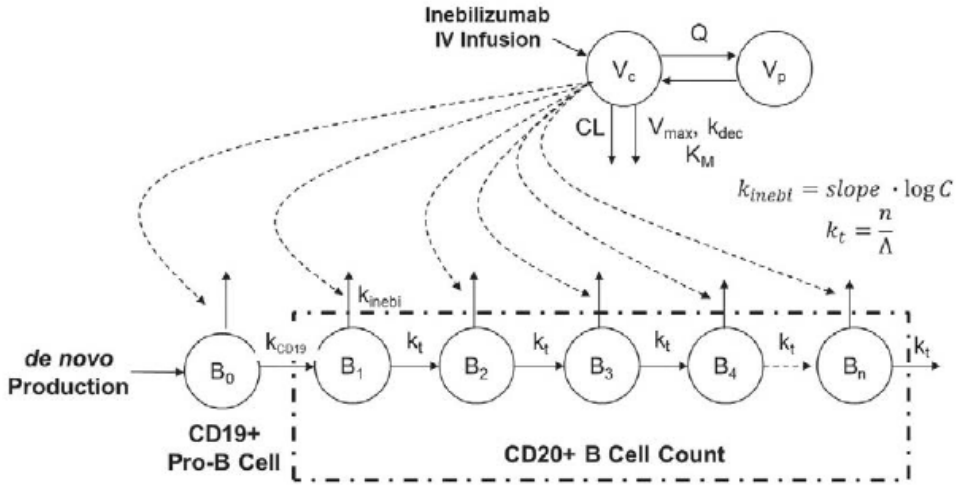
Table 4: Summary of data exclusions in the PK/PD datasets from study MINT

Analyte	Original Dataset	Data exclusions*		PK/PD Analysis Dataset
		C=1	C=2	
$CD20^+$ B cells	120 subjects with 661 measurable samples	11	7	116 subjects with 643 measurable samples

*C=1: Subjects without a non-BLQ record after exposure. C =2: Baseline-preceding records.

Based on a previous PK/PD model structure, a haematopoietic transit model was developed to describe the depletion of circulating CD20+ B cells. 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. The final structure of the PD model is shown in Figure 3.

Figure 3: Base PK/PD Model diagram



$$\frac{dB_0}{dt} = S_0 - k_{CD19} \cdot B_0 - k_{inebi} \cdot B_0$$

$$\frac{dB_1}{dt} = k_{CD19} \cdot B_0 - \frac{n}{\Lambda} \cdot B_1 - k_{inebi} \cdot B_1$$

$$\frac{dB_i}{dt} = \frac{n}{\Lambda} \cdot (B_{i-1} - Bi) - k_{inebi} \cdot B_i$$

$$B_{CD20} = \sum_{i=1}^{n} Bi$$

$$B_0 = \frac{S_0}{K_{CD19}}$$

$$B_i = \frac{S0 \cdot \Lambda}{n}$$

$$k_{inebi} = slope \cdot \log C$$

B_0: pro-B cell
B_i: $CD20^+$ B cells in each aging compartment
C: serum concentration of inebilizumab
CL: clearance
IV: intravenous
k_{CD19}: rate constant representing the maturation of pro-B to $CD20^+$ B cells in the circulation
k_{dec}: first-order rate constant describing the decrease of V_{max} over time
k_{inebi}: accelerated removal of $CD19^+$ pro-B and mature B cells by inebilizumab
K_M: concentration to achieve the half of V_{max}
V_c: volume of distribution in the central compartment
n: number of transit compartments
Q: intercompartmental clearance
V_p: volume of distribution in the peripheral compartment
V_{max}: maximum velocity of Michaelis–Menten equation
Λ: longevity (lifespan) of blood $CD20^+$ B cells
k_t: transit rate constant defined as the ratio of n and Λ.

The CD20+ B-cell data for the previous PKPD model came from two dose-ranging Phase 1 studies of inebilizumab in subjects with systemic sclerosis and multiple sclerosis, and from a pivotal study in subjects with neuromyelitis optica spectrum disorders (NMOSD). The PD effect of inebilizumab was described using a log-linear model. In this data there was a large interindividual variability of CD20+ B-cell lifespan across subjects. 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 (ref: Br J Clin Pharmacol. 2022;88(8):3803-3812).

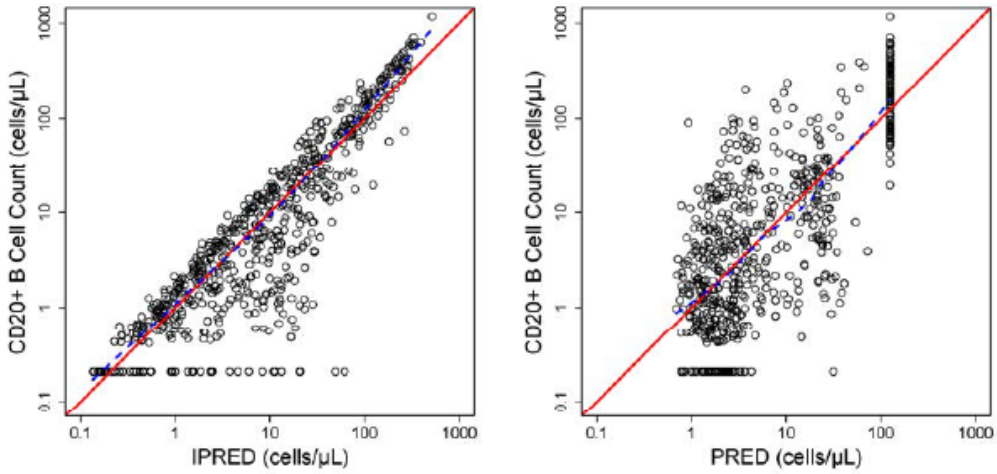
Covariate screening was conducted graphically and by linear regression or analysis of variance (ANOVA) on EBE's of the IIV of PD parameter estimates. Only covariates with a significant correlation ($p<0.01$) was further examined in a stepwise forward selection ($p<0.01$) and backward deletion ($p<0.001$) procedure. Baseline CD20+ B-cell count was identified as a statistically significant covariate on the PK/PD. For typical subjects, the estimated slope was 0.0120, baseline CD20+ B-cell count was 125 cells/µL, lifespan was 339 days, and KCD19 was 0.0410 day-1 (Table 5).

Table 5: Summary of inebilizumab final PK/PD parameters.

Parameter	Parameter Description	Final PopPK Model		Bootstrap Estimates Median (2.5, 97.5%tiles)
		Estimate (% RSE)	Shrinkage	
θ_1	Slope	0.0120 (4.63)	—	0.0121 (0.0107 - 0.0139)
θ_5	Impact of baseline CD20$^+$ B-cell count on slope	0.218 (31.5)	—	0.207 (0.086 - 0.365)
θ_2	Lifespan (day)	339 (23.4)	—	325 (124 - 835)
θ_3	Baseline CD20$^+$ B-cell count (cells/µL)	125 (9.31)	—	126 (106 - 149)
θ_4	K_{CD19} (day^{-1})	0.0410 (33.4)	—	0.0404 (0.00996 - 0.693)
ω_{slope}	IIV slope	35.7 (11.1)	16.7	35.3 (25.0 - 54.8)
$\omega_{Lifespan}$	IIV lifespan	128 (11.9)	19.3	128 (88.3 - 156)
ω_{CBASE}	IIV baseline CD20$^+$ B-cell count	69.9 (12.7)	16.8	68.8 (55.7 - 81.3)
ω_{KCD19}	IIV K_{CD19}	81.0 (48.4)	62.9	85.3 (1.61 - 210)
σ	Proportional error (%)	71.3 (5.32)	9.78	70.9 (63.8 - 77.4)

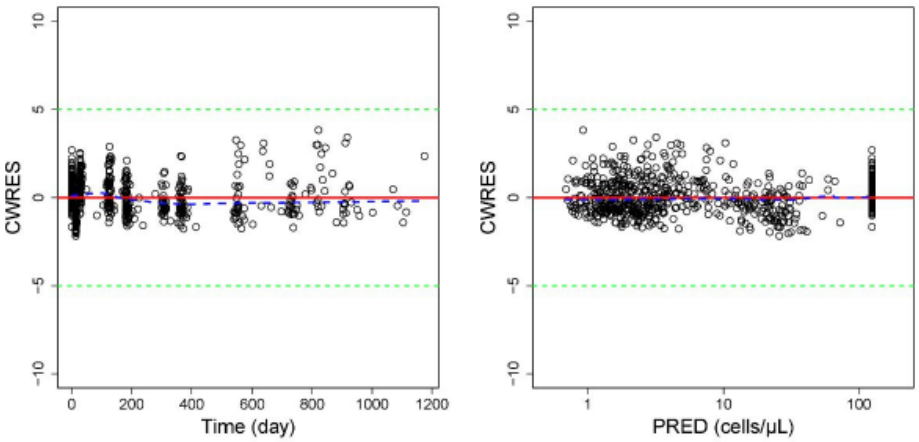
The η-shrinkage for slope, lifespan, and baseline CD20+ B-cell count was <20%. The η-shrinkage for K_{CD19} was 62.9%. The ε-shrinkage for the residual error was 9.78%. The final population PK/PD model was evaluated by goodness-of-fit plots, visual predictive check, numerical predictive check and bootstrap (n=1000).

Figure 4: Predicted versus observed CD20+ B-cell count for the final PK/PD model



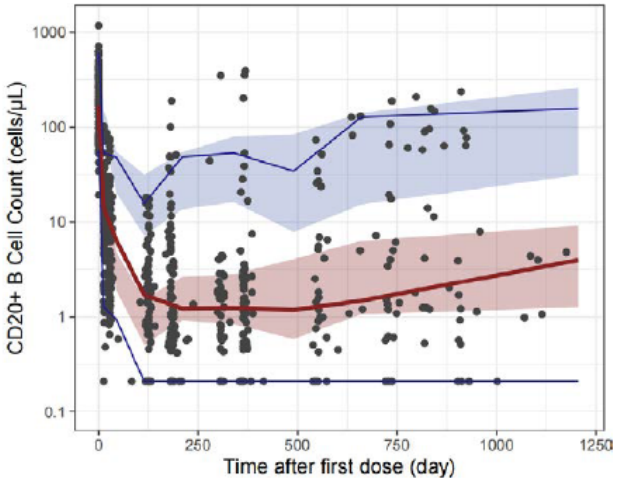
Observed versus individual predicted CD20$^+$ B-cell count (left) and observed versus population predicted CD20$^+$ B-cell count (right) for the final PK/PD model. Red solid lines represent the unit diagonal and blue dashed lines represent the lowess smooth curves.

Figure 5: Residual diagnostic plots for the final PK/PD model



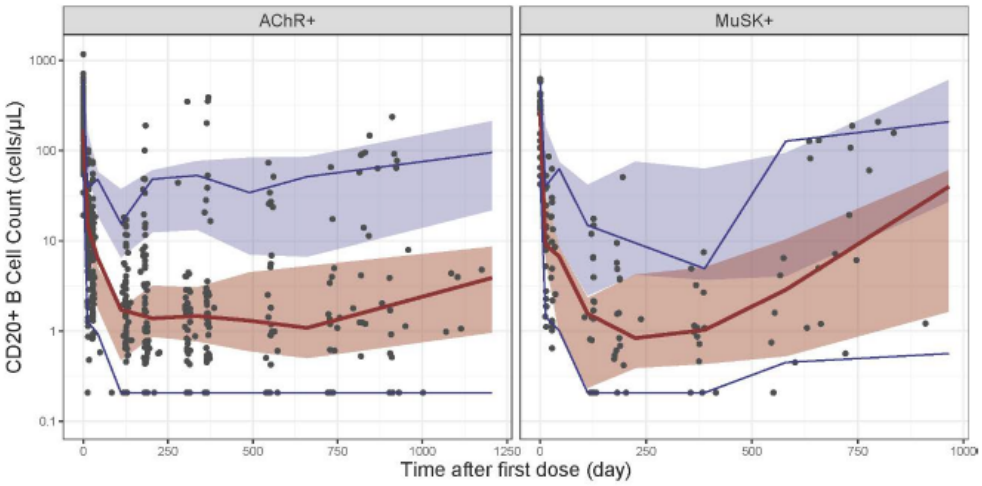
Conditional weighted residuals (CWRES) vs time (left) and population predicted CD20+ B-cell count (PRED, right). Points are individual data. Red solid lines represent the unit line at zero. Green dotted lines represent |CWRES| of 5. The blue dashed lines are smooth curves (lowess) showing the relationship between 2 variables.

Figure 6: VPC of inebilizumab CD20+ B-cell count vs. time profiles.



Points are observed CD20+ B-cell count, solid red line represent the median observed value, and solid blue lines represent 5%ile and 95%iles of the observed values. Red shaded areas represent the 95% CI of the median predicted values, and blue shaded areas represent the 95% CI of 95th predicted values.

Figure 7: VPC of inebilizumab CD20+ B-cell count vs. time profiles by cohort.



Points are observed CD20+ B-cell count, solid red line represents the median observed value, and solid blue lines represent 5%ile and 95%iles of the observed values. Red shaded areas represent the 95% CI of the median predicted values, and blue shaded areas represent the 95% CI of the 95th predicted values.

Table 6: Summary of CD20+ B-cell numerical predictive check

Range	Expected	Observation (%)
Above 95th percentile	5.00	6.84
Above 75th percentile	25.0	28.8
Above 50th percentile	50.0	55.8
Below 50th percentile	50.0	44.2
Below 25th percentile	25.0	14.9
Below 5th percentile	5.00	0

Exposure-response modelling

The previously developed final inebilizumab pop PK model was used to obtain empirical Bayes estimates of individual PK parameters of inebilizumab subjects from the study MINT. Steady-state exposure metrics (model predicted average concentration, model predicted peak concentration at steady state, and trough concentration at steady state) were computed and AUCss/tau (tau = 25 weeks).

Efficacy endpoints were change from baseline in MG-ADL and QMG score at Week 26 in the two different patient groups and in various combinations. Safety endpoints were COVID19, lymphopenia, urinary tract infection, back pain, headaches, and nasopharyngitis

Binary safety endpoints were explored by boxplots of exposure stratified by responses and the probability of response plotted versus exposure metrics or covariates, after binning according to quantiles of exposure or covariate values. If a trend was observed further evaluation by linear regression models was performed. Continuous endpoints were explored by exposure-response plots with loess lines. Efficacy endpoints were further evaluated by maximum effect or linear models if the graphical analysis indicated a trend.

Only one significant exposure-response relationship was identified for probability of lymphopenia (p=0.0159), however only 4 out of 121 treated subjects experienced lymphopenia.

2.3.3.2. Pharmacokinetics in the target population

The PK of inebilizumab in adults with gMG (anti-AChR-Ab+ and anti-MuSK Ab+ subjects) was investigated as a secondary objective in the ongoing pivotal Study VIB0551.P3.S1 (MINT; Study 20230049), a phase 3, randomized, double-blind, placebo controlled study.

Drug dosing and PK-sampling:

Subjects received IV infusions of either inebilizumab 300 mg or placebo on days 1 and 15 (all subjects), and day 183 (week 26) (anti-AChR-Ab+ subjects) of the RCP. Both groups then received inebilizumab every 6 months for the duration of the OLP.

Blood samples for assessment of serum concentrations of inebilizumab during the randomized-controlled period (RCP) were collected on days 1, 15, 29, 57, 85, and 183 (week 26) from anti-AChR-Ab+ and anti-MuSK Ab+ subjects, and on days 225, 267, and 365 for anti-AChR-Ab+ subjects. On inebilizumab dosing days, samples were collected predose and 15 minutes (± 5 minutes) after the end of infusion

PK-results

Inebilizumab PK parameter summary statistics are presented by dosing day for both the anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations in Table 7 and Table 8. Arithmetic mean (+SD) inebilizumab concentration-time figures are presented by subpopulation in Figure 8. Overall, there were no major differences between subpopulations.

Table 7: Descriptive Statistics of Serum Inebilizumab Pharmacokinetic Parameter Estimates Following IV Administration of 300 mg Inebilizumab to Patients With Either Anti AChR-Ab+ or Anti MuSK-Ab+ Myasthenia Gravis (I)

NCA Day	Statistic	t_{max} (day)	C_{max} (μg/mL)	AUC_{0-14d} (μg•day/mL)	AUC_{last} (μg•day/mL)	AUC_{inf} (μg•day/mL)
300 mg Inebilizumab to Patients with AChR+[a] Myasthenia Gravis						
1	N	87	87	84	87	ND
	Mean	0.080	113	881	874	ND
	SD	0.0066	33.5	241	313	ND
	Min	0.066	41.4	400	4.25	ND
	Median	0.080	111	862	862	ND
	Max	0.10	234	1480	1960	ND
	CV%	8	30	27	36	ND
	GeoMean	0.079	108	848	725	ND
15	N	90	90	90	90	74
	Mean	1.0	133	1140	2340	2520
	SD	3.5	51.3	455	1010	974
	Min	0.0	14.0	97.2	339	608
	Median	0.080	135	1140	2140	2320
	Max	17	243	2280	6040	6170
	CV%	353	38	40	43	39
	GeoMean	NC	120	1010	2120	2350
183	N	64	64	64	64	NR
	Mean	0.081	110	1090	2150	NR
	SD	0.0095	24.6	256	673	NR
	Min	0.052	60.8	626	1140	NR
	Median	0.078	108	1060	1990	NR
	Max	0.12	171	1770	4520	NR
	CV%	12	22	24	31	NR
	GeoMean	0.080	107	1060	2060	NR
300 mg Inebilizumab to Patients with MuSK+[a] Myasthenia Gravis						
1	N	20	20	20	20	ND
	Mean	0.081	115	945	971	ND
	SD	0.0044	26.8	233	263	ND
	Min	0.073	71.9	553	553	ND
	Median	0.081	112	909	915	ND
	Max	0.090	181	1530	1630	ND
	CV%	5	23	25	27	ND
	GeoMean	0.081	112	919	940	ND
15	N	20	20	20	20	16
	Mean	0.082	162	1370	2810	3000
	SD	0.0068	30.8	240	584	598
	Min	0.073	109	1070	1650	2100
	Median	0.080	158	1350	2910	3180
	Max	0.10	211	1790	3890	4180
	CV%	8	19	18	21	20
	GeoMean	0.081	159	1350	2750	2950

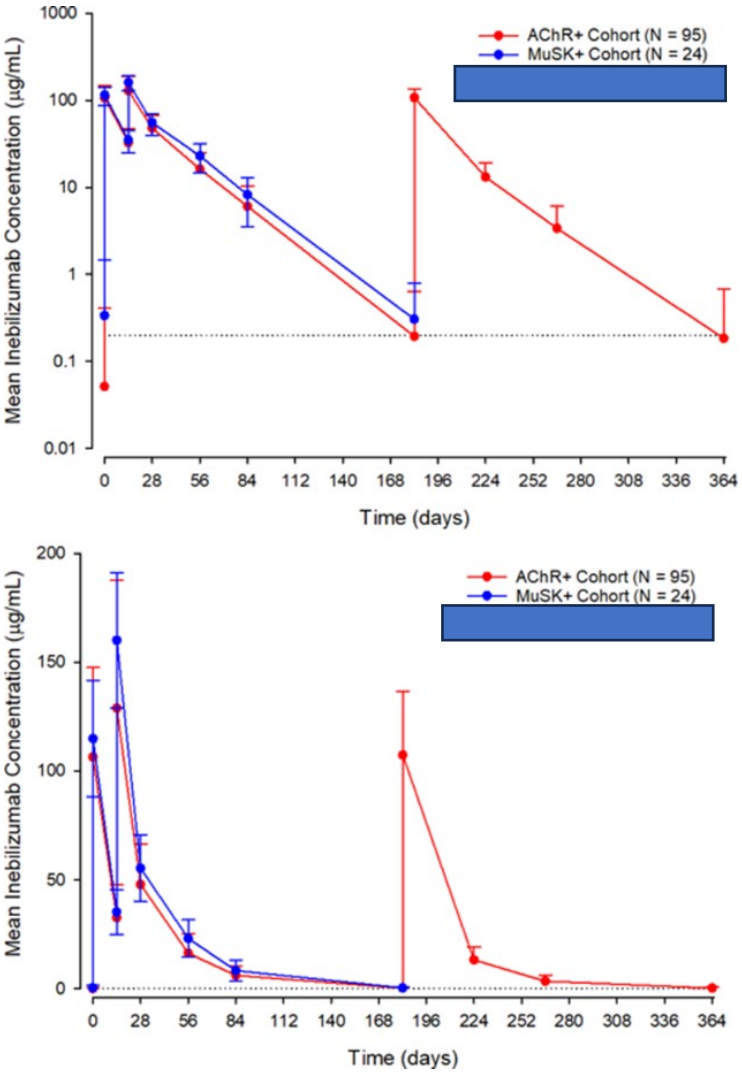
[a]AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.

Table 8: Descriptive Statistics of Serum Inebilizumab Pharmacokinetic Parameter Estimates Following IV Administration of 300 mg Inebilizumab to Patients With Either Anti AChR-Ab+ or Anti MuSK-Ab+ Myasthenia Gravis (II)

Statistic	$AUC_{cum,\ Day\ 15}$ (μg•day/mL)	$AUC_{cum,\ Day\ 183}$ (μg•day/mL)	$t_{1/2,z}$ (day)
300 mg Inebilizumab to Patients with AChR+[a] Myasthenia Gravis			
N	82	84	74
Mean	3320	4710	18.9
SD	1210	2020	4.67
Min	1240	600	9.79
Median	3150	4390	18.5
Max	7550	11 900	32.2
CV%	36	43	25
GeoMean	3120	4240	18.4
300 mg Inebilizumab to Patients with MuSK+[a] Myasthenia Gravis			
N	17	ND	16
Mean	3800	ND	19.5
SD	692	ND	3.66
Min	2430	ND	14.4
Median	3590	ND	18.5
Max	4920	ND	28.4
CV%	18	ND	19
GeoMean	3740	ND	19.2

AUCcum, Day 15 = AUC from time zero of the first dose to infinity following the second dose and was calculated using the following formula: AUC0-14d,Day1 + AUCinf,Day 15 for patients with calculable AUCinf on day 15. For patients without calculable AUCinf on day 15, AUC0-14d,Day1 + AUClast,Day 15 was used instead; AUCcum,Day 183 = AUC from time zero of the first dose to the last quantifiable concentration following last dose and was calculated using the following formula: AUC0-14d + AUClast,Day 15 + AUClast,Day 183 [a] AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively. Terminal half-life ($t_{1/2,z}$) only represents day 15.

Figure 8: Arithmetic Mean Concentration-time Profiles of Inebilizumab by Subpopulation in Patients With Either Anti-AChR-Ab+ Myasthenia Gravis or Anti-MuSK-Ab+ Myasthenia Gravis (Top Figure - Log Scale, Bottom Figure, Linear Scale)



Overall, 22 elderly (>65 years) were included in the MINT study (Table 9). Exposure, mean C_{max} and mean AUC, were comparable in elderly to in population patients <65 years. PK was therefore found not to be impacted by age.

Table 9: Age ranges studied in the elderly population

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
MINT study	18/119 (15.1%)	4/119 (3.4%)	0/119

2.3.4. Pharmacodynamics

2.3.4.1. Mechanism of action

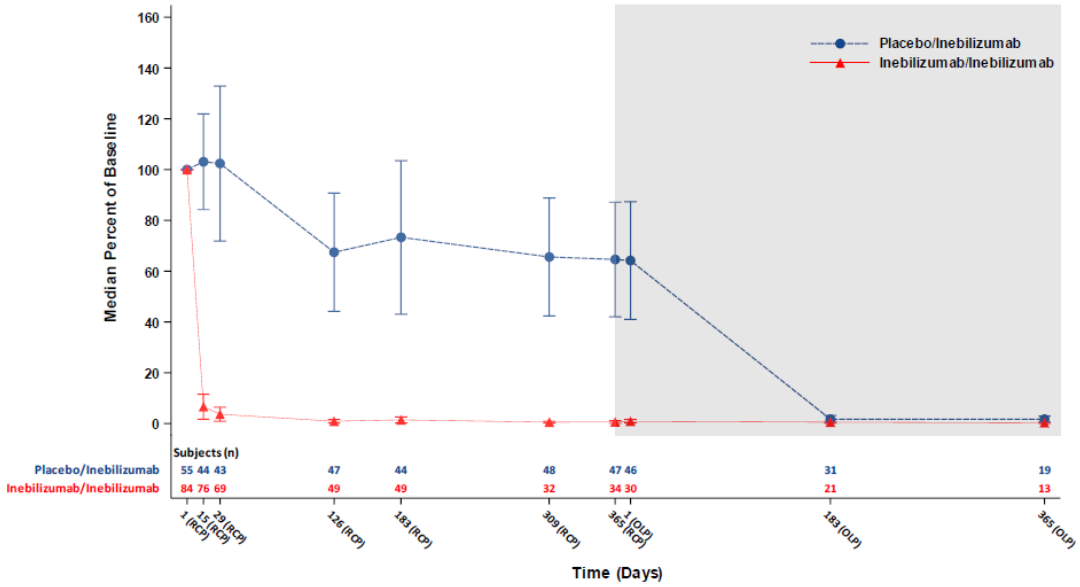
Inebilizumab is a CD19-directed B cell-depleting antibody that binds to the B cell-specific cell surface antigen CD19, resulting in antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis of CD19+ B cells.

2.3.4.2. Primary and secondary pharmacology

In the pivotal MINT study, CD20+ B cell counts were reduced below the lower limit of normal by week 4 in ≥ 99% of inebilizumab-treated subjects across all study populations (overall population, anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations) (Figure 9 and Figure 10). B cell counts remained below the lower limit of normal in ≥ 96% of inebilizumab-treated subjects across all study populations at RCP week 26, and in 92% of inebilizumab-treated anti-AChR-Ab+ subjects at RCP week 52

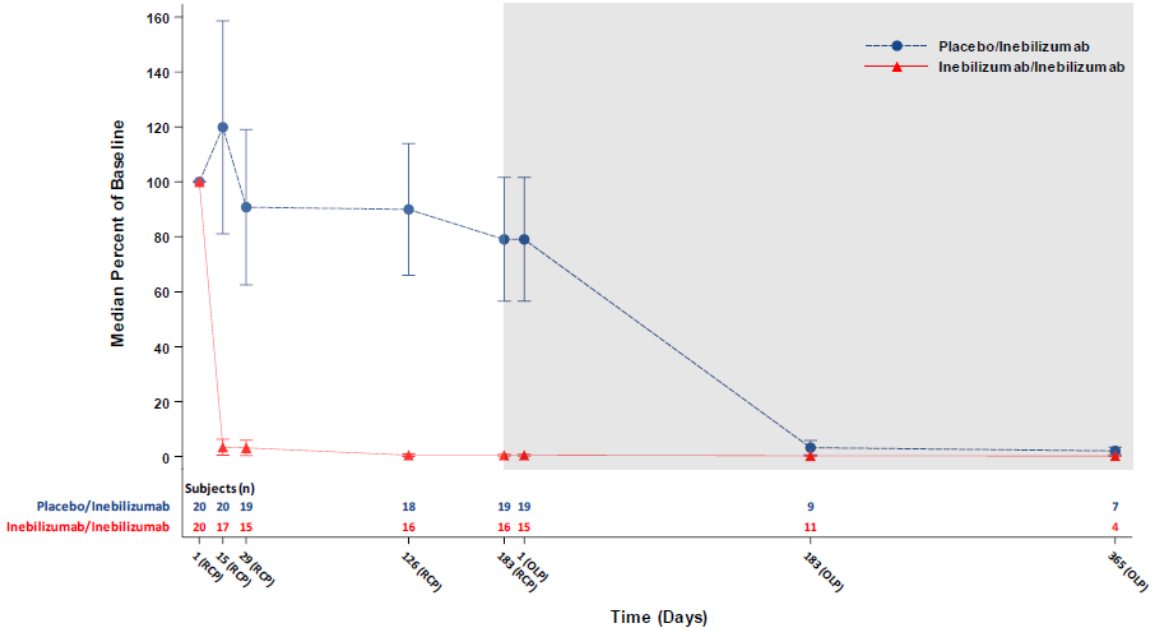
In the overall study population, CD20+ B cell counts were reduced to 6.51% of baseline 2 weeks after the initial infusion with inebilizumab and remained low throughout the RCP. In the AChR-Ab+ and MuSK-Ab+ subpopulations, CD20+ B cell counts were reduced to 6.67% and 3.42% of baseline by RCP week 2 with CD20+ B cell counts remaining low throughout the RCP. There were no substantial changes from baseline in CD20+ B cell counts in the placebo group across any RCP time points.

Figure 9: Median (± MAD) Percent of Baseline in CD20+ B Cell Counts in the Anti-AChR-Ab+ Subpopulation Throughout the Randomized Controlled Period and Open-label Period



anti-AChR-Ab+ = anti-acetylcholine receptor antibody positive; CD = cluster of differentiation; MAD = median absolute deviation; n = number of subjects with observed data; OLP = open-label period; RCP = randomized controlled period. Error bars represent Median Absolute Deviation

Figure 10: Median (± MAD) Percent of Baseline in CD20+ B Cell Counts in the Anti-MuSK-Ab + Subpopulation Throughout the Randomized Controlled Period and Open-label Period



anti-MuSK-Ab+ = anti-muscle-specific kinase antibody positive; CD = cluster of differentiation; MAD = median absolute deviation; n = number of subjects with observed data; OLP = open-label period; RCP = randomized controlled period. Error bars represent Median Absolute Deviation

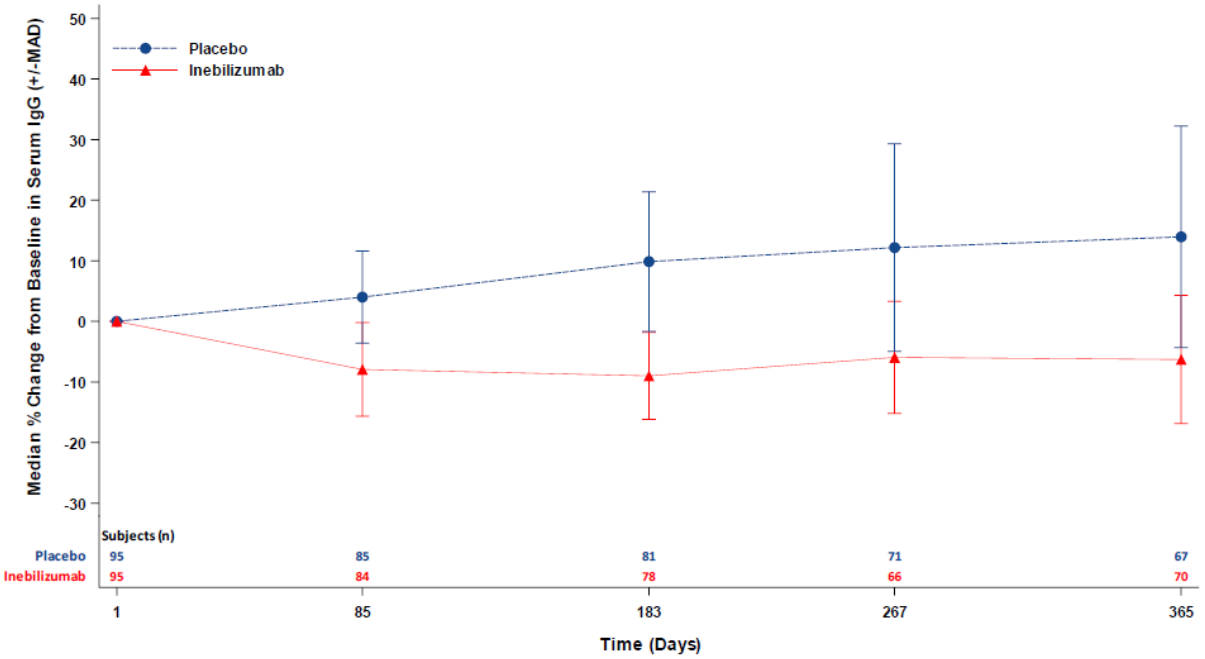
Total Immunoglobulin G

As supportive mechanistic evidence, total IgGs were evaluated throughout the RCP and OLP.

By week 26 of the RCP, a median percent change from baseline of -8.70%, -8.99%, and -8.06% was observed in the overall population, anti AChR Ab+ subpopulation and anti-MuSK-Ab+ subpopulation, respectively (Figure 11 and Figure 12).

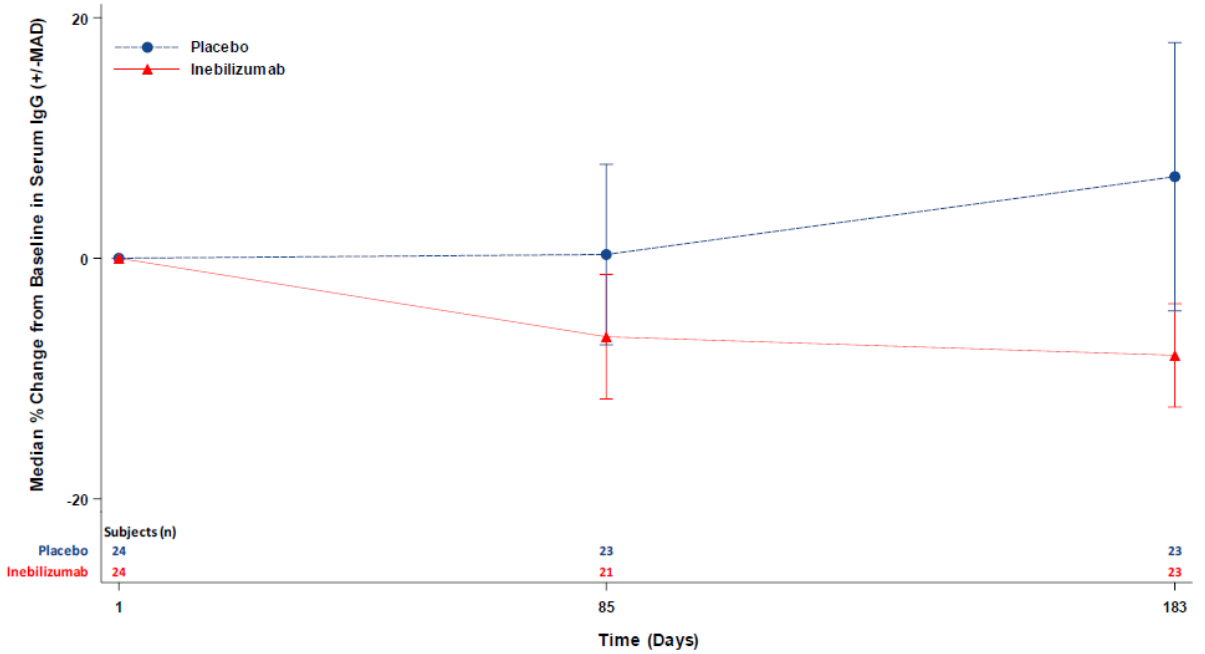
By week 26 of the OLP, placebo/inebilizumab patients experienced a median -9.84% change in IgG from baseline OLP (consistent with the RCP) in the overall population, with the anti AChR Ab+ and anti-MuSK-Ab+ subpopulations experiencing median -12.78% and -7.49% change in IgG from baseline OLP, respectively (Figure 11 and Figure 12).

Figure 11: Median Percent Change From Baseline in Serum Immunoglobulin G Levels by Week 52 (Randomized Controlled Period) – Safety Analysis Set: Anti-AChR-Ab+ Subpopulation



anti-acetylcholine receptor antibody positive;; Ig = immunoglobulin; MAD = median absolute deviation; n = number of subjects with observed data. Error bars represent Median Absolute Deviation.

Figure 12: Median Percent Change From Baseline in Serum Immunoglobulin G Levels by Week 26 (Randomized Controlled Period) – Safety Analysis Set: Anti-MuSK-Ab+ Subpopulation



anti-MuSK-Ab+ = anti-muscle-specific kinase antibody positive; Ig = immunoglobulin; MAD = median absolute deviation; n = number of subjects with observed data. Error bars represent Median Absolute Deviation.

Immunoglobulin G Subclasses

Immunoglobulin G subclass data demonstrated consistent changes from baseline as total IgG, which implies autoantibodies against AChR (IgG1, IgG2, IgG3) and MuSK (IgG4) were also reduced by treatment with inebilizumab.

In sum, the effectiveness of CD19+ B cell depletion in gMG and its downstream effects are supported by the observed reductions in total IgG levels, which include anti-AChR and anti-MuSK-specific IgGs.

Clinical immunogenicity

At any time by week 26 during RCP including baseline, the ADA prevalence for inebilizumab-treated subjects was 3.4% (4/119) in the overall population, 4.2% (4/95) in the anti AChR Ab% subpopulation, and 0 in the anti-MuSK Ab+ subpopulation. The ADA prevalence for placebo-treated subjects was 3.4% (4/119) in the overall population, 2.1% (2/95) in the anti AChR Ab+ subpopulation, and 8.3% (2/24) in the anti-MuSK Ab+ subpopulation (Table 10).

In the overall population, as well as in the anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, ADA status did not influence the change from baseline of Myasthenia Gravis Activities of Daily Living (MG-ADL) or Quantitative Myasthenia Gravis (QMG) scores at week 26. There was a limitation to data interpretability given a small size of subjects (N = 8) who were ADA positive.

By week 26 During the RCP, of 4 ADA positive subjects subject in the inebilizumab treatment group, there was 1 subject that had at least 1 treatment-emergent adverse event, which was mild (grade 1), did not cause investigational product (IP) discontinuation or dose interruption, and was classified as infusion related reaction.

Table 10: Anti-drug Antibody Response by Week 26 Randomized Controlled Period (Safety Analysis Set)

	Overall Population		AChR+[e] Subpopulation		MuSK+[e] Subpopulation	
Variable	Placebo N = 119	Inebilizumab N = 119	Placebo N = 95	Inebilizumab N = 95	Placebo N = 24	Inebilizumab N = 24
Subjects with at least 1 non-missing ADA result during the study	119	119	95	95	24	24
ADA not detected (negative) during the study, n (%)	115 (96.6%)	115 (96.6%)	93 (97.9%)	91 (95.8%)	22 (91.7%)	24 (100.0%)
ADA Incidence[a], n (%)	2 (1.7%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	1 (4.2%)	0 (0.0%)
ADA detected (positive) on study: ADA prevalence	4 (3.4%)	4 (3.4%)	2 (2.1%)	4 (4.2%)	2 (8.3%)	0 (0.0%)
Baseline[b] positive regardless postbaseline status	2 (1.7%)	3 (2.5%)	1 (1.1%)	3 (3.2%)	1 (4.2%)	0 (0.0%)
Only baseline positive	0 (0.0%)	3 (2.5%)	0 (0.0%)	3 (3.2%)	0 (0.0%)	0 (0.0%)
Postbaseline positive regardless baseline status	4 (3.4%)	1 (0.8%)	2 (2.1%)	1 (1.1%)	2 (8.3%)	0 (0.0%)
Only postbaseline positive	2 (1.7%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	1 (4.2%)	0 (0.0%)
Both baseline and postbaseline positive	2 (1.7%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Persistent positive[c]	1 (0.8%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Transient positive[d]	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)

AChR = acetylcholine receptor antibody positive; ADA = anti-drug antibody; MuSK = muscle-specific kinase specific antibody positive; N = number of subjects in the analysis set.
a Incidence is the proportion of the subjects with ADA positive postbaseline only or boosted their preexisting ADA (at least 4-fold over the baseline titer for China and 9-fold over the baseline titer for non-China countries) during the study period.
b Baseline was defined as the last valid value on or prior to the first dose of randomized controlled period.
c ADA postbaseline positive only and (at ≥ 2 postbaseline assessments [with ≥ 16 weeks between first and last positive] or positive at last postbaseline assessment).
d ADA postbaseline positive only and did not fulfill the criteria of persistent positive.

e AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively

2.3.5. Discussion on clinical pharmacology

Uplizna (inebilizumab) is an IgG1 kappa monoclonal antibody approved for the treatment of NMOSD. In this variation, the Applicant initially applied for the use of inebilizumab as an add-on to standard therapy for the treatment of adult patients with gMG. During the procedure, the indication was amended to the use of inebilizumab as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive . The NMSOD IV dosing regimen is also recommended for gMG. i.e. an initial IV loading dose of 300 mg, followed by a dose of 300 mg after 2 weeks and sustained by a maintenance dose of 300 mg every 6 months.

The PK of inebilizumab in gMG patients was investigated in the pivotal phase III study MINT. The recommended dosing regimen was used in the study. Inebilizumab in serum was adequately quantified using two validated sandwich ELISA methods. The two methods were not cross validated. An acceptable justification was provided for the absence of a cross validation. The immunogenicity of inebilizumab was investigated using two appropriately validated bridging ADA assays. Several biomarkers were quantified using qualified methods, i.e. immunoglobulins (IgA, IgM, IgG1-4) and CD20 positive (CD20+) B cells.

A previous pop PK model for inebilizumab was used to fit the data from Study MINT by external validation. In MINT, 190 subjects were anti-AChR-Ab+ and 48 subjects were anti-MuSK-Ab+ and contributed 932 measurable inebilizumab concentrations from 121 inebilizumab treated subjects. Data points 168 days post-dose with concentrations ≤1 µg/mL were underestimated and not well-captured by the model. These data points were primarily originating from the last visit where only 42 out of 181 data records were measurable. The model was refitted with MINT data for test of MG subtype as covariate.

The PK of inebilizumab in MINT study was determined using non-compartmental analysis, for the overall population and in the two subpopulation, anti-AChR-Ab+ positive patients and anti-MuSK-Ab+ patients. No clinically significant differences in PK in the two subpopulations were shown and the cumulative AUCcum,Day15 and maximum concentration were in range with data for NMOSD patients. PK-data were adequately reported in the SmPC.

A haematopoietic transit model was developed to describe the depletion of circulating CD20+ B cells by inebilizumab, based on the structure of a previous PK/PD model. A total of 643 CD20+ B-cell counts from 116 participants from Study MINT were included. The PD effect of inebilizumab was modelled as two effects: reducing influx from pro-B cells and accelerating CD20+ B-cell depletion. Effect of baseline CD20+ B-cell count was a statistically significant covariate and included on slope. The parameters of the final PK/PD model were estimated with reasonable precision and good concordance with bootstrap results

For exposure-response analyses, efficacy endpoints were change from baseline in MG-ADL and QMG score at Week 26 in the two different patient groups and in various combinations. Safety endpoints were COVID19, lymphopenia, urinary tract infection, back pain, headaches, and nasopharyngitis. No exposure response relations were identified for any efficacy or safety endpoint based on model-predicted average concentration and model predicted peak concentration at steady state.

In line with the mechanism of action (Inebilizumab is a CD19-directed B cell-depleting antibody that binds to the B cell-specific cell surface antigen CD19, resulting in antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis of CD19+ B cells), the CD20+ B-cells

declines to below LLOQ after treatment and the placebo arm drops as well in the OLP when administered inebilizumab.

Immunoglobulins were also measured as supportive evidence and here, a modest decline were seen, around 8% from baseline levels in the RCP and around 12% in the OLP. Results were consistent across different subgroups of IgG specific for the AChR (IgG1, 2 and 3) and MuSK (IgG4) subtypes.

Only four inebilizumab-treated patients developed ADA during the trial. Due to the low number, no impact on PK, efficacy or safety is expected nor observed.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of inebilizumab in patients with gMG have been adequately investigated in the pivotal MINT study both with regards to PK and PD. Appropriate model-based evaluation of the data was conducted. In conclusion, overall, the clinical pharmacology data supports the approval of inebilizumab for treatment of patients with gMG.

2.4. Clinical efficacy

2.4.1. Dose response study

The dosing regimen of inebilizumab in this study for the anti-AChR-Ab+ and MuSK-Ab+ subpopulations was 300 mg IV on RCP day 1 and day 15, followed by a single 300 mg infusion every 6 months thereafter. This regimen is the same as that administered to subjects with NMOSD in Study 1155 (Cree et al, 2019; Cree et al, 2024). In Study 1155, the dosing regimen was well tolerated and achieved rapid and durable depletion of CD-19-specific B-cells in the vast majority of subjects. Since there was no expected difference in inebilizumab PK between subjects with NMOSD and MG, the proposed dosing regimen was expected to be well tolerated and achieve a similar PD effect in subjects with MG.

2.4.2. Main study

MINT study: A Randomized, Double-Blind, Multicenter, Placebo-Controlled Phase 3 Study with Open-label Period to Evaluate The Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis (MINT).

Methods

Study MINT is an ongoing, phase 3, global, multicenter, randomized, double blind, placebo controlled, parallel group study with an OLP to evaluate the efficacy and safety of inebilizumab in adults with MG (protocol version 7.0). Eligible subjects were adults with either anti AChR Ab+ or anti MuSK Ab+ MG with moderate to severe disease activity (confirmed by the MGFA class at baseline).

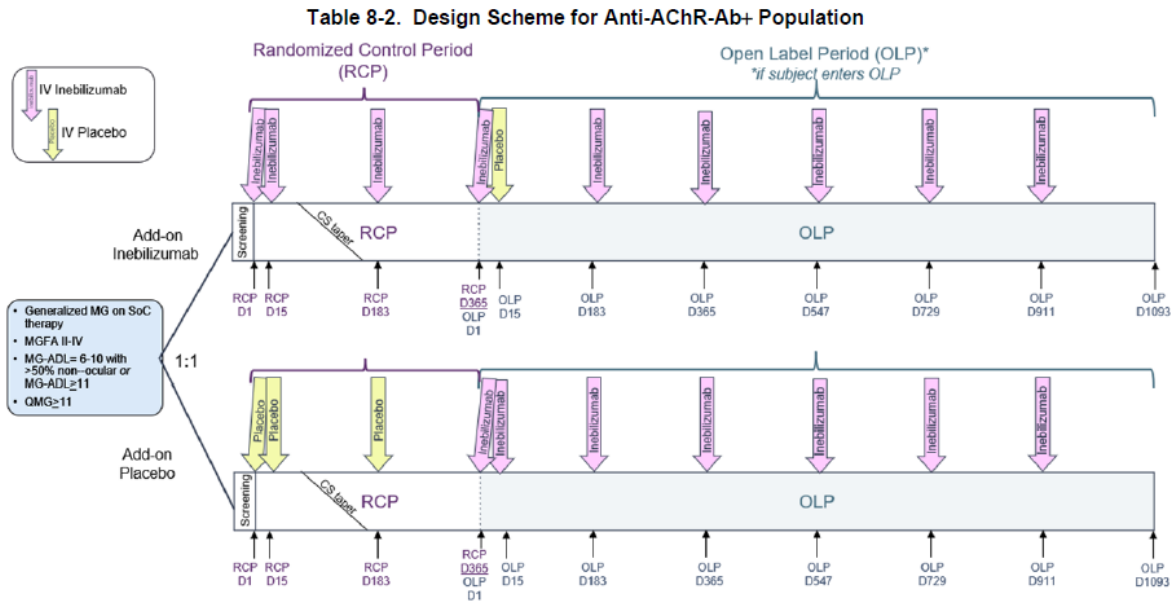
Subjects were randomized 1:1 to receive either IV infusions of 300 mg inebilizumab or placebo on days 1 and 15 (all subjects), and day 183 (anti AChR Ab+ subjects only) of the RCP.

Study duration is up to 4 years for subjects who chose to enter the optional OLP: Screening (4 weeks), RCP (26 or 52 weeks), and OLP (3 years). Subjects who chose not to participate in the OLP, or who discontinued IP during the OLP, had an option of entering the SFP for 2 years after the last dose of IP.

This study was conducted at 126 centers in Argentina, Belarus, Brazil, Canada, China, Denmark, France, Germany, India, Israel, Italy, Japan, Poland, Russia, South Korea, Spain, Taiwan, Turkey, Ukraine, and United States (US).

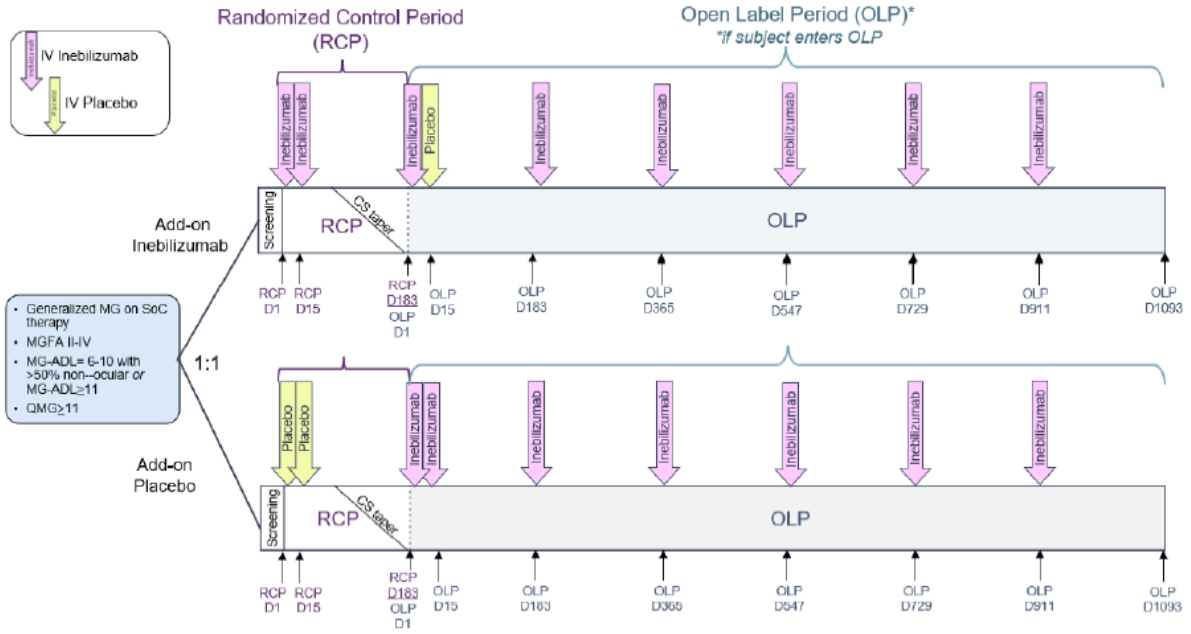
An unblinded, independent Data Monitoring Committee was used to evaluate safety data at regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. This study is ongoing. Data cutoff date was 28 May 2024.The analyses presented in this report are based on a database snapshot date of 09 September 2024 for RCP and OLP.

Figure 13: Design scheme for Anti-AChR-Ab+ Population



Anti-AChR-Ab+= acetylcholine receptor antibody positive; CS = corticosteroid; D = Day; IV = intravenous(ly); MG = Myasthenia Gravis; MG ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; OLP = Open label Period; QMG = Quantitative Myasthenia Gravis; RCP =Randomized Controlled Period; SoC= standard of care.

Figure 14: Design scheme for Anti-MuSK-Ab+ Population



CS = corticosteroid; D = Day; IV = intravenous(ly); MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MuSK-Ab+ = muscle-specific kinase antibody positive; OLP= Open-label Period; QMG = Quantitative Myasthenia Gravis; RCP = Randomized Controlled Period; SoC = standard of care.

Study participants

Study MINT enrolled a population with either anti AChR Ab+ or anti-MuSK-Ab+ gMG with moderate to severe disease activity (confirmed by the MG-ADL and QMG scores at baseline) and inadequate symptom control. The study design incorporated the same disease-specific inclusion and exclusion criteria across both anti-AChR-Ab+ or anti-MuSK-Ab+ gMG cohorts, facilitating the enrollment of a gMG patient population with similar disease characteristics, clinical presentations, and comparable levels of disease severity, regardless of autoantibody serostatus.

The inclusion criteria were designed to enroll subjects with moderate to severe disease activity to merit the use of a biological drug, as well as to enable adequate quantification of any improvement of their condition. Only subjects who had mild, moderate, or severe weakness affecting other than ocular muscles (MGFA class II, III, or IV, respectively) were eligible for the study. Subjects with MGFA classifications below II were ineligible as their disease was too mild and they had ocular signs and symptoms only. Subjects with MGFA classifications above IV were excluded as their disease was too severe and they required mechanical ventilation (Jaretzki et al, 2000).

Inclusion criteria:

To be included in this study, each individual must satisfy all the following criteria (protocol version 1.0):

1. Male or female subjects ≥ 18 years old.

2. Written informed consent and any locally required authorization (e.g, Health Insurance Portability and Accountability Act in the United States of America, European Union Data Privacy Directive in the European Union) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3. Diagnosis of MG defined as:

a. Positive serologic test for anti-AChR or anti-MuSK antibody titers as confirmed at screening (one retest allowed), and

b. At least one of the following:

- o History of abnormal neuromuscular transmission test results demonstrated by single-fiber electromyography or repetitive nerve stimulation; or
- o History of positive anticholinesterase test (e.g, edrophonium chloride test); or
- o Patient demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician; or
- o Clinical syndrome consistent with a diagnosis of MG, and not otherwise explained by another condition.

4. MGFA Clinical Classification Class II, III, or IV at the time of screening and randomization.

5. MG-ADL score of 6 or greater at screening and at randomization with > 50% of this score attributed to non-ocular items.

6. QMG score of 12 or greater at screening and at randomization.

7. Subjects may be on:

a. No immunosuppression, as long as the last dose of corticosteroid was at least 1 month prior to randomization, or

b. Corticosteroids only, with no dose increase within 4 weeks prior to randomization, or

c. One allowed non-steroidal IST, with continuous use for at least 6 months prior to randomization and no dose increase within 4 months prior to randomization

d. Combination of (1) corticosteroids with no dose increase within 4 weeks prior to randomization and (2) one allowed non-steroidal IST with continuous use for at least 6 months prior to randomization and no dose increase within 4 months prior to randomization.

Allowed ISTs, alone or in combination with corticosteroids, are azathioprine, mycophenolate mofetil, and mycophenolic acid.

8. Willing and able to comply with the protocol, complete study assessments, and return for follow-up visits.

9. Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective contraception method from the time of screening and for 6 months after the final dose of investigational period. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone level in the postmenopausal range). If the follicle-stimulating hormone level is not in the postmenopausal range in a subject with amenorrhea, she may still enroll in the study but must follow the same contraception requirements as women of childbearing potential.

10. Non-sterilized males who are sexually active with a female partner of childbearing potential must use a condom from Day 1 for the duration of the study and for 3 months after the last dose of IP. Because male condom is not a highly effective contraception method, it is strongly recommended that female partners of a male study subject also use a highly effective method of contraception throughout this period.

11. Vital signs, electrocardiogram (ECG), and laboratory parameters within the normal ranges at screening, or, if outside normal ranges, deemed not clinically significant by the Investigator.

Exclusion criteria:

If an individual meets any of the following criteria (protocol version 1.0.), he or she is **ineligible** for this study:

1. Any condition that, in the opinion of the Investigator, would place the patient at unacceptable risk of complications, interfere with evaluation of the IP, or confound the interpretation of patient safety or study results.

2. Lactating or pregnant females, or females who intend to become pregnant anytime from signing the informed consent form throughout the RCP plus 6 months following last dose of IP.

3. History of drug or alcohol abuse within < 1 year prior to screening, or any condition associated with poor compliance as judged by the Investigator.

4. Employees of the Sponsor, contract research organization, site staff, and their family members.

5. Currently committed to an institution by way of official or judicial order.

6. Subjects diagnosed with congenital myasthenic syndromes.

7. Known immunodeficiency disorder, including human immunodeficiency virus infection.

8. Thymectomy within ≤ 12 months prior to baseline (Day 1) visit or planned thymectomy during the duration of the RCP.

9. Receipt of the following medications or treatments at any time prior to randomization: Alemtuzumab (Lemtrada®, Campath®), total lymphoid irradiation, bone marrow transplant, T-cell vaccination therapy or Natalizumab (Tysabri®).

10. Receipt of rituximab (MabThera®, Rituxan®), ocrelizumab (Ocrevus®), ofatumumab (Arzerra®), obinutuzumab (Gazyva®), inebilizumab, or any experimental B-cell depleting agent within the 6 months prior to Day 1, unless the subject has a CD19+ B-cell count > one-half the lower limit of normal according to the central laboratory at screening.

11. Receipt within the 3 months prior to Day 1: tocilizumab (Actemra®), belimumab (Benlysta®), eculizumab (Soliris®), cyclophosphamide (Cytoxan®).

12. Receipt within the 4 weeks prior to Day 1: cyclosporine (except eye drops), tacrolimus (except topical), intravenous immunoglobulin (IVIg), plasma exchange (PLEX) treatment.

13. Current use of:

a. Prednisone > 60 mg/day or > 120 mg over a 2-day period (or equivalent dose of other corticosteroids)

b. Pyridostigmine > 480 mg/day or unstable dose in the 2 weeks prior to Day 1

c. Azathioprine > 3 mg/kg/day

d. Mycophenolate mofetil > 3 g/day or mycophenolic acid > 1440 mg/day

e. Methotrexate

14. Concurrent/previous enrollment in another clinical study involving an investigational treatment within 4 weeks or 5 half-lives of the investigational treatment, whichever is longer, prior to Day 1.

15. Receipt of a live attenuated vaccine within 4 weeks prior to randomization. Administration of inactivated (killed) vaccines is acceptable.

16. History of severe allergic or anaphylactic reactions to biologic agents or known allergy to any component of the IP formulation.

17. History of recurrent significant infections (e.g, requiring hospitalization or IV antibiotics).

18. Within 2 weeks prior to the screening visit: clinically significant active infection requiring antimicrobial medication but allowing chronic nail infections.

19. History of thymoma (imaging to evaluate for thymoma must have been performed prior to randomization per standard of care).

20. History of cancer, except for the following:

a. In situ carcinoma of the cervix treated with apparent success with curative therapy for > 12 months prior to screening

b. Cutaneous basal cell or squamous cell carcinoma treated with apparent success with curative therapy for > 12 months prior to screening

c. Prostate cancer treated with radical prostatectomy or radiation therapy with curative intent > 3 years prior to screening and without known recurrence or current treatment

21. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to screening.

22. Any of the following laboratory abnormalities at screening (one repeat test may be conducted to confirm results prior to randomization within the same screening period):

a. Elevated liver enzymes (aspartate aminotransferase or alanine aminotransferase > 2.5 × upper limit of normal.

b. Total bilirubin > 1.5 × upper limit of normal (unless due to Gilbert's syndrome)

c. Estimated glomerular filtration rate < 45 mL/min/1.73 m2

d. CD19+ B-cell count < one half the lower limit of normal

e. Absolute neutrophil count < 1.2 × 103 cells/μL

f. Platelet count < 75,000/μL (or < 75 × 109/L)

g. Hemoglobin < 8.0 g/dL

h. Total immunoglobulin < 600 mg/dL

23. Positive test for chronic hepatitis B infection at screening, defined as either (1) positive hepatitis B surface antigen or (2) a positive hepatitis B core antibody PLUS negative hepatitis B surface antibody. Note: Subjects with a positive hepatitis B surface antibody only, or a positive hepatitis B core antibody plus positive hepatitis B surface antibody and negative hepatitis B surface antigen, are eligible to enroll.

24. Positive test for hepatitis C virus antibody.

25. Positive human immunodeficiency virus test.

26. Blood transfusion within 4 weeks prior to screening or during the screening period

Treatments

Study treatment

The inebilizumab dosing regimen used in Study MINT was 300 mg administered as an IV infusion on day 1 and day 15 and every 6 months thereafter. This regimen is the same as that administered to subjects with NMOSD in Study 1155. In Study 1155, the dosing regimen was well tolerated and achieved rapid and durable depletion of CD19 specific B cells in the vast majority of subjects. Since there was no expected difference in inebilizumab PK between subjects with NMOSD and gMG, the proposed dose regimen was expected to be well tolerated and to achieve a similar PD effect in subjects with gMG.

The 300-mg dose is further supported by data from phase 1 studies in multiple sclerosis (Study CD-IA-MEDI-551-1102) and scleroderma (Study MI-CP200), in which B cell depletion was less complete and/or less durable at doses lower than 3 mg/kg (nominal 210 mg dose for a 70 kg patient).

The 300 mg dose resides at the efficacy plateau, minimizing the impact of PK variability. The second dose of inebilizumab on day 15 is timed to deplete newly circulating B cells mobilized from lymphoid and other tissues. Subsequent doses administered at 6 month intervals are timed to maintain the PD effect based on observations in Study 1155, in which CD20+ B cell counts were significantly reduced 8 days after the initial infusion and remained below the lower limit of normal in 100% of subjects at 4 weeks and 94% of subjects at 28 weeks.

The use of IV placebo is justified by the need to unambiguously assess the safety and efficacy of inebilizumab and to maintain blinding (subject, study center, investigator, sponsor) to assigned treatment during the RCP, thereby limiting bias. The use of premedication (steroid, antihistamine, and antipyretic) before each IP infusion in both treatment groups ensured maintenance of blinding and normalized risks associated with the medication.

Prior and concomitant treatments and rescue medications

During the Screening Period, immunosuppressive medications were allowed to be used; the dose could have been lowered but could not have been increased during the 4 weeks prior to randomization. Acetylcholinesterase inhibitors could have been used during screening, but the dose had to remain stable for the 2 weeks prior to randomization.

Corticosteroids could have been used during the Screening Period; the dose could have been lowered but it could not be increased within 4 weeks prior to randomization. Subjects who were already receiving a corticosteroid at the time of randomization continued to receive a corticosteroid. Subjects who were not already receiving a corticosteroid at time of randomization did not start corticosteroid treatment. Prednisone was used as the preferred oral corticosteroid, that was provided to the subject as part of study procedures. Subjects could have received up to 40 mg prednisone daily or 80 mg every other day or an equivalent dose of an alternate corticosteroid. Starting at the RCP week 4 visit, all subjects who were on corticosteroids were supposed to undergo the protocol-specified corticosteroid taper. Tapering occurred until a subject was on prednisone 5 mg daily, at which time the subject remained on that dose during the remainder of the RCP. Subjects who received corticosteroids at the time of OLP entry remained on

prednisone 5 mg daily or the dose that could be tapered further at the discretion of the Investigator.

Rescue therapy was allowed to be used in cases of mild to severe worsening of MG symptoms due to disease progression, infection, tapering of therapies, or certain medications. Rescue therapy is considered standard of care treatment, including IVIg and PLEX.

Pyridostigmine ≤ 480 mg/day can be used during screening, but the dose must be stable for 2 weeks prior to randomization.

Worsening of symptoms in MG can occur due to precipitating factors that include disease progression, infection, tapering of therapies, or certain medications (Wendell and Levine 2011). This worsening can range from mild to severe. If the worsening is clinically significant and the Investigator believes that the patient's health is in jeopardy, then rescue therapy can be given. The selection of rescue therapy is at the discretion of the Investigator. The protocol-allowed rescue therapy options include corticosteroids, IVIg, or PLEX. Corticosteroids will be considered rescue therapy if used to treat MG at a dose higher than the baseline dose at the start of the RCP. IVIg and PLEX will be considered rescue therapy when used to treat MG. IVIg is recommended over PLEX for subjects in this study since PLEX may remove the study drug from circulation, thus potentially decreasing its therapeutic effect (Khatri et al 2009). Subjects who are treated with a protocol-allowed rescue therapy can continue in the study. If a subject is on corticosteroids in the RCP and high-dose corticosteroids are used for rescue therapy, the subject should return to the prior corticosteroid dose after completion of the rescue therapy.

Objectives and endpoints

Table 11 displays the objectives and endpoints of this study.

Table 11: Objectives and endpoints of the MINT Study.

Objectives	Endpoints
Primary	
• To assess whether inebilizumab can reduce Myasthenia Gravis (MG)-related disability.	• Change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at week 26 in the overall study population, i.e., the Acetylcholine receptor antibody positive (anti-AChR-Ab+) and Muscle-specific kinase antibody positive (anti-MuSK-Ab+) populations.
Secondary	
• To evaluate whether inebilizumab can improve MG-related quality of life (QOL). • To evaluate the ability of inebilizumab to elicit minimal symptom expression. • To evaluate whether inebilizumab can reduce the frequency of MG exacerbations.	**Key secondary endpoints:** • Change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 26 in the overall study population. • Change from baseline in MG-ADL score at week 26 in the anti-AChR-Ab+ population. • Change from baseline in QMG score at week 26 in the anti-AChR-Ab+ population. • Change from baseline in MG-ADL score at week 26 in the anti-MuSK-Ab+ population. • Change from baseline in QMG score at week 26 in the anti-MuSK-Ab+ population.
	Other secondary endpoints: • Proportion of subjects with both (1) ≥ 3-point improvement in MG-ADL score at week 26 and (2) no use of rescue therapy between day 28 and week 26 in the overall study population, anti-AChR-Ab+ and anti-MuSK-Ab+, and at week 52 and no use of rescue therapy between day 28 and week 52 in AChR-Ab+, population. • Change from baseline in MG-ADL score at week 52 in the anti-AChR-Ab+ population. • Change from baseline in QMG score at week 52 in the anti-AChR-Ab+ population. • Change from baseline in Myasthenia Gravis Composite (MGC) score at week 26 in the overall study population, anti-AChR-Ab+ and anti-MuSK-Ab+ and at week 52 in anti-AChR-Ab+ population. • Change from baseline in Myasthenia Gravis Quality of Life-15, revised (MGQOL-15r) score at week 26 in the overall study population, anti-AChR-Ab+ and MuSK-Ab+ and at week 52 in anti-AChR-Ab+ population.

Objectives	Endpoints
	• Patient Global Impression of Change (PGIC) score at week 26 in the overall study population, anti-AChR-Ab+ and MuSK-Ab+ and at week 52 in anti-AChR-Ab+ population. • Time to first exacerbation by week 26 in the overall study population, anti-AChR-Ab+ and anti-MuSK-Ab+ and by week 52 for anti-AChR-Ab+ populations. • Proportion of subjects achieving minimal symptom expression (MSE), defined as MG-ADL = 0 or 1, at week 26.
• To evaluate the effect of inebilizumab on corticosteroid usage.	• The proportion of subjects with steroid tapered to ≤ 5 mg/day steroid at week 26 for the overall study population, AChR-Ab+ and MuSK-Ab+ and at week 52 for AChR-Ab+ population. • The proportion of subjects in whom steroid dose was reduced by ≥ 50% from baseline by week 26 for the overall study population, AChR-Ab+ and MuSK-Ab+ and by week 52 for AChR-Ab+ population.
• To evaluate the safety and tolerability of inebilizumab in MG.	• The safety and tolerability of inebilizumab as measured by the incidence of treatment-emergent adverse events, adverse events of special interest (AESIs), and treatment-emergent serious adverse events. • Clinical Laboratory • Vital signs • Electrocardiogram (ECG).
• To characterize the pharmacokinetic (PK) profile and immunogenicity of inebilizumab in subjects with MG.	• Anti-drug antibody status and titer during the study in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population. • Serum concentration of inebilizumab.
Exploratory	
• To evaluate whether inebilizumab can reduce fatigue in MG. • To evaluate whether inebilizumab can reduce healthcare resource utilization.	• Change in Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue score at week 26. • Myasthenia Gravis Foundation of America (MGFA) Post-Intervention Status (PIS) at week 26. • Healthcare resource utilization.
• To evaluate the pharmacodynamic (PD) profile of inebilizumab in MG	• PD profile, as measured by CD20+ B-cell count

AChR-Ab+= Acetylcholine receptor antibody positive; AESI = adverse events of special interest; ECG = electrocardiogram; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MS = minimal symptom expression; MGQOL-15r = Myasthenia Gravis Quality of Life-15, revised; MuSK-Ab+ = Muscle-specific kinase antibody positive; Neuro-QoL = Quality of Life in Neurological Disorders; PD = pharmacodynamic(s); PGIC = Patient Global Impression of Change; PIS = Post- Intervention Status; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QOL = quality of life

The MG-ADL scale assesses the impact of gMG on daily functions by measuring 8 signs or symptoms that are commonly affected in gMG. Each item is measured on a 4-point scale, where a score of 0 represents normal function and a score of 3 represents the loss of ability to perform that function. MG-ADL is a patient-reported outcome (PRO) that reflects impact of the disease on the patient's day-to-day function. The range of total MG-ADL score is 0-24, and the minimal important difference is a 2-point improvement (Muppidi et al 2011). The MG-ADL is composed of items related to patients' assessment of functional disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items).

The QMG is a 13-item direct physician assessment scoring system that quantifies disease severity, based on impairments of body functions and structures. The total QMG score ranges from 0 to 39, where higher scores indicated greater disease severity. The QMG score is composed of the following items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). An improvement of 2-3 points is considered meaningful for the patient.

The MGC is a 10-item instrument that measures the symptoms and signs of MG based on physician examination and patient history. Items relate to ptosis, double vision, eye closure, talking, chewing, swallowing, breathing, neck flexion, shoulder abduction, and hip flexion. Each item is scored on an ordinal scale with 4 possible categories and weighted. The total score ranges from 0 to 50, where higher scores indicating more severe impairments. A 3-point improvement in the MGC represents a meaningful improvement to most patients with MG.

The MGFA PIS is included as it provides a standard way of evaluating treatment response that is used widely by the MG community.

The MGQOL-15r is a disease-specific questionnaire that is included to evaluate whether treatment has an impact on patient-reported physical functioning, mental or psychological well-being, occupational status, and social interactions.

Sample size

Sample size was estimated using a 2-sided t-test. Approximately 230 subjects (188 subjects with AChR-Ab+ MG and 42 with MuSK-Ab+ MG) will be randomized at a 1:1 ratio to either receive inebilizumab or placebo. This sample size will provide more than 95% power to detect a true mean (population) treatment difference of 2 points in the MG-ADL score in the overall study population with a two- sided 0.05 alpha level assuming the common standard deviation is 4 using two-sided t-test.

The sample size of AChR-Ab+ subjects was also estimated using a 2-sided t-test, which will provide at least 90% power to detect a true mean (population) treatment difference of 2 points in change from baseline of MG-ADL with a 2-sided 0.05 alpha level. The sample size of MuSK-Ab+ population was estimated based on the feasibility of enrollment. Assuming the common standard deviation is 4 and a two- sided 0.05 alpha level, the minimum detectable treatment difference in MuSK-Ab+ population is 2.5.

Randomisation

Acetylcholine receptor antibody positive and MuSK-Ab+ subjects were randomized in a 1:1 ratio to receive inebilizumab or placebo, and were stratified by antibody status (AChR-Ab+ vs. MuSK-Ab+) and region (Japan vs. non-Japan). In the non-Japan population, subjects were further stratified according to baseline disease severity ("day 1 QMG score = 11-15" vs "day 1 QMG score = 16")

and baseline corticosteroid use (“prednisone > 5 mg/day” vs “prednisone dose ≤ 5 mg/day”) and randomized 1:1 to receive either inebilizumab or placebo within each stratum. In the Japan population, no further stratification was applied due to the small sample size, and subjects were randomized 1:1 to receive either IV inebilizumab or placebo. Treatment group randomization and assignment of IP kit numbers was managed by the interactive voice/web response system.

Blinding (masking)

This was a double-blind study in which the IV inebilizumab and IV placebo were matching in appearance. The Sponsor remained blinded until after the database lock for primary efficacy analysis, which occurred after all subjects completed week 26 or discontinued prior to week 26 visit. For the anti-AChR-Ab+ subjects who had not completed the 52-week RCP at the time of the primary analysis database lock, they completed the remaining visits during the RCP per protocol. To ensure the blinding of each subject’s treatment assignment during the study, the study site personnel, the Sponsor personnel who were directly associated with the conduct of the study, and the subjects remained blinded to the treatment assignment until the last subject had completed the study or, if a subject discontinued early from the study. Unblinded team members did not provide subject treatment assignment information to any blinded team member, study site personnel and the subjects.

Statistical methods

Analysis set

The following sets were defined:

Table 12: Analysis sets

Analysis Set	Definition
Full Analysis Set (FAS)	All subjects randomized who received at least 1 dose of investigational product in the study, and had a baseline MG-ADL assessment, and at least 1 post-baseline MG-ADL assessment. Subjects were analyzed according to the treatment randomized. The efficacy analysis for RCP was based on the FAS.
Safety Analysis Set (RCP)	All subjects who received any dose of investigational product during the RCP. Subjects were analyzed according to the treatments that they actually received. The safety, PD, and ADA analysis for RCP were based on the Safety Analysis Set. A subject who received any dose of inebilizumab during the RCP was included in the inebilizumab treatment group. A subject who received placebo only during the RCP was included in the placebo treatment group.
Open-label Analysis Set	All subjects who received any dose of inebilizumab during the OLP. The efficacy and safety for OLP were summarized based on Open-label Analysis Set.
Any inebilizumab Analysis Set	All subjects who received any dose of inebilizumab during the study. The efficacy and safety for the combined RCP and OLP were based on the Any inebilizumab Analysis Set unless otherwise specified.
Safety Follow up (SFP) Analysis Set	All subjects who entered the SFP.
Pharmacokinetic (PK) Analysis Set	All subjects who received any dose of inebilizumab during the RCP and had at least 1 quantifiable serum PK observation post first dose. The PK analysis was based on the PK Analysis Set. Subjects were analyzed according to the treatment that they actually received.
Per-protocol Analysis Set (PAS)	All subjects in the FAS who were sufficiently compliant with the protocol. Major reasons to exclude subjects from the PAS analysis set included: • Didn't meet eligibility of MG-ADL and/or QMG at day 1. • Didn't receive all day 1 and/or day 15 doses during the RCP per protocol. • Randomized at risk, for example, subject who was randomized while a serious adverse event is not resolved completely.

ADA = antidrug antibody; FAS = full analysis set; MG-ADL = Myasthenia Gravis Activities of Daily Living; OLP = open-label period; PAS = per-protocol analysis; PD = pharmacodynamics; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; RCP = randomized controlled period; SFP = safety follow-up.

Efficacy analyses were conducted on the Full Analysis Set (FAS).

The primary and secondary efficacy endpoints were analyzed using a composite strategy, which includes all data collected after randomization to the last visit during the RCP. The intercurrent events of early discontinuation and rescue therapy use were accounted for as follows:

- Binary efficacy endpoints: If a subject used rescue therapy after day 28 during the RCP or discontinued from the study early, the subject was considered a non-responder at the timepoints on or after the rescue therapy use or after the early discontinuation visit, whichever is earlier

- Continuous efficacy endpoints: if a subject used rescue therapy after day 28 during the RCP, the data collected on or after the initiation of the rescue therapy in the corresponding time

period were imputed using the subject's worst observation collected before initiation of the rescue therapy

Primary endpoint

For the primary analysis, the primary estimand is defined as follows:

1. Population: Subjects in the FAS.

2. Variable (endpoint): change from baseline in MG-ADL score at Week 26.

3. Intercurrent events:

    a. Rescue therapy initiated after Day 28 during the RCP will be analyzed using a composite strategy. The data collected on or after the initiation of the rescue therapy will be imputed using the subject's worst observation collected before initiation of the rescue therapy.

    b. Rescue therapy initiated on or before Day 28 during the RCP and treatment discontinuation will be addressed using a treatment policy strategy. Subjects who discontinue treatment early will be asked to attend scheduled evaluations until the end of RCP. The data collected after treatment discontinuation for reasons other than rescue therapy will be included in the analysis.

4. Population-level summary: Mean difference between inebilizumab and placebo.

Rationale for estimand: The occurrence of the intercurrent event of rescue therapy is informative about the effect of treatment. If a subject is administered rescue therapy after Day 28, it may be considered that the allocated treatment was not effective, and the subject was not successfully treated. Taking rescue therapy will confound treatment effect. The intercurrent event of treatment discontinuation is considered to be part of the treatments being compared, reflecting the intention-to-treat principle.

The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM) analysis with covariates of treatment group, baseline antibody status (AChR-Ab+ or MuSK-Ab+), baseline steroid use (daily prednisone dose≤ 5 mg vs. daily prednisone dose> 5 mg), baseline QMG score (as a binary variable: <16 vs. ≥ 16), baseline MG-ADL score, visits, the interaction between visit and treatment group. The estimate of the treatment effect estimator will be based on a contrast from this MMRM model. The variance-covariance matrix will be assumed to be unstructured. If the procedure doesn't converge, then a compound symmetric variance-covariance matrix will be applied.

The primary analysis will be conducted using the MMRM, which is valid under the missing at random (MAR) assumption. To assess the robustness of the treatment effect, for each estimand, additional sensitivity analyses utilizing multiple imputation approaches will also be conducted with the missing data imputed for the subjects who discontinue the study early based on the different missing data mechanism assumptions, including those expected to be more conservative such as missing not at random. For example, partial dropout reason-based multiple imputation assuming the trajectories for subjects in the inebilizumab group who discontinued the study early due to IP-related events are similar to those of the placebo subjects, whereas the remaining subjects who dropped out would be imputed assuming MAR. If a subject has monotone missing data (missing values occur at the end of data records) due to early discontinuation from the study, the reason for early discontinuation will be collected and sensitivity analyses using the same MMRM model as mentioned above will be conducted with missing data imputed. In addition, for MG-ADL and QMG, if intermittent missing is observed for the total score at a timepoint, the missing total score will be imputed using last observation carried forward before being included in the imputation described

below. The missing data in the placebo arm will be imputed using the mean of the non-missing values in the placebo arm. The missing data in the inebilizumab arm will be imputed using missing imputation approaches based on different missing data mechanism assumptions as listed in Table 3. The assumptions that will be used to impute the missing data are as follows:

- MAR: Assumes that the trajectory for subjects who dropped out in each arm are similar to those observed in their own treatment arm.

- Partial Dropout Reason-based Multiple Imputation (Partial-DRMI): Assumes that the trajectory for subjects in inebilizumab arm who dropped out for a treatment related reasons are similar to that of the placebo subjects, whereas the remaining subjects who have dropped out are imputed assuming MAR.

- DRMI: As for Partial-DRMI with treatment related reasons but also including protocol deviation.

Table 13: parameters for the imputation under MAR, partial-DRMI and DRMI

Reason for early discontinuation	**MAR**	**Partial-DRMI**	**DRMI**
Adverse Event	inebilizumab	Placebo	Placebo
Death	inebilizumab	Placebo	Placebo
Lack of efficacy or progressive disease	inebilizumab	Placebo	Placebo
Protocol-specified withdrawal criterion met	**inebilizumab**	**Placebo**	**Placebo**
Protocol deviation	inebilizumab	Inebilizumab	Placebo
Subject lost to follow up	inebilizumab	inebilizumab	inebilizumab
Withdrawal by subject for the following reasons: • **Adverse event** • **Lack of Efficacy** • **Progressive disease**	inebilizumab	**Placebo**	**Placebo**
Withdrawal by subject for the following reasons: • **Subject did not provide a reason** • **Other**	**inebilizumab**	**inebilizumab**	**inebilizumab**
Other	inebilizumab	**inebilizumab**	**inebilizumab**

Supplementary analysis will be performed for the primary efficacy endpoint using a treatment-policy strategy to address both intercurrent events of rescue therapy and treatment discontinuation

(i.e., including data collected after rescue therapy and treatment discontinuation in the analysis). The analyses for primary endpoint will also be conducted based on PAS as sensitivity analyses.

As supportive analyses, proportions of subjects with various improvement thresholds (≥ 2, 3, 4, 5, 6, 7, or 8 etc.) in MG-ADL at Week 26 (for overall study population, AChR-Ab+ population and MuSK-Ab+ population) and at Week 52 (for AChR-Ab+ population only) will be summarized. A subject is considered as a responder if he/she achieved improvement in MG-ADL≥ specific improvement thresholds and didn't receive rescue therapy between Day 28 (exclusive) and Week 26 (inclusive). If a subject used rescue therapy between Day 28 and Week 26 or discontinued the study before Week 26, the subject will be considered as a non-responder on or after the rescue therapy use and/or after the early discontinuation visit, whichever is earlier. The proportion of the responders will be analyzed using the Firth logistic regression utilizing composite strategy with covariates of treatment group, baseline antibody status, baseline steroid use, baseline QMG score (as a binary variable: <16 vs. > 16), and the baseline MG-ADL score. Firth logistic regression was utilized to mitigate small sample bias and to address the complete separation issues we may have. Similar analysis will be repeated at Week 52 for AChR+

population excluding the covariate of baseline antibody status. As additional sensitivity analyses, the proportion of the responders based on different improvement thresholds mentioned above will also be analyzed using the Firth logistic regression utilizing treatment-policy strategy regardless the rescue therapy use.

Key secondary endpoints

The key secondary efficacy endpoints are as follows:

- Change from baseline in QMG scores at Week 26 in the overall study population.

- Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.

- Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.

- Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.

- Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

The definitions of the primary estimand and the implementation of analysis methods for the key secondary endpoints are similar to those of the primary endpoint, except for differences in the population and the corresponding antibody endpoint. Similar sensitivity and supplementary analyses will be conducted in the same manner as for the primary endpoint.

Subgroup analysis

To explore the consistency of treatment effect, subgroup analyses will be performed on the FAS for the primary and the key secondary endpoints in the following subgroups as appropriate. Model based analyses will not be performed for subgroups with sample size less than 5% of the population

- Baseline antibody type (AChR-Ab+ vs. MuSK-Ab+)
- Gender: Male; Female
- Age: ≥18<65; ≥65 years
- Baseline MG duration: <4 years; ≥4 years
- Baseline steroid use: prednisone ≤20 mg/day; prednisone >20 mg/day
- Baseline IST use (Corticosteroid only, non-steroid IST only, Corticosteroid plus 1non-steroid IST)
- Baseline QMG: QMG ≤15; QMG ≥16

- Baseline MGFA class: class II; III; IV
- Region:
    - Region 1: Asia vs. Europe (Israel included) vs North America vs rest of world (Central America, South America, Australia, Turkey);
    - Region 2: US vs. non-US
    - Region 3: EU vs. non-EU
    - Region 4: Asia vs. non-Asia
    - Region 5: Japan vs. non-Japan
    - Region 6: China vs. non-China
- Country
- Racial/ethnic subgroups as needed for national/regional regulatory filings

These analyses are to be considered as exploratory and will be performed on the FAS.

With regards to subgroup analyses, it is noted that they were all conducted with the composite strategy for rescue therapy as intercurrent event. As no adjustment for multiplicity was planned, subgroup analyses are only to be considered in an exploratory sense.

Multiplicity

No interim analyses for efficacy were performed.

The type I error will be controlled across the primary and the key secondary endpoints at 0.05 (2-sided). A hierarchical approach will be used to control for multiplicity and the testing strategy is proposed as follows:

Step 1: Test the primary endpoint at a significance level (2-sided) of 0.05; if the p value is less than 0.05, then proceed to Step 2. Otherwise, no null hypothesis is rejected in the overall population.

Step 2: Test the key secondary endpoints at a significance level (2-sided) of 0.05 sequentially following the order below:

o Change from baseline in QMG score at Week 26 in the overall study population.

o Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.

o Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.

o Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.

o Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

SAP amendments

The statistical analyses were conducted according to the SAP (Version 3.0), dated 19 August 2024, which was finalized prior to the formal database lock. The SAP was amended twice. The most relevant amendment was the first one (version 2.0) where the following changes were implemented in accordance with protocol version 7: change the analysis to pooled analysis, the change of the primary analysis timepoint to Week 26, the update of endpoints and changes in the estimand including change in the proposed strategy to handle intercurrent event of use of rescue medication after Day 28. The last amendment to the SAP was made before database lock.

Results

Participant flow

Of the 238 randomized subjects, 190 subjects were anti-AChR Ab+ and 48 subjects were anti-MuSK Ab+. The primary analysis was conducted when the last subject had the opportunity to complete the week 26 visit, which represented the complete RCP for anti-MuSK-Ab+ subjects. In the anti-MuSK Ab+ subpopulation, 97.9% subjects completed the RCP. For anti-AChR-Ab+ subjects, the duration of the RCP was 52 weeks and it was still ongoing at the time of the primary analysis; therefore, 75.3% of the anti AChR Ab+ subjects had completed the RCP. The most common reason of discontinuation from RCP was withdrawal by subject (2 subjects [1.7% in inebilizumab group and 7 subjects [5.9% in placebo group). Death was the reason for discontinuation from RCP in 3 subjects (1.3% (inebilizumab 1 subject [0.8% placebo 2 subjects [1.7% all these subjects were anti-AChR Ab+ (Table 14).

In addition, 112 subjects (94.1% in the inebilizumab group and 110 subjects (92.4% in the placebo group completed treatment during the RCP (Table 14).

As of 09 September 2024, 94 subjects (79.0% in the inebilizumab group and 84 subjects (70.6% in the placebo group enrolled into OLP.

Table 14 Subject Disposition – All Randomized Subjects

	Overall Population			AChR+[a] Population			MuSK+ [a] Population		
Parameter	Placebo	Inebilizumab	Overall	Placebo	Inebilizumab	Overall	Placebo	Inebilizumab	Overall
Statistic	N = 119	N = 119	N = 238	N = 95	N = 95	N = 190	N = 24	N = 24	N = 48
Treated n (%)	119 (100%)	119 (100%)	238 (100%)	95 (100%)	95 (100%)	190 (100%)	24 (100%)	24 (100%)	48 (100%)
RCP									
Completed RCP	91 (76.5%)	99 (83.2%)	190 (79.8%)	68 (71.6%)	75 (78.9%)	143 (75.3%)	23 (95.8%)	24 (100%)	47 (97.9%)
Completed RCP and enrolled into OLP	83 (69.7%)	94 (79.0%)	177 (74.4%)	61 (64.2%)	70 (73.7%)	131 (68.9%)	22 (91.7%)	24 (100%)	46 (95.8%)
Completed RCP and didn't enroll into OLP	8 (6.7%)	5 (4.2%)	13 (5.5%)	7 (7.4%)	5 (5.3%)	12 (6.3%)	1 (4.2%)	0 (0.0%)	1 (2.1%)
Discontinued from RCP[b]	14 (11.8%)	5 (4.2%)	19 (8.0%)	13 (13.7%)	5 (5.3%)	18 (9.5%)	1 (4.2%)	0 (0.0%)	1 (2.1%)
Adverse event	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	2 (1.7%)	1 (0.8%)	3 (1.3%)	2 (2.1%)	1 (1.1%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of efficacy	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Progressive disease	2 (1.7%)	0 (0.0%)	2 (0.8%)	2 (2.1%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by subject	7 (5.9%)	2 (1.7%)	9 (3.8%)	6 (6.3%)	2 (2.1%)	8 (4.2%)	1 (4.2%)	0 (0.0%)	1 (2.1%)
Other	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinued from RCP and enroll into OLP	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RCP Treatment									
Completed treatment during RCP per protocol	110 (92.4%)	112 (94.1%)	222 (93.3%)	86 (90.5%)	88 (92.6%)	174 (91.6%)	24 (100%)	24 (100%)	48 (100%)
Did not complete treatment during RCP per protocol	9 (7.6%)	7 (5.9%)	16 (6.7%)	9 (9.5%)	7 (7.4%)	16 (8.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not complete treatment during RCP but completed RCP	0 (0.0%)	3 (2.5%)	3 (1.3%)	0 (0.0%)	3 (3.2%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pregnancy	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	2 (1.7%)	2 (0.8%)	0 (0.0%)	2 (2.1%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not complete treatment during RCP and did not complete RCP	9 (7.6%)	4 (3.4%)	13 (5.5%)	9 (9.5%)	4 (4.2%)	13 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of efficacy	2 (1.7%)	0 (0.0%)	2 (0.8%)	2 (2.1%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Progressive disease	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Overall Population			AChR+[a] Population			MuSK+[a] Population		
Parameter	Placebo	Inebilizumab	Overall	Placebo	Inebilizumab	Overall	Placebo	Inebilizumab	Overall
Statistic	N = 119	N = 119	N = 238	N = 95	N = 95	N = 190	N = 24	N = 24	N = 48
Protocol-specified withdrawal criterion met	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by subject	4 (3.4%)	2 (1.7%)	6 (2.5%)	4 (4.2%)	2 (2.1%)	6 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OLP									
Enrolled into OLP	84 (70.6%)	94 (79.0%)	178 (74.8%)	62 (65.3%)	70 (73.7%)	132 (69.5%)	22 (91.7%)	24 (100%)	46 (95.8%)
Completed OLP	1 (0.8%)	4 (3.4%)	5 (2.1%)	1 (1.1%)	1 (1.1%)	2 (1.1%)	0 (0.0%)	3 (12.5%)	3 (6.3%)
Discontinued from OLP	15 (12.6%)	17 (14.3%)	32 (13.4%)	13 (13.7%)	11 (11.6%)	24 (12.6%)	2 (8.3%)	6 (25.0%)	8 (16.7%)
Adverse event	2 (1.7%)	0 (0.0%)	2 (0.8%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	1 (4.2%)	0 (0.0%)	1 (2.1%)
Death	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (2.1%)
Physician disease	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by subject	4 (3.4%)	8 (6.7%)	12 (5.0%)	3 (3.2%)	3 (3.2%)	6 (3.2%)	1 (4.2%)	5 (20.8%)	6 (12.5%)
Other	8 (6.7%)	6 (5.0%)	14 (5.9%)	8 (8.4%)	6 (6.3%)	14 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
OLP Treatment									
Received any dose in OLP	84 (70.6%)	94 (79.0%)	178 (74.8%)	62 (65.3%)	70 (73.7%)	132 (69.5%)	22 (91.7%)	24 (100%)	46 (95.8%)
Completed treatment during OLP per protocol	2 (1.7%)	6 (5.0%)	8 (3.4%)	2 (2.1%)	2 (2.1%)	4 (2.1%)	0 (0.0%)	4 (16.7%)	4 (8.3%)
Did not complete treatment during OLP per protocol	14 (11.8%)	15 (12.6%)	29 (12.2%)	12 (12.6%)	10 (10.5%)	22 (11.6%)	2 (8.3%)	5 (20.8%)	7 (14.6%)
Did not complete treatment during OLP but completed OLP	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did not complete treatment during OLP and did not complete OLP	14 (11.8%)	15 (12.6%)	29 (12.2%)	12 (12.6%)	10 (10.5%)	22 (11.6%)	2 (8.3%)	5 (20.8%)	7 (14.6%)
Adverse event	2 (1.7%)	1 (0.8%)	3 (1.3%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	1 (4.2%)	1 (4.2%)	2 (4.2%)
Death	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Failure to meet continuation criteria	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (2.1%)
Physician disease	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	1 (0.8%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by subject	3 (2.5%)	5 (4.2%)	8 (3.4%)	2 (2.1%)	2 (2.1%)	4 (2.1%)	1 (4.2%)	3 (12.5%)	4 (8.3%)
Other	7 (5.9%)	6 (5.0%)	13 (5.5%)	7 (7.4%)	6 (6.3%)	13 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SFP									
Enrolled into SFP	11 (9.2%)	5 (4.2%)	16 (6.7%)	9 (9.5%)	5 (5.3%)	14 (7.4%)	2 (8.3%)	0 (0.0%)	2 (4.2%)
Completed SFP	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

AChR+= acetylcholine receptor antibody positive; MuSK+ = muscle-specific kinase antibody positive; N = Number of subjects in the analysis set; n = Number of subjects with observed data; OLP = Open Label Period; RCP = Randomized Controlled Period; SFP = Safety Follow up Period.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b There was 1 subject (1.1%) in placebo group in AChR+ subpopulation who discontinued treatment prior week 26.
Total includes placebo and Inebilizumab. The denominators of the percentages are the number of subjects randomized during RCP

Recruitment

First patient first visit: 15 October 2020

The study is ongoing. Data cutoff date was 28 May 2024. The analyses presented are based on a database snapshot date of 09 September 2024 for the RCP and OLP.

This study was conducted at 126 centers in Argentina, Belarus, Brazil, Canada, China, Denmark, France, Germany, India, Israel, Italy, Japan, Poland, Russia, South Korea, Spain, Taiwan, Turkey, Ukraine, United States (US).

Conduct of the study

The last protocol version is number 7.0.

The protocol changes (6 protocol amendments) are listed in the submitted version of the protocol, but no discussion or overview of the protocol changes and the potential impact on the results were provided by the Applicant.

Protocol Deviations

Critical and major protocol deviations in any treatment group during RCP and OLP are summarized in Table 15. During RCP, the incidence of subjects with any critical and major protocol deviations was similar between the 2 treatment groups (47.9+ vs 45.3+ inebilizumab vs placebo,

respectively). No notable differences in the incidence of protocol deviations was observed between anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations.

Subjects with any critical protocol deviation including late reporting of serious adverse events, pregnancy on-study, and late reporting of AESIs were reported in 4 subjects (3.4%) in inebilizumab group and 6 subjects (5.1%) in placebo group.

The most common major protocol deviations in both treatment groups were deviations related to study procedures and steroid tapering and (21.8% vs 16.2% and 15.1 vs 16.2% inebilizumab vs placebo, respectively) (Table 15). The most common eligibility deviation was subjects who did not meet MG specific inclusion criteria because of using the invalid paper source to capture the scores of MG-ADL, QMG, MGFA class etc. The most frequently reported major protocol deviations within the study procedure category involved the use of paper questionnaires instead of the designated digital questionnaires for newly enrolled subjects. These deviations occurred due to initial technical issues at certain sites and were not considered to impact the interpretability of the study results. These subjects continued participating in the study, and the sites were retrained according to the protocol deviation procedures. Regarding major deviations from the steroid tapering protocol, these occurred in subjects who did not reach a steroid dose of ≤7.5 mg at week 20 (day 141), primarily because of the investigator's evaluation of the individual subject's condition. Informed consent deviations (10.1% vs. 12.8% inebilizumab vs. placebo) mostly concerned subjects who had not signed a revised informed consent form at their subsequent study visit. In these cases, subjects signed the informed consent at the next available visit, and the sites were retrained on informed consent procedures. During the OLP, the incidence of subjects with any critical and major protocol deviations was 29.8% in the inebilizumab/inebilizumab group and 22.6% in the placebo/inebilizumab group. Subjects with any critical protocol deviation including late reporting of serious adverse events, pregnancy on-study, and late reporting of AESIs were reported in 4 subjects (4.3%) in inebilizumab/inebilizumab group and 3 subjects (3.6%) in placebo/inebilizumab group. The respective sites were re-trained on reporting procedures. The most common IP deviations were related to missing IP dose and when a subject was incorrectly stratified at randomization. An IP related critical protocol deviation occurred in 1 subject (1.1%) in the inebilizumab/inebilizumab treatment group and none in the placebo/inebilizumab group. This deviation was subject met IP discontinued criteria but did not discontinue from the IP. The most common major protocol deviations in both treatment groups were related to informed consent (17.0% and 10.7%, inebilizumab/inebilizumab and placebo/inebilizumab, respectively) (Table 15). Most of these cases involved subjects who were not reconsented with the revised informed consent form version during the visit after its implementation/approval. The respective sites were retrained on informed consent procedures. Overall, the nature of the protocol deviations that occurred during this study did not impact the interpretability of the study results.

Table 15: Critical and Major protocol deviations (FAS)

Variable	Randomized Controlled Period						Open-label Period	
	Overall Population		AChR+[a] Population		MuSK+[a] Population		Overall Population	
	Placebo N = 117 n (%)	Inebilizumab N = 119 n (%)	Placebo N = 93 n (%)	Inebilizumab N = 95 n (%)	Placebo N = 24 n (%)	Inebilizumab N = 24 n (%)	Placebo/ Inebilizumab N = 84 n (%)	Inebilizumab/ Inebilizumab N = 94 n (%)
Subjects with any critical and /or major protocol deviation	53 (45.3%)	57 (47.9%)	40 (43.0%)	47 (49.5%)	13 (54.2%)	10 (41.7%)	19 (22.6%)	28 (29.8%)
Subjects with any critical protocol deviation	6 (5.1%)	4 (3.4%)	4 (4.3%)	3 (3.2%)	2 (8.3%)	1 (4.2%)	3 (3.6%)	5 (5.3%)
Investigational product	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
serious adverse event, Pregnancy and AESI Reporting	6 (5.1%)	4 (3.4%)	4 (4.3%)	3 (3.2%)	2 (8.3%)	1 (4.2%)	3 (3.6%)	4 (4.3%)
Subjects with any major protocol deviation	53 (45.3%)	56 (47.1%)	40 (43.0%)	47 (49.5%)	13 (54.2%)	9 (37.5%)	17 (20.2%)	24 (25.5%)
Entry criteria not met	8 (6.8%)	10 (8.4%)	6 (6.5%)	9 (9.5%)	2 (8.3%)	1 (4.2%)	0 (0.0%)	0 (0.0%)
Excluded medication received	9 (7.7%)	5 (4.2%)	7 (7.5%)	4 (4.2%)	2 (8.3%)	1 (4.2%)	2 (2.4%)	2 (2.1%)
Informed consent	15 (12.8%)	12 (10.1%)	13 (14.0%)	10 (10.5%)	2 (8.3%)	2 (8.3%)	9 (10.7%)	16 (17.0%)
Investigational product	8 (6.8%)	14 (11.8%)	5 (5.4%)	13 (13.7%)	3 (12.5%)	1 (4.2%)	7 (8.3%)	4 (4.3%)
serious adverse event, Pregnancy and AESI Reporting	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Steroid Tapering[b]	19 (16.2%)	18 (15.1%)	12 (12.9%)	16 (16.8%)	7 (29.2%)	2 (8.3%)	0 (0.0%)	0 (0.0%)
Study procedures	19 (16.2%)	26 (21.8%)	15 (16.1%)	19 (20.0%)	4 (16.7%)	7 (29.2%)	2 (2.4%)	4 (4.3%)

AChR+ = acetylcholine receptor antibody positive; AESI = adverse events of special interest; MuSK+ = muscle-specific kinase antibody positive; N = Number of subjects in the analysis set; n = Number of subjects with observed data.
Critical protocol deviation: A deviation that was a significant departure from good clinical practice resulting in a life-threatening risk to an individual patient, or where the safety or well-being of trial patients was or had significant potential to be jeopardized or caused a significant portion of the clinical trial data to be potentially unreliable.
Major protocol deviation: A deviation that resulted or had the potential to result in non-life-threatening harm to an individual participant or had the potential to affect the safety and well-being of trial patients or the reliability of clinical trial data. The event did not pose a significant risk to the overall project, overall patient safety, or overall data quality/ integrity
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b Steroid Tapering Protocol Deviation: The subject did not reach steroid dose ≤ 7.5 mg at week 20

Baseline data

Baseline disease characteristics were generally balanced between inebilizumab and placebo treatment in the overall population, anti-AChR-Ab+, and anti-MuSK-Ab+ and between the anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulation groups (Table 16). The proportion of subjects with anti-AChR-Ab+ was higher than anti-MuSK-Ab+, consistent with the known anti-AChR-Ab+ MG epidemiology. In the overall population, the overall mean (SD) MG disease duration was 6.34 (7.12) years, the mean (SD) baseline MG-ADL score was 9.1 (2.8), the mean (SD) baseline QMG score was 17.0 (4.2), and the mean (SD) baseline MGC score was 18.8 (6.4). The most common baseline MGFA Class was III (50.9%) and II (44.4%). A majority of the subjects received corticosteroid treatment at baseline (92.4% overall; 63.6% corticosteroid only; 28.8% corticosteroid plus 1 non-steroid IST; 82.2% at a dose > 5 mg). The most common non-steroid IST at baseline was azathioprine (24.2%). Majority of the subjects also received acetylcholinesterase inhibitor at baseline (79.2% overall) (Table 17).

Table 16: Baseline Demographics (Randomized Controlled Period) - Full Analysis Set

Parameter Statistic	Overall Population Placebo N = 117	Overall Population Inebilizumab N = 119	Overall Population Overall N = 236	AChR+ [a] Population Placebo N = 93	AChR+ [a] Population Inebilizumab N = 95	AChR+ [a] Population Overall N = 188	MuSK+ [a] Population Placebo N = 24	MuSK+ [a] Population Inebilizumab N = 24	MuSK+ [a] Population Overall N = 48
Age (years)									
Mean (SD)	47.9 (15.0)	47.1 (15.7)	47.5 (15.3)	48.9 (15.4)	46.9 (16.3)	47.9 (15.9)	43.9 (12.8)	47.5 (13.3)	45.7 (13.0)
Median	48.0	46.0	47.5	51.0	46.0	48.0	44.0	47.0	46.0
Min, Max	(18, 80)	(18, 82)	(18, 82)	(18, 80)	(18, 82)	(18, 82)	(25, 73)	(21, 73)	(21, 73)
Age Category, n (%)									
18-64 years	101 (86.3%)	97 (81.5%)	198 (83.9%)	79 (84.9%)	76 (80.0%)	155 (82.4%)	22 (91.7%)	21 (87.5%)	43 (89.6%)
≥ 65 years	16 (13.7%)	22 (18.5%)	38 (16.1%)	14 (15.1%)	19 (20.0%)	33 (17.6%)	2 (8.3%)	3 (12.5%)	5 (10.4%)
Sex n (%)									
Female	65 (55.6%)	79 (66.4%)	144 (61.0%)	48 (51.6%)	60 (63.2%)	108 (57.4%)	17 (70.8%)	19 (79.2%)	36 (75.0%)
Male	52 (44.4%)	40 (33.6%)	92 (39.0%)	45 (48.4%)	35 (36.8%)	80 (42.6%)	7 (29.2%)	5 (20.8%)	12 (25.0%)
Race n (%)									
American Indian or Alaska Native	1 (0.9%)	0 (0.0%)	1 (0.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	54 (46.2%)	46 (38.7%)	100 (42.4%)	39 (41.9%)	31 (32.6%)	70 (37.2%)	15 (62.5%)	15 (62.5%)	30 (62.5%)
Black or African American	3 (2.6%)	2 (1.7%)	5 (2.1%)	2 (2.2%)	2 (2.1%)	4 (2.1%)	1 (4.2%)	0 (0.0%)	1 (2.1%)
White	56 (47.9%)	69 (58.0%)	125 (53.0%)	48 (51.6%)	60 (63.2%)	108 (57.4%)	8 (33.3%)	9 (37.5%)	17 (35.4%)
Other	1 (0.9%)	1 (0.8%)	2 (0.8%)	1 (1.1%)	1 (1.1%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	2 (1.7%)	1 (0.8%)	3 (1.3%)	2 (2.2%)	1 (1.1%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity n (%)									
n	117	118	235	93	94	187	24	24	48
Hispanic or Latino	8 (6.8%)	9 (7.6%)	17 (7.2%)	5 (5.4%)	8 (8.5%)	13 (7.0%)	3 (12.5%)	1 (4.2%)	4 (8.3%)
Not Hispanic or Latino	109 (93.2%)	109 (92.4%)	218 (92.8%)	88 (94.6%)	86 (91.5%)	174 (93.0%)	21 (87.5%)	23 (95.8%)	44 (91.7%)
Body mass index (kg/m^2)									
Mean (SD)	27.77 (8.77)	27.09 (6.24)	27.43 (7.59)	28.29 (8.95)	27.60 (6.50)	27.94 (7.80)	25.74 (7.86)	25.08 (4.68)	25.41 (6.41)
Median	25.83	26.08	25.90	26.26	26.17	26.17	23.97	24.96	24.49
Min, Max	(13.6, 59.5)	(15.4, 47.7)	(13.6, 59.5)	(15.5, 59.5)	(15.4, 47.7)	(15.4, 59.5)	(13.6, 49.7)	(17.3, 36.2)	(13.6, 49.7)
Body mass index (kg/m^2) n (%)									
Normal (≤ 25)	53 (45.3%)	50 (42.0%)	103 (43.6%)	40 (43.0%)	38 (40.0%)	78 (41.5%)	13 (54.2%)	12 (50.0%)	25 (52.1%)
Overweight (> 25-30)	28 (23.9%)	37 (31.1%)	65 (27.5%)	23 (24.7%)	28 (29.5%)	51 (27.1%)	5 (20.8%)	9 (37.5%)	14 (29.2%)
Obese (> 30-35)	17 (14.5%)	18 (15.1%)	35 (14.8%)	13 (14.0%)	16 (16.8%)	29 (15.4%)	4 (16.7%)	2 (8.3%)	6 (12.5%)
Morbidly Obese (> 35)	19 (16.2%)	14 (11.8%)	33 (14.0%)	17 (18.3%)	13 (13.7%)	30 (16.0%)	2 (8.3%)	1 (4.2%)	3 (6.3%)

AChR+ = acetylcholine receptor antibody positive; Max = maximum; Min = minimum; MuSK+ = muscle-specific kinase antibody positive; N = Number of subjects in the
analysis set; n = Number of subjects with observed data.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
Total includes placebo and Inebilizumab. The denominator of the percentage is the n under each variable

Table 17: Baseline Characteristics and Myasthenia Gravis History - Full Analysis Set

Parameter Statistic	Overall Population Placebo N = 117	Overall Population Inebilizumab N = 119	Overall Population Overall N = 236	AChR+ [a] Population Placebo N = 93	AChR+ [a] Population Inebilizumab N = 95	AChR+ [a] Population Overall N = 188	MuSK+ [a] Population Placebo N = 24	MuSK+ [a] Population Inebilizumab N = 24	MuSK+ [a] Population Overall N = 48
Antibody Status, n (%)									
AChR+ [a]	93 (79.5%)	95 (79.8%)	188 (79.7%)	93 (100%)	95 (100%)	188 (100%)			
MuSK+ [a]	24 (20.5%)	24 (20.2%)	48 (20.3%)				24 (100%)	24 (100%)	48 (100%)
MG Disease Duration [b] (years)									
Mean (SD)	6.73 (7.28)	5.94 (6.96)	6.34 (7.12)	7.17 (7.62)	6.11 (7.27)	6.64 (7.45)	5.05 (5.59)	5.27 (5.61)	5.16 (5.54)
Median	4.40	3.60	3.88	4.52	3.59	4.35	3.47	3.67	3.63
Min, Max	(0.1, 33.1)	(0.1, 30.6)	(0.1, 33.1)	(0.1, 33.1)	(0.1, 30.6)	(0.1, 33.1)	(0.2, 21.0)	(0.1, 24.9)	(0.1, 24.9)
MG Disease Duration, n (%)									
< 4 years	56 (47.9%)	63 (52.9%)	119 (50.4%)	43 (46.2%)	49 (51.6%)	92 (48.9%)	13 (54.2%)	14 (58.3%)	27 (56.3%)
≥ 4 years	61 (52.1%)	56 (47.1%)	117 (49.6%)	50 (53.8%)	46 (48.4%)	96 (51.1%)	11 (45.8%)	10 (41.7%)	21 (43.8%)
MG-ADL score									
Mean (SD)	9.1 (2.8)	9.0 (2.8)	9.1 (2.8)	9.3 (2.8)	9.1 (2.7)	9.2 (2.7)	8.3 (2.5)	8.8 (3.1)	8.5 (2.8)
Median	9.0	8.0	8.5	9.0	9.0	9.0	8.5	8.0	8.0
Min, Max	(2, 17)	(1, 17)	(1, 17)	(6, 17)	(1, 15)	(1, 17)	(2, 14)	(6, 17)	(2, 17)
QMG score									
n	115	115	230	91	93	184	24	22	46
Mean (SD)	17.3 (4.2)	16.7 (4.2)	17.0 (4.2)	17.4 (4.3)	16.9 (4.1)	17.1 (4.2)	17.2 (3.9)	16.1 (4.8)	16.7 (4.3)
Median	17.0	16.0	16.0	17.0	16.0	16.0	17.5	14.0	16.0
Min, Max	(10, 31)	(11, 35)	(10, 35)	(11, 31)	(11, 35)	(11, 35)	(10, 25)	(11, 27)	(10, 27)
Baseline QMG score, n (%)									
n	115	115	230	91	93	184	24	22	46
QMG ≤ 15	48 (41.7%)	51 (44.3%)	99 (43.0%)	39 (42.9%)	38 (40.9%)	77 (41.8%)	9 (37.5%)	13 (59.1%)	22 (47.8%)
QMG ≥ 16	67 (58.3%)	64 (55.7%)	131 (57.0%)	52 (57.1%)	55 (59.1%)	107 (58.2%)	15 (62.5%)	9 (40.9%)	24 (52.2%)
MGC score									
n	115	117	232	91	94	185	24	23	47
Mean (SD)	19.6 (6.3)	18.1 (6.4)	18.8 (6.4)	19.6 (6.5)	18.0 (6.0)	18.8 (6.3)	19.5 (5.7)	18.7 (7.7)	19.1 (6.7)
Median	19.0	17.0	18.0	18.0	17.0	18.0	19.5	17.0	18.0
Min, Max	(3, 35)	(0, 38)	(0, 38)	(5, 35)	(0, 34)	(0, 35)	(10, 32)	(11, 38)	(10, 38)
Baseline MGFA Class, n (%)									
n	116	118	234	92	95	187	24	23	47

II	48 (41.4%)	56 (47.5%)	104 (44.4%)	36 (39.1%)	43 (45.3%)	79 (42.2%)	12 (50.0%)	13 (56.5%)	25 (53.2%)
III	61 (52.6%)	58 (49.2%)	119 (50.9%)	49 (53.3%)	49 (51.6%)	98 (52.4%)	12 (50.0%)	9 (39.1%)	21 (44.7%)
IV	7 (6.0%)	4 (3.4%)	11 (4.7%)	7 (7.6%)	3 (3.2%)	10 (5.3%)	11 (45.8%)	5 (21.7%)	16 (34.0%)
Corticosteroid/ Immunosuppressive therapy (IST) use, n (%)									
Corticosteroid only	68 (58.1%)	82 (68.9%)	150 (63.6%)	56 (60.2%)	69 (72.6%)	125 (66.5%)	12 (50.0%)	13 (54.2%)	25 (52.1%)
non-steroid IST only	9 (7.7%)	8 (6.7%)	17 (7.2%)	8 (8.6%)	5 (5.3%)	13 (6.9%)	1 (4.2%)	3 (12.5%)	4 (8.3%)
Corticosteroid plus 1 non-steroid IST	39 (33.3%)	29 (24.4%)	68 (28.8%)	28 (30.1%)	21 (22.1%)	49 (26.1%)	11 (45.8%)	8 (33.3%)	19 (39.6%)
Types of immunosuppressive treatments at baseline									
Prednisone (or equivalent)	107 (91.5%)	111 (93.3%)	218 (92.4%)	84 (90.3%)	90 (94.7%)	174 (92.6%)	23 (95.8%)	21 (87.5%)	44 (91.7%)
Daily dose ≤ 5 mg	11 (9.4%)	13 (10.9%)	24 (10.2%)	7 (7.5%)	9 (9.5%)	16 (8.5%)	4 (16.7%)	4 (16.7%)	8 (16.7%)
Daily dose > 5 mg	96 (82.1%)	98 (82.4%)	194 (82.2%)	77 (82.8%)	81 (85.3%)	158 (84.0%)	19 (79.2%)	17 (70.8%)	36 (75.0%)
Daily dose ≤ 20 mg	67 (57.3%)	82 (68.9%)	149 (63.1%)	54 (58.1%)	63 (66.3%)	117 (62.2%)	13 (54.2%)	19 (79.2%)	32 (66.7%)
Daily dose > 20 mg	40 (34.2%)	29 (24.4%)	69 (29.2%)	30 (32.3%)	27 (28.4%)	57 (30.3%)	10 (41.7%)	2 (8.3%)	12 (25.0%)
Azathioprine	29 (24.8%)	28 (23.5%)%	57 (24.2%)	22 (23.7%)	20 (21.1%)	42 (22.3%)	7 (29.2%)	8 (33.3%)	15 (31.3%)
Mycophenolate mofetil	16 (13.7%)	7 (5.9%)	23 (9.7%)	13 (14.0%)	5 (5.3%)	18 (9.6%)	3 (12.5%)	2 (8.3%)	5 (10.4%)
Mycophenolic acid	0 (0.0%)	1 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tacrolimus (Japan only)	3 (2.6%)	1 (0.8%)	4 (1.7%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	2 (8.3%)	1 (4.2%)	3 (6.3%)
Subject received Acetylcholinesterase Inhibitor at baseline	93 (79.5%)	94 (79.0%)	187 (79.2%)	80 (86.0%)	84 (88.4%)	164 (87.2%)	13 (54.2%)	10 (41.7%)	23 (47.9%)

AChR+ = acetylcholine receptor antibody positive; IST = immunosuppressive therapy; Max = maximum; Min = minimum; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MuSK+ = muscle specific kinase antibody positive; N = number of subjects in the analysis set; n = number of subjects with observed data; QMG = Quantitative Myasthenia Gravis; RCP = Randomized Controlled Period.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b MG disease duration = (Date of first dose in RCP - Date of MG diagnostic)/365.25.
The denominator of the percentage is the n under each variable. Total includes placebo and Inebilizumab.

Numbers analysed

Table 18: Analysis population All randomised subjects: overall population (top), AChR+ population (middle) and MuSK+ population (bottom)

Population	Placebo N = 119	Inebilizumab N = 119	Total N = 238
Full Analysis Set[a]	117 (98.3%)	119 (100%)	236 (99.2%)
Safety Analysis Set[b]	119 (100%)	119 (100%)	238 (100%)
Open-label Analysis Set[c]	84 (70.6%)	94 (79.0%)	178 (74.8%)
Any Inebilizumab Analysis Set[d]	84 (70.6%)	119 (100%)	203 (85.3%)
PK Analysis Set[e]	119 (100%)	119 (100%)	238 (100%)
Safety Follow up Analysis Set[f]	11 (9.2%)	5 (4.2%)	16 (6.7%)
Per-protocol Analysis Set[g]	106 (89.1%)	109 (91.6%)	215 (90.3%)

Population	Placebo N = 95	Inebilizumab N = 95	Total N = 190
Full Analysis Set[a]	93 (97.9%)	95 (100%)	188 (98.9%)
Safety Analysis Set[b]	95 (100%)	95 (100%)	190 (100%)
Open-label Analysis Set[c]	62 (65.3%)	70 (73.7%)	132 (69.5%)
Any Inebilizumab Analysis Set[d]	62 (65.3%)	95 (100%)	157 (82.6%)
PK Analysis Set[e]	95 (100%)	95 (100%)	190 (100%)
Safety Follow up Analysis Set[f]	9 (9.5%)	5 (5.3%)	14 (7.4%)
Per-protocol Analysis Set[g]	85 (89.5%)	88 (92.6%)	173 (91.1%)

Population	Placebo N = 24	Inebilizumab N = 24	Total N = 48
Full Analysis Set[a]	24 (100%)	24 (100%)	48 (100%)
Safety Analysis Set[b]	24 (100%)	24 (100%)	48 (100%)
Open-label Analysis Set[c]	22 (91.7%)	24 (100%)	46 (95.8%)
Any Inebilizumab Analysis Set[d]	22 (91.7%)	24 (100%)	46 (95.8%)
PK Analysis Set[e]	24 (100%)	24 (100%)	48 (100%)
Safety Follow up Analysis Set[f]	2 (8.3%)	0	2 (4.2%)
Per-protocol Analysis Set[g]	21 (87.5%)	21 (87.5%)	42 (87.5%)

N is Number of subjects randomized.
a Full Analysis Set includes all randomized subjects who received at least one dose of IP in the study and have baseline MG-ADL and at least one post-baseline MG-ADL observation. Subjects are analyzed according to the
treatment randomized.
b Safety Analysis Set includes all subjects who received any dose of IP. Subjects are analyzed according to the treatment they actually received during the RCP. Subject who received only placebo during the RCP are included
in placebo group. Subject who received any Inebilizumab are included in Inebilizumab group.
c The Open-label Analysis Set includes all subjects who received any dose of Inebilizumab during the OLP.
d The Any Inebilizumab Analysis Set includes all subjects who received any dose of Inebilizumab.
e Pharmacokinetic Analysis Set includes all subjects who received IP and have at least one quantifiable serum PK observation post first dose. Subjects are analyzed according to the treatment they actually received.
f Safety Follow up Analysis Set includes all subjects who entered into the safety follow up period.
g The per-protocol Analysis Set includes all subjects in the full analysis set who are sufficiently compliant with the protocol.

Only two randomised patients are excluded from the FAS.

Outcomes and estimation

Primary and key secondary endpoints

Primary efficacy endpoint

Table 19 shows results for the primary efficacy endpoint using the composite and treatment policy strategies.

Table 19: Change From Baseline at Week 26 in Myasthenia Gravis Activities of Daily Living Overall Population – Randomized Controlled Period (Full Analysis Set)

	Overall Population	
Variable	Placebo N = 117	Inebilizumab N = 119
Change from baseline in MG-ADL at week 26		
Using Composite Strategy		
n	105	111
LS Mean	-2.2	-4.2
Difference		-1.9
95% CI		(-2.9, -1.0)
p-value		<0.0001
Using Treatment-policy Strategy		
n	105	111
LS Mean	-3.0	-4.3
Difference		-1.3
95% CI		(-2.2, -0.4)
p-value		0.0067

AChR+ = acetylcholine receptor antibody positive; LS = Least squares; CI = confidence intervals; MG-ADL = Myasthenia Gravis Activities of Daily Living; MMRM = mixed-effects model for repeated measures; MuSK+ = muscle-specific kinase antibody positive; N =Number of subjects in the analysis set; n = Number of subjects with assessments at week 26; QMG = Quantitative Myasthenia Gravis; RCP = Randomization controlled period.
Baseline is defined as the last valid value on or prior to the first dose of RCP.
Composite Strategy: If a subject used rescue therapy after day 28 during RCP, the data collected on or after the initiation of the rescue therapy were imputed using the subject's worst observation collected before initiation of the rescue therapy.
Treatment-policy Strategy: The analyses include all data collected by week 26 regardless the rescue therapy use.
Estimate of the mean change from treatment group is compared to the placebo group using a repeated measures analysis.
The MMRM model for overall population is Change from baseline = Treatment + baseline antibody status (AChR+ vs MuSK+) + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (QMG ≤ 15 vs QMG ≥ 16) + baseline MG-ADL score + visit + treatment x visit.

Key secondary endpoints

The key secondary endpoints are presented following the hierarchy as explained in methods. Inebilizumab demonstrated a statistically significant improvement in the first 4 out of 5 key secondary endpoints (Table 20, Table 21, Table 22).

Table 20: Change From Baseline at Week 26 in Quantitative Myasthenia Gravis in Overall Population – Randomized Controlled Period – (Full Analysis Set)

	Overall Population	
Variable	Placebo N = 117	Inebilizumab N = 119
Change from baseline in QMG at week 26		
Using Composite Strategy		
n	103	107
LS Mean	-2.3	-4.8
Difference		-2.5
95% CI		(-3.8, -1.2)
p-value		0.0002
Using Treatment-policy Strategy		
n	103	107
LS Mean	-2.9	-4.9
Difference		-2.0
95% CI		(-3.3, -0.7)
p-value		0.0028

AChR+ = acetylcholine receptor antibody positive; LS = Least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MMRM = mixed-effects model for repeated measures; MuSK+ = muscle-specific kinase antibody positive; N =Number of subjects in the analysis set; n = Number of subjects with assessments at week 26; QMG = Quantitative Myasthenia Gravis; RCP = Randomization controlled period.
Baseline was defined as the last valid value on or prior to the first dose of RCP.
Composite strategy: The analyses included all data collected by week 26. If a subject used rescue therapy after day 28 during RCP, the data collected on or after the initiation of the rescue therapy were imputed using the subject's worst observation collected.
Treatment-policy Strategy: The analyses included all data collected by week 26 regardless the rescue therapy use.
Estimate of the mean change from treatment group is compared to the placebo group using a repeated measures analysis.
The MMRM model for overall population is Change from baseline = Treatment + baseline antibody status (AChR+ vs MuSK+) + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (continuous variable) + baseline MG-ADL score + visit + treatment x visit.

Table 21: Change From Baseline in Myasthenia Gravis Activities of Daily Living and Quantitative Myasthenia Gravis in Anti-AChR-Ab+ Subpopulation Randomized Controlled Period – (Full Analysis Set)

	Change From Baseline in MG-ADL at Week 26		Change From Baseline in QMG at Week 26	
Variable	Placebo N = 93	Inebilizumab N = 95	Placebo N = 93	Inebilizumab N = 95
Using Composite Strategy				
n	82	87	80	85
LS Mean	-2.4	-4.2	-2.0	-4.4
Difference		-1.8		-2.5
95% CI		(-2.9, -0.7)		(-3.9, -1.0)
p-value		0.0015		0.0011
Using Treatment-policy Strategy				
n	82	87	80	85
LS Mean	-3.0	-4.4	-2.3	-4.6
Difference		-1.4		-2.2
95% CI		(-2.5, -0.3)		(-3.8, -0.7)
p-value		0.0131		0.0042

AChR+ = acetylcholine receptor antibody positive; LS = Least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MMRM = mixed-effects model for repeated measures; MuSK+ = muscle-specific kinase antibody positive; N =Number of subjects in the analysis set; n = Number of subjects with assessments at week 26; QMG = Quantitative Myasthenia Gravis; RCP = Randomization controlled period.
Baseline is defined as the last valid value on or prior to the first dose of RCP.
Composite Strategy: If a subject used rescue therapy after day 28 during RCP, the data collected on or after the initiation of the rescue therapy were imputed using the subject's worst observation collected before initiation of the rescue therapy. Treatment-policy Strategy: The analyses include all data collected by week 26 regardless the rescue therapy use.
Estimate of the mean change from treatment group was compared to the placebo group using a repeated measures analysis.

The model for change from baseline in MG-ADL = Treatment + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (QMG≤15 vs QMG≥16) + baseline MG-ADL score + visit + treatment x visit.
The model for change from baseline in QMG = Treatment + baseline antibody status (AChR+ vs MuSK+) + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (continuous variable) + baseline MG-ADL score + visit + treatment x visit.

Table 22: Change From Baseline in Myasthenia Gravis Activities of Daily Living and Quantitative Myasthenia Gravis in Anti-MuSK-Ab+ Subpopulation Randomized Controlled Period – (Full Analysis Set)

	Change From Baseline in MG-ADL at Week 26		Change From Baseline in QMG at Week 26	
Variable	Placebo N = 24	Inebilizumab N = 24	Placebo N = 24	Inebilizumab N = 24
Using Composite Strategy				
n	23	24	23	23
LS Mean	-1.7	-3.9	-3.0	-5.2
Difference		-2.2		-2.3
95% CI		(-4.2, -0.2)		(-5.3, 0.7)
p-value		0.0297		0.1326
Using Treatment-policy Strategy				
n	23	24	23	23
LS Mean	-2.9	-3.8	-4.1	-5.3
Difference		-0.9		-1.2
95% CI		(-2.7, 1.0)		(-4.0, 1.6)
p-value		0.3415		0.3825

AChR+ = acetylcholine receptor antibody positive; LS = Least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MMRM = mixed-effects model for repeated measures; MuSK+ = muscle-specific kinase antibody positive; N =Number of subjects in the analysis set; n = Number of subjects with assessments at week 26; QMG = Quantitative Myasthenia Gravis; RCP = Randomization controlled period.
Baseline is defined as the last valid value on or prior to the first dose of RCP.
Composite Strategy: If a subject used rescue therapy after day 28 during RCP, the data collected on or after the initiation of the rescue therapy were imputed using the subject's worst observation collected before initiation of the rescue therapy. Treatment-policy Strategy: The analyses include all data collected by week 26 regardless the rescue therapy use.
Estimate of the mean change from treatment group was compared to the placebo group using a repeated measures analysis.
The model for change from baseline in MG-ADL = Treatment + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (QMG≤15 vs QMG≥16) + baseline MG-ADL score + visit + treatment x visit.
The model for change from baseline in QMG = Treatment + baseline antibody status (AChR+ vs MuSK+) + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (continuous variable) + baseline MG-ADL score + visit + treatment x visit.

Upon request, the Applicant provided the *ad hoc* supplementary analysis of changes from baseline in MG-ADL and QMG at week 26 in the overall population, anti-AChR-Ab+, and anti/MuSK-Ab+ subpopulations, respectively, that implemented a hypothetical strategy for handling rescue therapy use with a jump to reference imputation (Table 23).

Table 23: Overview of the Key Efficacy Results Using Hypothetical Strategy for Rescue Therapy Use (Randomized Controlled Period - Full Analysis Set)

	Overall Population		Anti-AChR-Ab+ Subpopulation		Anti-MuSK-Ab+ Subpopulation	
Variable	Placebo N = 117	Inebilizumab N = 119	Placebo N = 93	Inebilizumab N = 95	Placebo N = 24	Inebilizumab N = 24
Change from baseline in MG-ADL at week 26						
N	116	117	92	93	24	24
LS Mean	-2.7	-4.2	-2.8	-4.2	-2.3	-3.9
Difference		-1.5		-1.4		-1.7
95% CI		(-2.4, -0.6)		(-2.5, -0.4)		(-3.5, 0.2)
p-value		0.0015		0.0088		0.0779

Change from baseline in QMG at week 26						
N	114	113	90	91	24	22
LS Mean	-2.7	-4.8	-2.3	-4.4	-3.3	-5.2
Difference		-2.1		-2.1		-1.9
95% CI		(-3.4, -0.8)		(-3.5, -0.7)		(-4.8, 1.1)
p-value		0.0013		0.0040		0.2113

Anti-AChR-Ab+ = acetylcholine receptor antibody positive; anti-MuSK-Ab+ = muscle-specific kinase antibody positive; MG-ADL = Myasthenia Gravis Activities of Daily Living; MMRM = mixed model for repeated measures; N = number of subjects in the analysis set; n = number of subjects with assessments at week 26; QMG = Quantitative Myasthenia Gravis; RCP = randomized controlled period
Baseline is defined as the last valid value on or prior to the first dose of RCP.
Hypothetical strategy for rescue therapy use, where data following rescue therapy use are imputed based on jump to reference imputation.
Estimate of the mean change from treatment group is compared to the placebo group using a repeated measures analysis.
The MMRM model for overall population is:
Change from baseline = Treatment + baseline antibody status (AChR+ vs MuSK+) + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (as a continuous variable for change in QMG scores and as a binary variable for MG-ADL scores: QMG≤15 vs QMG≥16) + baseline MG-ADL score + visit + treatment x visit.
The MMRM model for AChR-Ab+ subpopulation and MuSK-Ab+ subpopulation is:
Change from baseline = Treatment + baseline steroid use (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg) + baseline QMG score (as a continuous variable for change in QMG scores and as a binary variable for MG-ADL scores: QMG≤15 vs QMG≥16) + baseline MG-ADL score + visit + treatment x visit

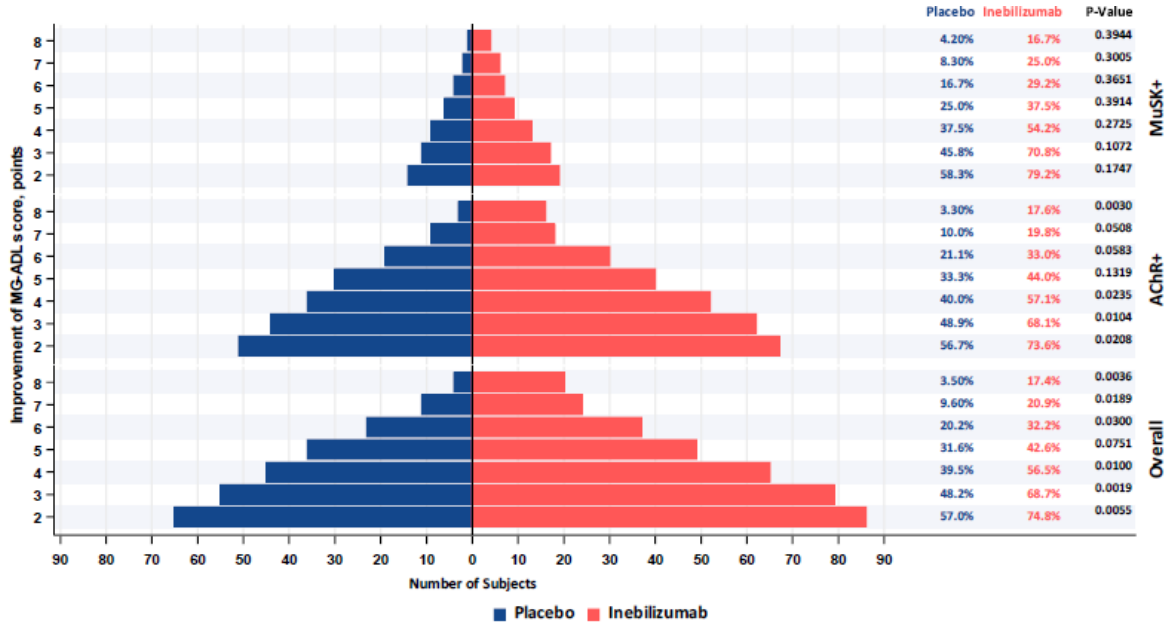
Exploratory endpoints

A number of secondary/exploratory endpoints were evaluated in addition to the primary and key secondary endpoints. I.e. they were not type-1 error controlled, so can be only supportive in nature.

Responder analyses for the primary endpoint (composite strategy)

For ≥3-point improvement in MG-ADL score with no rescue therapy use (between day 28 and week 26), the differences between inebilizumab and placebo in the proportions were 19.8%, 18.5%, and 23.4% for the overall study population, anti-AChR-Ab+ subpopulation and anti-MuSK-Ab+ subpopulation, respectively (Figure 15).

Figure 15: proportion of subjects with various improvements from baseline at week 26 in MG-ADL using composite strategy randomised controlled period (full analysis set)

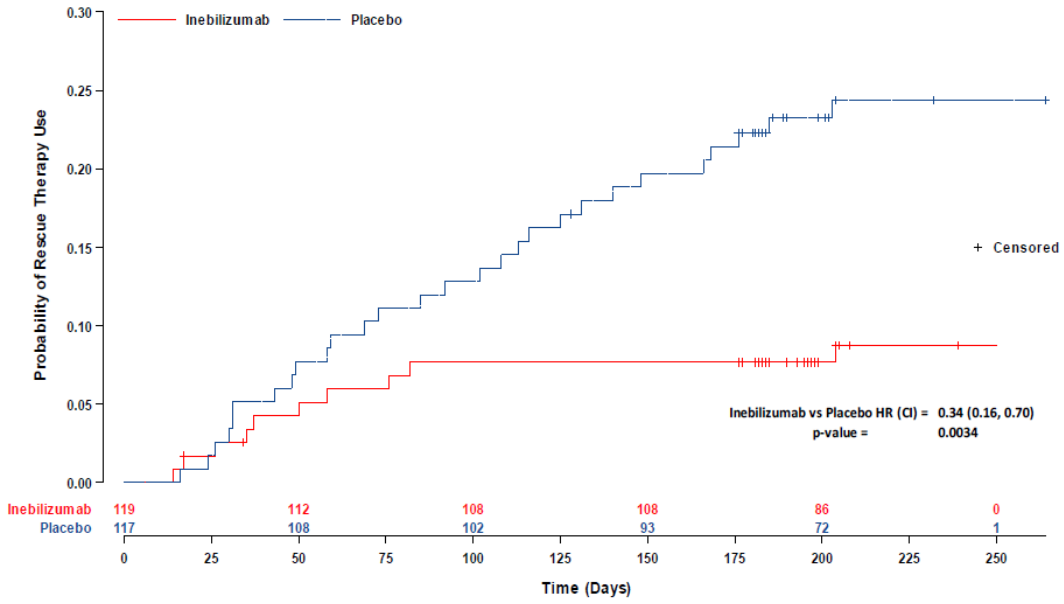


AChR+= acetylcholine receptor antibody positive; MG-ADL = Myasthenia Gravis Activities of Daily Living; MuSK+ = muscle-specific kinase antibody positive.
If a subject used rescue therapy after day 28 or discontinued from the study early, the subject was considered as a non-responder at the timepoints after the rescue therapy use or after the early discontinuation visit, whichever is earlier.

Rescue therapy

Inebilizumab treatment during RCP significantly delayed the time to first rescue therapy use compared to placebo in the overall population (Figure 16) and the proportion of subjects with any rescue therapy event was lower in the inebilizumab group vs placebo group (8.4% vs 23.9%, respectively, 95% CI: -21.7, -3.9). These results were consistent in the anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations. A high dose steroid (at a dose higher than baseline) rescue therapy use was reported in the overall population by week 26 in 5 subjects (4.2% in the inebilizumab group and 7 subjection (6.0%) in the placebo group.

Figure 16: Time to First Rescue Therapy Use Using Treatment-Policy Strategy by Week 26 in Overall Population - Randomized Controlled Period (Full Analysis Set)



Change From Baseline in MGC Score at Week 26 in the Overall Study Population, Anti AChR Ab+ and Anti MuSK Ab+ Subpopulations:

Inebilizumab improved MGC scores compared with placebo at week 26 in the overall population using the composite strategy (LS Mean 7.3 vs 4.7, difference -2.7, 95% CI: 4.6, 0.7, as well as in anti AChR Ab+ and anti MSK Ab+ subpopulations.

Proportion of Subjects With Minimal Symptom Expression at Week 26:

A higher percentage of subjects in the inebilizumab group achieved MSE at week 26 (MG-ADL score = 0 or 1 and no rescue therapy between day 28 and week 26) in the overall population (18.3% vs 9.6% inebilizumab vs placebo, respectively).

Delayed Time to First Exacerbation:

Inebilizumab delayed the time to first exacerbation compared with placebo in the overall population by week 26 and reduced the risk of exacerbation (hazard ratio [HR] of 0.41 (95% CI: 0.24, 0.70).

Similar results were observed by week 26 in anti AChR Ab+ subpopulation with HR of 0.49 (95% CI: 0.27, 0.90) and in the anti-MuSK Ab+ subpopulation with HR of 0.21 (95% CI: 0.06, 0.79).

Figure 17: Time to First Exacerbation by Week 26 Using Treatment-policy Strategy (Randomized Controlled Period) - Full Analysis Set

	Overall Population		AChR+ Population		MuSK+ Population	
	Placebo N = 117	Inebilizumab N = 119	Placebo N = 93	Inebilizumab N = 95	Placebo N = 24	Inebilizumab N = 24
Number (%) of subjects with Exacerbation	41 (35.0%)	19 (16.0%)	30 (32.3%)	16 (16.8%)	11 (45.8%)	3 (12.5%)
Number (%) of subjects with rescue therapy use	28 (23.9%)	10 (8.4%)	22 (23.7%)	9 (9.5%)	6 (25.0%)	1 (4.2%)
Number (%) of subjects with MG crisis	1 (0.9%)	2 (1.7%)	1 (1.1%)	2 (2.1%)	0	0
Number (%) of subjects with significant symptomatic worsening	25 (21.4%)	11 (9.2%)	18 (19.4%)	9 (9.5%)	7 (29.2%)	2 (8.3%)
Number (%) of censored subjects	76	100	63	79	13	21
Median time to exacerbation (days) [a]	NA	NA	NA	NA	NA	NA
95% CI [a]	(NA-NA)	(NA-NA)	(NA-NA)	(NA-NA)	(85.00-NA)	(196.00-NA)
Hazard ratio [b]		0.41		0.49		0.21
95% CI [b]		(0.24-0.70)		(0.27-0.90)		(0.06-0.79)
P-value [b]		0.0013		0.0210		0.0204

An exacerbation is defined as Use of protocol defined rescue therapy, or Myasthenic crisis or Significant symptomatic worsening. MG crisis is defined as worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation, except when these measures are employed during routine postoperative management. Significant symptomatic worsening is defined as MG-ADL total score of 3 or a 2-point worsening from baseline on any one of the individual items other than double vision or eyelid droop.
a Based on Kaplan-Meier method.
b Based on Cox regression method, with common covariates of treatment group, baseline steroid use status (daily prednisone dose ≤ 5 mg vs daily prednisone dose > 5 mg), baseline QMG score (QMG ≤ 15 vs QMG ≥16), and baseline MG-ADL score, and additional covariate, baseline antibody status (AChR-Ab+ or MuSK-Ab+), for the overall population.

Anti-AChR-Ab+ population week 52:

Proportion of Subjects With MG-ADL ≥3-Point Improvement at **Week 52**

At week 52 in the anti-AChR-Ab+ subpopulation, the proportion of subjects with ≥ 3-point improvement in MG-ADL score with no use of rescue therapy (between day 28 and week 52) was greater in the inebilizumab group (75.9%) vs placebo (40.5%).

Change From Baseline in MG-ADL Score at **Week 52** in the Anti-AChR-Ab+ Subpopulation:

Across the 52-week RCP in the anti-AChR-Ab+ subpopulation, inebilizumab treatment continuously improved MG-ADL scores compared to placebo (week 52 LS Mean -4.8 vs -1.8, respectively; difference -3.0; 95% CI: -4.1, -1.8 using composite strategy and LS Mean -5.1 vs -3.0, respectively; difference -2.2; 95% CI: -3.3m -1.1 using treatment policy). A greater difference between treatment groups in favor of inebilizumab was observed at week 52, compared to week 26.

Change From Baseline in QMG Score at Week 52 in the Anti-AChR-Ab+ Subpopulation:

In the anti-AChR-Ab+ subpopulation, inebilizumab treatment continuously improved QMG scores compared to placebo through week 52 (week 52 LS Mean -5.7 vs -1.4, respectively; difference -4.3; 95% CI: -5.9, -2.7). These results were numerically consistent between composite strategy and treatment policy strategy analyses.

Change From Baseline in MGC Score at Week 52 in the Anti AChR Ab+ population:

By week 52, MGC scores were further improved in the anti AChR Ab+ subpopulation compared with placebo using the composite strategy (LS Mean 8.7 vs 3.1, difference 5.6, 95% CI: 8.0, 3.2). The

change from baseline in MGC scores by week 26 and 52 using treatment-policy strategy was consistent with the composite strategy.

Delayed Time to First Exacerbation:

Inebilizumab delayed time to first exacerbation compared to placebo in the anti AChR Ab+ subpopulation by week 52 and reduced the risk of exacerbation (HR of 0.40, 95 CI: 0.23, 0.70).

Reduction of Steroid Use

Proportion of Subjects With Steroid Dose Modifications

At baseline, the daily steroid use > 5 mg was similar between inebilizumab and placebo groups (82.4% vs 82.1% overall population; 85.3% vs 82.8% in the anti-AChR-Ab+ subpopulation, 70.8% vs 79.2% in the anti-MuSK Ab+ subpopulation, respectively).

At week 26, the proportion of subjects with a daily steroid dose of ≤ 5 mg was similar between the inebilizumab and placebo groups among those who had a baseline dose of > 5 mg (87.4% vs 84.6% in the overall population; 85.9% vs 88.9% in the anti-AChR-Ab+ subpopulation for inebilizumab and placebo, respectively). In the anti-MuSK Ab+ subgroup, a higher proportion of subjects achieved the steroid taper at week 26 in the inebilizumab group, compared with the placebo group: 94.1% vs 68.4%, respectively. At week 52, the proportion of subjects with a daily steroid dose of ≤5 mg in the anti AChR Ab+ subpopulation was 90.9% vs 93.3%, inebilizumab vs placebo, respectively.

Proportion of Subjects Achieving ≥50% Steroid Reduction

At week 26, the proportion of subjects who achieved ≥ 50% steroid reduction was similar between the inebilizumab and placebo groups among those subjects that had a baseline dose of > 5 mg (60.0 vs 67.0% overall population; 60.3% vs 68.1% in the anti AChR Ab+ subpopulation; 58.8% vs 63.2% in the anti-MuSK Ab+ subpopulation. At week 52, the anti AChR Ab+ subpopulation results were also consistent (63.6% vs 65.0%, inebilizumab vs placebo).

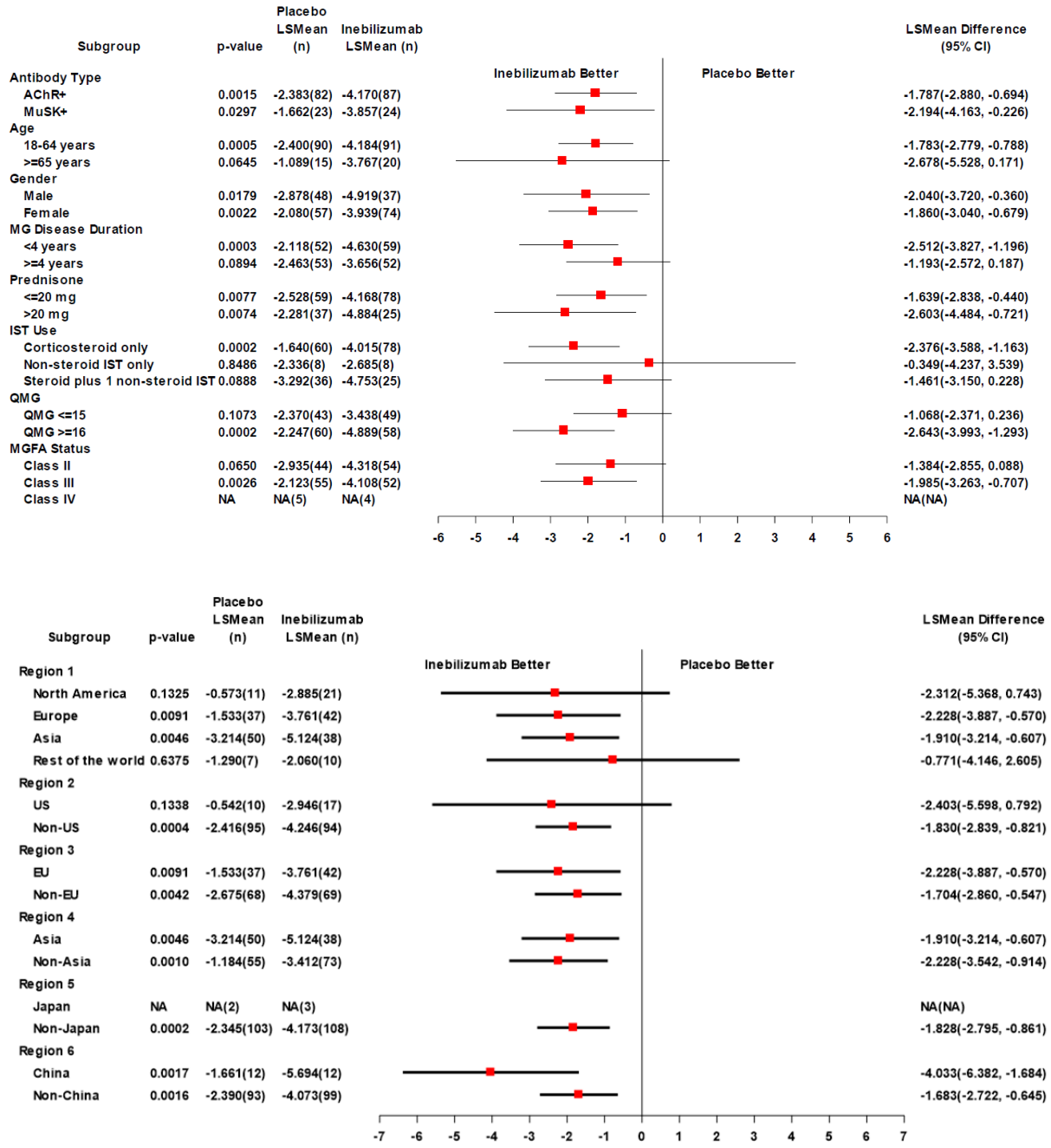
Ancillary analyses

Subgroup Analysis

Inebilizumab demonstrated directionally consistent efficacy for the primary endpoint of change in MG-ADL score at week 26 in the overall study population across all subgroups (Figure 18).

In addition, inebilizumab showed a similar and consistent efficacy for the key secondary endpoint of change in QMG score at week 26 in the overall population across all subgroups

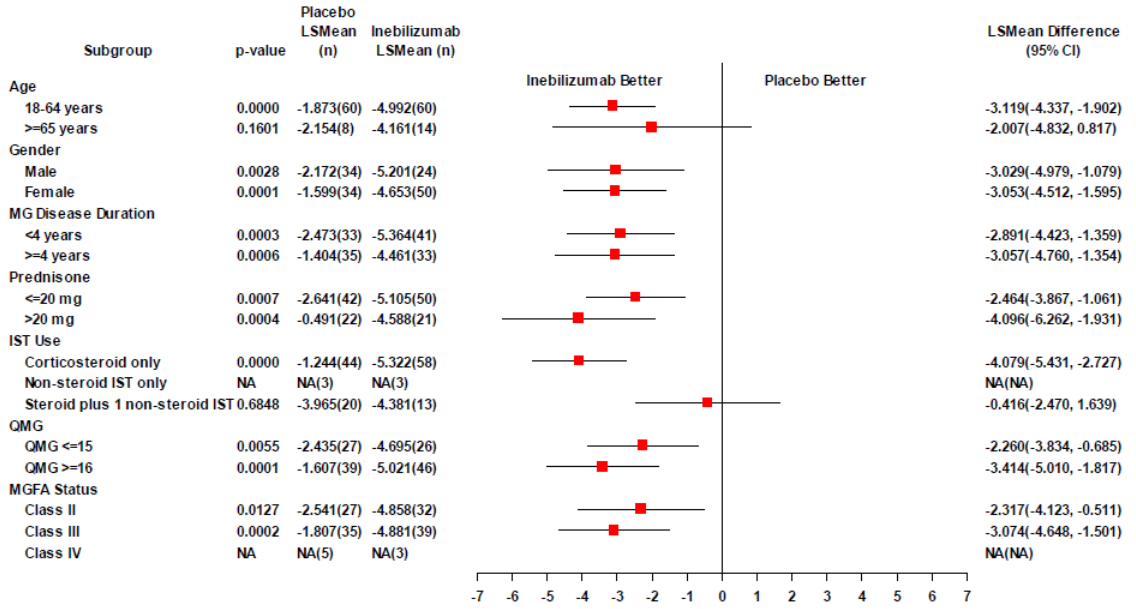
Figure 18: Forest Plot of Change From Baseline in Myasthenia Gravis Activities of Daily Living Score at Week 26 in Overall Population Using Composite Strategy– Randomized Controlled Period (Full Analysis Set)



AChR+ = acetylcholine receptor antibody positive; IST = immunosuppressive therapy; LS Mean = Least squares mean; MG = Myasthenia Gravis; MGFA = Myasthenia Gravis Foundation of America; MuSK+ = muscle-specific kinase antibody positive; n = Number of subjects with observed data; QMG = Quantitative Myasthenia Gravis.
LS Means were not calculated for subgroups with sample size less than 5% of the population

At week 52, the MG-ADL score change showed similar directionality across all subgroups within the anti-AChR-Ab+ subpopulation, as defined by the baseline characteristics (Figure 19).

Figure 19: Forest Plot of Change From Baseline in Myasthenia Gravis Activities of Daily Living Score at Week 52 in AChR+ Population Using Composite Strategy– Randomized Controlled Period (Full Analysis Set)



AChR+ = acetylcholine receptor antibody positive; IST = immunosuppressive therapy; LS Mean = Least squares mean; MG = Myasthenia Gravis; MGFA = Myasthenia Gravis Foundation of America; MuSK+ = muscle-specific kinase antibody positive; n = Number of subjects with observed data; QMG = Quantitative Myasthenia Gravis.
LS Means were not calculated for subgroups with sample size less than 5% of the population

Open Label period

The sponsor designed the RCP and OLP of Study MINT as a single study. The OLP is still ongoing.

All subjects who completed the RCP had the option to enroll in OLP of 3 years (156 weeks) for both subpopulations. In the OLP, further tapering of azathioprine, mycophenolate mofetil, mycophenolic acid, tacrolimus (if applicable), and corticosteroids was recommended.

Following the RCP, subjects from an active treatment group who elected to enter the OLP received inebilizumab 300 mg IV on OLP day 1, IV placebo on OLP day 15 (to avoid potential unblinding), and inebilizumab 300 mg IV on OLP week 26 (day 183), week 52 (day 365), week 78 (day 547), week 104 (day 729), and week 130 (day 911). Subjects from a placebo treatment group who elected to enter the OLP received inebilizumab 300 mg IV on OLP day 1, day 15, week 26 (day 183), week 52 (day 365), week 78 (day 547), week 104 (day 729), and week 130 (day 911). Safety Follow-up Period: Includes 2 years after the last IP dose would take place for subjects who did not enter the OLP or who discontinued the IP during the OLP.

As of the cut-off date (28 May 2024), a total of 94 subjects (79.0%) in the inebilizumab group and 84 subjects (70.6%) in the placebo group enrolled into the OLP.

Change From Baseline in MG-ADL Score During OLP

Among subjects in the anti AChR Ab+ subpopulation originally randomized to placebo who were switched to inebilizumab in the OLP, mean improvement in MG-ADL score was observed in subjects at week 26 of the OLP. The improvement was similar to that observed in the inebilizumab group upon initiation of treatment in the RCP. The mean (SD) change in MG ADL score at OLP week 52 was 6.3 (3.4) for the inebilizumab/inebilizumab group and 6.1 (3.2) for the inebilizumab/placebo group (Table 24).

Among subjects in the anti-MuSK Ab+ subpopulation originally randomized to placebo who were switched to inebilizumab in the OLP, mean improvement in MG-ADL was observed in subjects at week 26 of the OLP. The improvement was similar to that observed in the inebilizumab group upon initiation of treatment in the RCP. The mean (SD) change in MG ADL score at OLP week 52 was 6.0 (3.8) for the inebilizumab/inebilizumab group and 6.1 (4.1) for the inebilizumab/placebo group) (Table 24).

Table 24: Summary of MG-ADL Using Treatment-policy Strategy During Combined RCP and OLP – Any Inebilizumab Analysis Set

	AChR+[a] Population		MuSK+[a] Population	
	Placebo/ Inebilizumab N = 62	Inebilizumab/ Inebilizumab N = 95	Placebo/ Inebilizumab N = 22	Inebilizumab/ Inebilizumab N = 24
OLP day 1 - Change from baseline				
n	60	69	22	24
Mean	-3.1	-5.4	-3.1	-4.0
SD	3.5	3.0	3.3	3.5
(Min, Max)	(-12, 10)	(-13, 3)	(-9, 4)	(-12, 4)
OLP week 26 - Change from baseline				
n	52	60	17	20
Mean	-5.2	-5.9	-5.1	-5.6
SD	3.1	3.3	3.9	3.4
(Min, Max)	(-12, 5)	(-12, 3)	(-10, 5)	(-15, 0)
OLP week 52 - Change from baseline				
n	38	40	14	14
Mean	-6.1	-6.3	-6.1	-6.0
SD	3.2	3.4	4.1	3.8
(Min, Max)	(-15, 2)	(-14, 3)	(-14, 2)	(-15, -1)
OLP week 78 - Change from baseline				
n	23	27	7	8
Mean	-5.4	-6.2	-7.0	-7.9
SD	4.1	2.8	2.7	4.4
(Min, Max)	(-11, 6)	(-13, 0)	(-10, -3)	(-16, -2)

AChR+ = acetylcholine receptor antibody positive; anti-AChR-Ab+ = Anti-acetylcholine receptor specific antibodies; anti-MuSK-Ab+ = Anti-muscle-specific kinase specific antibodies; Max = maximum; MG-ADL = Myasthenia Gravis Activities of Daily Living; Min = minimum; MuSK+ = muscle-specific kinase antibody positive; N = Number of subjects in the analysis set; n = Number of subjects with observed data. The denominator of the percentage is the n under each variable; OLP = Open-label period; RCP = Randomized controlled period; SD = standard deviation.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
Baseline was defined as the last valid value on or prior to the first dose of RCP

Change in QMG Score From Baseline During the OLP

Among subjects in the anti AChR Ab+ subpopulation originally randomized to placebo who were switched to inebilizumab in the OLP, mean improvement in QMG was observed in subjects at week 26 of the OLP. The improvement was similar to that observed in the inebilizumab group upon initiation of treatment in the RCP. The mean (SD) change in QMG score at OLP week 52 was 7.6 (4.4 for the inebilizumab/inebilizumab group and 7.1 [5.6] for the inebilizumab/placebo group) (Table 25).

Among subjects in the anti-MuSK Ab+ subpopulation originally randomized to placebo who were switched to inebilizumab in the OLP, mean improvement in QMG was observed in subjects at week 26 of the OLP. The improvement was similar to that observed in the inebilizumab group upon initiation of treatment in the RCP. The mean (SD) change in QMG score at OLP week 52 was 8.8 (6.1) for the inebilizumab/inebilizumab group and 9.4 (5.5) for the inebilizumab/placebo group) (Table 25).

Table 25: Summary of QMG Using Treatment-policy Strategy During Combined RCP and OLP – Any Inebilizumab Analysis Set

	AChR+[a] Population		MuSK+[a] Population	
	Placebo/ Inebilizumab N = 62	Inebilizumab/ Inebilizumab N = 95	Placebo/ Inebilizumab N = 22	Inebilizumab/ Inebilizumab N = 24
OLP day 1 - Change from baseline				
n	58	67	22	22
Mean	-3.3	-6.6	-4.2	-5.0
SD	4.2	5.2	5.3	4.7
(Min, Max)	(-14, 6)	(-18, 5)	(-18, 5)	(-13, 2)
OLP week 26 - Change from baseline				
n	50	58	17	19
Mean	-6.2	-7.4	-7.6	-5.9
SD	5.1	5.0	5.0	4.8
(Min, Max)	(-21, 5)	(-19, 3)	(-18, 2)	(-14, 2)
OLP week 52 - Change from baseline				
n	36	38	13	13
Mean	-7.1	-7.6	-9.4	-8.8
SD	5.6	4.4	5.5	6.1
(Min, Max)	(-21, 8)	(-17, 4)	(-21, 1)	(-21, -1)
OLP week 78 - Change from baseline				
n	23	27	7	7
Mean	-6.8	-7.7	-7.4	-9.3
SD	6.4	4.0	5.7	5.2
(Min, Max)	(-21, 3)	(-14, -2)	(-15, 2)	(-16, -2)

AChR+ = acetylcholine receptor antibody positive; anti-AChR-Ab+ = Anti-acetylcholine receptor specific antibodies; anti-MuSK-Ab+ = Anti-muscle-specific kinase specific antibodies; Max = maximum; MG-ADL = Myasthenia Gravis Activities of Daily Living; Min = minimum; MuSK+ = muscle-specific kinase antibody positive; N = Number of subjects in the analysis set; n = Number of subjects with observed data. The denominator of the percentage is the n under each variable; OLP = Open-label period; RCP = Randomized controlled period; SD = standard deviation.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
Baseline was defined as the last valid value on or prior to the first dose of RCP

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of Efficacy for trial MINT

Title: A Randomized, Double-Blind, Multicenter, Placebo-Controlled Phase 3 Study with Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis	
Study identifier	Protocol number: VIB0551.P3.S1 (MINT; Amgen reference: (20230049) EudraCT: 2020-000949-14 ClinicalTrials.gov: NCT 04524273
Design	Study VIB0551.P3.S1 (MINT; 20230049) is a randomized, double-blind, multicenter, placebo-controlled phase 3 study with an open-label period (OLP) to evaluate the efficacy and safety of inebilizumab in adults with MG. Adult subjects aged ≥ 18 years with acetylcholine receptor antibody positive (AChR-Ab+) or muscle-specific kinase antibody positive (MuSK-Ab+) generalized MG were included.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks for the anti-AChR-Ab+ population and 26 weeks for the anti-MuSK-Ab+ subpopulation with an optional 3-year OLP An optional 3-year OLP With 2-year safety follow-up period
Hypothesis	Superiority		
Treatments groups	RCP Phase Inebilizumab		119 (out of 238) subjects were randomized (1:1 ratio) to the inebilizumab group (intravenous (IV) inebilizumab 300 mg on day 1, day 15, and week 26(day 183) of the 52-week RCP. Week 26 dosing in RCP for the anti-MuSK-Ab+ subpopulation only
	RCP Phase Placebo		119 (out of 238) subjects were randomized (1:1 ratio) to the placebo group intravenous (IV) placebo on day 1, day 15, and week 26 (day 183) of the 52-week RCP. Week 26 dosing in RCP for the anti-MuSK-Ab+ subpopulation only
	OLP Phase Inebilizumab		300 mg inebilizumab IV on day 1, blinded 300 mg inebilizumab or placebo on day 15, then inebilizumab 300 mg IV every 6 months thereafter
Endpoints and definitions	Primary endpoint	Change from baseline in MG-ADL score at week 26 in the overall study population (anti-AChR-Ab+ and anti-MuSK-Ab+ populations).	Change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at week 26 in the overall study population, i.e., the Acetylcholine receptor antibody positive (anti-AChR-Ab+) and Muscle-specific kinase antibody positive (anti-MuSK-Ab+) populations. Baseline is defined as the last valid value on or prior to the first dose of RCP.
	Key Secondary Endpoint	Change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 26 in the overall study population	Change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 26 in the overall study population.
	Key Secondary Endpoint	Change from baseline in MG-ADL score at week 26 in the anti-AChR-Ab+ population.	Change from baseline in MG-ADL score at week 26 in the anti-AChR-Ab+ population.

	Key Secondary Endpoint	Change from baseline in QMG score at week 26 in the anti-AChR-Ab+ population.	Change from baseline in QMG score at week 26 in the anti-AChR-Ab+ population.
	Key Secondary Endpoint	Change from baseline in MG-ADL score at week 26 in the anti- MuSK-Ab+ population.	Change from baseline in MG-ADL score at week 26 in the anti-MuSK-Ab+ population.
	Key Secondary Endpoint	Change from baseline in QMG score at week 26 in the anti-MuSK-Ab+ population.	Change from baseline in QMG score at week 26 in the anti-MuSK-Ab+ population.
	Additional secondary endpoint	Change from baseline in MG-ADL score at week 52 in the anti-AChR-Ab+ population.	Change from baseline in MG-ADL score at week 52 in the anti-AChR-Ab+ population.
	Additional secondary endpoint	Change from baseline in QMG score at week 52 in the anti-AChR-Ab+ population.	Change from baseline in QMG score at week 52 in the anti-AChR-Ab+ population.
	Additional Secondary endpoint	Rescue therapy use by week 26 in the overall population	Proportion of subjects who used rescue therapy by week 26 in the overall population
	Additional Secondary endpoint	Time to first exacerbation by week 26 in the overall population	Time to first exacerbation by week 26 in the overall population
Database lock	Study is still ongoing. Data cutoff date for the primary analysis: 28 May 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Of the 238 randomized subjects, 190 subjects were anti-AChR-Ab+ and 48 subjects were anti-MuSK-Ab+. Overall, 112 subjects (94.1%) in the inebilizumab group and 110 subjects (92.4%) in the placebo group completed treatment during the RCP. As of data cutoff date, 94 subjects (79.0%) in the inebilizumab group and 84 subjects (70.6%) in the placebo group enrolled into OLP. Baseline Demographics: -Sex: 39% men, 61% women - Age: mean (SD) age at baseline was 47.5 (15.3) years - Race: American Indian or Alaska Native (0.4%), Asian (42.4%), Black or African American (2.1%), Black (0.7%), White (53%), Other (0.8%), Not Reported (1.3%) - Ethnicity: Hispanic/Latino 7.2%, Not Hispanic or Latino 92.8% Time point description and assessments: per protocol: -RCP: at weeks 0-2-4-8-12-18-26 or EDV (early discontinuation visit) -OLP: at weeks 0-2-13, 26-39-52, 65-78-104, 130-156 or EDV		

Descriptive statistics and estimate variability	Treatment group	Placebo *{as per above terminology}*	Inebilizumab *{as per above terminology}*
	Change from baseline in the MG-ADL score at Week 26 in overall population Number of subjects Mean (SD)	 105 -2.4 (3.6)	 111 -4.2 (3.7)
	Change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 26 in the overall study population Number of subjects Mean (SD)	 103 -2.3 (5.0)	 107 -4.4 (4.8)
	Change from baseline in MG-ADL score at week 26 in the anti-AChR-Ab+ population. Number of subjects Mean (SD)	 82 -2.5 (3.5)	 87 -4.2 (3.7)
	Change from baseline in QMG score at week 26 in the anti-AChR-Ab+ population Number of subjects Mean (SD)	 80 -2.2 (4.8)	 85 -4.3 (4.9)
	Change from baseline in MG-ADL score at week 26 in the anti-MuSK-Ab+ population. Number of subjects Mean (SD)	 23 -1.9 (3.8)	 24 -4.1 (3.6)
	Change from baseline in QMG score at week 26 in the anti-MuSK-Ab+ population Number of subjects Mean (SD)	 23 -2.9 (5.9)	 22 -5.0 (4.7)
	Change from baseline in MG-ADL score at week 52 in the anti-AChR-Ab+ population Number of subjects Mean (SD)	 68 -1.8 (3.9)	 74 -5.1 (3.3)
	Change from baseline in MG-ADL score at week 52 in the anti-AChR-Ab+ population Number of subjects Mean (SD)	 66 -1.5 (5.2)	 71 -6.1 (5.8)

	Rescue therapy use by week 26 in the overall population Number of subjects n(%)	117 28 (23.9%)	119 10 (8.4%)
Effect estimate per comparison	Change from baseline in the MG-ADL score at Week 26 in overall population	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-4.2 vs -2.2
		Difference	-1.9
		95% CI	(-2.9, -1.0)
		P-value	<0.0001
	Change from Baseline in QMG score at Week 26 in overall population	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-4.8 vs. -2.3
		Difference	-2.5
		95% CI	(-3.8, -1.2)
		P-value	0.0002
	Change from Baseline in MG-ADL score at Week 26 in Anti-AChR Ab+ Subpopulation	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-4.2 vs. -2.4
		Difference	-1.8
		95% CI	(-2.9, -0.7)
		P-value	0.0015
	Change from Baseline in QMG score at Week 26 in Anti-AChR Ab+ Subpopulation	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-4.4 vs. -2.0
		Difference	-2.5
		95% CI	(-3.9, -1.0)
		P-value	0.0011
	Change from Baseline in MG-ADL score at Week 26 in Anti-MuSK Ab + Subpopulation	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-3.9 vs. -1.7
		Difference	-2.2
		95% CI	(-4.2, -0.2)
		P-value	0.0297
	Change from Baseline in QMG score at Week 26 in Anti-MuSK Ab + Subpopulation	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-5.2 vs. -3.0
		Difference	-2.3

		95% CI	(-5.3, -0.7)
		P-value	0.1326
	Change from Baseline in MG-ADL score at Week 52 in Anti-AChR Ab+ Subpopulation	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-4.8 vs. –1.8
		Difference	-3.0
		95% CI	(-4.1, -1.8)
		Nominal P-value	<0.0001
	Change from Baseline in MG-ADL score at Week 52 in Anti-MuSK Ab+ Subpopulation	Comparison groups	Inebilizumab vs. Placebo
		LS Mean	-5.7 vs. –1.4
		Difference	-4.3
		95% CI	(-5.9, -2.7)
		Nominal P-value	<0.0001
	Rescue therapy use by week 26 in the overall population	Comparison groups	Inebilizumab vs. Placebo
		Difference in proportions	-12.8%
		95% CI	(-21.7%, -3.9%)
		Nominal P-value	0.0049
	Time to first exacerbation by week 26 in the overall population	Comparison groups	Inebilizumab vs. Placebo
		Hazard ratio	0.41
		95% CI	(0.24, 0.70)
		Nominal P-value	0.0013
Notes	Inebilizumab showed a statistically significant and clinically meaningful benefit versus placebo in improvement of MG-ADL (MG-related disability) and QMG (disease severity) scores, respectively at week 26 across the overall gMG population. For the anti-AChR-Ab+ subpopulation, improvement was statistically significant and clinically meaningful in both MG-ADL and QMG scores. In the anti-MuSK-Ab+ subpopulation, inebilizumab demonstrated statistically significant and clinically meaningful benefit in improvement of MG-ADL and a clinically meaningful benefit in QMG, though it did not reach statistical significance for the latter.. Of the 4 subjects (3.4%) in the inebilizumab group who did not complete the RCP, 1 discontinued due to adverse events (AE)s. Two subjects withdrew consent. 15 subjects discontinued study drug during the OLP; 1 subject (0.8%) discontinued due an AE and 5 subjects withdrew consent. As of the data cutoff, no subjects have completed the study.		
Analysis description	N/A		

2.4.3. Discussion on clinical efficacy

The Applicant has sought the following extension of indication (new indication in **bold**):

<u>Neuromyelitis optica spectrum disorders (NMOSD)</u>

Uplizna is indicated as monotherapy for the treatment of adult patients with NMOSD who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive (see section 5.1).

Generalized myasthenia gravis (gMG)

Uplizna is indicated as an add-on to standard therapy for the treatment of adult patients with gMG (see section 5.1).

The following gMG indication has been agreed upon:

Generalized myasthenia gravis (gMG)

Uplizna is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive

Design and conduct of clinical studies

No dose-response studies were conducted. A similar dosing regimen as for the already approved NMOSD has been proposed. This is acceptable.

One pivotal trial in patients with gMG who were anti-AChR Ab+ and anti-MuSK Ab+ was conducted to support the use of inebilizumab in gMG.

In this case, there is a mechanistic rationale to use B-cell depletion for the treatment of gMG and it is acceptable to have only one pivotal trial.

The pivotal MINT trial was a multinational, double-blind, placebo-controlled trial with RCP of 26 and 52 weeks (52 weeks for the anti-AChR Ab+ patients only) and an OLP of up to 3 years.

The trial was conducted in 126 centers in Argentina, Belarus, Brazil, Canada, China, Denmark, France, Germany, India, Israel, Italy, Japan, Poland, Russia, South Korea, Spain, Taiwan, Turkey, Ukraine, and United States (US).

The gMG patients included had moderate to severe disease activity. Anti-AChR Ab+ are the most common subtype of gMG with the anti-MuSK-Ab+ being rare, with a more severe phenotype and more treatment resistant. Anti-MuSK Ab+ are usually anti-AChR Ab negative. All patients were positive for either anti-AChR or anti-MuSK antibodies.

The primary endpoint was amended during the study in protocol version 7.0. In the former plan, the anti-AChR Ab+ patients had a planned primary evaluation at week 52. This is now a secondary endpoint and will inform on the sustained effect in the anti-AChR Ab+ patients. Amendments to the primary endpoint and estimand strategies were formalized and pre-specified in the protocol and SAP prior to database lock, and are therefore statistically valid. The Applicant justified the use of the pooled population based on the expectation that a CD19 B cell depleting therapy would provide comparable efficacy across both subgroups, and highlighted that the majority of the study population consisted of AChR-Ab+ patients and that the treatment effect plateaued by week 26, making this a clinically meaningful and analytically practical time point for all patients. Although the change in the estimand was introduced late, the Applicant provided extensive supportive analyses under composite, treatment policy, and hypothetical strategies.

After the double-blind period, 26 weeks for anti-MuSK Ab+ patients and 52 weeks for the anti-AChR Ab+ patients, patients could roll over in an OLP with a planned duration of up to 3 years.

Overall, in- and exclusion criteria in the MINT trial are acceptable. Patients with moderate to severe gMG defined as: MGFA Clinical Classification Class II, III, or IV at the time of screening and randomization; MG-ADL score of 6 or greater at screening and at randomization with > 50% of this score attributed to non-ocular items and QMG score of 12 or greater at screening and at randomization, were included. Patients with a MGFA class I (ocular symptoms only) or MGFA class V (intubation with and without mechanical ventilation) were not included in the trial.

The inebilizumab dosing regimen was the same as that approved for the indication NMOSD, that is 300 mg inebilizumab IV on Day 0, 15 and every 6 months thereafter. As there are no expected differences in the PK and depletion of B-cells between patients with gMG and NMOSD, this is considered acceptable. Pre-medication was administered according to label (corticosteroid, antihistamines and anti-pyretic) approximately 30-60 minutes prior to each administration.

Corresponding placebo was administered at Day 0, 15 for both anti-AChR-Ab+ and anti-MuSK-Ab+ patients and at Day 183 (week 26) for the Anti-AChR-Ab+ patients since they have an endpoint assessment at week 52 as well (previously planned primary evaluation time point before the protocol amendment 7).

The inebilizumab dosing regimen in the OLP was for those randomized to placebo in the RCP: OLP day 1, day 15, week 26 (day 183), week 52 (day 365), week 78 (day 547), week 104 (day 729), and week 130 (day 911). Those randomized to inebilizumab in the RCP: OLP day 1, week 26 (day 183), week 52 (day 365), week 78 (day 547), week 104 (day 729), and week 130 (day 911). Overall, the administered treatments are done in an acceptable way.

Certain concomitant IST were allowed during the trial, however they had to be stable during the 4 weeks prior to randomization. ISTs allowed were corticosteroids (if already on treatment prior to trial entry) and non-steroid IST (azathioprine, mycophenolate mofetil and mycophenolic acid). Corticosteroids were tapered during the randomized controlled period to a maintenance dose of 5 mg prednisone (or equivalent). Acetylcholine esterase inhibitor (pyridostigmine) dose had to be stable from 2 weeks prior to randomization and $\leq$ 480 mg/day. Other IST were not allowed in the trial. IVIg, PLEX and corticosteroids were used as rescue medication and was administered based on the investigators judgement. Corticosteroids were to be tapered to prior dose after rescue treatment.

The evaluation of efficacy was based mainly on the MG-ADL, subjective assessment of MG symptoms by the patient) and QMG, (quantitative evaluation of relevant muscle groups by the physician) scales.

The primary endpoint was change from baseline in MG-ADL score at week 26 in the overall study population (anti-AChR Ab+ and anti-MuSK Ab+).

Key secondary endpoints were 1) change from baseline in QMG score at week 26 in the overall population, 2) change from baseline in MG-ADL score at week 26 in the AChR-Ab+ population, 3) change from baseline in QMG score at week 26 in the AChR-Ab+ population, 4) change from baseline in MG-ADL score at week 26 in the MuSK-Ab+ population and 5) change from baseline in the QMG score at week 26 in the MuSK-Ab+ population.

Use of both MG-ADL (patient perspective) and QMG (physician perspective) is considered relevant.

Several definitions of responders and related secondary/exploratory endpoints were used. MGC, MG-QoL15r and PGIC were also used as specific scales but not as primary or key secondary endpoints and they are considered supportive only.

The selected endpoints are standard methods for evaluation of MG and have previously been used in several clinical studies in this condition. This is acceptable.

The current protocol version is number 7.0. The protocol changes are listed in the submitted version of the protocol, but no discussion or overview of the protocol changes and the potential impact on the results were provided by the Applicant. In protocol version 7, regarding the primary endpoint: Revised the primary endpoint to state that MG-ADL score will be measured for the overall study population at Week 26, instead of separately for the 2 populations at different timepoints (ie, Week 52 for AChR-Ab+ subjects). The shortened duration is based on previous study experience with inebilizumab in NMOSD, in which CD19-mediated B-cell depletion was efficacious within 26 weeks. The Applicant claimed that the pooling of the 2 populations is supported by the expectation that a CD19 B-cell-depleting drug will offer similar levels of efficacy in both populations, as CD19+ B-cells are expressed earlier in development than CD20+ B-cells. This was followed by a number of new endpoints and relocation of endpoints to being secondary and not exploratory. Also the total number of patients enrolled were updated to 230 in total, 188 for the for anti-AChR-Ab+ and 42 for the anti-MuSK-Ab+. In the CHMP SA from 2020, it was in fact advised not to have different timepoints for the primary evaluation for the two patient populations (for AChR-Ab+ and anti-MuSK-Ab+), as it may be considered to be two separate trials.

Statistical methods: Sample size was estimated using a two-sided t-test. Approximately 188 subjects with AChR-Ab+ and 42 subjects with MuSK-Ab+ were planned to be randomized. This sample size was calculated to provide more than 95% power to detect a two-point mean treatment difference in MG-ADL score in the overall study population at a two-sided significance level of 0.05, assuming a common standard deviation of 4. For the AChR-Ab+ population specifically, the sample size was estimated to provide at least 90% power to detect the same treatment difference under the same assumptions. The assumed standard deviation of 4 was not based on internal or empirical data but was justified in the SAP as being derived from publicly available competitor studies using MG-ADL in a similar population. The sample size for the MuSK-Ab+ population was determined based on feasibility, and a minimum detectable treatment difference of 2.5 points was calculated. However, no formal power calculation was provided.

Participants were randomized 1:1 into the treatment and placebo group. Randomization was stratified according to antibody status (AChR-Ab positive vs. MuSK-Ab positive) and region (Japan vs. non-Japan). In the non-Japan population, further stratification factors were baseline disease severity (QMG score 11–15 vs. ≥16), and baseline corticosteroid use (prednisone >5 mg/day vs. ≤5 mg/day), with the threshold of 5 mg/day defined in the SAP but not formally justified. In Japan, where only six subjects were randomized, no additional stratification was applied. Japan was selected as a separate stratification factor to account for regional treatment differences, including the allowance of tacrolimus in that population.

Multiple analysis sets were employed to support different study objectives. The FAS was used for the main analyses in the primary and key secondary efficacy endpoints, was a mITT population that included all randomized subjects who received at least one dose of IP, had a baseline MG-ADL assessment, and at least one post-baseline MG-ADL measurement. This definition excluded two subjects (0.8% of the randomized population), both from the placebo arm in the AChR+ population, due to missing either the baseline assessment, post-baseline data, or both. The safety analysis set included all randomized subjects, confirming that all received at least one dose of study treatment. Although, in theory, the two excluded subjects from the placebo arm could have had favourable outcomes, they had no usable baseline/post-baseline MG-ADL data and therefore would not have contributed to the MMRM-based primary analysis even if retained in the FAS. As both exclusions occurred in the placebo arm and the maximum possible impact on responder rates

is negligible, the treatment effect estimate is not meaningfully affected, and no further request was pursued.

The primary and key secondary endpoints (MG-ADL, QMG) were analysed using a consistent estimand strategy and methodology based on the FAS. Both integer-valued endpoints had sufficient ranges (MG-ADL: 0–24; QMG: 0–39) and were treated as continuous variables in the analyses. The primary analysis for each was conducted using a MMRM, including fixed effects for treatment, visit, treatment-by-visit interaction, baseline MG-ADL score, antibody status, baseline prednisone dose, and QMG severity. An unstructured covariance matrix was prespecified, with compound symmetry as fallback. Although QMG severity was modelled as a binary variable in the MMRM per SAP Version 3 (<16 vs. ≥16), it was defined as a continuous covariate included in the MMRM per Protocol Version 7. The divergence between Protocol v7 and SAP v3 regarding the coding of QMG severity was implementation-driven and does not appear to materially affect the results.

Intercurrent events were handled using a prespecified hybrid estimand strategy. Rescue therapy initiated after day 28 was addressed using a composite strategy, where post-rescue data were replaced by the subject's worst pre-rescue observation. Early rescue therapy (on or before day 28) and treatment discontinuation were handled using a treatment policy strategy, whereby all collected data were retained. This combination approach diverged from scientific advice, which recommended the treatment policy strategy as the primary method (this was, however, included as a prespecified supplementary analysis, thereby partially aligning with the advice and enhancing the robustness of the treatment effect estimation). During the assessment, the Applicant was requested to provide supplementary results using the hypothetical strategy for handling the intercurrent event of use of rescue to understand the effect of inebilizumab on its own.

As per missing data, the number of subjects with missing MG-ADL and QMG assessments has been provided. There was no apparent tendency for missing measurements to be concentrated in either treatment arm. The proportion of observations that were missing was relatively small.

Finally, the population in the estimand is defined as "subjects in the FAS" by the Applicant. However, the population should have been defined as target population with no reference to trial features or analysis populations.

The Mixed Effects framework assumes normality of residuals. Even though the overall and AChR-Ab+ populations had adequate sample sizes and a large number of repeated measures per subject, making violations of the normality assumption for model residuals unlikely, the assumption of normality of residuals from the fixed effects MMRM model should still be empirically verified. This is particularly important for the MuSK-Ab+ subgroup, which demonstrated a statistically significant treatment effect on MG-ADL at Week 26 under the composite strategy but not under the treatment policy strategy, and showed no statistical significance for the key secondary endpoint (QMG) with any of the estimands. Given the small sample size of 48 subjects and the strategy-dependent result, the validity of the observed treatment effect in this subgroup relies heavily on the correctness of the model assumptions. Both visual and numerical assessments of residual normality, such as residual plots, QQ-plots and the Shapiro Wilk test, have been provided for the primary and key secondary endpoints in the overall population, the AChR-Ab+ population, and especially the MuSK-Ab+ subgroup, to confirm the appropriateness of the model and the credibility of the results. From the QQ-plots, it appears that the distribution of residuals can be reasonably approximated by a Gaussian distribution. The investigations and discussions in the presented references provide adequate assurance regarding the robustness of the MMRM results.

In addition, for the MuSK-Ab+ population, the confidence intervals provided from the bootstrap procedure were consistent with the model-based confidence intervals. This provides assurance of the robustness of the results for the anti-MuSK-AB+ subgroup.

Study-wise type I error was controlled using a predefined testing hierarchy, containing one primary and five key secondary endpoints. The testing hierarchy was implemented and followed. In the hierarchy, hypotheses concerning the overall population were prioritised over those concerning the AChR-Ab+ population, which was again prioritised over the MuSK-Ab+ population. Hypotheses concerning MG-ADL were prioritised over those concerning QMG. No multiplicity control was implemented for subgroup or exploratory analyses.

Efficacy data and additional analyses

238 patients were randomized in the pivotal trial MINT, 190 patients were AChR-Ab+ and 48 patients were MuSK-Ab+. The RCP was 26 weeks for the MuSk-Ab+ patients and 52 weeks for the AChR-Ab+ patients.

Anti-MuSK Ab+ patients:

All MuSK-Ab+ patients except one placebo patient (withdrawal by patient) completed the RCP and all patients completed the randomized treatment. All patients except 2 placebo patients rolled over into the OLP phase OLP which is still ongoing.

Anti-AChR Ab+ patients:

At the data cut-off of 28 May 2024, 75.3% of patients had completed the RCP (52 weeks). Of those, 68.9% rolled over into the OLP. 18 patients (18.9%) discontinued the RCP: 13 placebo patients (reasons were death (n=2), lack of efficacy/progressive disease (n=3) and withdrawal by patient (n=6)) and 5 inebilizumab patients (one AE and one death and withdrawal by subject). The majority (91.6%) of AChR-Ab+ patients had completed the treatment in the RCP. One patient discontinued treatment prior to week 26 (placebo). Hence, the majority of patients completed the trial with no concerns about the drop-out rate.

Critical protocol deviations were reported for 3.4% and 5.1% in the active and placebo arm, respectively. They concerned late reporting of serious Adverse Events (SAEs) and adverse events of special interest (AESIs) and pregnancy on study drug.

Major protocol deviations were observed for 47.9% vs 45.3% for inebilizumab vs placebo, respectively. Major PDs related to study procedures were e.g. use of paper source to capture information instead of digital solutions (MG-ADL scores, QMG and MGFA class etc). This was due to technical issues in the beginning of the study at some sites. Sites were retrained in the proper procedures where major protocol deviations had occurred. Major protocol deviations related to steroid tapering were also observed. It seems plausible that the nature of the protocol deviations would not have impacted the study results.

Baseline characteristics:

Mean age was 47 years with 84% being below 65 years of age. Two thirds were women as expected from the known epidemiology. Around 80% of patients were anti-AChR-Ab+, and around 20% anti-MuSK-Ab+. Distribution of antibody status, MG disease duration, severity, concomitant treatment was mostly evenly distributed between placebo and inebilizumab treatment arms and between serotypes. Mean disease duration was app. 6 years (range 0.1-33 years), with 50% of patients having a disease duration of > 4 years. Mean baseline MG-ADL score was around 9 (MG-ADL score range is 0-24 with higher score for increasing disease severity). Mean baseline QMG

score was around 17 (QMG score ranges from 0-39 with higher score for increasing disease severity).

Most patients were in the MGFA class II and III, only around 5% were MGFA class IV. Of note, MGFA class V are patients who are intubated and these were not included in the pivotal trial. A sentence in section 4.4 in the SmPC was added to inform that these patients were not studied.

At baseline, more than 90% were on concomitant corticosteroids, either alone (~60%) or in combination with a non-steroid immunosuppressive therapy (~30%). Around 80% received an acetylcholinesterase inhibitor (pyridostigmine) at baseline.

Overall, baseline characteristics were evenly distributed between treatment arms and between serotypes of gMG (anti-AChR-Ab+ and anti-MuSK-Ab+).

A total of 236 patients were in the FAS, 117 on placebo and 119 on inebilizumab. Apparently, 2 anti-AChR-Ab+ patients from the placebo group were not included in the FAS.

Primary endpoint

The primary endpoint change from baseline in MG-ADL score at week 26 for the overall population was met with a treatment difference to placebo of -1.9 (95% CI: -2.9; -1.0) using the composite strategy. The LS mean absolute change from baseline was -2.2 and -4.2 points for placebo and inebilizumab, respectively.

Using the treatment policy strategy, the treatment difference was -1.3 (95% CI: -2.2; -0.4). The LS mean absolute change from baseline was –3.0 and -4.3 points for placebo and inebilizumab, respectively.

The magnitude of the treatment difference of *ad hoc* requested supplementary analyses with a hypothetical strategy where rescue therapy is handled with a jump to reference imputation was -1.5 points (-2.4 to -0.6, p=0.0015). The LS mean absolute change from baseline was –2.7 and -4.2 points for placebo and inebilizumab, respectively.

For the analysis of the primary endpoint, it is unclear why the Applicant has chosen the strategy called a composite strategy. The composite strategy was used only to handle rescue medication initiated after day 28, reflecting an assumption of treatment failure. All other intercurrent events, including early rescue and discontinuation, were handled using the treatment policy strategy. The primary analysis thus implemented a hybrid estimand combining these two approaches and not the treatment policy strategy (the preferred and advised strategy). The larger effect observed under the composite strategy likely reflects the penalization of placebo subjects who required rescue therapy, in contrast to the treatment policy approach, which retained their post-rescue outcomes. In the middle, the hypothetical strategy reflects the effect of inebilizumab on its own. Nonetheless, all strategies resulted in statistically significant findings, and the inclusion of the treatment policy analysis provides reassurance regarding the robustness and interpretability of the results.

Key secondary endpoints

The next endpoint in the hierarchy was the key secondary endpoint change from baseline in QMG score at week 26 for the overall population and was met with a treatment difference to placebo of -2.5 (95% CI: -3.8; -1.2) using the composite strategy and -2.0 (95% CI: -3.3; -0.7) for the treatment policy strategy. The MCID for QMG is 3 points.

In the anti-AChR-Ab+ patients, the treatment difference in change from baseline at week 26 for MG-ADL was -1.8 (95% CI: -2.9; -0.7) and QMG -2.5 (95% CI: -3.9; -1.0) (composite strategy).

Using treatment policy, the treatment difference in change from baseline at week 26 for MG-ADL was -1.4 (95% CI: -2.5; -0.3) and QMG -2.2 (95% CI: -3.8; -0.7).

In the anti-MuSK-Ab+ patients the treatment difference in change from baseline at week 26 for MG-ADL was -2.2 (95% CI: -4.2; -0.2) and QMG -2.3 (95% CI: -5.3; +0.7) (composite strategy). Using treatment policy, the treatment difference in change from baseline at week 26 for MG-ADL was -0.9 (95% CI: -2.7; +1.0) and QMG -1.2 (95% CI: -4.0; +1.6).

In conclusion, the primary and key secondary endpoints were statistically significant with 95% CI below zero, except the last key secondary endpoint: change from baseline in QMG score at week 26 (day 183) in the anti-MuSK Ab+ subpopulation (composite strategy). When using the treatment policy, the 4th and 5th key secondary endpoints – the ones in the anti-MusK Ab+ subpopulation – were not statistically significant.

Clinical relevance

Although statistically significant, the magnitude of effect of the primary endpoint were below the minimally clinically important difference of 2 points, especially with the treatment policy strategy (-1.3 (95% CI: -2.2; -0.4)) which is the most conservative and preferred. Therefore, the Applicant was requested to justify the clinical relevance.

The Applicant provided responder analyses based on multiple MG-ADL thresholds (e.g., ≥2,3,4,5,6,7 and 8-point improvement) using logistic regression and Cochran–Mantel–Haenszel methods, and repeated measures using multiple imputation under the composite and treatment-policy strategies with MAR, pDRMI, and DRMI assumptions for the overall population and also divided in serotypes. Overall, for all both serotypes, a higher proportion of patients treated with inebilizumab were MG-ADL responders with differences to placebo around 10-20%.

A secondary endpoint (not in hierarchy) was ≥3-point improvement in MG-ADL score with no rescue therapy (week 26-28) and here the treatment differences were around 20%, with 48.2% responders in the placebo group and 68.7% in the inebilizumab group in the overall population and for the different serotypes similar proportions were seen.

Hence, although the MCID is below the 2 points, when looking at the responder analyses, there is a clinically relevant effect of inebilizumab versus placebo on gMG for both the anti-AChR-Ab+ and anti-MuSK-Ab+ patients.

<u>Rescue therapy</u>

Only IVIg and PLEX were considered as rescue therapy per protocol. Most patients received IVIg as rescue therapy and only few patients were treated with PLEX. At week 26, more patients in the placebo group had received rescue therapy with 8.4% vs 23.9% in inebilizumab and placebo, respectively. At week 52 the numbers were 11.6% and 34.4%, respectively. Similar results were seen in the two serotypes.

A high steroid dose (i.e. higher than at baseline) were seen in few patients (4.2% in the inebilizumab group and 6.0% in the placebo group). Hence, overall, the placebo group received more rescue therapy than did the inebilizumab group.

<u>Persistence of efficacy (week 52)</u>

Initially, the primary evaluation of efficacy for the anti-AChR-Ab+ patients were at week 52, but it was changed to week 26 as for the anti-MuSK-Ab+ patients. Hence, the anti-AChR-Ab+ patients had a placebo-controlled period of 52 weeks.

Efficacy at week 52 was evaluated for the anti-AChR-Ab+ patients on change from baseline in MG-ADL, ≥3 points responder, QMG and MGC and time to exacerbation. Overall, it seemed that the effect was sustained until week 52 with even greater separation from placebo compared to week 26.

Change from baseline in MG-ADL to week 52

- Composite strategy: LS Mean (95% CI) -1.8 (-2.7, -1.0) and -4.8 (-5.6, -4.0) for placebo and inebilizumab, respectively. Treatment difference of -3.0 (95% CI: -4.1, -1.8).
- Treatment policy: LS Mean (95% CI) -3.0 (-3.8, -2.1) and -5.1 (-5.9, -4.3) for placebo and inebilizumab, respectively. Treatment difference of -2.2 (95% CI: -3.3, -1.1).

Also, the proportion of patients with a ≥ 3-point improvement in MG-ADL score with no use of rescue therapy (between day 28 and week 52) was greater in the inebilizumab group (75.9%) vs. placebo (40.5%). Supportive results were also seen QMG and MGC scores at week 52 as well as number of patients with exacerbations. In conclusion, the effect of inebilizumab in anti-AChR-Ab+ patients appeared to be sustained up to week 52.

Exploratory endpoints.

All exploratory endpoints were supportive of an effect of inebilizumab for the treatment of gMG. The number of exacerbations were less for patients treated with inebilizumab, with 41 (35%) placebo patients experiencing an exacerbation compared to 19 (16%) in the inebilizumab patients at week 26. It is noted that 1 placebo patient and 2 inebilizumab patients experienced an MG crisis.

As per the corticosteroid use, patients were allowed to be on corticosteroids when entering the trial, although no dose increase were allowed within 4 weeks prior to randomisation. The steroid tapering was done irrespective of clinical status in a protocol defined tapering schedule. All patients were tapered to 5 mg if possible. Baseline use of > 5 mg corticosteroids was similar in the treatment groups and in the serostatus groups, i.e. around 80% were on corticosteroid treatment in the trial. Fewer anti-MuSk-Ab+ patients in the inebilizumab group used >5 mg corticosteroid at baseline compared to placebo (70.8% vs. 79.2%) and for those patients 94.1% tapered to ≤ 5 mg at week 26 compared to 68.4% in the placebo group.

For the anti-AChR-Ab+ patients, similar proportions tapered to ≤ 5 mg at week 26 and 52 in the inebilizumab and placebo groups. Also the proportions of patients able to achieve a ≥50% reduction in steroid use were similar between the treatment groups.

Hence, it seems that only for the anti-MuSK-Ab+ patients, inebilizumab treatment was associated with a larger proportion of patients being able to taper to 5 mg corticosteroid. Since this is an exploratory endpoint, the results should be interpreted with caution.

Quality of life scores (MGQOL and PGIC) both demonstrated a trend of improvement.

Subgroup analyses

Relevant subgroups were evaluated for the primary and key secondary endpoints (MG-ADL and QMG change from baseline). Change from baseline to weeks 26 and 52 (w52 for anti-AChR-Ab+ patients only) in MG-ADL were more or less consistent across the subgroups evaluated (age, gender, MG disease duration, background medication (corticosteroid only, non-steroid IST only or a combination of those), baseline MGFA status and regions. Hence, no subgroup was identified from those evaluated where a different treatment effect would be expected.

Open-label period (OLP) of MINT

As of the cut-off date (28 May 2024), a total of 94 subjects (79.0%) in the inebilizumab group and 84 subjects (70.6%) in the placebo group enrolled into the OLP. Anti-AChR-Ab+ patients after the RCP of 52 weeks and anti-MuSK-Ab+ patients after 26 weeks.

Anti-AChR-Ab+ patients

In the anti-AChR-Ab+ patients, mean change from baseline in MG-ADL at week 52 was -3.0 (-3.8, -2.1) for placebo and -5.1 (-5.9, -4.3) for inebilizumab (treatment policy strategy).

At entry in the OLP, at Day 1, the mean change in MG-ADL from baseline (baseline defined as the last valid value on or prior to the first dose of RCP) was -3.1 (placebo->inebilizumab) and -5.4 (inebilizumab->inebilizumab) and at week 78 it was -5.4 and -6.2 for placebo->inebilizumab and inebilizumab->inebilizumab, respectively (treatment policy strategy). I.e. the placebo group seems to benefit from the start of inebilizumab, although the number of patients at week 78 is lower due to the trial is ongoing. The results of the OLP for the anti-AChR-Ab+ patients support a sustained effect on MG-ADL.

Anti-MuSK-Ab+ patients

In the anti-MuSK-Ab+ patients, the mean change from baseline to week 26 in MG-ADL was -2.9 for placebo and -3.8 for inebilizumab (treatment policy strategy).

At entry in the OLP, at Day 1, the mean change in MG-ADL from baseline (baseline defined as the last valid value on or prior to the first dose of RCP) was -3.1 (placebo->inebilizumab) and -4.0 (inebilizumab->inebilizumab) and at week 78 it was -7.0 and -7.9 for placebo->inebilizumab and inebilizumab->inebilizumab, respectively (treatment policy strategy). The week 78 data are based on very few patients (7 placebo and 8 inebilizumab patients). Similar results were seen with QMG. In conclusion, placebo patients that rolled over to inebilizumab in the OLP seemed to benefit by initiating inebilizumab on the MG-ADL and QMG scores.

2.4.4. Conclusions on the clinical efficacy

Clinically relevant and statistically significant reductions in symptom scores as measured by patients and physicians in anti-AChRAb and anti-Musk-Ab positive gMG patients were demonstrated in the single pivotal phase 3 study MINT. Efficacy is considered demonstrated for inebilizumab for the treatment of gMG.

2.5. Clinical safety

Introduction

Inebilizumab is a humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody that binds with high affinity to cluster of differentiation (CD)19 cell surface antigen expressed on B cells.

This report focuses on the safety data from the pivotal Study VIB0551.P3.S1 (MINT, Amgen Study 20230049), a phase 3, randomized, double-blind, placebo controlled study of inebilizumab in adults with gMG.

The safety data of inebilizumab in subjects with NMOSD are described in the Initial MAA. Due to differences in study design and patient populations, no safety data are pooled in this application. However, high-level side-by-side comparisons between the safety profiles observed in subjects with gMG and NMOSD are provided.

Patient exposure

All safety data collected up to the data cutoff date for the RCP (week 26 for the anti-MuSK-Ab+ subpopulation and week 52 for the anti-AChR-Ab+ subpopulation) as well as all the safety data collected up to the data cutoff date for the OLP were included in the safety analyses.

Safety analyses for the RCP are based on the Safety Analysis Set, which includes all subjects who received any dose of IP. Subjects were analyzed according to the treatment that they received. Safety analyses for the OLP are based on the Open-label Analysis Set, which includes all subjects who received any dose of inebilizumab during the OLP. Safety analyses for the combined RCP and OLP are based on the Any Inebilizumab Analysis Set, which includes all subjects who received any dose of inebilizumab during the study up to the data cutoff date.

During the RCP, there were 3 planned doses of IP for subjects who were anti-AChR-Ab+ (300 mg inebilizumab or placebo on day 1, day 15, and week 26) and 2 planned doses of IP for subjects who were anti-MuSK-Ab+ (300 mg inebilizumab or placebo on day 1 and day 15). All planned doses were received by 92.6% of subjects in the inebilizumab group and 90.5% of subjects in the placebo group in the anti-AChR-Ab+ subpopulation and 100% of subjects in the inebilizumab group and placebo group in the anti-MuSK Ab+ subpopulation (Table 27).

For the primary analysis, overall, across the RCP and the OLP, 203 subjects received 1 or more doses of inebilizumab (Table 28).

A total of 238 subjects were randomized, 190 subjects were anti AChR Ab+ and 48 subjects were anti MuSK Ab+.

For the supplemental analysis, overall, across the RCP and the OLP, 207 subjects received 1 or more doses of inebilizumab. Duration of inebilizumab exposure was at least 1 year for 141 subjects (68.1%) in the overall population. Duration of inebilizumab exposure was at least 2 years for 53 subjects (25.6%) in the overall population.

Table 27. Exposure to investigational product. Randomized controlled period (safety analysis set)

	Overall Population		AChR+ Subpopulation[d]		MuSK+ Subpopulation[d]	
	Placebo	Inebilizumab	Placebo	Inebilizumab	Placebo	Inebilizumab
	N = 119	N = 119	N = 95	N = 95	N = 24	N = 24
Number of doses received						
1	2 (1.7%)	1 (0.8%)	2 (2.1%)	1 (1.1%)	0	0
2	31 (26.1%)	30 (25.2%)	7 (7.4%)	6 (6.3%)	24 (100%)	24 (100%)
3	86 (72.3%)	88 (73.9%)	86 (90.5%)	88 (92.6%)	0	0
Duration of the exposure (days)[a]						
n	119	119	95	95	24	24
Mean	226.8	232.1	257.8	264.3	104.1	104.5
SD	78.0	75.0	53.1	43.2	1.1	1.6
Median	271.0	272.0	272.0	272.0	104.0	104.0
(Q1, Q3)	(105.0, 273.0)	(115.0, 274.0)	(268.0, 274.0)	(271.0, 276.0)	(104.0, 105.0)	(104.0, 105.0)
(Min, Max)	(90, 406)	(90, 369)	(90, 406)	(90, 369)	(102, 106)	(102, 110)
Dose amount administered (mg)[b]						
n	119	119	95	95	24	24
Mean	0.0	819.3	0.0	874.7	0.0	600.0
SD	0.0	139.2	0.0	94.5	0.0	0.0
Median	0.0	900.0	0.0	900.0	0.0	600.0
(Q1, Q3)	(0.0, 0.0)	(600.0, 900.0)	(0.0, 0.0)	(900.0, 900.0)	(0.0, 0.0)	(600.0, 600.0)
(Min, Max)	(0, 0)	(300, 900)	(0, 0)	(300, 900)	(0, 0)	(600, 600)
Treatment compliance (%)[c]						
n	119	119	95	95	24	24
Mean	96.92	97.76	96.14	97.19	100.00	100.00
SD	11.47	9.44	12.74	10.50	0.00	0.00
Median	100.00	100.00	100.00	100.00	100.00	100.00
(Q1, Q3)	(100.00, 100.00)	(100.00, 100.00)	(100.00, 100.00)	(100.00, 100.00)	(100.00, 100.00)	(100.00, 100.00)
(Min, Max)	(33.3, 100.0)	(33.3, 100.0)	(33.3, 100.0)	(33.3, 100.0)	(100.0, 100.0)	(100.0, 100.0)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; SD = standard deviation.
RCP = Randomized controlled period, OLP = Open label period.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b Duration of the exposure = Date of the last dose in RCP – Date of the first dose in RCP + 90

c Total dose was estimated based on actual volume administered, if dose was not fully administered. The dose administered = 300 mg x actual volume received/planned volume.
d Treatment compliance for an individual subject = [Total number of doses received]/ [Total number of doses planned per protocol] x100%

Table 28 Exposure to Inebilizumab Combined RCP and OLP (Any Inebilizumab Analysis Set)

	Overall Population N = 203	AChR+ Subpopulation[b] N = 157	MuSK+ Subpopulation[b] N = 46
Number of inebilizumab doses received			
1	2 (1.0%)	2 (1.3%)	0
2	20 (9.9%)	14 (8.9%)	6 (13.0%)
3	53 (26.1%)	46 (29.3%)	7 (15.2%)
4	44 (21.7%)	27 (17.2%)	17 (37.0%)
5	48 (23.6%)	37 (23.6%)	11 (23.9%)
6	20 (9.9%)	15 (9.6%)	5 (10.9%)
7	16 (7.9%)	16 (10.2%)	0
Mean	4.2	4.2	4.0
SD	1.4	1.5	1.2
Median	4.0	4.0	4.0
(Q1, Q3)	(3.0, 5.0)	(3.0, 5.0)	(3.0, 5.0)
(Min, Max)	(1, 7)	(1, 7)	(2, 6)
Duration of the exposure (days)[a]			
1 - 183	21 (10.3%)	15 (9.6%)	6 (13.0%)
184 - 365	54 (26.6%)	47 (29.9%)	7 (15.2%)
366 - 547	38 (18.7%)	23 (14.6%)	15 (32.6%)
548 - 729	49 (24.1%)	40 (25.5%)	9 (19.6%)
730 - 911	16 (7.9%)	10 (6.4%)	6 (13.0%)
>911	25 (12.3%)	22 (14.0%)	3 (6.5%)
Mean	515.5	520.1	500.0
SD	279.3	288.0	249.6
Median	462.0	461.0	465.5
(Q1, Q3)	(273.0, 643.0)	(272.0, 644.0)	(279.0, 639.0)
(Min, Max)	(90, 1265)	(90, 1265)	(102, 1050)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; SD = standard deviation.
RCP = Randomized controlled period, OLP = Open label period.
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b Duration of the exposure = Date of the last dose in RCP – Date of the first dose in RCP + 90

Adverse events

Summaries of the subject incidence of adverse events in the RCP using Safety Analysis Set, the OLP using Open-label Analysis Set, and the combined RCP and OLP using Any Inebilizumab Analysis Set are detailed below in Table 29, Table 30 and Table 31, respectively.

Table 29: Summary of Treatment-emergent Adverse Events – Randomized Controlled Period (Safety Analysis Set)

	Overall Population		Anti-AChR-Ab+ Population		Anti-MuSK-Ab+ Population	
	Placebo	Inebilizumab	Placebo	Inebilizumab	Placebo	Inebilizumab
Subject With	N = 119	N = 119	N = 95	N = 95	N = 24	N = 24
At least one event	87 (73.1%)	96 (80.7%)	70 (73.7%)	77 (81.1%)	17 (70.8%)	19 (79.2%)
At least one investigational product related event	22 (18.5%)	20 (16.8%)	15 (15.8%)	15 (15.8%)	7 (29.2%)	5 (20.8%)
At least one event of ≥ grade 3 severity	13 (10.9%)	12 (10.1%)	11 (11.6%)	10 (10.5%)	2 (8.3%)	2 (8.3%)
Death (grade 5 severity)	2 (1.7%)	1 (0.8%)	2 (2.1%)	1 (1.1%)	0	0
At least one serious event	16 (13.4%)	10 (8.4%)	15 (15.8%)	8 (8.4%)	1 (4.2%)	2 (8.3%)
At least one investigational product related serious event	0	3 (2.5%)	0	3 (3.2%)	0	0
At least one event leading to discontinuation of investigational product	1 (0.8%)	3 (2.5%)	1 (1.1%)	2 (2.1%)	0	1 (4.2%)
At least one event leading to dose interruption	1 (0.8%)	0	1 (1.1%)	0	0	0

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; SD = standard deviation.
RCP = Randomized controlled period, OLP = Open label period.
Total includes placebo and Inebilizumab.
Subjects were counted once for each category regardless of the number of events.
Grade 3: Severe, grade 4: Life-threatening, grade 5: Fatal
Serious adverse event criteria: death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, persistent or significant medical event, congenital anomaly/birth defect (in the offspring of the subject). disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.

Table 30: Summary of Treatment-emergent Adverse Events – Open-label Period (Open-Label Analysis Set)

	Overall Population		Anti-AChR-Ab+ Population		Anti-MuSK-Ab+ Population	
Subject With	Placebo/ Inebilizumab N = 84	Inebilizumab/ Inebilizumab N = 94	Placebo/ Inebilizumab N = 62	Inebilizumab/ Inebilizumab N = 70	Placebo/ Inebilizumab N = 22	Inebilizumab/ Inebilizumab N = 24
At least one event	42 (50.0%)	60 (63.8%)	28 (45.2%)	44 (62.9%)	14 (63.6%)	16 (66.7%)
At least one investigational product related event	13 (15.5%)	16 (17.0%)	8 (12.9%)	10 (14.3%)	5 (22.7%)	6 (25.0%)
At least one event of ≥ grade 3 severity	5 (6.0%)	8 (8.5%)	3 (4.8%)	6 (8.6%)	2 (9.1%)	2 (8.3%)
Death (grade 5 severity)	0	1 (1.1%)	0	1 (1.4%)	0	0
At least one serious event	6 (7.1%)	8 (8.5%)	3 (4.8%)	7 (10.0%)	3 (13.6%)	1 (4.2%)
At least one investigational product related serious event	1 (1.2%)	1 (1.1%)	0	1 (1.4%)	1 (4.5%)	0
At least one event leading to discontinuation of investigational product	1 (1.2%)	2 (2.1%)	1 (1.6%)	0	0	2 (8.3%)
At least one event leading to dose interruption	0	0	0	0	0	0

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; SD = standard deviation.
RCP = Randomized controlled period, OLP = Open label period.
Total includes placebo and Inebilizumab.
Subjects were counted once for each category regardless of the number of events.
Grade 3: Severe, grade 4: Life-threatening, grade 5: Fatal
Serious adverse event criteria: death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, persistent or significant medical event, congenital anomaly/birth defect (in the offspring of the subject).

Table 31: Summary of Treatment-emergent Adverse Events Combined Randomized Controlled Period and Open-label Period (Any Inebilizumab Analysis Set)

	Overall Population		Anti-AChR-Ab+ Population		Anti-MuSK-Ab+ Population	
Subject With	Placebo/ Inebilizumab N = 84	Inebilizumab/ Inebilizumab N = 119	Placebo/ Inebilizumab N = 62	Inebilizumab/ Inebilizumab N = 95	Placebo/ Inebilizumab N = 22	Inebilizumab/ Inebilizumab N = 24
At least one event	69 (82.1%)	106 (89.1%)	52 (83.9%)	84 (88.4%)	17 (77.3%)	22 (91.7%)
At least one investigational product related event	22 (26.2%)	33 (27.7%)	12 (19.4%)	23 (24.2%)	10 (45.5%)	10 (41.7%)
At least one event of ≥ grade 3 severity	9 (10.7%)	19 (16.0%)	6 (9.7%)	15 (15.8%)	3 (13.6%)	4 (16.7%)
Death (grade 5 severity)	0	2 (1.7%)	0	2 (2.1%)	0	0
At least one serious event	14 (16.7%)	17 (14.3%)	11 (17.7%)	14 (14.7%)	3 (13.6%)	3 (12.5%)
At least one investigational product related serious event	1 (1.2%)	4 (3.4%)	0	4 (4.2%)	1 (4.5%)	0
At least one event leading to discontinuation of investigational product	1 (1.2%)	5 (4.2%)	1 (1.6%)	2 (2.1%)	0	3 (12.5%)
At least one event leading to dose interruption	0	0	0	0	0	0

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; SD = standard deviation.
RCP = Randomized controlled period, OLP = Open label period.
Total includes placebo and Inebilizumab.
Subjects were counted once for each category regardless of the number of events.
Grade 3: Severe, grade 4: Life-threatening, grade 5: Fatal
Serious adverse event criteria: death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, persistent or significant medical event, congenital anomaly/birth defect (in the offspring of the subject).

Common adverse event

Adverse events reported for ≥ 5% of subjects in either group (overall population) are summarized for the overall population and by subpopulation during the RCP, OLP and Combined RCP and OLP after the first inebilizumab exposure in Table 32, Table 33, and Table 34, respectively.

Table 32: Treatment-Emergent Adverse Events (≥ 5% In either group in overall population) by Preferred Term Randomized Controlled Period (Safety Analysis Set)

	Overall Population		Anti-AChR-Ab+ Subpopulation		Anti-MuSK-Ab+ Subpopulation	
Preferred Term (MedDRA version 23.0)	Placebo N = 119	Inebilizumab N = 119	Placebo N = 95	Inebilizumab N = 95	Placebo N = 24	Inebilizumab N = 24
Headache	8 (6.7%)	18 (15.1%)	6 (6.3%)	11 (11.6%)	2 (8.3%)	7 (29.2%)
COVID-19	12 (10.1%)	13 (10.9%)	9 (9.5%)	11 (11.6%)	3 (12.5%)	2 (8.3%)
Cough	4 (3.4%)	8 (6.7%)	4 (4.2%)	6 (6.3%)	0	2 (8.3%)
Nasopharyngitis	3 (2.5%)	8 (6.7%)	2 (2.1%)	8 (8.4%)	1 (4.2%)	0
Urinary tract infection	3 (2.5%)	8 (6.7%)	2 (2.1%)	8 (8.4%)	1 (4.2%)	0
Infusion-related reaction	3 (2.5%)	7 (5.9%)	2 (2.1%)	6 (6.3%)	1 (4.2%)	1 (4.2%)
Arthralgia	8 (6.7%)	5 (4.2%)	6 (6.3%)	3 (3.2%)	2 (8.3%)	2 (8.3%)
Diarrhoea	8 (6.7%)	4 (3.4%)	4 (4.2%)	4 (4.2%)	4 (16.7%)	0
Upper respiratory tract infection	7 (5.9%)	4 (3.4%)	5 (5.3%)	3 (3.2%)	2 (8.3%)	1 (4.2%)
Hypertension	8 (6.7%)	2 (1.7%)	6 (6.3%)	2 (2.1%)	2 (8.3%)	0

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019; MedDRA = medical dictionary of regulatory activities.
Subjects were counted once for each preferred term regardless of the number of events.

Table 33: Treatment-Emergent Adverse Events (≥ 5% In either group in overall population) by Preferred Term Open label Period (Safety Analysis Set)

	Overall Population		Anti-AChR-Ab+ Subpopulation		Anti-MuSK-Ab+ Subpopulation	
Preferred Term (MedDRA version 23.0)	Placebo/ Inebilizumab N = 84	Inebilizumab/ Inebilizumab N = 94	Placebo/ Inebilizumab N = 62	Inebilizumab/ Inebilizumab N = 70	Placebo/ Inebilizumab N = 22	Inebilizumab/ Inebilizumab N = 24
COVID-19	3 (3.6%)	8 (8.5%)	2 (3.2%)	5 (7.1%)	1 (4.5%)	3 (12.5%)
Nasopharyngitis	1 (1.2%)	7 (7.4%)	1 (1.6%)	5 (7.1%)	0	2 (8.3%)
Blood immunoglobulin M decreased	2 (2.4%)	6 (6.4%)	2 (3.2%)	4 (5.7%)	0	2 (8.3%)
Upper respiratory tract infection	7 (8.3%)	4 (4.3%)	3 (4.8%)	4 (5.7%)	4 (18.2%)	0
Pyrexia	5 (6.0%)	3 (3.2%)	4 (6.5%)	2 (2.9%)	1 (4.5%)	1 (4.2%)
Cough	6 (7.1%)	2 (2.1%)	4 (6.5%)	1 (1.4%)	2 (9.1%)	1 (4.2%)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019; MedDRA = medical dictionary of regulatory activities.
Subjects were counted once for each preferred term regardless of the number of events.

Table 34: Treatment-Emergent Adverse Events (≥ 5% In either group in overall population) after first inebilizumab exposure Combined RCP and OLP (Any inebilizumab Analysis Set)

Preferred Term	Overall Population Total N = 203, n (%)	Anti-AChR-Ab+ Subpopulation Total N = 157, n (%)	Anti-MuSK-Ab+ Subpopulation Total N = 46, n (%)
Subjects with at least 1 event	147 (72.4%)	112 (71.3%)	35 (76.1%)
COVID-19	24 (11.8%)	18 (11.5%)	6 (13.0%)
Headache	21 (10.3%)	13 (8.3%)	8 (17.4%)
Cough	16 (7.9%)	11 (7.0%)	5 (10.9%)
Nasopharyngitis	14 (6.9%)	12 (7.6%)	2 (4.3%)
Upper respiratory tract infection	14 (6.9%)	9 (5.7%)	5 (10.9%)
Pyrexia	13 (6.4%)	11 (7.0%)	2 (4.3%)
Urinary tract infection	10 (4.9%)	10 (6.4%)	0 (0.0%)
SARS-CoV-2 test positive	10 (4.9%)	5 (3.2%)	5 (10.9%)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019; MedDRA = medical dictionary of regulatory activities.
Total includes placebo/inebilizumab and inebilizumab/inebilizumab

Adverse Events by Severity

Randomized Controlled Period

Mild (grade 1) (35.3% inebilizumab, 26.1% placebo) and moderate (grade 2) (35.3% inebilizumab, 36.1% placebo) treatment-emergent adverse events were the most common events across inebilizumab and placebo treatment groups in the overall population.

Inebilizumab group: Of the 119 subjects in the overall population inebilizumab group, at least 1 treatment-emergent adverse event of grade 5 or grade 4 was reported in 1 subject (0.8%) each; grade 3 treatment-emergent adverse events were reported in 10 subjects (8.4%). Of these subjects, IP related grade 5 and grade 3 treatment-emergent adverse events occurred in 1 subject (0.8%) and 3 subjects (2.5%), respectively.

Grade 3 treatment-emergent adverse events: COVID-19 (2 subjects [1.7%]), iron deficiency anemia, coronary artery thrombosis, glaucoma, anal abscess (IP related), COVID 19 pneumonia, herpes zoster disseminated (IP related), urinary tract infection bacterial, fall, fibula fracture, (IP related), tibia fracture, intervertebral disc protrusion, osteonecrosis, cervical cord compression, and syncope (1 subject [0.8%] each). Some subjects experienced multiple events.

Grade 4 treatment-emergent adverse events: MG crisis that occurred in 1 subject (0.8%) which was not considered related to IP per investigator.

Grade 5 treatment-emergent adverse events: septic shock, acute respiratory distress syndrome (ARDS), and pneumonitis that occurred in the same 1 subject (0.8%) and were considered related to IP. All of the above developed following hospitalization for an MG crisis (grade 5, not related to IP per investigator).

Open-label Period

During the OLP, for most of the subjects in the overall population who experienced treatment-emergent adverse events, events were of mild (grade 1) or moderate (grade 2) severity.

Inebilizumab/inebilizumab group:

Grade 3 treatment-emergent adverse events: COVID-19 pneumonia (2 subjects [2.1%]), retinal artery occlusion, dental caries, pneumonia viral, vaginal hemorrhage, pulmonary embolism, and deep vein thrombosis (1 subject [1.1%] each). Some subjects experienced multiple events.

Grade 4 treatment-emergent adverse events: diverticular perforation, intestinal hemorrhage, COVID-19 pneumonia, pelvic abscess, and pulmonary embolism that occurred in 1 subject (1.1%) each. Some subjects experienced multiple events.

Grade 5 treatment-emergent adverse events: acute myocardial infarction that occurred in 1 subject (1.1%).

Placebo/inebilizumab group:

Grade 3 treatment-emergent adverse events: acute myocardial infarction, enteritis infectious, pneumonia, dehydration, lumbar spinal stenosis, and uterine polyp that occurred in 1 subject (1.2%) each. Some subjects experienced multiple events.

Grade 4 treatment-emergent adverse events: altered state of consciousness that occurred in 1 subject (1.2%).

Across RCP and OLP in Any Inebilizumab Analysis Set

Consistent with the individual results in RCP and OLP, during the combined RCP and OLP period, a majority of the subjects in the overall population experienced either mild (grade 1) or moderate (grade 2) treatment-emergent adverse events. No major differences were identified between anti AChR Ab+ and anti-MuSK Ab+ subpopulations.

Inebilizumab/inebilizumab group: Of the 119 subjects in the overall population, at least 1 treatment-emergent adverse events of grade 5 was reported in 2 subjects (1.7%), grade 4 in 3 subjects (2.5%), and grade 3 in 14 subjects (11.8%).

Placebo/inebilizumab group: Among the 84 subjects in the overall population, there were no treatment-emergent adverse events of grade 5. At least 1 treatment emergent adverse events of grade 4 was reported in 1 subject (1.2%) and grade 3 in 4 subjects (4.8%).

Serious adverse event/deaths/other significant events

Serious Adverse Events

During the RCP, at least 1 treatment-emergent serious adverse event occurred in 10 subjects (8.4%) in the inebilizumab group and 16 subjects (13.4%) in the placebo group in the overall population. Summary of serious treatment-emergent adverse events by SOC and PT is provided in Table 35.

Table 35: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term Randomized Controlled Period (Safety Analysis Set)

	Overall Population		AChR+[a] Population		MuSK+[a] Population	
System Organ Class Preferred Term	Placebo N = 119 n (%)	Inebilizumab N = 119 n (%)	Placebo N = 95 n (%)	Inebilizumab N = 95 n (%)	Placebo N = 24 n (%)	Inebilizumab N = 24 n (%)
Subjects with at least 1 event	16 (13.4%)	10 (8.4%)	15 (15.8%)	8 (8.4%)	1 (4.2%)	2 (8.3%)
Blood and lymphatic system disorders	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anemia megaloblastic	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pancytopenia	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	3 (2.5%)	1 (0.8%)	3 (3.2%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Atrial fibrillation	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardio-respiratory arrest	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Coronary artery stenosis	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Coronary artery thrombosis	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Eye disorders	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Glaucoma	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Gastrointestinal disorders	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inguinal hernia	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Umbilical hernia	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations	5 (4.2%)	7 (5.9%)	4 (4.2%)	5 (5.3%)	1 (4.2%)	2 (8.3%)
Bone abscess	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
COVID-19	3 (2.5%)	2 (1.7%)	2 (2.1%)	2 (2.1%)	1 (4.2%)	0 (0.0%)
COVID-19 pneumonia	1 (0.8%)	2 (1.7%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (4.2%)
Herpes zoster disseminated	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Sepsis	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Septic shock	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection bacterial	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	1 (0.8%)	2 (1.7%)	1 (1.1%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Fall	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fibula fracture	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Infusion-related reaction	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Tibia fracture	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	2 (1.7%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dehydration	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Magnesium deficiency	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Osteonecrosis	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	3 (2.5%)	2 (1.7%)	3 (3.2%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Myasthenia gravis crisis	3 (2.5%)	2 (1.7%)	3 (3.2%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ovarian rupture	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Acute respiratory distress syndrome	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pneumonitis	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Respiratory distress	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypotension	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019, MedDRA = medical dictionary of regulatory activities
Subjects were counted once for each system organ class and preferred term regardless of the number of events.
Serious adverse event criteria: death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, persistent or significant medical event, congenital anomaly/birth defect (in the offspring of the subject).

During the OLP, at least 1 treatment-emergent serious adverse event occurred in 8 subjects (8.5%) in the inebilizumab/inebilizumab group and 6 subjects (7.1%) in the placebo/inebilizumab group in the overall population. A summary of serious treatment emergent adverse events by SOC and PT is provided in Table 36.

Table 36: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term Open label Period (Safety Analysis Set)

	Overall Population		AChR+[a] Population		MuSK+[a] Population	
System Organ Class Preferred Term	Placebo/ Inebilizumab N = 84 n (%)	Inebilizumab/ Inebilizumab N = 94 n (%)	Placebo/ Inebilizumab N = 62 n (%)	Inebilizumab/ Inebilizumab N = 70 n (%)	Placebo/ Inebilizumab N = 22 n (%)	Inebilizumab/ Inebilizumab N = 24 n (%)
Subjects with at least 1 event	6 (7.1%)	8 (8.5%)	3 (4.8%)	7 (10.0%)	3 (13.6%)	1 (4.2%)
Cardiac disorders	1 (1.2%)	1 (1.1%)	1 (1.6%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Acute myocardial infarction	1 (1.2%)	1 (1.1%)	1 (1.6%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Eye disorders	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Retinal artery occlusion	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	0 (0.0%)	2 (2.1%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Diverticular perforation	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Intestinal hemorrhage	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Infections and infestations	3 (3.6%)	5 (5.3%)	1 (1.6%)	4 (5.7%)	2 (9.1%)	1 (4.2%)
COVID-19	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
COVID-19 pneumonia	0 (0.0%)	3 (3.2%)	0 (0.0%)	3 (4.3%)	0 (0.0%)	0 (0.0%)
Cystitis	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Enteritis infectious	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Pelvic abscess	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Pneumonia	1 (1.2%)	2 (2.1%)	1 (1.6%)	1 (1.4%)	0 (0.0%)	1 (4.2%)
Pneumonia viral	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Dehydration	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	1 (1.2%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	1 (4.5%)	0 (0.0%)
Lumbar spinal stenosis	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Musculoskeletal pain	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Clear cell renal cell carcinoma	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Altered state of consciousness	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Reproductive system and breast disorders	1 (1.2%)	1 (1.1%)	1 (1.6%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Uterine polyp	1 (1.2%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vaginal hemorrhage	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Vascular disorders	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019, MedDRA = medical dictionary of regulatory activities
Subjects were counted once for each system organ class and preferred term regardless of the number of events.
Serious adverse event criteria: death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, persistent or significant medical event, congenital anomaly/birth defect (in the offspring of the subject).

Across RCP and OLP in any inebilizumab set, serious adverse events reported for more than 1 subject were (COVID-19 (5 subjects, 2.5%), COVID-19 pneumonia (3 subjects, 1.5%), MG crisis (2 subjects, 1%), pneumonia (3 subjects, 1.5%), and acute myocardial infarction (2 subjects, 1%).

Deaths

A total of 4 deaths were reported as of the 28 May 2024 cutoff date, with 3 subjects who died during the RCP (2 subjects in placebo vs. 1 subject in inebilizumab), and 1 subject (inebilizumab/inebilizumab) during OLP. All 4 deaths were reported from the same site. Three death events were not related to IP. One death (ARDS, septic shock, and pneumonitis) reported for 1 subject in inebilizumab group during RCP, was assessed as related to IP by the investigator. All fatal cases were considered to have severe MG based on the QMG score at baseline (all scores > 18).

Death Events During Randomized Controlled Period

Inebilizumab treatment group:

One subject suffered a fatal MG crisis, ARDS, pneumonitis, and septic shock.

Medical history included anti AChR Ab+ MG since 2013 with difficulty speaking, change in voice, nasal regurgitation, difficulty in chewing, difficulty swallowing and breathing. At screening, the total MG-ADL score was 12, QMG score was 20 and MGFA category was IIIB. No additional medical history was provided.

Day 1 of the first dose of inebilizumab was on Q4 2021 and last dose was on day 26 On day 57 after the first dose of inebilizumab, the subject was admitted to the hospital due to MG exacerbation. One day after admission, intravenous Ig was started as a rescue therapy. However, the subject's condition did not improve. The subject was moved to the intensive care unit and on Day 66 , the subject underwent perianal surgery On Day 75 , subject developed difficulty breathing, hypoxia, and tachypnoea and one day later, the subject was intubated and put on ventilator support. On Day 83 the investigator reported the subject died with cause of death MG crisis leading to ARDS. Two months later the government hospital's death certificate listed cause of death as septic shock and pneumonitis. An autopsy was not performed. The investigator attributed the event of MG crisis as not related to the IP, and the events of pneumonitis, septic shock and ARDS as related to the IP.

Placebo group:

One subject suffered a fatal cardio-respiratory arrest. At screening, the total MG-ADL score was 7, QMG score was 19 and MGFA category was IIB. No medical history was provided.

The subject started placebo on Q4 2021 and the last dose was on day 189 On Eleven months after starting placebo, the subject was discharged in hemodynamically stable condition from the hospital where the subject was an inpatient for MG crisis, for which the subject received intravenous Ig and plasma exchange. Few days later, the subject experienced a fatal cardio-respiratory arrest. The event occurred 213 days after the last dose of placebo. The investigator assessed the fatal event as not related to the IP.

One subject suffered a fatal respiratory distress. At screening, the total MG-ADL score was 13, QMG score was 18 and MGFA category was IIB. The subject's medical history included diabetes mellitus and hypertension

Day 1 of placebo was on Q2 2021 and the last dose was on day 198 On day 289 after first placebo administration the subject started experiencing dyspnea and difficulty swallowing and was

admitted to the hospital. The same day, the subject died of respiratory distress. The event occurred 91 days after the last dose of placebo. The investigator assessed the fatal event as not related to the IP.

Death Events During Open-label Period

Inebilizumab/inebilizumab treatment group:

One subject suffered a fatal acute myocardial infarction At screening, the total MG-ADL score was 9, QMG score was 20 and MGFA category was IIIA. The subject's medical history included hypertension.

Day 1 of inebilizumab was on Q1 2022 and the last dose was on day 565). 63 days after the last dose, while in route to the hospital after complaining of chest pains; a short time later, the subject experienced a fatal acute myocardial infarction and died . Per autopsy report, there was evidence of left ventricular hypertrophy and narrowing of the lumen of coronaries The investigator considered the adverse event to be unrelated to the IP.

Adverse Events of Special Interest

Cytopenia

During RCP: In the overall population, cytopenia was reported in 3 subjects (2.5%) in the inebilizumab group and 11 subjects (9.2%) in the placebo group (Table 37).

Lymphopenia was reported in 1 subject (0.8%) in the inebilizumab group and 1 subject (0.8%) in the placebo group. Neutropenia was reported in 1 subject (0.8%) in the inebilizumab group and in 2 subjects (1.7%) in the placebo group.

During combined RCP and OLP in Any Inebilizumab set: In the overall population, cytopenia was reported for 14 subjects (6.9%). Lymphopenia and neutropenia were reported for 4 subjects (2.0%) each (Table 38).

All cytopenia cases were mild (grade 1) or moderate (grade 2) in severity. One subject in the placebo/inebilizumab group during OLP experienced a grade 2 neutropenia which led to discontinuation of study IP. This event was assessed as related to study IP by the investigator.

Of note, there were 3 subjects who experienced iron deficiency anemia (1 grade 3 in inebilizumab group during RCP and 2 in Inebilizumab/Inebilizumab group during OLP) which were not captured as AESI by either investigator or sponsor. All these events did not result in study IP discontinuation and were assessed as not related to study IP by the investigator.

Infusion-related Reaction

During RCP: In the overall population, IRR was reported in 12 subjects (10.1%) in the inebilizumab group and 7 subjects (5.9%) in the placebo group (Table 37).

During combined RCP and OLP in Any Inebilizumab set: In the overall population, IRR was reported in 20 subjects (9.9%) (Table 38).

All cases were mild or moderate in severity except 1 subject who experienced 2 IRR events of grade 3. The first event occurred after the first infusion. The subject experienced mild headache and dizziness, nausea, vomiting, vertigo, fatigue, blood pressure decreased, intermittent head tightness without photophobia or phonophobia. Symptoms resolved after treatment with diphenhydramine HCl and acetaminophen. The subject experienced another IRR 1 day after second inebilizumab infusion. The subject experienced headache, nausea, vomiting (once), a little shortness of breath, and sinus bradycardia. Symptoms resolved after treatment with diphenidol,

acetaminophen, and prochlorperazine maleate. The event was reported as a serious adverse event due to prolongation of hospitalization. Both of the 2 IRR events were considered related to IP by the investigator and no action was taken with regard to the study IP.

None of the IRRs led to discontinuation of study IP.

The common signs and symptoms (reported for more than 1 subject) associated with IRR after exposure to inebilizumab included headache (5 subjects, 2.5%), dysgeusia (2 subjects, 1.0%), hypotension (2 subjects, 1.0%), and somnolence (2 subjects, 1.0%).

Opportunistic Infections

During RCP: A similar percentage of subjects reported an opportunistic infection between inebilizumab group and placebo group in the overall population (0.8% vs 1.7%, respectively) (Table 37). All subjects reported events of herpes zoster. One subject from the inebilizumab group reported a serious adverse event (disseminated herpes zoster of grade 3). The subject was hospitalized due to disseminated herpes zoster involving chest, back, arms and leg 2 days after the third dose of the IP. The event led to study IP discontinuation and was considered related to the study IP by investigator. The event resolved 5 days after treatment.

During combined RCP and OLP in Any Inebilizumab set: Hepatitis B reactivation occurred in 1 subject (0.8%) in the inebilizumab/inebilizumab group during the OLP. This was considered a nonserious, moderate event (grade 2), which was related to IP and led to IP discontinuation and was resolving. In addition, herpes zoster disseminated occurred in 1 subject (0.8%) in the inebilizumab/inebilizumab and was considered a severe serious adverse event (grade 3) (Table 38).

Serious Hypersensitivity Reactions

No anaphylaxis or serious hypersensitivity reaction cases were reported.

Serious Infections

During RCP: Serious infections were reported in 7 subjects (5.9%) in the inebilizumab group and 5 subjects (4.2%) in the placebo group. COVID-19 and COVID-19 pneumonia were reported in ≥ 1 subject in both inebilizumab and placebo groups with similar percentage in each group. In addition, in the inebilizumab group, bone abscess, Herpes zoster disseminated, and septic shock were reported in 1 subject (0.8%) each (Table 37).

During combined RCP and OLP in Any Inebilizumab set: In the overall population, serious infections reported for more than 1 subject included COVID-19 pneumonia (5 subjects [4.2%]), COVID-19 (3 subjects [2.5%]), and pneumonia (2 subjects [1.7%]) (Table 38).

Table 37: Treatment-emergent Adverse Events of Special Interest – Sponsor Defined Randomized Controlled Period (Safety Analysis Set)

Adverse Events of Special Interest Category[b] Preferred Term	Overall Population Placebo N = 119 n (%)	 Inebilizumab N = 119 n (%)	AChR+[a] Population Placebo N = 95 n (%)	 Inebilizumab N = 95 n (%)	MuSK+[a] Population Placebo N = 24 n (%)	 Inebilizumab N = 24 n (%)
Subjects with at least one event of special interest	24 (20.2%)	21 (17.6%)	17 (17.9%)	15 (15.8%)	7 (29.2%)	6 (25.0%)
Cytopenia	11 (9.2%)	3 (2.5%)	6 (6.3%)	3 (3.2%)	5 (20.8%)	0 (0.0%)
Anemia	2 (1.7%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	1 (4.2%)	0 (0.0%)
Anemia megaloblastic	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cytopenia	3 (2.5%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (8.3%)	0 (0.0%)
Leukopenia	1 (0.8%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Lymphocyte count decreased	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphopenia	1 (0.8%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Neutropenia	2 (1.7%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	1 (4.2%)	0 (0.0%)
Pancytopenia	2 (1.7%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Infusion-related reaction	7 (5.9%)	12 (10.1%)	6 (6.3%)	8 (8.4%)	1 (4.2%)	4 (16.7%)
Dizziness	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysarthria	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysgeusia	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Headache	1 (0.8%)	4 (3.4%)	1 (1.1%)	2 (2.1%)	0 (0.0%)	2 (8.3%)
Hypotension	1 (0.8%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Infusion-related reaction	3 (2.5%)	6 (5.0%)	2 (2.1%)	5 (5.3%)	1 (4.2%)	1 (4.2%)
Peripheral swelling	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pruritus	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	1 (0.8%)	1 (0.8%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)

Adverse Events of Special Interest Category[b] Preferred Term	Overall Population Placebo N = 119 n (%)	 Inebilizumab N = 119 n (%)	AChR+[a] Population Placebo N = 95 n (%)	 Inebilizumab N = 95 n (%)	MuSK+[a] Population Placebo N = 24 n (%)	 Inebilizumab N = 24 n (%)
Opportunistic infections	2 (1.7%)	1 (0.8%)	1 (1.1%)	1 (1.1%)	1 (4.2%)	0 (0.0%)
Herpes zoster	2 (1.7%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Herpes zoster disseminated	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Serious infections	5 (4.2%)	7 (5.9%)	4 (4.2%)	5 (5.3%)	1 (4.2%)	2 (8.3%)
Bone abscess	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
COVID-19	3 (2.5%)	2 (1.7%)	2 (2.1%)	2 (2.1%)	1 (4.2%)	0 (0.0%)
COVID-19 pneumonia	1 (0.8%)	2 (1.7%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (4.2%)
Herpes zoster disseminated	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Sepsis	1 (0.8%)	0 (0.0%)	1 (1.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Septic shock	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection bacterial	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019, MedDRA = medical dictionary of regulatory activities
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b Subjects were counted once for each category and preferred term regardless of the number of events.
The sponsored defined Infusion-related reaction (IRR) includes any signs or symptoms experienced by patients during the infusion of IP or any adverse event occurring within 24 hours of IP administration for which alternative explanation is not clearly attributable.
One subject with serious Infusion Related Reaction was included under AESI category of serious hypersensitivity reaction by mistake and should be removed from the total count of serious hypersensitivity reactions.

Table 38: Treatment-emergent Adverse Events of Special Interest – Sponsor Defined Combined Randomized Controlled Period and Open-label Period (Any inebilizumab analysis set)

Adverse Events of Special Interest Category[b] Preferred Term	Overall Population Placebo/ Inebilizumab N = 84 n (%)	Overall Population Inebilizumab/ Inebilizumab N = 119 n (%)	AChR+[a] Population Placebo/ Inebilizumab N = 62 n (%)	AChR+[a] Population Inebilizumab/ Inebilizumab N = 95 n (%)	MuSK+[a] Population Placebo/ Inebilizumab N = 22 n (%)	MuSK+[a] Population Inebilizumab/ Inebilizumab N = 24 n (%)
Subjects with at least one event of special interest	12 (14.3%)	32 (26.9%)	7 (11.3%)	23 (24.2%)	5 (22.7%)	9 (37.5%)
Cytopenia	6 (7.1%)	8 (6.7%)	3 (4.8%)	7 (7.4%)	3 (13.6%)	1 (4.2%)
Anemia	1 (1.2%)	2 (1.7%)	0 (0.0%)	2 (2.1%)	1 (4.5%)	0 (0.0%)
Cytopenia	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Leukopenia	1 (1.2%)	2 (1.7%)	0 (0.0%)	2 (2.1%)	1 (4.5%)	0 (0.0%)
Lymphopenia	1 (1.2%)	3 (2.5%)	1 (1.6%)	3 (3.2%)	0 (0.0%)	0 (0.0%)
Neutropenia	1 (1.2%)	3 (2.5%)	1 (1.6%)	2 (2.1%)	0 (0.0%)	1 (4.2%)
Red blood cell count decreased	1 (1.2%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infusion-related reaction	3 (3.6%)	17 (14.3%)	3 (4.8%)	11 (11.6%)	0 (0.0%)	6 (25.0%)
Dizziness	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Dysgeusia	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (4.2%)
Headache	0 (0.0%)	5 (4.2%)	0 (0.0%)	3 (3.2%)	0 (0.0%)	2 (8.3%)
Hypotension	1 (1.2%)	1 (0.8%)	1 (1.6%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Influenza like illness	1 (1.2%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infusion-related reaction	0 (0.0%)	8 (6.7%)	0 (0.0%)	6 (6.3%)	0 (0.0%)	2 (8.3%)
Insomnia	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Nausea	1 (1.2%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	1 (1.2%)	1 (0.8%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Vertigo	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)

Adverse Events of Special Interest Category[b] Preferred Term	Overall Population Placebo N = 84 n (%)	Overall Population Inebilizumab N = 119 n (%)	AChR+[a] Population Placebo N = 62 n (%)	AChR+[a] Population Inebilizumab N = 95 n (%)	MuSK+[a] Population Placebo N = 22 n (%)	MuSK+[a] Population Inebilizumab N = 24 n (%)
Opportunistic infections	0 (0.0%)	2 (1.7%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (4.2%)
Hepatitis B reactivation	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Herpes zoster disseminated	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Serious infections	3 (3.6%)	12 (10.1%)	1 (1.6%)	9 (9.5%)	2 (9.1%)	3 (12.5%)
Bone abscess	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
COVID-19	0 (0.0%)	3 (2.5%)	0 (0.0%)	3 (3.2%)	0 (0.0%)	0 (0.0%)
COVID-19 pneumonia	0 (0.0%)	5 (4.2%)	0 (0.0%)	4 (4.2%)	0 (0.0%)	1 (4.2%)
Cystitis	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Enteritis infectious	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Herpes zoster disseminated	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pelvic abscess	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pneumonia	1 (1.2%)	2 (1.7%)	1 (1.6%)	1 (1.1%)	0 (0.0%)	1 (4.2%)
Pneumonia viral	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Septic shock	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection bacterial	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)

AChR+= acetylcholine receptor antibody positive; anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; anti- MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; MuSK+= muscle-specific kinase antibody positive; N = Number of subjects in analysis set; n = Number of subjects with observed data; RCP = Randomized controlled period; RCP = Randomized controlled period, OLP = Open label period; COVID-19 = coronavirus disease – 2019, MedDRA = medical dictionary of regulatory activities
a AChR+ and MuSK+ represent anti-AChR-Ab+ and anti-MuSK-Ab+ subpopulations, respectively.
b Subjects were counted once for each category and preferred term regardless of the number of events.
The sponsored defined Infusion-related reaction (IRR) includes any signs or symptoms experienced by patients during the infusion of IP or any adverse event occurring within 24 hours of IP administration for which alternative explanation is not clearly attributable.
One subject with serious Infusion Related Reaction was included under AESI category of serious hypersensitivity reaction by mistake and should be removed from the total count of serious hypersensitivity reactions.

Laboratory findings

Hematology

Lymphocytes

During the RCP overall, lymphocyte counts were lower in the inebilizumab group compared to the placebo group. During the RCP at week 2, lymphocyte counts decreased from baseline in inebilizumab group (median percent change form baseline 15.33%) and no significant change from baseline in placebo (median percent change form baseline 6.14%). By week 8, lymphocyte count had a median percent change form baseline of -5.49% in the inebilizumab group. At week 26,

lymphocyte count was similar to counts that were observed at week 2, where lymphocyte counts decreased from baseline in inebilizumab group (median percent change form baseline -15.08%). By week 52, the low lymphocyte count trended back to baseline.

For OLP, the lymphocyte levels trended back to the OLP baseline level.

Analysis of the worst toxicity postbaseline showed that by week 26 (in overall population) and week 52 (anti AChR Ab+ subpopulation only), inebilizumab group had a higher incidence of ≥ 2 grade worsening in lymphocyte count decreased (18.8% vs 12.0% and 23.7% vs 15.1%, inebilizumab vs placebo at week 26 and at week 52, respectively).

During the OLP, lymphocyte count decrease was similar between inebilizumab/inebilizumab and placebo/inebilizumab groups. No clinically meaningful finding in shift analysis for other parameters.

Neutrophils

During the RCP, neutrophil counts increased in both inebilizumab and placebo groups at week 2 (median percent change: 10.63% vs 7.04% in inebilizumab vs placebo, respectively) and at week 4 (2.08% vs 7.78% in inebilizumab vs placebo, respectively). By week 8, neutrophil counts returned to baseline. Starting from week 12 through week 52, neutrophil count trended down from baseline. At week 26, neutrophil counts decreased in both inebilizumab and placebo groups in the overall population (median percent change: -9.32% vs -16.82% in inebilizumab vs placebo, respectively). At week 52, neutrophil counts decreased in both inebilizumab and placebo groups in the anti AChR Ab+ subpopulation (median percent change: -12.14% vs -26.69% in inebilizumab vs placebo, respectively). In the overall population during the RCP, there were no subjects in the inebilizumab group with grade 2 neutrophil count decrease compared to 4 subjects (3.4%) in the placebo group. Grade 3 neutrophil count decrease was observed in 1 subject (0.9%) in the inebilizumab group and none in the placebo group.

During the OLP, neutrophil counts remained stable. In the overall population during the OLP, grade 2 neutrophil count decreases were observed in 3 subjects (3.5%) in the inebilizumab/inebilizumab group and 1 subject (1.3%) in the placebo/inebilizumab group. Grade 3 neutrophil count decreases were observed in 2 subjects (2.3%) in the inebilizumab/inebilizumab group and 1 subject (1.3%) in the placebo/inebilizumab group.

Chemistry

No notable differences between treatment groups were observed for laboratory parameters. There were no reports of Hy's Law cases by RCP week 26, week 25, and during the OLP.

Immunoglobulins

Overall Ig levels in the anti AChR Ab+ and anti-MuSK Ab+ subpopulations decreased over time in inebilizumab-treated subjects during the RCP and the trend continued during OLP (Figure 20 and Figure 21). Placebo/inebilizumab subjects in the OLP had similar decreases over time in Ig levels as inebilizumab/inebilizumab subjects.

These results were consistent in the anti AChR Ab+ and anti-MuSK Ab+ subpopulations for IgA (Figure 22 and Figure 23), IgG (Figure 24 and Figure 25), and IgM levels (Figure 26 and Figure 27).

In the overall population, median percentage change from baseline to the end of the RCP and OLP are summarized below.

- Total Ig levels:

    - By RCP week 26, total Ig levels demonstrated a 12.84% median reduction from baseline in the inebilizumab group and a 9.51% median increase from baseline in the placebo group.
    - By OLP week 52, total Ig levels demonstrated a 19.64% median reduction from baseline in the inebilizumab/inebilizumab group and a 9.50% median reduction from baseline in the placebo/inebilizumab group.
- IgA levels:
    - By RCP week 26, IgA levels demonstrated a 25.41% median reduction from baseline in the inebilizumab group and a 3.01% median increase from baseline in the placebo group.
    - In the overall population (RCP), IgA levels below the lower limit of normal were reported for 1.9% of subjects in the placebo group and 14.9% in the inebilizumab group.
    - In the anti-AChR-Ab+ subpopulation (RCP), IgA levels below the lower limit of normal were reported for 2.5% of subjects in the placebo group and 15.4% in the inebilizumab group.
    - In the anti-MuSK-Ab+ subpopulation (RCP), IgA levels below the lower limit of normal were reported for 0% of subjects in the placebo group and 13.0% in the inebilizumab group.
    - By OLP week 52, IgA levels demonstrated a 46.15% median reduction from baseline in the inebilizumab/inebilizumab group and a 30.06% median reduction from baseline in the placebo/inebilizumab group.
- IgG levels:
    - By RCP week 26, IgG levels demonstrated an 8.70% median reduction from baseline in the inebilizumab group and a 10.41% median increase from baseline in the placebo group.
    - In the overall population (RCP), IgG levels below the lower limit of normal were reported for 7.7% of subjects in the placebo group and 28.7% in the inebilizumab group.
    - In the anti-AChR-Ab+ subpopulation (RCP), IgG levels below the lower limit of normal were reported for 9.9% of subjects in the placebo group and 30.8% in the inebilizumab group.
    - In the anti-MuSK-Ab+ subpopulation (RCP), IgA levels below the lower limit of normal were reported for 0% of subjects in the placebo group and 21.7% in the inebilizumab group.
    - By OLP week 52, IgG levels demonstrated a 11.64% median reduction from baseline in the inebilizumab/inebilizumab group and a 3.61% median reduction from baseline in the placebo/inebilizumab group.
- IgM levels:
    - By RCP week 26, IgM levels demonstrated a 29.33% median reduction from baseline in the inebilizumab group and a 4.84% median increase from baseline in the placebo group.
    - In the overall population (RCP), IgM levels below the lower limit of normal were reported for 3.8% of subjects in the placebo group and 15.8% in the inebilizumab group.
    - In the anti-AChR-Ab+ subpopulation (RCP), IgM levels below the lower limit of normal were reported for 4.9% of subjects in the placebo group and 16.7% in the inebilizumab group.

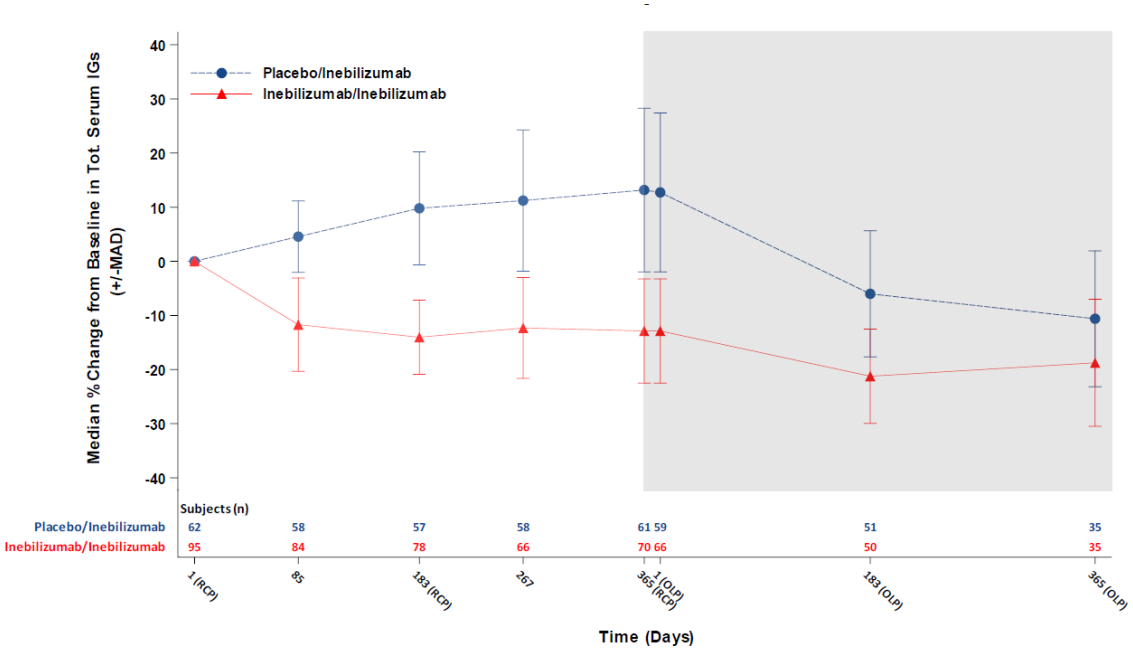
- In the anti-MuSK-Ab+ subpopulation (RCP), IgM levels below the lower limit of normal were reported for 0% of subjects in the placebo group and 13.0% in the inebilizumab group.
- By OLP week 52, IgM levels demonstrated a 41.73% median reduction from baseline in the inebilizumab/inebilizumab group and a 32.56% median reduction from baseline in the placebo/inebilizumab group.

In the overall population during combined RCP and OLP, no subjects with severe IgG hypogammaglobulinemia (< 300 mg/dL) developed infections. Of the 83 subjects who developed infections, IgG levels representing moderate hypogammaglobulinemia (300 to < 500 mg/dL) were found in 11 subjects. Mild changes in the IgG levels did not increase the incidence of infections.

Of the 83 subjects who developed infections, low IgM levels (≤ 30 mg/dL) were observed in 27 subjects. Eleven subjects had low levels of IgM but did not develop infections.

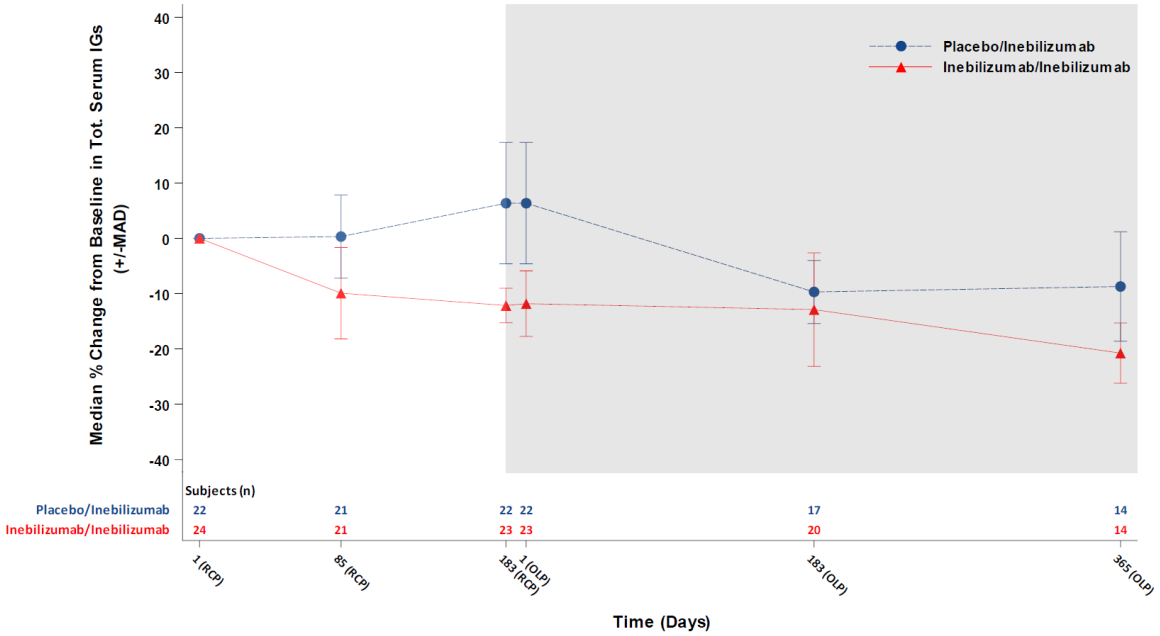
Of the 83 subjects who developed infections, low IgA levels (≤ 70 mg/dL) were observed in 30 subjects. Twelve subjects had low IgA levels but did not develop infections.

Figure 20: Median Percent Change From Baseline in Total Serum Immunoglobin Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti-AChR-Ab+ Population



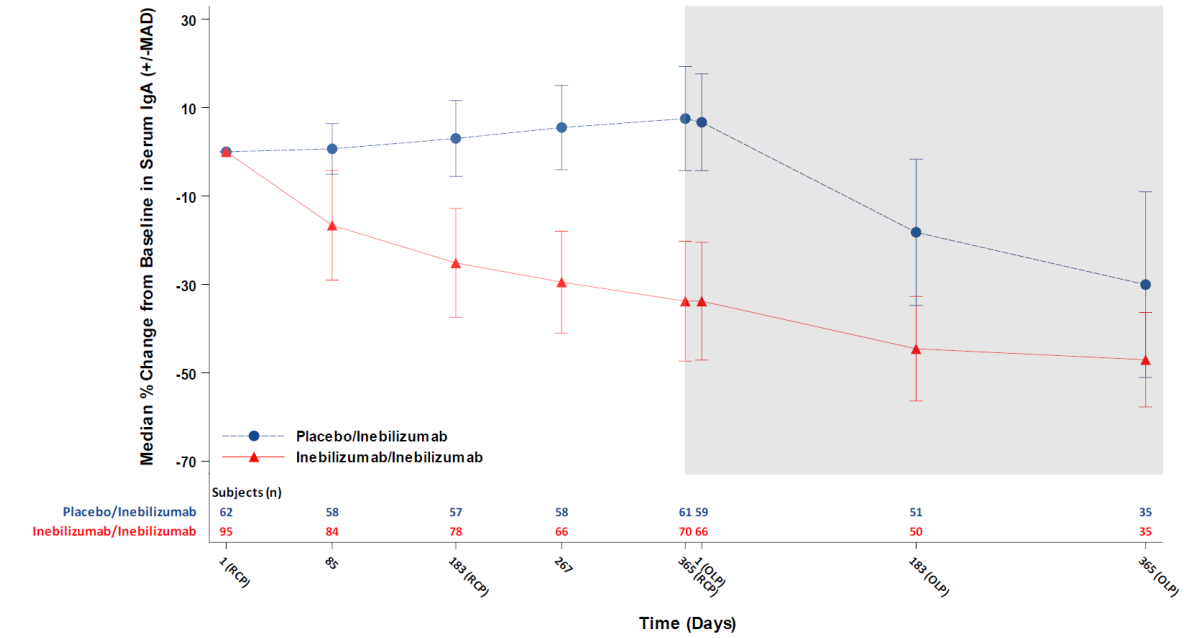
anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 21: Median Percent Change From Baseline in Total Serum Immunoglobin Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti-MuSK-Ab+ Population



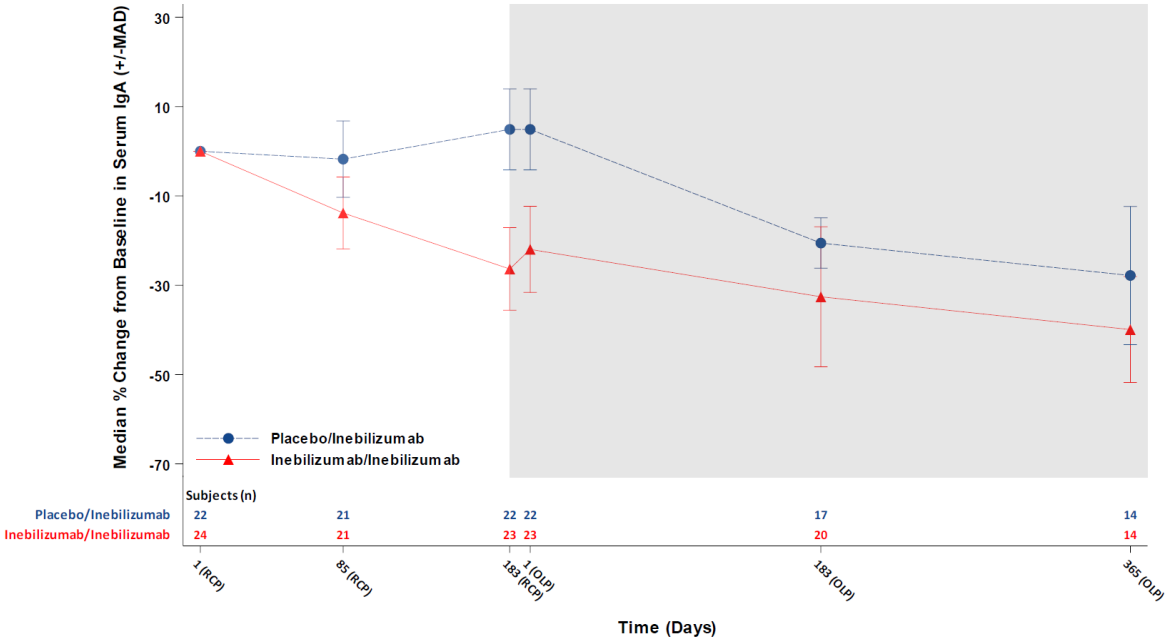
anti-MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 22: Median Percent Change From Baseline in Serum Immunoglobin A Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti-AChR-Ab+ Population



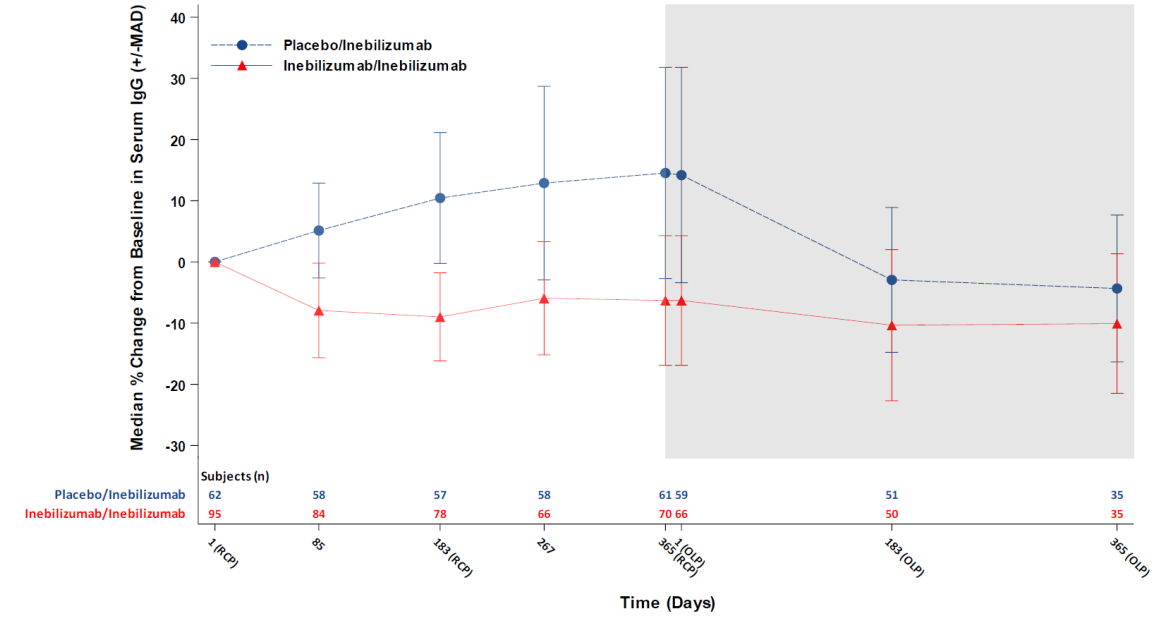
anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 23: Median Percent Change From Baseline in Serum Immunoglobin A Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti- MuSK-Ab+ Population



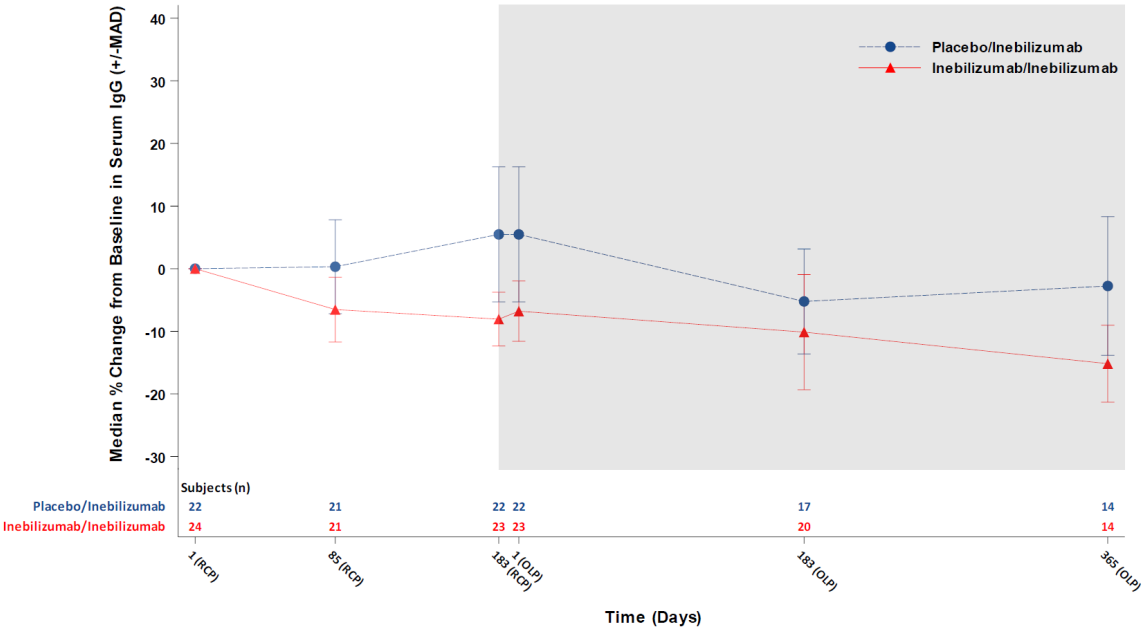
anti-MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 24: Median Percent Change From Baseline in Serum Immunoglobin G Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti-AChR-Ab+ Population



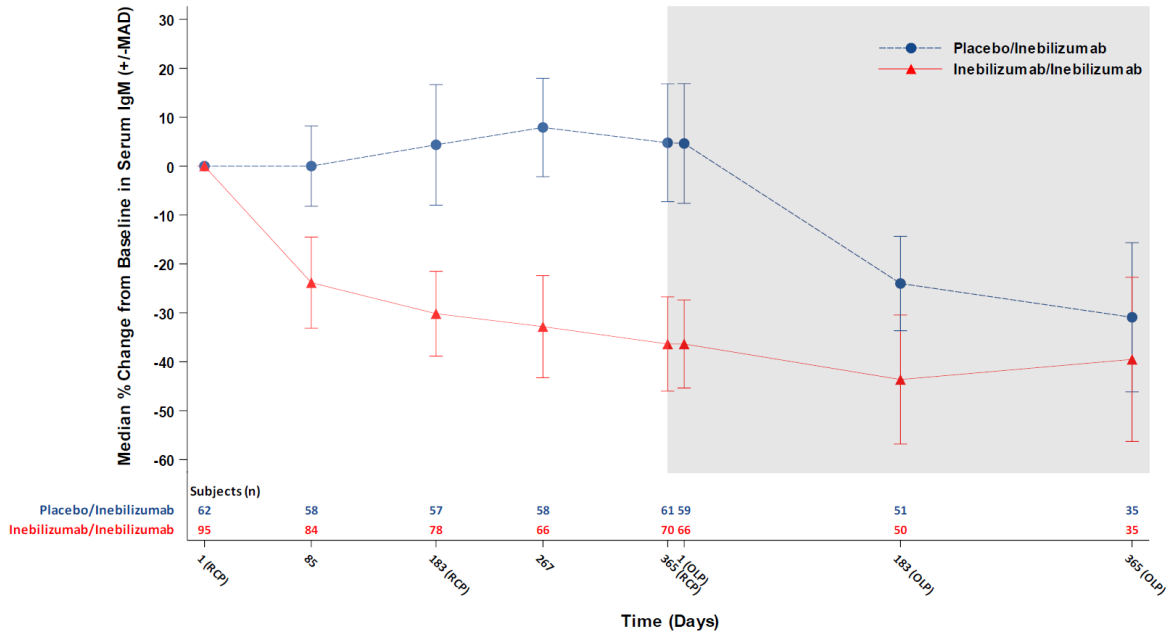
anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 25: Median Percent Change From Baseline in Serum Immunoglobin G Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti- MuSK-Ab+ Population



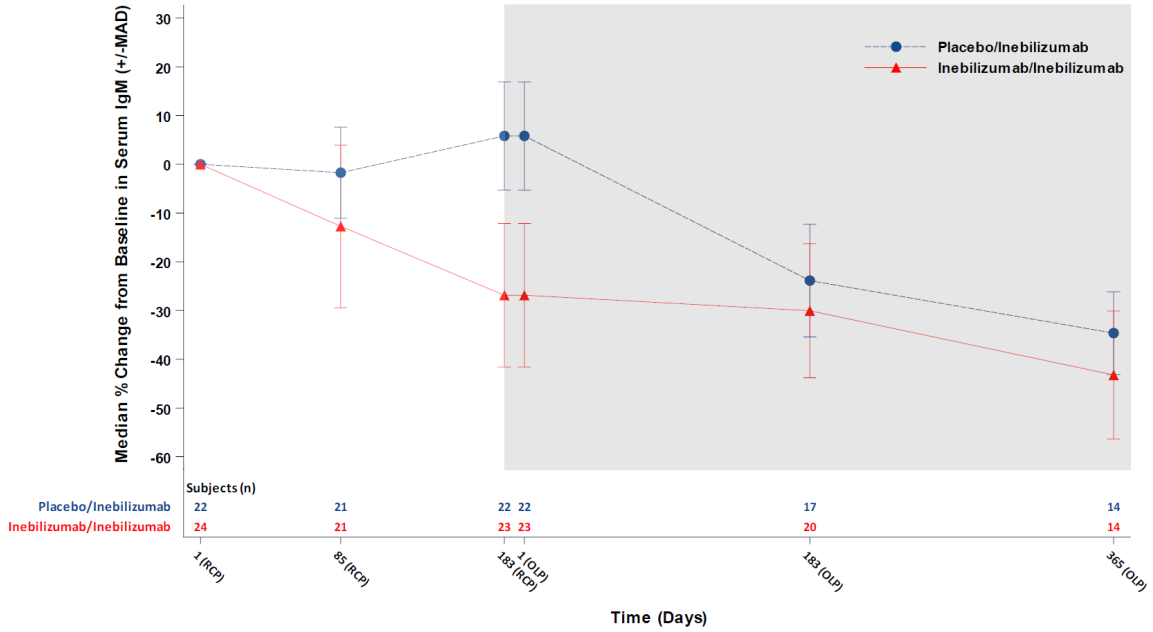
anti-MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 26: Median Percent Change From Baseline in Serum Immunoglobin M Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti-AChR-Ab+ Population



anti-AChR-Ab+= Anti-acetylcholine receptor specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Figure 27: Median Percent Change From Baseline in Serum Immunoglobin M Levels During Combined RCP and OLP – Any Inebilizumab Analysis Set: Anti- MuSK-Ab+ Population



anti-MuSK-Ab+= Anti-muscle-specific kinase specific antibodies; n =Number of subjects with observed data; OLP = Open-label period; RCP = Randomized controlled period.
Error bars represent Median Absolute Deviation (MAD).

Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no clinically significant changes in vital signs in either treatment group during the study.

Electrocardiograms

During the RCP, no abnormal ECG results were clinically significant at baseline through week 52. There were no subjects in the RCP at week 26 for the anti-MuSK-Ab+ population or at week 52 for the anti-AChR-Ab+ population with abnormal, potentially clinically significant ECG readings for both the placebo and inebilizumab groups.

Physical Findings

No notable differences between treatment groups were observed in weight during the RCP in the anti-AChR-Ab+ subpopulation and anti-MuSK-Ab+ subpopulation, or during the OLP.

Suicide Events

There was no notable difference between treatment groups in suicidal events per the summary of Columbia Suicide Severity Rating Scale. Across RCP and OLP in any inebilizumab group, suicide ideation or suicide attempt was reported for 4 subjects. Two subjects (1 in the inebilizumab group and 1 in the placebo group) reported suicide ideation. Two subjects in the inebilizumab group reported suicide attempt. One of these subjects reported aborted suicidal attempt, actual suicidal attempt, and suicidal behavior present at week 52 during the RCP. The other subject reported multiple aborted attempts and interrupted suicidal attempts during the RCP and OLP. There were no completed suicides during any study period. No corresponding adverse events were reported by the investigators.

Safety in special populations

Intrinsic Factors

The effects of intrinsic factors on the adverse event profile of inebilizumab were assessed by subgroup analyses of adverse events reported during the RCP in Study MINT. Summaries are provided for the following groups

- age (≥ 18 < 65 years vs ≥ 65 years):
- sex (male vs female):
- race (American Indian or Alaska Native, Asian, Black or African American, White, other, not reported):
- ethnicity (not Hispanic or Latino, Hispanic or Latino, missing)

No formal clinical studies have been conducted to investigate the effect of renal or hepatic impairment on inebilizumab. Subjects with mild to moderate decrease in glomerular filtration rate and mild to moderate hepatic impairment were included in previous inebilizumab clinical studies. Based on population pharmacokinetic analysis, inebilizumab clearance was comparable in gMG subjects with normal and mild/moderate impaired hepatic function and subjects with normal and mild/moderate impaired renal function.

Extrinsic Factors

The effect of region on the adverse event profile of inebilizumab was assessed by subgroup analyses of adverse events reported during the RCP in Study MINT.

Summaries are provided in the following groups:

- Region 1 (Asia vs Europe (Israel included) vs North America vs rest of world (Central America, South America, Australia, Turkey):
- Region 2 (US vs non-US):
- Region 3 (EU vs non-EU):
- Region 4 (Asia vs non-Asia):
- Region 5 (Japan vs non-Japan):
- Region 6 (China vs non-China):

There were more severe and serious events in patients >=65 compared to patients <65, in male compared to female, in Asian compared to White and in the different regions. The differences were both seen in the placebo group and Inebilizumab group except for patients >=65. However, the small numbers of subjects in the >=65 subgroup limit interpretation of the comparisons.

Use in Pregnancy and Lactation

Cumulatively through 10 June 2024 from all sources, there were 21 pregnancies reported in which patients were exposed to inebilizumab prior to or during pregnancy. These included a total of 6 pregnancies from study sources and 15 pregnancies from non study sources. Cumulatively through10 June 2024, there were no reports of infants receiving breast milk from mothers being treated with inebilizumab. Specifically for Study MINT, there was 1 report of exposure during pregnancy in a subject during the treatment period. On Q1 2022 the subject began treatment with inebilizumab Seventeen days later, , the subject received the last dose of inebilizumab before

confirmed pregnancy. The subject discontinued the study treatment on Day 58 after first infusion . The subject gave birth to an *on term* (37-42 weeks) infant with APGAR score and birth weight values within the normal range There were no complications during childbirth. There were no reports of paternal exposure in Study MINT.

Inebilizumab is a humanized IgG1 monoclonal antibody and Igs are known to cross the placental barrier. There are no adequate data on the developmental risk associated with the use of inebilizumab in pregnant women. However, transient peripheral B cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B cell depleting antibodies during pregnancy. B cell levels in infants following maternal exposure to inebilizumab have not been studied in clinical trials. The potential duration of B cell depletion in such infants, and the impact of B cell depletion on vaccine safety and effectiveness, is unknown. Women of childbearing potential should use contraception while receiving inebilizumab and for 6 months after the last infusion of inebilizumab. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity: however, they have shown a B cell depletion in the fetal livers of progeny.

Regarding use in lactation, there are no data on the presence of inebilizumab in human milk, the effects on a breastfed infant, or the effects on milk production. Human IgG is excreted in human milk, and the potential for absorption of inebilizumab to lead to B cell depletion in the breastfed infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for inebilizumab and any potential adverse effects on the breastfed infant from inebilizumab or from the underlying maternal condition.

Safety related to drug-drug interactions and other interactions

Formal drug-drug interaction studies have not been conducted for inebilizumab.

Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of inebilizumab, a humanized IgG1κ monoclonal antibody. The primary elimination pathway for inebilizumab is clearance by the reticuloendothelial system in the same way as that for an endogenous IgG. Therefore, the potential risk of PK interactions between inebilizumab and other drugs is low. Based on population analysis, commonly used small molecule drugs by subjects with gMG (prednisolone and methylprednisolone) had no effect on inebilizumab PK.

As with other B cell depleting drugs, concomitant usage of inebilizumab and other immunosuppressant drugs may increase the risk of infection.

Treatment with inebilizumab led to reduced peripheral CD20+ B cell counts below the lower limit of normal. As with other B cell depleting drugs, concomitant usage of inebilizumab and other immunosuppressant drugs may result in an increased risk of infection. In Study MINT, more than 20% of subjects in the inebilizumab group during the RCP concomitantly used other immunosuppressants. In general, the safety profile of inebilizumab was acceptable in the gMG study population. Major interactions may occur with other biologic immunosuppressants including anti-TNF therapies, abatacept, anakinra, and tocilizumab. If immunosuppressants are used concomitantly with inebilizumab, patients may need to be monitored for signs and symptoms of infections during the concomitant treatment

Discontinuation due to adverse events

In the overall population during the RCP, 3 subjects (2.5%) in the inebilizumab group and 1 subject (0.8%) in the placebo group experienced at least 1 event resulting in permanent

discontinuation of the IP. No PT was reported for more than 1 subject (inebilizumab group: thyroid mass, herpes zoster disseminated, and intervertebral disc protrusion; placebo group: MG crisis).

In the overall population during the OLP, 2 subjects (2.1%) in the inebilizumab/inebilizumab group and 1 subject (1.2%) in the placebo/inebilizumab group experienced at least 1 event resulting in permanent discontinuation of the IP. No PT was reported for more than 1 subject (inebilizumab/inebilizumab group: fatigue and hepatitis B reactivation; placebo/inebilizumab group: neutropenia).

Post marketing experience

The first approval for marketing worldwide for inebilizumab was in the United States on 11 June 2020 for the indication of NMOSD. As of 11 June 2024, 38 countries have granted marketing approval for inebilizumab for NMOSD . Postmarketing patient exposure estimates are based on unit sales data and converted to patient-time estimates. The estimated cumulative number of patient-years of exposure to inebilizumab for the Amgen territories (US, EU/European Economic Area, Switzerland, and Brazil) was 2045 patient-years. The estimated cumulative number of patient-years of exposure to inebilizumab through 10 June 2024 for Japan, South Korea, and Taiwan was 464 patient-years. The estimated cumulative number of patient-years of exposure to inebilizumab through 30 June 2024 for Chinawas 1931 patient-years.

A cumulative summary of postmarketing adverse reactions that have been reported for inebilizumab up to 10 June 2024 is presented in Appendix 2 of the PBRER/PSUR covering the reporting period 11 December 2023 to 10 June 2024 (Refer to Module 5 for the PBRER/PSUR). These adverse reactions include serious and nonserious reactions from spontaneous sources (reports from health care professionals, consumers, scientific literature, and regulatory authorities) as well as serious adverse reactions from noninterventional studies and other noninterventional solicited sources. The table referred to in the PBRER/PSUR presents event count by source (spontaneous and noninterventional postmarketing study). The summary tabulation is arranged by primary SOC and PT in the internationally agreed order. As of 10 June 2024, Amgen received cumulatively a total of 449 adverse drug reactions (ADRs) from medically confirmed and unconfirmed spontaneous sources of which 88 were serious ADRs and 361 were nonserious ADRs. During that same time frame, a total of 476 serious adverse reactions were received from noninterventional postmarketing sources. A review of the postmarketing data concluded that the overall benefit-risk balance of inebilizumab for its approved indication remains favorable.

2.5.1. Discussion on clinical safety

The safety of inebilizumab is well known for the treatment of NMOSD. In this submission the patient population differ from the initial MAA and therefore, this assessment will focus on the clinically significant differences in safety for patients with gMG compared to the known safety profile of inebilizumab in NMOSD patients.

Safety data

The safety assessment of inebilizumab in this submission is based on data from the RCP and the open label period OLP of Study MINT (data cut-off date 28 May 2024 for RCT and OLP). A supplemental safety analysis was conducted with a data cut-off date of 01 September 2024.

Overall, across the RCP and the OLP, 207 patients received 1 or more doses of inebilizumab. The median duration of inebilizumab in the overall population was 462.0 days and the median number of doses received was 4.0 doses. 41 patients (20,2%) in the overall population received

inebilizumab for more than 2 years and 128 patients (63%) received inebilizumab for at least 1 year.

In the subpopulations, duration of exposure was at least 2 years for 32 patients (20.4%) in the anti-AChR-Ab+ subpopulation and 9 patients (19.6%) in the anti-MuSK-Ab+ subpopulation. Duration of exposure was at least 1 year for 95 patients (60.5%) in the anti-AChR-Ab+ subpopulation and 33 patients (71.7%) in the anti-MuSK-Ab+ subpopulation.

In the supplemental analysis, 207 patients received 1 or more doses of inebilizumab, 53 patients (25.6%) in the overall population received inebilizumab for more than 2 years and 141 patients (68.1%) received inebilizumab for at least 1 year.

Despite the low prevalence of the disease (approximately 10-20 per 100 000), the safety database is considered small and does not fulfil the recommendations according to the current Guideline ("To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300-600 patients should be adequate." Though the safety database is considered small, over 100 patients were exposed to inebilizumab for at least one year, which is acceptable per EMA guideline CPMP/ICH/375/95. Considering the anticipated chronic treatment with inebilizumab, long-term safety data are required, and further results of the OLE awaited.

Adverse events

During the RCT, the incidence of treatment emergent adverse events (TEAS) was 80.7% in the inebilizumab group and 73.1% in the placebo group. Serious adverse events in the overall population occurred in 10 patients (8.4%) in the inebilizumab group, three cases were assessed as related (2.5%). In the placebo group, 16 patients (13.4%) experienced serious adverse events, none of which was assessed as related. Grade ≥3 AEs were reported for 12 patients (10.1%) in the inebilizumab group and 13 (10.9%) in the placebo group. Three deaths were reported in the overall population during RCP, with 1 patient (0.8%) in the inebilizumab treatment group and 2 patients (1.7%) in the placebo group. TEAEs leading to IP discontinuation in the overall population occurred in 3 patients (2.5%) in the inebilizumab group and in 1 patient (0.8%) in the placebo group.

During the OLP, the incidence of TEAEs was 63.8% in the inebilizumab/inebilizumab group and 50% in the placebo/inebilizumab group. SAEs in the overall population occurred in 8 patients (8.5%) in the inebilizumab/inebilizumab group and 6 patients (7.1%) in the placebo/inebilizumab group. Discontinuation occurred in 2 patients (2.1%) in the inebilizumab/inebilizumab group. One death was reported in the inebilizumab/inebilizumab treatment group.

In the Any Inebilizumab Analysis Set, TEAEs occurred in 175 patients (86.2%). SAEs occurred in 23 patients (11.3%). Discontinuation in the overall population occurred in 6 patients (3.0%). Death was reported in 2 patients (1.0%) in the overall population with 1 death during RCP and another death during OLP.

Overall, similar incidence of TEAEs, SAEs, Grade ≥3 AEs and discontinuations were observed in the anti-AChR Ab+ and anti-MuSK Ab+ subpopulations.

Overall, the frequencies of the different categories of AEs (e.g. AEs, SAEs, Grade ≥3 AEs etc.) in the study MINT were similar to the observed frequencies in the initial MAA.

Common adverse events

In the RCP, the most common AEs by PT in the inebilizumab group were headache (15.1% for inebilizumab vs. 6.7% for placebo), COVID-19 (10.9% vs. 10.1%), Cough (6.7% vs. 3.4%), Nasopharyngitis (6.7% vs. 2.5%) and Urinary tract infection (6.7% vs. 2.5%).

In the OLP, the most frequently reported AEs were COVID-19 (8.5% for inebilizumab/inebilizumab vs. 3.6% for placebo/inebilizumab), Nasopharyngitis (7.4% vs. 1.2%) and Blood immunoglobulin M decreased (6.4% vs. 2.4%).

In the Any Inebilizumab Analysis Set, the most frequently reported AEs were COVID-19 (11.8%), headache (10.3%) and cough (7.9%) in the overall population.

Overall, the most common AEs were consistent with the known safety profile of inebilizumab. However, headache (15.1% vs. 6.7%) and cough (6.7% vs. 3.4%) were reported more frequent in the RCP in the inebilizumab group compared to placebo. Headache and cough have been added to the ADR table in the SmPC section 4.8. This is endorsed since the imbalance in cough remained when excluding events related to infections.

Adverse Events by Severity

During the RCT, adverse events were mostly mild to moderate in severity (70.6% in the inebilizumab group and 62.2% in the placebo group). Grade 3 treatment-emergent adverse events were reported in 10 patients (8.4%) in the inebilizumab group. Three grade 3 events were assessed as related by the Investigator; anal abscess, herpes zoster disseminated and IRR. One grade 4 event of MG crisis was not considered related by the Investigator and one patient with a fatal (grade 5) events of septic shock, ARDS, and pneumonitis was assessed as related to inebilizumab by the Investigator. The Same patient had MG crisis, which was assessed as not related to inebilizumab. The event is further assessed below.

During the OLP, the proportion of patients with mild (33.0% inebilizumab/inebilizumab, 26.2% placebo/inebilizumab), moderate (22.3% inebilizumab/inebilizumab, 17.9% placebo/inebilizumab) and severe AEs (5.3% inebilizumab/inebilizumab, 4.8% placebo/inebilizumab) were overall similar between the groups. Two severe events of pneumonia and enteritis infectious (one in each group) was assessed as related by the investigator. Grade 4 events were reported in 2 (2.1%) patients in the inebilizumab/inebilizumab group and 1 (1.2%) patient in the placebo/inebilizumab group. There was one patient with a fatal (grade 5) event of acute myocardial infarction. The grade 4 and 5 events were not considered related by the investigator.

Serious Adverse Events

Serious adverse events were reported for 8.4% of patients in the inebilizumab group and 13.4% of patients in the placebo group during the RCP. COVID-19, COVID-19 pneumonia and Myasthenia gravis crisis were reported in 2 patients (1.7%) each. All other events occurred in 1 patient. The 2 events of Myasthenia gravis crisis were assessed as not related to inebilizumab. Serious infections and infestations were reported for 7 patients (5.9%) in the inebilizumab group. Serious infections are further assessed below.

During the OLP, serious adverse events occurred in 8.5% of patients in the inebilizumab/inebilizumab group and 7.1% of patients in the placebo/inebilizumab group. In the inebilizumab/inebilizumab all SAEs were reported for single patient each, except for COVID-19 pneumonia and pneumonia, which occurred in 3 patients (3.2%) and 2 patients (2.1%), respectively. No SAEs occurred in more than 1 patient in the placebo/inebilizumab group.

Overall, the SAEs reported does not raise any new safety concerns.

Deaths

As of the cutoff date 28 May 2024, a total of 4 deaths were reported. Three fatal cases were reported during the RCP; 2 patients in the placebo group (cardio-respiratory arrest and respiratory distress) and 1 patient in the inebilizumab group (MG crisis, ARDS, pneumonitis and septic shock). One fatal case was reported during the OLP in the inebilizumab/inebilizumab group (acute myocardial infarction). Three of the fatal cases were assessed as not related by the investigator and 1 fatal case of ARDS, septic shock and pneumonitis was assessed as related to inebilizumab by the Investigator. In the patient with acute myocardial infarction comorbidities included hypertension, left ventricular hypertrophy and narrowing of the lumen of coronaries.

Severe infection is a known risk of inebilizumab and it is agreed that the treatment could have increased the susceptibility to infections in the fatal case of MG crisis, ARDS, pneumonitis and septic shock.

No fatal cases were reported from 29 May 2024 to 01 September 2024. Of note, 1 patient withdrew consent on the 23 September 2024 and died on 22 November 2024. Before the withdrew of consent, the patient was in the OLP in the inebilizumab/inebilizumab group. The cause of death was reported as invasive squamous carcinoma cervical and assessed as not related to inebilizumab by the Investigator. Malignancy is an important potential risk in the RMP and risk minimization measures is included in the SmPC section 4.3 and 4.4.

Adverse Events of Special Interest

Cytopenia

During the RCP, cytopenia was reported for 2.5% of patients in the inebilizumab group and 9.2% of patients in the placebo group. Lymphopenia and neutropenia were reported in 1 patient (0.8%) each in the inebilizumab group.

In the Any Inebilizumab group, cytopenia was reported for 14 patients (6.9%). The most common subtype of cytopenia was lymphopenia (2.0%) and neutropenia (2.0%). All cytopenia cases were mild (grade 1) or moderate (grade 2) in severity. One patient in the placebo/inebilizumab group during OLP experienced a grade 2 neutropenia which led to discontinuation of study IP. This event was assessed as related to study IP by the investigator.

Lymphopenia and neutropenia are well described in the SmPC section 4.8.

Infusion-related Reaction

During the RCP, infusion-related reactions were reported for a total of 12 patients (10.1%) in the inebilizumab group and 7 patients (5.9%) in the placebo group. The SmPC section 4.8. has been updated to reflect this.

In the Any Inebilizumab group, IRR was reported in 20 patients (9.9%). All cases were mild or moderate in severity except 1 patient who experienced 2 IRR events of grade 3. Both of the 2 IRR events were considered related to inebilizumab by the investigator. None of the IRRs led to discontinuation of treatment.

Information about pre-medication and serious infusion reactions is already included in the SmPC section 4.4. and Infusion-related reactions is an Important identified risk in the RMP.

Serious Hypersensitivity Reactions

No anaphylaxis cases were reported.

Opportunistic Infections

Opportunistic infections were reported for 1 patient (0.8%) in the inebilizumab group and 2 patients (1.7%) in the placebo group during the RCP. The event in the inebilizumab group was disseminated herpes zoster of grade 3. The event led to discontinuation of treatment and was considered related to the inebilizumab by the Investigator. The event resolved 5 days after treatment. Herpes zoster is already included in the ADR table in the SmPC section 4.8 and relevant risk minimization measures is included in in section 4.4 of the SmPC.

In the Any Inebilizumab group, hepatitis B reactivation occurred in 1 patient (0.8%) in the inebilizumab/inebilizumab group during the OLP. This was considered a nonserious, moderate event (grade 2). The event led to discontinuation of treatment and was considered related to the inebilizumab by the Investigator. Relevant risk minimization measures are included in section 4.3 and 4.4 of the SmPC and section 4.4. has been updated accordingly.

Opportunistic infections were balanced between inebilizumab and placebo groups of Study MINT, no opportunistic infections were reported in the study with NMOSD patients.

Serious Infections

Serious infections were reported in 7 patients (5.9%) in the inebilizumab group and 5 patients (4.2%) in the placebo group. COVID-19 and COVID-19 pneumonia were reported in 2-3 patients in both inebilizumab and placebo groups with similar percentage in each group. In addition, in the inebilizumab group, bone abscess, herpes zoster disseminated, and septic shock were reported in 1 patient (0.8%) each.

In the Any Inebilizumab group, serious infections reported for more than 1 patient included COVID-19 pneumonia (4.2%), COVID-19 (2.5%), and pneumonia (1.7%).

Serious infections were reported at a higher frequency in Study MINT compared to the study in NMOSD patients. The difference can be attributed to COVID-19.

During the RCP and OLP, no new AESIs were reported from 29 May 2024 to 01 September 2024.

Overall, the risk of IRRs, hypersensitivity, cytopenia and infections and risk minimisation measures are described in the SmPC and no new safety concerns were found based on the AESI evaluation.

Immune complex disease was also an AESI in the study. The Applicant confirmed that no events related to immune complex disease were identified during the study.

Laboratory findings

Hematology

No clinically meaningful trends were identified in the average changes from baseline in hemoglobin, haematocrit, eosinophils, leukocytes, eosinophils/leukocytes, basophils, basophils/leukocytes, erythrocytes, mean corpuscular volume and platelets.

Overall, lymphocyte counts were lower in the inebilizumab group than the placebo group during the RCP, which is consistent with the mechanism of action of the drug. With longer-term exposure at week 52 in the RCT and during the OLP, the lymphocyte levels trended back to the baseline level. The Inebilizumab group had a higher incidence of ≥ 2 grade worsening in lymphocyte count decreased compared to placebo ay week 26 (18.8% vs. 12.0%).

Neutrophil levels increased in both treatment groups at Weeks 2 and returned to baseline at week 8. Starting from week 12 through week 52, neutrophil count trended down from baseline. During the OLP, neutrophil counts remained stable. During the RCP, there were 1 patient with grade 3

neutrophil count decrease. No patients in the inebilizumab group had grade 2 neutrophil count decrease. During the OLP, grade 2 neutrophil count decreases were observed in 3 patients (3.5%) in the inebilizumab/inebilizumab group and 1 patient (1.3%) in the placebo/inebilizumab group. Grade 3 neutrophil count decreases were observed in 2 patients (2.3%) in the inebilizumab/inebilizumab group and 1 patient (1.3%) in the placebo/inebilizumab group.

The increased risk of infections associated with neutropenia and lymphopenia is reflected in the SmPC.

Chemistry

No clinically meaningful trends were identified in the average changes from baseline in albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, bilirubin, calcium, chloride, creatinine, gamma-glutamyl transferase, magnesium, potassium, protein, albumin, sodium or glucose.

Immunoglobulins

Immunoglobulin levels decreased with inebilizumab use. The decrease in serum immunoglobins was a concern at the MAA, as it may over time lead to increased risk of serious and/or opportunistic infections. As a consequence, warnings on the risk of infection relating to decreased levels of immunoglobulins is indicated in section 4.4 of the SmPC, and monitoring of immunoglobulins is also detailed in section 4.2 of the SmPC. In Study MINT, a greater reduction of total Ig and IgG from baseline was seen compared to the reduction seen in NMOSD patients, this might be attributed to disease-specific pathology.

Vital signs, Electrocardiograms

Overall, there were no notable changes from baseline in vital sign parameters (heart rate, systolic BP, and diastolic BP), physical findings or ECG parameters during the RCP and OLP and data were similar to the known safety profile.

Suicide Events

There was no notable difference between treatment groups in suicidal events per the summary of Columbia Suicide Severity Rating Scale.

Safety in special populations

Subgroup analyses showed more severe and serious events in patients ≥65 compared to patients <65, in male compared to female, in Asian compared to White and in the different regions. The differences were both seen in the placebo group and inebilizumab group except for patients ≥65. However, the small numbers of subjects in the ≥65 subgroup limit interpretation of the comparisons.

Renal and hepatic impairment has not been formally studied for inebilizumab.

There were 1 exposure during pregnancy in Study MINT. No conclusions can be drawn based on the event.

Drug-drug interactions

Concomitant use of inebilizumab and other immunosuppressant drugs may increase the risk of infection. Patients concomitantly receiving other immunosuppressive agents is included as missing information in the safety concerns in the RMP.

Discontinuations due to adverse events

During the RCP, 3 patients (2.5%) in the inebilizumab group and 1 patient (0.8%) in the placebo group discontinued the treatment. All events were reported for 1 participant each (inebilizumab group: thyroid mass, herpes zoster disseminated, and intervertebral disc protrusion; placebo group: MG crisis).

During the OLP, 2 patients (2.1%) in the inebilizumab/inebilizumab group and 1 patient (1.2%) in the placebo/inebilizumab group discontinued the treatment. All events were reported for 1 participant each (inebilizumab/inebilizumab group: fatigue and hepatitis B reactivation; placebo/inebilizumab group: neutropenia).

Post marketing experience

Overall, the post-marketing safety data are in line with the known safety profile. No conclusions can be drawn on the serious adverse events due to limited data. No new safety concerns are raised.

2.5.2. Conclusions on clinical safety

Overall, available safety data from the study MINT in patients with gMG is consistent with the known safety profile for inebilizumab in NMOSD patients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 39: Summary of Safety Concerns

Important identified risks	• Infusion-related reactions • Infections, including serious infections
Important potential risks	• Viral reactivation and opportunistic infections • Progressive multifocal leukoencephalopathy (PML) • Malignancy • Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women
Missing information	• Safety in patients ≥ 65 years

	• Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents

Pharmacovigilance plan

Table 40: on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20230064 (Previously VIB0551.P4.S4) An Observational Pregnancy Safety Study in Women with Neuromyelitis Optica Spectrum Disorder (NMOSD) and Generalized Myasthenia Gravis (gMG) Exposed to UPLIZNA (NMOSD indication: ongoing; gMG indication: planned) Ongoing	The registry is conducted to better characterize how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The specific objectives are: • To assess pregnancy and birth outcomes in female patients with NMOSD and gMG, exposed to inebilizumab commercial product (UPLIZNA) during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception. • To describe major congenital malformations, minor congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.	• Use in pregnancy and breastfeeding • Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Protocol submission Interim study report Final study report	October 2021 July 2026 July 2033
Study 20257092 (Previously VB-4149) CorEvitas SPHERES (Synergy of Prospective Health & Experimental Research for Emerging Solutions) Registry for Neuromyelitis Optica Spectrum Disorder (NMOSD) (NMOSD indication) Ongoing	To prospectively study the natural history of NMOSD and the comparative effectiveness and comparative safety of approved and off-label medications used in the treatment of NMOSD, as well as to systematically evaluate the burden for patients with this disease and to describe treatment utilization patterns. Adverse events of special interest (Targeted Events) including the important risks and missing information such as serious infections, malignancies, severe hypersensitivity reactions/anaphylaxis, and pregnancy will be evaluated.	• Infusion-related reactions • Infections, including serious infections • Viral reactivation, and opportunistic infections • PML • Malignancy • Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years	First Patient In Final study report	June 2021 December 2028

Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD), Immunoglobulin G4-related disease, and Generalized Myasthenia Gravis (gMG)Treated With inebilizumab in Europe (NMOSD indication: ongoing; IgG4-RD and gMG indications: planned) Ongoing	• To describe demographic, clinical and treatment characteristics of patients at the time of first inebilizumab treatment • To describe inebilizumab treatment patterns in the first 12 months following treatment initiation in terms of dosing, duration of treatment, frequency of drug discontinuation, switching, and use of add-on therapies • To quantify the incidence of adverse events of special interest, including serious infections, opportunistic infections, hepatitis B reactivations, serious infusion-related reactions, and malignancies.	• Infusion-related reactions • Infections, including serious infections • Viral reactivation and opportunistic infections • PML • Malignancy • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years • Use in pregnancy and breastfeeding	Protocol submission Final study report	March 2022 December 2032

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20230115 (Previously HZNP-UPL-401) A safety study of NMOSD patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study (NMOSD indication) Ongoing	• To understand the long-term effects of inebilizumab. • To assess specific safety, laboratory, and other measures in patients with NMOSD, during long-term treatment with inebilizumab and following its discontinuation.	• Infusion-related reactions • Infections, including serious infections • Viral reactivation, and opportunistic infections • PML • Malignancy • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years	Protocol submission Final study report	March 2022 August 2028

Risk minimisation measures

Table 41: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Infusion-related reactions	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.8, Section 5.1 • PL Section 2 and Section 4 • Recommendation to receive treatment under the supervision of a physician experienced with NMOSD, IgG4-RD, or gMG and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions is provided in SmPC Section 4.2 • Recommendations to use prophylaxis medications (corticosteroid, antihistamine, and antipyretic) prior to each inebilizumab infusion are provided in SmPC Section 4.2 and 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Infections, including serious infections	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8. • PL Section 2 and Section 4 • Recommendations to obtain a recent (ie, within 6 months) CBC including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for treatment discontinuation in the case of serious infections and recurrent infections is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Viral reactivation and opportunistic infections	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8 • PL Section 2 and Section 4 • Recommendations to obtain a recent (ie, within 6 months) CBC including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for HBV screening and evaluation for active tuberculosis and test for latent infection before administration of inebilizumab is included in SmPC Section 4.2 • Recommendation for treatment discontinuation in the case of serious opportunistic infection or recurrent infections is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Progressive multifocal leukoencephalopathy	Routine risk minimization measures: • SmPC Section 4.3 and 4.4 • PL Sections 2 and 4 • Recommendation to evaluate further at the first sign or symptom suggestive of PML, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JCV DNA, with repeat neurological assessments to be considered is included in SmPC Section 4.4 • Recommendation for treatment suspension if signs and symptoms of PML should occur and to discontinue	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402 Real-World Observational Study (NMOSD, IgG4-RD, and gMG

	treatment if PML is confirmed is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card	indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Malignancy	Routine risk minimization measures: • SmPC Sections 4.3 and 4.4 • PL Section 2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • Recommendations on monitoring newborns for B-cell depletion and to not administer live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant are included in SmPC Section 4.4 and Section 4.6 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Recommendation to consider consulting with a qualified specialist to assess whether a protective immune response has been mounted is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD and gMG indications)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Safety in patients ≥ 65 years	Routine risk minimization measures: • SmPC Sections 4.2 and 5.2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Use in pregnancy and breastfeeding	Routine risk minimization measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6, and PL Section 2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD, IgG4-RD, and gMG indications) • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information (continued)		
Patients concomitantly receiving other immunosuppressive agents	Routine risk minimization measures: • SmPC Sections 4.4 and 4.5 • PL Section 2 1. Recommendations to consider the potential for increased immunosuppressive effects in the presence of concomitant immunosuppressive therapy are included in SmPC Section 4.4 and Section 4.5 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

CBC = complete blood count; gMG = generalized myasthenia gravis; IgG4-RD = immunoglobulin G4-related disease; IV = intravenous; JCV = John Cunningham virus; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; PL = Package Leaflet; PML = progressive multifocal leukoencephalopathy; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4 ,4.5, 4.6, 4.8, 5.1, 5.2, and 7 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

In addition, the list of local representatives in the PL is being revised.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The same dosage, presentation, and route of administration (IV infusion) of Uplizna (inebilizumab) will be used for the new proposed indication (gMG). Uplizna remains to be administered in an in-patient or out-patient hospital setting under the supervision of a doctor experienced in treating patients with such a condition.
- Analysis of available safety data from pivotal Study MINT has not identified significant updates to the overall safety information for inebilizumab in the gMG adult patient population. The safety profile of inebilizumab was similar in NMOSD patients and gMG patients and is consistent with the known mechanism of B cell depletion.

- The adult gMG patient population who will be administered Uplizna is not expected to substantially differ from the NMOSD adult patient population in terms of ability to read and comprehend the patient leaflet (PL).
- The design and layout of the proposed PL in this variation remains consistent with the approved PL.
- The concept and style of writing and language used (lay language) is the same as the previous approved PL.
- The updates do not affect the layout of critical safety sections of the PL.
- The updated text can be clearly translated into other EU languages.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

gMG is a rare chronic autoimmune neuromuscular condition that causes fluctuating weakness of muscles of varying severity, ranging from difficulties in performing daily tasks to life-threatening respiratory insufficiency (Lehnerer et al, 2022; Finnis and Jayawant, 2011).

3.1.2. Available therapies and unmet medical need

Anticholinesterase inhibitors and ISTs are standard of care for gMG and have reduced mortality and improved quality of life (Evoli et al, 2023). Approximately 85% to 90% of gMG patients respond to these therapies; however, efficacy has limited durability and there are adverse effects associated with long term use that lead to reduced quality of life (Urban et al, 2018). Additionally, compared to anti AChR Ab+ patients, anti-MuSK-Ab+ patients often have a poorer response to standard therapies such as anticholinesterase inhibitors, and are more likely to remain steroid dependent, despite the addition of other ISTs (Gilhus et al, 2019).

More recently, several therapeutics targeting the complement pathway (eculizumab/Soliris, ravulizumab/Ultomiris, and zilucoplan/Zilbrysq) have been approved for the treatment of anti-AChR-Ab+ gMG, however, these therapies have not been studied in anti-MuSK-Ab+ gMG, considering that IgG4 antibodies do not activate complement (Evoli et al, 2023). Other therapies targeting the neonatal fragment crystallizable receptors have also been approved for use in the treatment of either anti-AChR-Ab+ gMG (efgartigimod alfa/Vyvgart) or both anti AChR Ab+ and anti-MuSK-Ab+ gMG subgroups (rozanolixizumab/Rystiggo, and nipocalimab/Imaavy) (Evoli et al, 2023). Neonatal fragment crystallizable receptors blockers reduce the overall levels of circulating pathogenic autoantibodies by inhibiting the IgG salvage mechanism, but do not directly target the B cells responsible for producing the pathogenic autoantibodies.

3.1.3. Main clinical studies

One pivotal study was conducted: A Randomized, Double-Blind, Multicenter, Placebo-Controlled Phase 3 Study with Open-label Period to Evaluate The Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis (**MINT**)

Eligible subjects were adults with either anti AChR Ab+ or anti MuSK Ab+ MG with moderate to severe disease activity (confirmed by the MGFA class at baseline).

Subjects were randomized 1:1 to receive either IV infusions of 300 mg inebilizumab or placebo on days 1 and 15 (all subjects), and day 183 (anti AChR Ab+ subjects only) of the RCP.

Study duration is up to 4 years for subjects who chose to enter the optional OLP: screening (4 weeks), RCP (26 or 52 weeks), and OLP (3 years). Subjects who chose not to participate in the OLP, or who discontinued IP during the OLP, had an option of entering the SFP for 2 years after the last dose of IP.

3.2. Favourable effects

The primary endpoint was change from baseline in MG-ADL score at week 26 for the overall population and showed a treatment difference to placebo of -1.3 (95% CI: -2.2; -0.4) using the treatment policy strategy. The LS mean absolute change from baseline was –3.0 and -4.3 points for placebo and inebilizumab, respectively. MG-ADL is a patient-reported outcome reflecting day-to-day function.

The next endpoint in the hierarchy was the key secondary endpoint change from baseline in QMG score at week 26 for the overall population and was met with a treatment difference to placebo of -2.0 (95% CI: -3.3; -0.7) using the treatment policy strategy. The LS mean absolute change from baseline was –2.9 and -4.9 points for placebo and inebilizumab, respectively. QMG is physician based and quantifies the disease severity.

In the anti-AChR Ab+ patients, the treatment difference in change from baseline at week 26 for MG-ADL was 1.4 (95% CI: -2.5; -0.3) and QMG -2.2 (95% CI: -3.8; -0.7) (treatment policy strategy).

In the anti-MuSK Ab+ patients the treatment difference in change from baseline at week 26 for MG-ADL was -0.9 (95% CI: -2.7; +1.0) and QMG -1.2 (95% CI: -4.0; +1.6) (treatment policy strategy).

A number of exploratory endpoints were reported:

Responder analyses were presented for 2-8 points improvement in MG-ADL at week 26 (Composite strategy) for treatment and placebo arms divided in serotypes. Overall, for all three serotypes, a higher proportion of patients treated with inebilizumab were MG-ADL responders with differences to placebo around 10-20%.

Another endpoint (not in hierarchy) was ≥3-point improvement in MG-ADL score with no rescue therapy (week 26-28) and here the treatment differences were around 20%, with 48.2% responders in the placebo group and 68.7% in the inebilizumab group in the overall population and for the different serotypes similar proportions were seen.

At week 26, more patients in the placebo group had received rescue therapy (IVIg/PLEX): 8.4% vs 23.9% in inebilizumab and placebo, respectively. At week 52 the numbers were 11.6% and 34.4%, respectively. Similar results were seen in the two serotypes. Most patients received IVIg as rescue therapy.

Anti-AChR-Ab+ patients entered the OLP of the pivotal MINT trial after 52 weeks and the anti-MuSK-Ab+ patients after 26 weeks. As of the cut-off date (28 May 2024), a total of 94 subjects (79.0%) in the inebilizumab group and 84 subjects (70.6%) in the placebo group had been enrolled into the OLP. Patients randomized to inebilizumab in the double-blind period seemed to have a sustained response on inebilizumab and the placebo treated patients seemed to benefit from initiating inebilizumab. Only few patients have been treated for 78 weeks and the trial is ongoing.

3.3. Uncertainties and limitations about favourable effects

The present extension of indication relies on a single, pivotal trial (MINT trial), so the results are expected to be statistically compelling and clinically relevant. Inebilizumab demonstrated a statistically significant improvement in the first 4 out of 5 key secondary endpoints (3 out of 5 when using treatment policy). Despite the magnitude of effect of the primary endpoint, change from baseline in MG-ADL to weeks 26, were below the MCID of 2 points, especially with the treatment policy strategy (-1.3 (95% CI: -2.2; -0.4)) the responder analyses showed a clinically relevant reduction in gMG symptoms compared to placebo. In addition, the results are supported by the physician-based outcome QMG with a change from baseline in QMG to weeks 26 of 2.0 (95% CI: -3.3; -0.7) which is considered supportive as well as additional analyses and sensitivity analyses.

3.4. Unfavourable effects

The safety profile of inebilizumab is consistent with its mechanism of action (anti-CD19 monoclonal antibody leading to B-cell depletion) with reported cases of infusion-related reactions, infections, neutropenia, lymphopenia and decreases in immunoglobulins.

In the RCT, the most common AEs by preferred term in the inebilizumab group were headache (15.1% for inebilizumab vs. 6.7% for placebo), COVID-19 (10.9% vs. 10.1%), cough (6.7% vs. 3.4%), nasopharyngitis (6.7% vs. 2.5%) and urinary tract infection (6.7% vs. 2.5%).

Overall, the most common AEs were consistent with the known safety profile of inebilizumab. However, headache (15.1% vs. 6.7%) and cough (6.7% vs. 3.4%) were reported more frequent in the RCP in the inebilizumab group compared to placebo and have been added to the adverse drug reactions table in the SmPC section 4.8. The high frequency of COVID-19, reflect that the RCT were conducted during the global COVID-19 pandemic.

Serious adverse events were reported for 8.4% of patients in the inebilizumab group and 13.4% of patients in the placebo group during the RCP. COVID-19, COVID-19 pneumonia and myasthenia gravis crisis were reported in 2 patients (1.7%) each. All other events occurred in 1 patient. The 2 events of Myasthenia gravis crisis were assessed as not related to inebilizumab. Serious infections and infestations were reported for 7 patients (5.9%) in the inebilizumab group.

As of the cutoff date 28 May 2024, a total of 4 deaths were reported. Three fatal cases were reported during the RCP; 2 patients in the placebo group (cardio-respiratory arrest and respiratory distress) and 1 patient in the inebilizumab group (MG crisis, ARDS, pneumonitis and septic shock). One fatal case was reported during the OLP in the inebilizumab/inebilizumab group (acute myocardial infarction). Three of the fatal cases were assessed as not related by the investigator and 1 fatal case of ARDS, septic shock and pneumonitis was assessed as related to inebilizumab by the Investigator. Severe infection is a known risk of inebilizumab and it is agreed that the treatment could have increased the susceptibility to infections in the fatal case of MG crisis, ARDS, pneumonitis and septic shock.

Opportunistic infections were reported for 1 patient (0.8%) in the inebilizumab group and 2 patients (1.7%) in the placebo group during the RCT. The event in the inebilizumab group was disseminated herpes zoster of grade 3. In the Any Inebilizumab group, hepatitis B reactivation occurred in 1 patient (0.8%) in the inebilizumab/inebilizumab group during the OLP. This was considered a nonserious, moderate event (grade 2).

3.5. Uncertainties and limitations about unfavourable effects

The main safety database consisted of a total of 207 patients receiving 1 or more doses of inebilizumab, 41 patients received inebilizumab for more than 2 years and 128 patients received inebilizumab for at least 1 year. Considering the anticipated chronic treatment with inebilizumab, long-term safety data are required, and further results of the OLE awaited.

Since inebilizumab is intended for chronic administration and considering that neutropenia, lymphopenia and decreases in immunoglobulin (consistent with the mechanism of action of inebilizumab) were common during the study and previous study in NMODS, a risk of infections (including opportunistic infections) cannot be excluded for patients receiving long-term treatment. A section is included in section 4.4 of the SmPC and serious infections, viral reactivation and opportunistic infections are included as important potential risks in the RMP.

Due to a death of probable PML in the previous NMODS study, the SmPC includes a section for PML in section 4.4. and PML has been included in the RMP as an important potential risk. There were no reports of PML in study MINT.

Given the limited long-term safety data at current stage, the potential impact of treatment with inebilizumab on the development of malignancies is unknown. A section is already included in section 4.4 of the SmPC and malignancy is included as important potential risks in the RMP.

There is missing information with regard to the safety in some populations; in patients concomitantly receiving other immunosuppressive medications and in pregnant or lactating women. Specific sections are already included in the SmPC section 4.4. and 4.5. and these groups are included as missing information in the RMP.

3.6. Effects Table

*Table 42: **Effects Table for Uplizna for gMG (data cut-off: 28 May 2024)***

Effect	Short description	Unit	Treatment Inebilizumab (N = 119)	Control placebo (N = 117)	Uncertainties / Strength of evidence	Ref
Favourable Effects						
MG-ADL	Reduction in MG-ADL change from baseline at **Week 26** in the overall study population		111 vs. 105 (LS mean -4.3 vs. -3.0; difference -1.3; 95% CI: -2.2, -0.4)		**Unc**: **1)** overall an effect size not close to the MCID of 2 points difference in MG-ADL. **2)** One pivotal trial	MINT Study 20230049
QMG	Reduction in QMG change from baseline at **Week 26** in the overall study population		107 vs. 103 (LS mean -4.9 vs. -2.9; difference -2.0; 95% CI: -3.3, -0.7)		**Unc:** **1)** overall an effect size not close to the MCID of 3 points difference in QMG **2)** One pivotal trial	
Unfavourable Effects						
Infections	Infections and infestations (SOC)	%	42.9	36.1	Identified risk	MINT Study 20230049
Serious infections	Infections and infestations (SOC)	%	5.9	4.2	Identified risk	

Effect	Short description	Unit	Treatment Inebilizumab (N = 119)	Control placebo (N = 117)	Uncertainties / Strength of evidence	Ref
Opportunistic infections	Definition unclear from CSR.	%	0.8	1.7	Potential risk due to neutropenia, lymphopenia and immunoglobulin decrease	
Infusion related reaction	Definition unclear from CSR.	%	10.1	5.9	Identified risk	

Abbreviations: MG-ADL: Myasthenia Gravis – Activity of Daily Living

All favourable results are based on an estimand strategy that uses treatment policy to handle the intercurrent events of use of rescue medications (at any time point) and treatment discontinuation.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The single pivotal trial has demonstrated an effect size for the primary endpoint MG-ADL that are below the MCID of 2 points. However, the results are statistically robust and there is good internal consistency with clinically important secondary endpoints (e.g. QMG). Responder analyses for the primary endpoint MG-ADL was in favour of inebilizumab and it is demonstrated that inebilizumab is efficacious for the treatment of gMG.

The safety profile of inebilizumab is consistent with its mechanism of action (anti-CD19 monoclonal antibody leading to B-cell depletion) with reported cases of infusion-related reactions, infections, neutropenia, lymphopenia and decreases in immunoglobulins. There are serious identified risks (Infusion-related reactions and infections, including serious infections) and potential risks (viral reactivation and opportunistic infections, PML and malignancy) with inebilizumab therapy which is considered to be manageable with the current labelling and monitoring. A long-term safety study with inebilizumab, in order to monitor immunoglobulins and evaluate the risk of adverse events, within the Infections and infestations SOC, is ongoing and included in the RMP.

With the caution needed due to the limitations of the safety database, particularly in the long-term, it appears that the safety profile of inebilizumab in patients with gMG is manageable and consistent with the known safety profile.

3.7.2. Balance of benefits and risks

Inebilizumab has shown to be efficacious for the treatment of gMG. Despite a modest effect size on the population level in the primary and key secondary endpoints MG-ADL and QMG, the responder analyses showed a clinically relevant effect.

The safety profile of inebilizumab was consistent with its mechanism of action and the known safety profile in NMODS patients. The identified risks are considered manageable.

3.8. Conclusions

The overall B/R of Uplizna is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	type II	I, II, IIIA, and IIIB
A.6	A.6 Change in ATC Code / ATC Vet Code	type IA	I

Extension of indication to include add-on to standard therapy for the treatment of adult patients with generalised myasthenia gravis (gMG) for Uplizna, based on primary analysis results from Study MINT (VIB0551.P3.S1); this is a pivotal phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab in adults subjects with myasthenia gravis. As a consequence, sections 4.1, 4.2, 4.4 ,4.5, 4.6, 4.8, 5.1, 5.2, and 7 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the RMP has also been endorsed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

Update of the ATC code of inebilizumab to L04AG10 in line with the 2024 ATC INDEX.

The group of variations leads to amendments to the annexes I, II, IIIA, and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II, IIIA, and IIIB and to the Risk Management Plan (RMP) are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Uplizna in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Uplizna is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Uplizna have access to/are provided with the following educational package:

A patient card

The **patient card** shall contain the following key messages:

- Information that inebilizumab treatment may increase the risk of infections, including serious infections, viral reactivation, opportunistic infections, and PML
- A warning message on seeking early medical care in case of signs and symptoms of infection and PML
- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency that the patient is receiving inebilizumab
- Contact details of treating physician/centre
- Cross-reference to the Package Leaflet

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Uplizna is not similar to Soliris, Vyvgart and Rystiggo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMA/VR/0000257358'