11 November 2021
EMA/266309/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Uplizna

International non-proprietary name: inebilizumab

Procedure No. EMEA/H/C/005818/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AC	Adjudication Committee
ADA	Anti-Drug Antibodies
ADCP	Antibody-Dependent Cellular Phagocytosis
ADCC	Antibody-Dependent Cellular Cytotoxicity
AEs	Adverse Events
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AQP4-IgG	Aquaporin-4 Immunoglobulin G antibodies
ARR	Annualised relapse rate
AS	Active Substance
AST	Aspartate Aminotransferase
AUC_{0-7d}	Area Under the Concentration-Time Curve from hour 0 to day 7
AUC_{inf}	Area under the concentration-time curve from dosing extrapolated to infinity
AUClast	Area under the concentration-time curve from dosing to last measurable timepoint
BSE	bovine spongiform encephalopathies
C_{max}	Maximum Observed Concentration
CI	Confident Interval
CHO	Chinese Hamster Ovary
CL	Clearance
CL/F	Apparent Clearance
CNS	Central Nervous System
CPHM	Cox Proportional Hazards Model
CPPs	critical process parameters
CQAs	Critical quality attributes
DB	Double Blind
DDI	Drug-Drug Interaction
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EMC	expected maximum change
E-R	Exposure-Response
FDA	Food and Drug Administration
FP	Finished Product
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
huCD19 Tg	human CD19 transgenic
ICH	International Council for Harmonisation
IDMC	Data Monitoring Committee
Ig	immunoglobulin
INN	International nonproprietary name
IP	Investigational Product
IPCs	in-process controls
ITT	Intent-To-Treat
IST	Immunosuppressive Therapy
IVIG	Intravenous Immune Globulin
IV	Intravenous
HED	Human Equivalent Dose

HR	Hazard Ratio
JP	Japan Pharmacopoeia
LLN	Lower Limit of Normal
MRI	Magnetic Resonance Imaging
mAb	monoclonal Antibody
MCB	master cell bank
MVM	mouse minute virus
NMOSD	Neuromyelitis Optica Spectrum Disorders
NOAEL	No Observed Adverse Effect Level
Q	Inter-compartmental clearance
OR	Odds Ratio
Ph. Eur.	European Pharmacopoeia
PML	Progressive Multifocal Leukoencephalopathy
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
popPK	Population PK
PPQ	process performance qualification
PRS	Primary Reference Standard
PRV	pseudorabies virus
PT	Preferred Term
QbD	Quality-by-Design
REO3	reovirus type 3
RCP	Randomised-Controlled Period
RPN	risk priority number
TEAE	Treatment Emergent Adverse Events
TESAE	Treatment Emergent Serious Adverse Events
TK	Toxicokinetics
TSE	transmissible spongiform encephalopathies
TTC	Threshold of Toxicological Concern
$t_{1/2}$	half-life
RMP	Risk Management Plan
SA	Scientific Advice
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneous
SFP	Safety Follow-up Period
SmPC	Summary of product characteristics
SOC	System Organ Class
UF/DF	Ultrafiltrate/Diafiltrate
US	United States
USP	US Pharmacopoeia
Vc	Volume of distribution in the central compartment
Vp	Volume of distribution in the peripheral compartment
V_{max}	Maximum velocity of Michaelis-Menten equation
WCB	Working Cell Bank
WRS	Working Reference Standards
XMuLV	Xenotropic Murine Leukemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viela Bio submitted on 23 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Uplizna, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 November 2020.

Uplizna, was designated as an orphan medicinal product EU/3/17/1856 on 20 March 2017 in the following condition: Neuromyelitis optica spectrum disorder (NMOSD).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Uplizna as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Uplizna

The applicant applied for the following indication:

Uplizna is indicated for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) to reduce the risk of attacks and associated worsening of disability.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0428/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0428/2020 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0428/2020.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.4.2. New active substance status

The applicant requested the active substance inebilizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice (SA) on the development relevant for the indication subject to the present indication.

Date	Reference	SAWP co-ordinators
21 November 2013	EMEA/H/SA/2664/1/2013/III	Dr. Monique Wakelkamp Dr. Jan Mueller-Berghaus
23 April 2015	EMEA/H/SA/2664/1/FU/1/2015/II	Dr. Kerstin Wickström Prof. Luca Pani

There are no available scientific guidelines for the development of products intended for the treatment of NMOSD.

SA on Uplizna was provided to MedImmune, as the clinical trial sponsor, in 2013 including questions on Chemical, Pharmaceutical and Biological development, toxico-Pharmacological development and Clinical development (EMEA/H/SA/2664/1/2013/III). Regarding this last section, SA was provided to the applicant for several aspects including mechanisms of action, study population, study design features (randomisation scheme and particularly the use of a placebo-controlled trial), sample size estimations, primary endpoint (definition of the event and role of adjudication committee), secondary endpoints and pharmacokinetics (PK) and pharmacodynamics (PD) modelling.

Advices given regarding the chemical, pharmaceutical and biological development have been followed by the applicant.

Of note, the CHMP showed some concerns on the inclusion of Aquaporin-4 Immunoglobulin G antibodies (AQP4-IgG) seronegative patients: (1) paucity of scientific evidence supporting this role; (2) potential negative impact for the assessment derived from the inclusion of a heterogeneous group [AQP4-IgG seropositive and AQP4-IgG seronegative are different. Additionally, AQP4- is a heterogeneous group itself]; (3) the study was not powered for assessing the efficacy of inebilizumab in AQP4-IgG seronegative patients based on sample size considerations and the analysis plan presented by the applicant (EMEA/H/SA/2664/1/2013/III).

Instead of using the time to first on-trial adjudicated relapse as primary efficacy endpoint, the SA EMEA/H/SA/2664/1/2013/III recommended using investigator-confirmed attacks for the primary analyses and to conduct sensitivity analyses using the adjudicated cases. This advice has not been followed by the applicant. However, all pivotal trials for Inebilizumab, Eculizumab and Satralizumab used adjudicated events (relapses) for primary endpoint.

The applicant's proposal of hierarchical key secondary endpoints was endorsed during the SA. The proposal included the following endpoints to be evaluated only in AQP4-IgG seropositive subjects in this order: (1) expanded disability status scale (EDSS) worsening, (2) change in low-contrast visual acuity, (3) number of attack-related medical facility visits, (4) change in quality of life by short-form-36 and (5) time from Day-1 to onset of confirmed attack on or before Day-183. In the submitted application, key secondary endpoints evaluated in AQP4-IgG seropositive and in the full-study population included: (1) EDSS worsening, (2) change in binocular low-contrast visual acuity, (3) cumulative total magnetic

resonance imaging (MRI) lesions and (4) number of NMOSD-related in-patient hospitalisations. The proposed and endorsed hierarchical order during SA was not fully followed.

A following SA was obtained in 2015 regarding the use of Placebo-controlled trial without background immunosuppressive therapy (IST) (EMEA/H/SA/2664/1/FU/1/2015/II), which agreed with placebo use under certain conditions to limit placebo exposure (e.g. unequal randomisation; use of a time-to-event outcome; limiting the time on placebo in a given patient to a maximum of 6.5 months). These conditions were met in current pivotal study.

The applicant held a pre-submission meeting with the Product Lead and Regulatory Affairs team November 2019 and received written feedback from the Rapporteur and Co-Rapporteur teams in March 2020.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kirstine Moll Harboe Co-Rapporteur: Fátima Ventura

The application was received by the EMA on	23 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 October 2021

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Uplizna on	11 November 2021
The CHMP adopted a report on similarity of inebilizumab with eculizumab and satralizumab on (see Appendix on similarity)	11 November 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Neuromyelitis optica spectrum disorder (NMOSD; also known as Devic's syndrome and previously known as neuromyelitis optica [NMO]) is a rare, chronic, autoimmune, inflammatory, disorder of the central nervous system (CNS) manifesting clinically as optic neuritis, myelitis, and certain brain and brainstem syndromes. Cases clinically diagnosed as NMOSD may include AQP4-IgG seropositive patients and AQP4-IgG seronegative patients.

2.1.2. Epidemiology

The epidemiology of NMOSD is complex and differs greatly depending on the region and the ethnicity of the study population. The incidence of NMOSD is estimated between 0.05-0.4 per 100,000 population, and the prevalence estimates vary from 0.5-10 per 100,000 population. The prevalence among white people is ~1/100,000 population, with an annual incidence of <1/million population. Among East Asians, the prevalence is higher, at ~3.5/100,000 population, while the prevalence in African people may be up to 10/100,000 population.

AQP4-antibody disease has a high female-to-male ratio (up to 9:1), and its mean age at onset of ~40 years is later than that seen in multiple sclerosis, though onset can occur throughout the lifespan. Onset in childhood occurs very rarely and the paediatric manifestation of NMOSD is poorly understood.

2.1.3. Aetiology and pathogenesis

Neuromyelitis optica spectrum disorder is a distinct, although heterogeneous, disease (Wingerchuk et al, 2007). A defining feature of NMOSD is the presence of serum AQP4-IgG, which is detected in about 80-90% of NMOSD patients (Jarius and Wildemann, 2010; Pittock and Lucchinetti, 2016). Aquaporin-4 is the most abundant water channel expressed on the plasma membrane of astrocytes throughout the CNS. AQP4-IgG is thought to be pathogenic by causing astrocyte loss through complement-dependent mechanisms, antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC), and/or by unfavourably altering astrocyte physiology by reducing expression of key water channel proteins (Ratelade and Verkman, 2012).

Pathogenic AQP4-IgG is produced by B-lineage cells, specifically a subpopulation of CD19-positive (CD19+) CD20-negative (CD20-) B cells showing morphological and phenotypical properties of

plasmablasts (Chihara et al, 2011). These cells are increased selectively in the peripheral blood of NMOSD patients (Chihara et al, 2011; Kim W et al, 2011; Greenberg et al, 2012), and are further expanded in the periphery; they are also found in the CNS at the time of NMOSD attack (Chihara et al, 2011; Kowarik et al, 2017).

Even using the most reliable assays, there are subsets of subjects who do not test seropositive for AQP4-IgG who may still present with NMOSD phenotype. Some of the "seronegative" NMOSD patients have antibodies to myelin-oligodendrocyte glycoprotein (Kitley et al, Nov 2012; Kitley et al, 2014), and others may have autoantibodies that have not yet been identified. Different etiological mechanisms may be involved in AQP4-IgG seronegative NMOSD (Kitley et al, Sep 2012; Mader et al, 2011; Jarius et al, 2012).

Occasionally, patients without detectable serum AQP4-IgG are later found to be seropositive. There may be technical explanations in some cases, but antibody levels also increase with clinical relapses and decrease with immunosuppressive therapy in some patients. Therefore, retesting should be considered before B-cell or antibody-targeted therapies (plasma exchange, immunosuppressive drugs) are instituted and in seronegative patients who relapse.

2.1.4. Clinical presentation, diagnosis

The diagnosis of NMOSD relies on a clinician's assessment of a patient's history and findings being consistent with consensus international clinical criteria for NMOSD (2015 International Panel on NMO Diagnosis (IPND) criteria) (Table 1).

Table 1: IPND Neuromyelitis Optica Spectrum Disorders Diagnostic Criteria

TABLE. DIAGNOSTIC CRITERIA FOR NMOSD IN ADULTS	
AQP4+ NMOSD	
Positive test for AQP4-IgG[a]	
Exclusion of alternate diagnoses	
At least 1 of the following:	
Optic neuritis	
Acute myelitis	
Area postrema syndrome	
Acute brainstem syndrome	
Symptomatic cerebral syndrome w/ NMOSD-typical brain lesion	
Symptomatic narcolepsy OR acute diencephalic clinical syndrome with NMOSD-typical diencephalic lesions.	

AQP4- or AQP4 status unknown NMOSD	
Negative or inconclusive test for AQP4-IgG[a]	
Exclusion of alternative diagnoses	
At least 1 of the following :	
Optic neuritis	
Acute myelitis with LETM	
Area postrema syndrome	
If only 1 of above present, then also 1 of following:	
Acute brainstem syndrome	
Symptomatic cerebral syndrome w/ NMOSD-typical brain lesion	
Symptomatic narcolepsy OR acute diencephalic clinical syndrome WITH NMOSD-typical diencephalic lesions	
PLUS THE FOLLOWING MRI FINDINGS	
Acute optic neuritis	Brain MRI normal or with nonspecific white matter lesions OR optic nerve hyperintense lesion or T1 Gd+ lesion extending over more than half the optic nerve or involving optic chiasm
Acute myelitis	Associated intramedullary lesion extending over 3 or more contiguous segments (LETM) OR focal spinal cord atrophy over 3 or more contiguous segments and compatible history
Area postrema syndrome	Dorsal medulla/area postrema lesions
Acute brainstem lesion	Periependymal brainstem lesions
Abbreviations: AQP4, aquaporin-4; Gd+, gadolinium positive; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; NMOSD, neuromyelitis optica spectrum disorders. [a] cell-based assay preferred for AQP4 antibody testing	

The disease is characterised by attacks of predominantly ON and longitudinally extensive transverse myelitis, and, less frequently, affecting the brain and brainstem. Commonly reported symptoms include ocular pain, unilateral and bilateral loss of visual acuity that can reach blindness, loss of sensation, weakness including paraplegia, bladder and bowel dysfunction, paroxysmal tonic spasms of the trunk and limbs, and Lhermitte's phenomenon (Wingerchuk et al, 2007).

Up to 90% of patients with NMOSD have relapsing episodes of ON and myelitis rather than following a monophasic course (Ghezzi et al, 2004; Wingerchuk et al, 1999). The monophasic NMOSD is a recognizable clinical entity but the criteria that accurately predict long-term adherence to a monophasic course cannot currently be defined. An interval longer than 4 weeks between index attacks indicates relapsing disease (Wingerchuk et al, 2015). A second attack occurs within 1 year of onset in 60% of seropositive patients and within 3 years in 90% of patients. Few patients who experience an NMOSD relapse have a full recovery. More than half of patients with NMOSD have permanent blindness or paralysis as the result of NMOSD relapses. If inflammation compromises brainstem regions involved in breathing or heart function, which occurs rarely, NMOSD relapses can be fatal due to neurogenic respiratory failure (Oh and Levy, 2012).

Differential diagnosis between NMOSD and conditions that may cause myelitis and ON by other mechanisms is important to establish as some MS immunotherapies appear to aggravate NMOSD.

2.1.5. Management

Patients who are AQP4-IgG seropositive should be assumed to be at risk for relapse indefinitely and preventive treatment should be considered, even in the setting of a prolonged clinical remission (Wingerchuk et al, 2015).

Current treatments for NMOSD are aimed at prevention of attacks, acute management of attacks, and amelioration of persistent symptoms. Patients with NMOSD have been treated prophylactically for attack prevention with off-label IST such as azathioprine, mycophenolate mofetil, daily prednisone, or rituximab. High-dose steroids and plasmapheresis are generally used for the acute management of attacks. Symptomatic treatments are used to address symptoms, which can include general and neuropathic pain (e.g, anti-epileptics, anti-spasmodics, anti-depressants, or analgesics), bowel (e.g, laxatives), bladder (e.g, bethanechol), and fatigue and depression (e.g, psychotherapy or medication) disorders (Kessler et al, 2016).

Since 2019 to the date of this report, two new therapies have been authorised in the EU for the treatment of APQ4-IgG seropositive NMOSD patients. Blockade of complement-mediated damage by eculizumab is approved for AQP4-IgG+ NMOSD patients with a relapsing course of the disease (2019). Satralizumab, a humanised interleukin-6 (IL-6) receptor antagonist is for the treatment of NMOSD in adult and adolescent patients from 12 years of age who are AQP4-IgG positive. There are other treatment strategies being tested in phase I and II for treatment of NMOSD.

Results of uncontrolled studies with rituximab, a chimeric monoclonal antibody (mAb) against the human CD20 molecule, provide low level evidence for utility of B-cell depletion as a means of preventing attacks in NMOSD (Cree et al, 2005; Jacob et al, 2008; Bedi et al, 2011; Kim SH et al, 2011; Ip et al, 2013). B-cell analysis of rituximab failures revealed the presence of CD19+/CD20- plasmablasts (unpublished data, Dr Larry Steinman, Stanford University), which supports the need for a more comprehensive B cell-depleting therapy than rituximab for effective treatment of this disease. CD19 is expressed on a wider lineage of B cells, from pro-B to plasmablasts and some plasma cells, compared to CD20. It is therefore conceivable that direct depletion of CD19+ B cells could be more effective in reducing the risk for NMOSD attack by more effectively depleting plasmablasts producing AQP4-IgG.

The preventive therapy has been regarded as beneficial, and the scarce published data provide an indication of a preventive effect to an extent; consensus treatment regimens have been published and are widely used throughout the world with an apparent clinical benefit. Nevertheless, an adequate evidence base of randomised controlled trials has been lacking to support these currently used treatment options. Thus, an unmet medical need for highly effective and specific therapies has long been prevalent.

2.2. About the product

Inebilizumab is a humanised, affinity-optimised, afucosylated IgG1 kappa (IgG1κ) mAb that binds to the B cell-specific surface antigen CD19, resulting in a profound depletion of B cells; these include plasmablasts and some plasma cells via ADCC and ADCP mechanisms.

Inebilizumab is generated by expression of the human CD19-specific mAb 16C4 in a fucosyltransferase-deficient Chinese hamster ovary producer cell line, thereby generating a homogenously afucosylated antibody with enhanced antibody-dependent cellular cytotoxicity.

The claimed indication was the following:

> *Uplizna is indicated for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) to reduce the risk of attacks and associated worsening of disability (see section 5.1).*

The approved indication is the following:

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

2.3. Type of Application and aspects on development

N/A

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as concentrate for solution for infusion containing 100 mg of inebilizumab as active substance (AS).

Other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, trehalose dihydrate, polysorbate 80 and water for injection.

The product is available in glass vials, each vial containing 100 mg of inebilizumab in a concentration of 10 mg/mL as described in section 6.5 of the SmPC. The final concentration after dilution is 1.0 mg/mL.

2.4.2. Active substance

2.4.2.1. General information

The AS, inebilizumab (INN) is a recombinant humanised IgG1κ monoclonal antibody (mAb) directed against CD19 and therefore targets the B-lineage plasmablasts.

The Chinese Hamster Ovary (CHO)-cell line used for inebilizumab expression has been designed to be fucosyltransferase-deficient (i.e. lost the ability to transfer fucose), and the N-linked oligosaccharides attached at the residue Asn-301 are therefore homogenously afucosylated without core fucosylation thereby increasing the antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activities.

2.4.2.2. Manufacture, process controls and characterisation

Inebilizumab AS is manufactured by a standard mAb manufacturing process at an AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC) manufacturing site in Maryland USA. Good Manufacturing Practice (GMP) compliance has been documented for all sites involved.

Description of manufacturing process and process controlsThe manufacturing process of inebilizumab AS encompasses cell culture, harvest and primary capture, purification including orthogonal dedicated virus clearance steps, concentration, formulation and filtration to final fill. Dilution buffer and excipient addition buffer are added to the product in quantities calculated to achieve the target composition.

The manufacturing process, process parameters (including criticality assignment), the material inputs and process outputs (in-process controls (IPCs), microbial controls, and performance attributes) are summarised. The purpose of each step is clearly stated, and a brief description is provided. Several critical process parameters (CPPs) and IPCs have been identified. The acceptance criteria for the process parameters and IPCs, as well as action limits for process outputs, are also included and generally justified by process characterisation data. The manufacturing process and process controls are considered acceptable.

Control of materials

All raw materials used in the cell banking, cell culture and purification processes are either tested according to in-house criteria or according to US pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), or Japan Pharmacopoeia (JP). Importantly, excipients are tested according to Ph. Eur. Materials are inspected upon receipt, and supplier certificates of analysis are reviewed. The internal specifications for the non-compendial raw materials are available.

The cell culture media and nutrient feeds are confirmed to be free of animal proteins.

Supplier certificates of analysis and certificate of origin are available for all raw materials of biological origin and transmissible spongiform encephalopathies (TSE) Certificate of Suitability is provided for all relevant materials of animal origin or a risk assessment was considered sufficient. Based on the provided risk assessment, the confirmed bovine spongiform encephalopathies (BSE)-free status of the animal and selective sourcing from 'negligible BSE risk'-countries, it is agreed that the risk for BSE is sufficiently low for these two raw materials.

A detailed description of the source, history and generation of the cell substrate is provided giving no reason for concern. The CHO-cell line used for inebilizumab expression is fucosyltransferase-deficient and has therefore lost the ability to transfer fucose, resulting in a homogenously afucosylated antibody.

The cell banking system employed for inebilizumab is a standard two-tiered system. All cell banks have been tested in accordance with relevant guidelines and the results confirm the suitability of the master cell bank (MCB) and WCB. Cell line stability has been sufficiently demonstrated.

In conclusion, the control of material section is considered to contain sufficient information.

Control of critical steps and intermediates

In-process bioburden controls are in place for all AS manufacturing steps with associated acceptance criteria for the Production Bioreactor step, and action limits for the rest of the steps. In-process endotoxin controls are in place for all steps from harvest and onwards.

Hold times for the AS process intermediates have been validated.

Process validation and evaluation

Process validation has been performed with three consecutive and successful batches at the commercial scale manufactured with the commercial Process 3 process. The manufacturing process for AS is considered validated.

Efficient and robust clearance of the process-related impurities was demonstrated, supporting that testing for these impurities can be omitted from the AS release specification. The data also demonstrate efficient clearance of host cell protein, which remains controlled at AS release.

Manufacturing process development

History and comparability

Four manufacturing processes were used during the development: Pilot Process (for non-clinical toxicology), Process 1 (for clinical trials), Process 2 (for clinical trials including the pivotal trial), and Process 3 (used for commercial manufacturing). Process 2, and not Process 3 material, has been used for manufacturing the pivotal phase 2/3 clinical batches.

Overall, the manufacturing history and comparability exercises are described in sufficient detail and the results support comparability of product quality when manufactured with the different processes during development. The test panel included in the comparability exercise covers relevant attributes.

Critical quality attributes, control strategy and process characterisation

Critical quality attributes (CQAs) and control strategy: The assigned CQAs are supported. The proposed control strategy is found sufficiently comprehensive to ensure acceptable quality of CQAs.

Process characterisation: Extensive process characterisation studies have been executed to determine the impact of the process parameters on product quality, resulting in parameter classification as critical or non-critical process parameters. Several elements of Quality-by-Design (QbD) (risk assessments, multivariate design of experiments, statistical tools) are applied. The results from the process characterisation support the acceptance ranges presented.

A robust process understanding is demonstrated and the classification of CPP and non-CPP is supported with an extensive number of identified CPPs.

Lastly, contact materials which may introduce leachables have been evaluated based on the vendor-provided extractable data. As all leachable exposures were below the appropriate Threshold of Toxicological Concern (TTC) level, it is agreed that these contact materials pose a negligible safety risk.

Characterisation

Inebilizumab has been sufficiently characterised in accordance with EMA/CHMP/BWP/532517/2008, 'Guideline on development, production, characterisation and specification for monoclonal antibodies and related products'.

The primary sequence, secondary and tertiary structure and post translational modifications of inebilizumab were characterised by state-of-the-art analytical methods and found to be consistent with the expected theoretical values. Moreover, inebilizumab has the expected biological properties. Inebilizumab contains N-linked glycosylation at position Asn-301 of each heavy chain in the Fc part of the molecule. As expected, the detected glycoforms were afucosylated as inebilizumab is expressed in a cell line engineered to produce afucosylated structures.

Product variants of inebilizumab are defined as variants with no impact on safety or efficacy. Safety evaluations concluded that the presence of these variants pose no or minimal risk to patients as the variants are either naturally occurring within endogenous proteins (such as glycation and Asn-388 and Asn-393 deamidation (acidic variants)) or will be processed *in vivo* (such as cleavage of additional C-terminal lysine (basic variants)). The characterisation and evaluation of the safety and efficacy of these variants is considered sufficient and acceptable.

Impurities

Levels of product-related impurities in representative inebilizumab AS batches from manufacturing processes 1, 2, and 3 were evaluated. In general, low levels of product-related impurities were found.

The characterisation study also concluded that the maximum levels found in representative AS batches had no effect on the biological activity or PK of the product, as determined by one or several relevant assays. During the assessment limits for certain product-related impurities in AS and FP at release and stability were tightened to better reflect process capability. Process-related impurities arise from the cell substrates, cell culture, and purification processing Data from manufacturing history and small-scale clearance studies demonstrated that during the manufacturing process, Process-related impurities are robustly cleared to levels below clinically relevant specifications and levels defined in EU, FDA or WHO guidelines and /or controlled at the level of the AS.

The characterisation and evaluation of product and process related impurities is acceptable.

2.4.2.3. Specification

The AS specifications include general tests, test for total protein, purity, potency identity, impurities, and safety.

Upon request, some specification limits have been recalculated and tightened.

The proposed AS release specifications are accepted for the initial marketing authorisation.

Analytical methods and acceptance criteria

The panel of methods used to assure the quality of the AS is considered broad and in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. All methods are validated and considered suitable for their intended use. Product specific verification of the compendial methods was conducted, confirming that inebilizumab AS does not inhibit or in other ways affect the methods.

Acceptance criteria are set according to one of three approaches: Published limits approach, Stability limits approach or Non-stability limits approach. The Stability limits approach takes into consideration process and assay variation along with process capability evaluated through batch data and rate of change during stability. The Non-stability approach is based on findings from product characterisation and manufacturing process capability.

Batch analysis

The submitted batch data from process 1 , process 2 and process 3 batches confirm batch consistency within each process, and low variation between manufacturing processes as confirmed in process development comparability studies.

Reference materials

A two-tiered reference standard system has been introduced for inebilizumab, comprising of a Primary Reference Standard (PRS) and Working Reference Standards (WRS).

Container closure

Compatibility between the container closure and inebilizumab AS has been evaluated through the AS stability studies.

2.4.2.4. Stability

Stability studies based on ICH guidelines have been conducted for the active substance.

Relevant parameters were selected to study the stability profile of the active substance.

The analytical methods were validated and are described in the relevant sections of the dossier. The data from primary stability and supporting stability studies support the proposed shelf life at the designated storage condition in the proposed container closure system.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The inebilizumab finished product (FP) is a sterile, concentrate for solution for infusion. It has a label claim of 100 mg of inebilizumab in a 10 mL volume. The FP is aseptically filled into 10R clear glass vials (single use) closed with elastomeric stoppers, capped with an aluminium seal and packaged as 3 vials per carton, sufficient for preparation of a single 300 mg dose.

Besides the active ingredient, inebilizumab, the composition comprises only compendial excipients, typically used for formulating mAbs: L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, trehalose dihydrate, polysorbate 80 and water for injection. The excipients were chosen to provide optimal buffering capacity, enhance stability, and protect the antibody during manufacture and storage.

An overfill is applied for the vials to ensure a deliverable volume of 10 mL.

Formulation development and robustness

The proposed commercial FP formulation is overall the same as the formulation used during the clinical trials. Importantly, Process 2 and Process 3 formulations and vial presentations are identical, hence the inebilizumab FP tested in the pivotal clinical study corresponds to the intended commercial presentation.

The results from univariate and multivariate studies support the robustness of the intended commercial formulation. The rationale used to select the final composition/formulation has been sufficiently described.

Manufacturing process development – history and comparability

The FP was produced using three different processes: Process 1, Process 2 and Process 3, the current, commercial formulation. The changes between FP manufacturing processes are summarised. The comparability study including inebilizumab FP from the Process 2 and Process 3 is found sufficient with confirmation of comparable product quality and stability.

Process characterisation

Process characterisation studies have been executed to determine the impact of the process parameters on product quality, resulting in parameter classification (non-CPP versus CPP). Several elements of QbD (risk assessments, multivariate design of experiments, statistical tools) are applied, but no design space is claimed. The process characterisation presented is considered sufficiently comprehensive. The results from the process characterisation support most of the acceptance ranges presented in in the dossier.

Product-contact material compatibility and photosensitivity

A material product compatibility study was conducted to confirm that no meaningful change occurred to the FP quality when inebilizumab FP was exposed to various product-contact materials at worst-case

conditions and at manufacturing-representative durations. The results are acceptable. The risk of leachables from product contact materials was also evaluated and found sufficiently low.

Photosensitivity was evaluated by worst-case cumulative light exposures.

Collectively, robust process and environmental-impact understanding are demonstrated and the classification of CPP/non-CPP and the control strategy is supported.

Compatibility and in-use stability

The section on compatibility includes in-use stability testing. The inebilizumab FP must be diluted in 0.9% (w/v) saline prior to IV bag dose administration. Biochemical compatibility of the inebilizumab FP was assessed using intravenous (IV) bags containing saline and with an administration set with a 0.2 µm in-line filter. The results confirm biochemical compatibility at both in-use storage temperatures. In the SmPC, the claimed in-use storage is 2-8°C for up to 24 hours or 4 hours at room temperature for diluted product. In addition to the biochemical compatibility study, an in-use microbial challenge study was conducted with samples stored at 2-8°C and at room temperature and the results support the maximum intended hold times.

2.4.3.2. Manufacture of the product and process controls

The batch size of inebilizumab FP 100mg/10mL is defined.

Description of manufacturing process, process controls and GMP

Inebilizumab finished product is manufactured and tested at EU GMP-compliant sites. Sufficient proof of GMP compliance has been provided. The FP is released in the EEA by Almac Pharma services, Ireland.

The FP manufacturing process is overall standard for monoclonal antibodies. The AS is thawed, mixed with dilution buffer, sterile filtered, filled into vials; vials are fully stoppered and crimped, and visual inspection is performed before secondary packaging and labelling. The FP is 100% visually inspected, acceptable quality limit sampling is performed, and the FP is bulk packaged, and shipped to the packaging, labeling and storage site. Before and after visual inspection, the vials are stored at 2-8°C.

Reprocessing (refiltration) during FP manufacturing is not presented in the dossier.

Overall, the description of the manufacturing process is found to be satisfactory with each manufacturing step being clearly summarised in a table with the important features (incoming materials, filters and product contact disposables, critical and non-critical process parameters, IPCs and performance attributes). Acceptance ranges for process parameters and process controls have been presented and are in general supported by the process characterisation studies.

The bioburden limit before sterile filtration is in line with guideline requirements. The hold times have been defined and are supported by the presented hold time validation data (see also *Process validation and/or evaluation*).

There are no intermediates isolated in the FP manufacturing process.

The minimal and maximal batch sizes are established for inebilizumab FP fill.

Process validation and/or evaluation:

The process validation studies comprise Process Performance Qualification (PPQ), qualification of in-process hold times, aseptic process validation, container closure integrity testing, filter validation, and shipping qualification.

Consecutive PPQ batches were manufactured at the commercial FP manufacturing site with parameters and testing results meeting the defined ranges.

The hold times have been sufficiently qualified.

Filter validation was performed, and data has been included in accordance with guideline requirements. The aseptic filling has been sufficiently validated with media fills performed at simulated routine production and at worst-case challenge.

In conclusion, the activities at the FP manufacturing site can be considered sufficiently validated.

2.4.3.3. Product specification

The specification for the finished product includes control of identity, purity and impurity, potency and other general tests. The finished product specification was established in line with ICH Q6B and Ph. Eur. monograph 2031 on monoclonal antibodies for human use.

Upon request, some specification limits have been recalculated and slightly tightened. The proposed FP release specifications are accepted for the initial marketing authorisation.

Analytical methods and acceptance criteria

Many analytical methods used for release and stability testing of FP are equal to those used for the AS or are compendial.

Methods for analysis used for both AS and FP, and justification for specifications for these analyses is given in the AS part.

The compendial methods have been verified using inebilizumab FP, to show that the sample material itself does not inhibit the assays.

Batch analysis data

All batch release data from process 1, process 2 , and process 3 batches were within the specifications in place at the time of testing. These data, show a high degree of batch consistency within and across processes.

Reference standard

The same reference standard as used for the AS analyses is used at the FP level. Please refer to the AS part.

Container closure system

Inebilizumab FP is stored in a 10 mL Type 1 clear and colorless glass vial with an elastomeric stopper and a mist grey flip-off aluminium seal. Schematic drawings of the container closure system are provided. The choice of the container closure system is in line with pharmaceutical standards and the components comply with pharmacopoeial requirements.

The primary container closure system has been analysed with respect to extractables according to Ph. Eur. and the results are acceptable.

Overall, the suitability of the FP primary container closure was demonstrated through FP protection studies (protection from light, moisture and microbiological contamination), extractables studies, elemental impurities study, compatibility studies (based on stability data including total protein to evaluate possible adsorption) and withdrawal performance studies.

The FP vials are individually labelled and placed in a paperboard carton (3 vials per carton). The secondary packaging components comprise of an opaque paperboard carton to protect the FP from light exposure and an internal paperboard carton partition to secure the vials during transportation.

The FP container closure system is considered suitable for storage of inebilizumab.

Impurities

A risk evaluation concerning the presence of nitrosamine impurities in the FP has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the AS or the related FP. Therefore, no additional control measures are deemed necessary.

2.4.3.4. Stability of the product

The proposed shelf-life for Uplizna FP is 3 years at 2–8°C.

Stability studies were performed in line with ICH and CHMP guidelines on a suitable number of batches representative of the final commercial product. Relevant parameters were selected to study the stability of the finished product. The analytical methods were appropriately validated.

Photostability has been tested in one FP PV batch, in accordance with ICH Q1B.

Elemental impurities, originating from the AS and FP manufacturing processes or from the container closure system were evaluated according to ICH Q3D 'Guideline for Elemental Impurities', with respect to parenteral formulations.

In-use stability results, performed as part of the compatibility studies (described in P.2), support the maximum intended hold times of 4h at 25ºC and 24h at 2-8ºC of FP diluted into 0.9% (w/v) saline solution. The results demonstrate that there was no change (only change within method variability) in appearance, purity, charge isoforms, and potency, or any undesired changes in protein concentration when FP was diluted into 0.9% (w/v) saline, or upon subsequent agitation and hold, with all administration components tested. There was no sub-visible particle formation upon dilution, or upon subsequent agitation and hold at the final timepoint compared to the initial timepoint. Also, any sub-visible/visible particles observed for samples obtained through the injection port (pre-in-line filter) are removed after passing through the in-line filter (post-in-line filter).

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.4.3.5. Adventitious agents

Non-Viral Adventitious Agents

The cell banks have been sterility-tested for bacteria, fungi and mycoplasma using Ph. Eur. methods.

No material of human origin is used in the manufacturing process of inebilizumab. All animal-derived ingredients are discussed with regards to TSE/BSE risk and the detailed risk assessments following the EMA/410/01 'Guideline Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy' support an acceptably low risk for introduction of BSE-TSE infectious agents. Supplier

information with certificates of analysis and origin as well as Certificates of Suitability (TSE) where relevant have been provided for the materials. For two animal-derived raw materials, Certificate of Suitability were not provided, but the provided risk assessment is considered sufficient.

Viral Adventitious Agents

The bioburden and mycoplasma testing are conducted according to Ph. Eur. Testing for viral contaminants is conducted using a 28-day *in vitro* assay for adventitious viruses with MRC-5, Vero, CHO-K1, and 324K cells as detector cells. The test is compliant with ICH Q5A(R1), and the result for three PPQ batches verifies the absence of viral contamination, as well as mycoplasma and bioburden.

A comprehensive programme has been employed to test, evaluate, and eliminate the potential risks of adventitious and endogenous viral agents in accordance with ICH Q5A, and includes: 1) Control of raw materials, facilities, and procedures used in manufacturing; 2) Viral testing and characterisation of the cell banks used in GMP manufacturing; 3) Viral testing of unprocessed bulk; and 4) Viral clearance assessment of the purification process.

The viral clearance capacity of the inebilizumab AS purification process was confirmed by conducting viral clearance studies for relevant steps, using qualified scale down models in accordance with ICH Q5A. Four model viruses were used for the virus validation; Xenotropic Murine Leukemia Virus (XMuLV), reovirus type 3 (REO3), pseudorabies virus (PRV), and mouse minute virus (MVM). The selected model viruses are supported. Global reduction factors were satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for nonenveloped viruses.

In conclusion, the risk of contamination of the inebilizumab AS with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of viral contaminants in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity, demonstrated for the inebilizumab purification process.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Overall, the quality of inebilizumab AS and FP has been well evaluated and presented by the applicant.

Inebilizumab AS is expressed in CHO cells and further processed by a standard monoclonal antibody manufacturing process. No excipients of animal or human origin are used. Critical in-process controls are in place. The manufacturing history of the AS and FP is overall described in sufficient detail and comparability is supported. The AS and FP processes are considered validated.

Inebilizumab has been sufficiently characterised and all identified impurities have either been evaluated to be present at non-significant levels, to be cleared from the product through downstream processing or are controlled on the release specification.

The AS and FP specifications are extensive, and the analytical methods used are generally considered valid and capable of controlling the quality of the AS and FP at both release and during shelf-life. The specification limits are considered acceptable for the initial marketing authorisation.

Inebilizumab remains stable at the proposed storage conditions and shelf-lives.

A nitrosamine risk evaluation has been provided, confirming that AS and FP manufacturing processes are not conductive to nitrosamine formation and the raw materials, excipients, materials used in manufacturing, and the primary packaging material does not contain nitrosamines or nitrosating reagents.

The applicant agreed to Recommendations.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical package included 6 pivotal GLP-conducted toxicology studies (four repeated dose toxicity studies, one Fertility and embryofetal development study and one pre and postnatal development study) and several *in vitro* and *in vivo* supportive PD studies

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Several *in vitro* and *in vivo* pharmacology studies were conducted to determine the binding characteristics, effector function and efficacy of inebilizumab.

A series of assays were employed to optimise the binding affinity of the humanised anti-CD19mAb 3649 and identify the humanised, affinity-optimised monoclonal antibody variant 16C4. This humanised, affinity-optimised monoclonal variant binds specifically to human CD19 approximately twice as strongly as does the humanised antibody (study No ONC551-0001). The binding properties including the affinity, dissociation, and internalisation of anti-CD19 affinity-matured version mAb 16C4 (the fucosylated form of inebilizumab) were further examined in Daudi human Burkitt lymphoma cells used as model B lymphocytes. The results indicate that mAb 16C4 possesses the desired qualities of enhanced binding, slower dissociation, and minimal internalisation favorable for achieving ADCC. Furthermore, measurement of the equilibrium binding constants demonstrated an approximate 10-fold increase in the binding of afucosylated human IgG1-Fc to the human activating Fcγ receptor, FcγRIIIA and its murine homologue, FcγRIV over the fucosylated form (study No ONC551-0002).

It was shown that inebilizumab mediated ADCC when tested with B lymphoma cell lines as targets but showed no complement-dependent cytotoxicity in the presence of B lymphoma targets and human serum from healthy donors (study No ONC551-0003). This ADCC was further evaluated against normal human peripheral B cells, lymphocytic leukemia tumour cells and acute lymphoblastic leukemia tumour cells demonstrating the ADCC of inebilizumab (study No ONC551-0004). In another study inebilizumab also displayed ADCC by significantly depleting both human peripheral blood mononuclear cell differentiated plasma cells as well as freshly isolated plasma cells from human bone marrow (study No RIA551-0002).

Evaluated by flow cytometry analysis anti-CD19 mAb 16C4 (the fucosylated form of inebilizumab) had poor cross-reactivity with CD19 on the surface of B cells from baboon, rhesus monkey, African green

monkey, or cynomolgus monkey but bound well to CD19 expressed on B cells of humans (study No ONC551-0008). Similarly, in three separate *in vitro* experiments there was no detectable binding of inebilizumab to IgM positive B cells from rabbit blood (study No RIA551-0005).

In another tissue cross-reactivity study (study No MI-0007) inebilizumab stained B cells within human and huCD19 Tg mouse tissues, but not within the rat. Inebilizumab-specific staining unrelated to B cells occurred in multiple tissues and cell types in all 3 species tested; however, the staining pattern, intensity and frequency in the human tissue panel were more similar to the staining pattern noted in the rat.

Characterisation of human CD19 Tg mice as a pharmacologically relevant species was carried out in study No ONC551-009. The binding of inebilizumab to CD19 on human B cells was comparable to its binding to human CD19 on B cells from huCD19 Tg mice. In huCD19 Tg mice, inebilizumab bound to B cells from blood, spleen, bone marrow, and the peritoneal cavity. Inebilizumab is specific for human CD19 and does not react with murine surface markers on B or non-B cells.

The *in vivo* pharmacological activity of inebilizumab was evaluated in huCD19 Tg mice as the relevant species since this mAb was specific for human CD19 and had poor cross-reactivity with CD19 on the surface of B cells from rat, rabbit, baboon, rhesus monkey, African green monkey, or cynomolgus monkey. In study No ONC551-0010 the specific depletion and recovery of B cells in normal blood and tissues was shown in huCD19 Tg mice at single intravenous (IV) doses of inebilizumab (10 to 250 µg/mouse). At 250 µg treatment the duration of B-cell depletion was dose-dependent (sustained for more than 10 weeks post treatment) and recovery of B cells to levels and maturities similar to control animals was seen 14 to 16 weeks after treatment. It was suggested B cell-activating factor likely plays a role in promoting B cell recovery. Inebilizumab also caused inhibition of antibody responses.

Two *in vivo* studies were undertaken to characterise the pharmacological activity of inebilizumab in a B cell–dependent model of experimental autoimmune encephalomyelitis (EAE) (Chen et al, 2014 and Chen et al, 2016). In this model a single dose of 250 µg inebilizumab effectively depleted CD19+ B cells and plasma cells in EAE mice, resulting in a global reduction of autoantibodies in blood and in the CNS (Chen et al, 2014). Thus, inebilizumab was effective in targeting pathogenic B cells in a preclinical neuroinflammatory setting.

The efficacy of inebilizumab was investigated in a second autoimmune mouse model Sle1-hCD19 Tg exhibiting classical autoimmune manifestations including high levels of autoantibodies, skewed B cell subsets, and profoundly activated B and T cells (study No RIA551-0003). Inebilizumab was shown to deplete blood and tissue B cells in the Sle1-huCD19 Tg mice in a dose-dependent manner. B cells in blood, spleen and bone marrow were reduced by >90% and total serum immunoglobulin, and autoantibodies. Some inflammatory markers in circulation were also decreased and others were increased.

A huCD19 TG murine model of scleroderma also demonstrated the efficacy of inebilizumab in depleting pathogenic B cells. Animals displayed sustained depletion of B-cell populations, including depletion of antibody secreting cells, and had reduced serum immunoglobulins and autoantibodies (study No RIA551-0001).

Preliminary PK and PD data of inebilizumab in human CD19 transgenic mice was determined in study No ONC551-0011. Following a single IV bolus injection of inebilizumab at doses of 0.5, 1.0, 2.5, or 12.5 mg/kg to female human CD19 transgenic mice the maximum concentration (C_{max}) increased in a dose-dependent manner within the dose-range of 0.5 to 12.5 mg/kg, the area under the concentration-time curve from dosing extrapolated to infinity (AUC_{inf}) increased in a more than dose-proportional manner at this dose range and the terminal half-life ($t_{1/2}$) increased with increasing doses. In the same setting

inebilizumab treatment led to marked B-cell depletion in blood, bone marrow and spleen with different effects on B-cell recovery. Between one and three weeks, blood, bone marrow, and spleen B cells remained depleted in mice treated at doses of with 1, 2.5, or 12.5 mg/kg.

In general, the *in vitro* and *in vivo* studies were comprehensive and relevant. Proof of concept and mode of action were established and are supported.

2.5.2.2. Secondary pharmacodynamic studies

No secondary PD studies of inebilizumab were conducted. Due to the specific receptor targeting, low biodistribution to non-target tissues and low cross-reactivity the absence of dedicated secondary PD studies was accepted.

2.5.2.3. Safety pharmacology programme

Dedicated safety pharmacology studies were not performed. The potential for exaggerated pharmacology on the neurological, cardiovascular, and respiratory systems was assessed through cage side observations and detailed physical examinations conducted during the repeat-dose toxicology studies. No effects on these systems were observed. Inebilizumab is a biotechnology-derived product that achieves highly specific receptor targeting therefore in accordance with the ICH guideline S7A the omission of dedicated safety pharmacology studies is supported.

2.5.2.4. Pharmacodynamic drug interactions

Non-clinical PD drug-drug interaction (DDI) studies were not conducted. As inebilizumab is highly specific for human CD19 the absence of studies investigating PD DDI was endorsed.

2.5.3. Pharmacokinetics

Inebilizumab specifically recognises human CD19 and has poor cross-reactivity to rodent, rabbit or nonhuman primate CD19. Therefore, human CD19 transgenic mice were selected as the relevant animal species to evaluate the pharmacokinetics of inebilizumab. With the exception of the initial non-GLP (good laboratory practice) PK/PD study (study No ONC551-0011), the PK and toxicokinetics (TK) of inebilizumab in huCD19 Tg mice were assessed as part of the toxicity studies.

2.5.3.1. Methods of analysis

A sandwich ELISA method was developed and qualified for the quantification of inebilizumab in mouse serum from the PK/PD Study ONC551-0011. An electrochemiluminescent, solution-phase, bridging immunoassay that uses MSD technology (Method SOP CT050091) was developed and validated by MedImmune for the detection and titration of anti-drug antibodies (ADA) to inebilizumab in mouse serum (MedImmune Validation Report CTVR0045).

The electrochemiluminescent sandwich immunoassay for measurement of inebilizumab in mouse serum was adequately validated with regards to accuracy, precision, range of quantification (20 ng/mL to 2000 ng/mL), dilutional linearity, hook effect (concentrations up to 64000 ng/mL), specificity, antibody interference, robustness, stability (three freeze-thaw cycles, for up to 16 hours at room temperature, 15 days at 5 ± 3°C and up to 45 days at -80 ±10°C). The selectivity of the assay was affected since anti-inebilizumab antibodies at concentrations of 50 ng/mL (at the LQC level) and 1500 ng/mL (at the LQC and HQC levels) interfered with the assay's ability to measure inebilizumab (study CTVR-0044).

An electrochemiluminescent, solution-phase, bridging immunoassay for detection of anti-inebilizumab antibodies in mouse serum met the acceptance criteria for accuracy and precision of classification and titre, intermediate precision, repeatability, robustness, selectivity, specificity and matrix stability. Anti-inebilizumab antibody levels of 0.5 µg/mL were detectable in the presence of 25 µg/mL of inebilizumab. This is supported (study CTVR-0045).

2.5.3.2. Absorption

In study ONC551-0011, following a single IV administration of inebilizumab to female huCD19 Tg mice at 0.5, 1, 2.5 and 12.5 mg/kg doses (n = 24/group), the C_{max} increased dose-proportionally within the 0.5 to 12.5 mg/kg dose range. The systemic exposure (AUC_{inf}) increased in a more than dose-proportional manner at this dose range. This was consistent with the presence of an antigen sink. A decrease in clearance and an increase in terminal $t_{1/2}$ of inebilizumab were observed with an increasing dose of inebilizumab.

In study No 08-2083, following the first IV administration of inebilizumab, a more than dose-proportional increase in exposure was observed in the area under the concentration-time curve from hour 0 to day 7 (AUC_{0-7d}) within the 0.675 to 36.6 mg/kg dose range. Following the last administration of inebilizumab, parallel terminal phases with similar clearance values and $t_{1/2}$ were observed after the mid- (3.71 mg/kg) and high- (36.6 mg/kg) doses. The clearance rates in the mid- and high-dose groups were typical of clearance of a human IgG1 antibody in mice in the absence of an antigen sink, which is consistent with the having depleted CD19+ B lymphocytes in the mid and high dose groups. No appreciable gender difference in TK was observed during the treatment period in the mid and high dose groups. Only animals from the 0.675 mg/kg dose group (6/13, 4 females and 2 males) showed anti-inebilizumab antibodies development. Titres ranged from 1:10 to 1:20480 by the end of the study. The immunogenicity results were consistent with the depletion and recovery kinetics of B lymphocytes observed in inebilizumab-treated groups as the development of anti-inebilizumab antibodies is dependent upon antibody producing B cells. One animal from the control group had consistently detectable anti-inebilizumab antibodies.

In study No 08-2084, following the first IV administration of inebilizumab in huCD19 Tg mice, systemic exposure increased in a more than dose-proportional manner, consistent with the presence of antigen sink. The nonlinearity was less pronounced at steady state (Day 71), consistent with B cell depletion and consequent reduction of the antigen sink. From the immunogenicity screening assay, no pre-existing anti-inebilizumab antibodies were detected. During the dosing phase, 2 out of 17 animals from the control group and 2 out of 9 animals from the 0.5 mg/kg dose group (2 females) were positive for anti-inebilizumab antibodies. Titres ranged from 1:10 to 1:1280.

In study No 09-2153, following both the first and the 26th IV injection of inebilizumab, exposure (C_{max} and AUC_{0-7d}) was dose-proportional in the 2 dose groups (3 and 30 mg/kg) for both male and female huCD19 Tg mice. $t_{1/2}$ were shorter and clearance was faster in female than in males. Steady-state was reached by the 13th dose. With regards to immunogenicity 2/14 animals (2 females) tested in Group 1 and 2/14 animals tested in Group 2 developed inebilizumab antibodies.

In study No 10-2237, following the first subcutaneous (SC) administration of inebilizumab, exposure (C_{max} and AUC_{0-7d}) was approximately dose-proportional for the 3 and 30 mg/kg dose groups. Following the 13th SC administration of inebilizumab, apparent clearance (CL/F) and $t_{1/2}$ were similar between the 2 dose groups, with mean $t_{1/2}$ values of 18.2 and 20.6 days, and mean CL/F of 3.49 and 4.63 mL/kg/d for the 3 and 30 mg/kg doses, respectively. Following the IV administration of inebilizumab at 30 mg/kg, $t_{1/2}$ was similar to that of the SC doses and estimated to be 20.9 day. Clearance was estimated as 4.83 mL/kg/d. The bioavailability of 104% was estimated for SC at 30 mg/kg. No anti-inebilizumab antibodies were detected in animals in the 30 mg/kg/wk SC or IV groups. Positive results for antibodies in 4 control

mice and 1/14 mice in the 3 mg/kg/week (SC) group in the predose phase were considered to be false positives.

In general, TK data for inebilizumab showed that exposure increased in a dose-proportional manner and was independent of sex. Immunogenicity samples were not collected from the TK groups, the impact of ADA on TK profiles and TK parameters was not analysed.

2.5.3.3. Distribution

Tissue distribution of inebilizumab was carried out in the Fischer-344 rat because antigen-specific or cross-reactive binding studies previously showed that the staining pattern of human tissue panel was more similar to the staining pattern in the rat (study No MI-0007).

Following a single IV injection in male and female Fischer-344 rats the tissue distribution pattern of inebilizumab compared with a control afucosylated antibody R347afuc was evaluated by immunohistochemistry analysis (study No ONC551-0012). The presence of R347afuc or inebilizumab in Group Nos 1 and 2 was detected within the vasculature, most prominently at Day 3 and somewhat diminished at Day 7. There was no detectable membrane-bound or intracellular signal in any of the tissues examined, except for the testes. Testes analysed from Group No 2 males (treated with 25 mg/kg inebilizumab) at necropsy Day 3 and Day 7 had detectable signal of rare cells within the seminiferous tubules.

Therefore, the potential testicular toxicity of inebilizumab was investigated in study No 08-2087. Fischer 344 rats were injected IV once weekly with 0, 2.5, or 25 mg/kg inebilizumab for 1 month (5 injections). Histopathology evaluation at 1 month revealed no macro- or microscopic findings in the testes of treated rats and no evidence of testicular toxicity.

In study No AAO00141, male huCD19 Tg mice received a total of 9 weekly IV injections of inebilizumab while female huCD19 Tg mice received a total of 5 weekly IV injections of inebilizumab at the doses of 3 or 30 mg/kg. Following the first and last IV bolus administration of inebilizumab, systemic exposure increased in an approximately dose-proportional manner in the tested range of 3 to 30 mg/kg. Fetal-to-maternal inebilizumab concentration percent ratios were 114% and 31.1% for dose groups 3 and 30 mg/kg, respectively. Adequate exposure of fetus to inebilizumab was demonstrated by detecting inebilizumab in the serum of fetuses at levels comparable or exceeding the levels measured in the corresponding maternal animals.

In study No 62509, following 3 and 30 mg/kg intravenous (bolus) injection of inebilizumab on Gestation Days 6, 9, 12, 15, and 18 and on Lactation Days 1, 4, 7, 10, 14, 17, and 20 maternal serum concentrations of inebilizumab were approximately dose proportional on lactation day 21. Mean concentrations of inebilizumab in pup serum on postnatal day 21 were only slightly lower compared to maternal serum concentrations at the same interval; mean concentrations were similar in male and female pups. No inebilizumab was detected in serum samples collected from the control group dams or pups at the time of weaning. Comparable maternal and pup serum levels of inebilizumab on Lactation Day/Postnatal Day 21 indicated inebilizumab is excreted into the milk.

2.5.3.4. Metabolism

No studies of metabolism of inebilizumab were conducted. Inebilizumab is a humanised IgG1κ monoclonal mAb, which is expected to be degraded to small peptides and amino acids. According to the guideline ICH S6(R1) on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals the expected metabolism is the degradation to small peptides and individual amino acids and thus the absence of metabolism studies can be accepted.

2.5.3.5. Excretion

No studies of excretion of inebilizumab were conducted. Due to the large molecular size, inebilizumab is not expected to be excreted in urine. As inebilizumab is expected to be degraded to small peptides and individual amino acids the omission of excretion studies was endorsed.

2.5.3.6. Pharmacokinetic drug interactions

Nonclinical PK DDI studies were not performed for inebilizumab. Inebilizumab is a humanized mAb where the primary elimination pathway is clearance by the reticuloendothelial system. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in clearance of inebilizumab. Therefore, the potential risk of interaction between inebilizumab and other drugs is low. This is endorsed.

2.5.4. Toxicology

The use of the transgenic huCD19 mouse model for the toxicology programme of inebilizumab, is supported in accordance with ICH S6(R1). No other animal species was considered relevant, as binding to human CD19 does not occur in standard toxicology models in rodents and monkeys. In contrast, the huCD19 Tg mouse model showed similar binding and effector function, as found in human cells by demonstrated the pharmacologic effect of CD19+ B-cell depletion and recovery in blood and tissues. With no viable alternative, it is therefore endorsed that the nonclinical *in vivo* programme is performed primarily in this model.

2.5.4.1. Single dose toxicity

Two non-GLP single dose toxicity studies were conducted in huCD19 Tg mice with IV doses of 2.5, 10, or 40 mg/kg for a 7-day observation period (ONC551-0013) and 0.5, 10, or 50 mg/kg for a maximum observation period of 28-days (ONC551-0014). The second study was conducted with animals of both genders, while this aspect is not clear in relation to the first study. The lack of GLP compliance is acceptable.

Results from these studies showed that B-cell depletion occurred at all doses with a dose-dependent decrease and recovery pattern. No changes were seen in other cell populations (e.g. T-cells, NK-cells). Additionally, histopathological examination showed inebilizumab-related findings in spleen and lymph nodes, as a reduction of follicles/germinal centres most evident at high doses. In general, findings were consistent with the expected pharmacology of inebilizumab and no observed adverse effect level (NOAEL) values of ≥ 40 mg/kg and ≥ 50 mg/kg were determined for single dose administration in the two studies.

2.5.4.2. Repeat dose toxicity

Four GLP compliant repeat-dose toxicity studies were conducted with inebilizumab in huCD19 transgenic mice. Inebilizumab was well tolerated at once weekly IV administration at doses up to 36.6 mg/kg for 1 month (total of 5 administrations; Study a08-2083) and at doses up to 30 mg/kg for 3 months (total of 13 administrations; Study 08-2084) or 6 months (total of 26 administrations; Study 09-2153). Furthermore, a 3-month study was conducted comparing SC and IV administration of inebilizumab, showing that the pharmacological effects of B-cells depletion were independent of the route of administration at doses up to 30 mg/kg once weekly (total of 13 administrations; Study 10-2237). However, as IV is the intended clinical administration route, SC administration will only briefly be discussed. All four studies had a long recovery period (35 to 45 weeks), corresponding to the B220+ B lymphocytes returning to a level of > 25% of control.

Primary findings were to a large degree consistent between studies and with the expected pharmacological effect of inebilizumab on B lymphocytes. These findings included decreases in B220+ lymphocytes in blood, spleen and bone marrow, decreased spleen weight, microscopic findings of decreased size of the white pulp compartment of the spleen due to lymphocyte depletion, and decreased size and cellularity of the B lymphocyte areas of the mediastinal and mesenteric lymph nodes. A small number of changes unrelated to the pharmacological effect was detected in the studies, most of which were reversable after the recovery period and therefore not considered adverse.

Non-pharmacological related findings of a more severe character were observed in the 3-month SC and IV study (study 10-2237), as an increased incidence of skin changes and bronchiolo-alveolar adenomas. Unscheduled euthanisations occurred due to severe skin ulcerations/infections in both SC and IV dose groups, without any apparent dose response but with a majority of cases occurring in the SC group. The applicant argued that it could be an exacerbation of skin sores commonly seen in mice in combination with the immunosuppressive effect of the test article. This explanation is considered plausible, thus indicating that a general risk of infection exists with the use of inebilizumab. However, it is puzzling that the skin lesions were detected only in this particular study (study 10-2237) and not in the three other repeat-dose studies (study 08-2083, 08-2084 and 09-2153). Additionally, an increased incidence of bronchiolo-alveolar adenomas (50%) were detected in males at end recovery in the IV 30 mg/kg/week group in study 10-2237. Results from a background study in untreated huCD19 Tg mice revealed that bronchiolo-alveolar adenomas occur in males at an incidence of 3.4% to 8.9%, depending on the age of the mouse (Iverson et al, 2017). However, there is still a long way from 8.9% to the observed incidence of 50%. According to the applicant, various factors were explored, including the phenotype of the transgenic animals and material used on the study, without identifying the cause of the skin lesions or bronchiolo-alveolar adenomas. When specifically considering the most recent 3-month study with SC and IV administration, in relation to the alveolar adenoma findings in Study 10-2237, the applicant adds that the weight of evidence suggests that this was an incidental background finding and is not considered to represent a risk to patients. It was not observed in other studies and is an expected background finding for this mouse strain and gender.

In relation to the skin ulcerations, the applicant adds that these were also observed in the 6-month study, but were not considered test article-related as they were observed in both the control and test article treated animals with no dose-dependence. Furthermore, in terms of data from clinical trials, although observations of skin ulcerations were seen in subjects treated with inebilizumab, these were infrequent, possible complications of the underlying disease, or assessed by investigator as not related to inebilizumab.

A general IV NOAEL=30 mg/kg/week is considered acceptable based on the conducted repeat-dose studies and the argumentation presented above. However, a SC NOAEL of 30 mg/kg/week is not endorsed based on the pronounced skin lesion detected. However, since the route of administration is IV and the clinical relevance of the finding therefore is considered low, the issue will not be further pursued.

TK parameters were evaluated in a single-dose study and in all four repeat-dose studies. In the single-dose study and in the 1- and 3-months repeat-dose studies, systemic exposure (measured by AUC) appeared to increase in a more than dose-proportional manner. This was consistent with the presence of an initial antigen sink. However, the non-linearity was less pronounced at the end of the 3-months study (Day 71), which is consistent with B-cell depletion and consequent reduction of the antigen sink. In the 6-months repeat-dose study (09-2153), inebilizumab exposure (C_{max} and $AUC_{0\text{-}7d}$) was dose-proportional in the 2 dose groups (3 and 30 mg/kg). After SC administration in the 3-months repeat-dose study (10-2237), inebilizumab exposure was approximately dose proportional following the first SC injection but less than dose proportional following the 13th SC injection in both dose groups (3 and 30 mg/kg). A tendency toward a lower drug exposure (lower C_{max} and AUC) were seen in females compared

to males in the 6-month study and at low doses in the 1-month study. However, none of the repeat dose toxicity studies included TK data for the control groups, despite the presence of ADA in control animals. The applicant justified the lack of TK data from control group animals used in the repeated dose toxicity studies based on the 3Rs principles. The repeated dose toxicity studies were conducted in transgenic mice, from which limited volumes of blood can be collected. Inclusion of separate TK groups would be required. As for the presence of anti-inebilizumab antibodies in animals from control groups, the applicant suggests that this represents false positives. Owing to the small amount of blood able to be collected from individual mice, the ADA samples were only evaluated in the screening tier and not subjected to a confirmatory test.

Interspecies comparison data was presented by the applicant, as a comparison of doses and exposures over a 6-month treatment period in huCD19 Tg mice and human patients. Data obtained at the NOAEL of 30 mg/kg/week iv from the 6-month repeat-dose GLP chronic toxicology study (Study 09-2153) in huCD19 Tg mice were used for the comparison and the dose was successfully corrected to human equivalent dose (HED) using the generic allometric scaling factor proposed by the FDA*. When comparing the total dose received during 6-months of treatment in mice and humans, an HED-based safety factor of 6.9-fold was determined. Furthermore, an exposure-based safety margin of 55-fold existed when using accumulated AUC_{26week} data from female huCD19 Tg mice with the lowest systemic exposure. The calculated safety margins are supported, as well as the NOAEL determination.

* *Guidance for industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.* 2005 FDA

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted, which is acceptable in accordance with ICH S6.

2.5.4.4. Carcinogenicity

In accordance with the weight of evidence approach outlined in ICH S6 (R1), the applicant has presented argumentation for waiving of carcinogenicity studies. It is agreed, that data from a 2-year carcinogenicity study in human transgenic CD19 mice do not seem to provide much additional clinically relevance, due to the limited interpretability of study results, as a lack of historical reference data. Additionally, the applicant argues that findings from the 6-months repeat-dose study in huCD19 Tg mice, showed no adverse organ weight changes, detected masses, or histological findings suggestive of proliferative or pre-neoplastic lesions, which is endorsed. It should furthermore be mentioned that the mice in the 6-months study received a higher number of treatments with shorter duration between, than expected in the clinical setting. In line with the SA EMEA/H/SA/2664/1/2013/III, experience from other B-cell depleting agents (i.e. rituximab, belimumab, alemtuzumab) was taken into consideration, showing no increased risk of malignancies and for rituximab this was supported by data from a 11-year period of using rituximab in the clinical programme. The applicant did not include the mAb ocrelizumab in their weight of evidence discussion. Ocrelizumab is also a B-cell depleting agent (targeting CD20 positive B-cells), for which, in contrast to the previously mentioned, there is as clinical signal regarding breast cancer. The presented rationale for omitting carcinogenicity studies is however considered acceptable, due to the reasons listed above.

2.5.4.5. Reproductive and developmental toxicity

A GLP compliant combined male and female fertility and embryofetal development study was conducted with IV doses of 0, 3 and 30 mg/kg/week for 9 and 5 weekly dose administrations in male and females, respectively. The conduct of a combined study is accepted, and the study is considered sufficient to cover

all aspects of fertility and embryofetal development. A dose-dependent treatment-related reduction in fertility index (96%, 76% and 64% in control, 3 and 30 mg/kg/week group respectively) were noted. However, the reason for the reduced fertility index was unclear, since no impact on estous/diestrous were detected in females and no effect on male reproductive organs (i.e. right and left epididymis, left cauda epididymis, left testis, seminal vesicles with and without fluid, right testis and prostate), sperm motility or number of male mice that mated was seen. The section 5.3 of the Summary of product characteristics (SmPC) states that a treatment-related reduction in fertility index has been observed in a non-clinical study.

Systemic exposure of inebilizumab was confirmed in the fetuses in the combined fertility and embryofetal development study (see PK section). No impact was detected on embryofetal development (i.e. malformations, variations), however, a marked difference was seen in huCD19+ B-cells in fetal livers from progeny of dosed mice compared to undosed (population average of 60.7% in undosed compared to 0.32% and 0.15% in dosed progeny). This shows that inebilizumab crosses the placenta and causes huCD19+ B-cell depletion in fetuses.

A pre- and postnatal development study were conducted in huCd19 Tg mice with IV administration of inebilizumab at doses of 3 and 30 mg/kg. The study was initiated on GD6 and therefore provided an overlap with the combined fertility and embryofetal development study, covering the whole reproductive and developmental period as requested by guideline. Findings suggestive of an impairment in normal B-cell function in the F1 generation at all doses correlated with above mentioned findings of inebilizumab placenta crossing and B-cell depletion from the combined fertility and embryofetal development study. A fetal and newborn B-cell depletion in case of in utero exposure in humans is therefore expected. This is reflected in section 4.6 and 5.3 of SmPC.

As no adverse effects on the F_0 dams, F_1 growth, survival, and reproductive development and performance, and F_2 fetuses were detected at any dosage level, the NOAEL for F_0 maternal, F_1 systemic and reproductive, and F_2 embryo/fetal developmental toxicity was considered to be 30 mg/kg/dose. However, malignant lymphoma was identified in 2 F_1 females at 3 mg/kg and 1 F_1 female at 30 mg/kg on PND 357. The finding accentuates the weakness of the model due to lack of sufficient historical data, but it is agreed with the applicant that given the advanced age of the females and lack of a dose response pattern, the relationship to the test article is uncertain. Furthermore, no particular malignant lymphoma concern was highlighted for other B-cell depleting agents on the market, as addressed under carcinogenicity subsection. A statistically significantly increase in startle response was noted in F1 males of the 30 mg/kg dose group but not in the females. Even though, the finding does not correlate with other neurobehaviour parameters, it is still considered to be test article related. The NOAEL of 30 mg/kg for developmental neurotoxicity is therefore not endorsed. However, as the clinical relevance is unclear and a sufficient caution for use in pregnant women is included in the SmPC section 4.6, the issue is not further pursued.

From the non-clinical point of view, information in the two sections of the SmPC is generally considered adequate.

No juvenile animal studies have been conducted. This is acceptable, as the medicinal product is indicated for adult patients only.

2.5.4.6. Local Tolerance

Local tolerance after IV and SC injection was assessed as a part of the conducted repeat-dose studies. No gross or histopathological changes attributed to IV injection were seen, whereas, slight reversable acute to subacute inflammation were presented at the SC injection site. As the clinical route of

administration is IV, the evaluation of local tolerance is considered sufficient and no further studies are necessary.

2.5.4.7. Other toxicity studies

A study was conducted in order to assess potential cross-reactivity of inebilizumab with cryosection of human, rat (Fischer-344) and huCD19 Tg mouse tissues (MI-0007). In tissues from human and huCD19 Tg mice, membranous staining pattern were localised to B-cells primarily in lymphatic tissue but also to scattered B-cells in various other tissues. None-B-cell related staining were seen in various tissue from all three species, however, the staining was cytoplasmic in nature, and it is anticipated by the applicant that any potential intracellular cross-reactive epitope would not be accessible to a large molecule such as inebilizumab under *in vivo* conditions. The applicant states GLP compliance of the study, however, this is questioned due to e.g. lack study directors' signature at a compliance statement in the report. However, no demand for GLP compliance exists for these types of studies according guideline.

In order to exclude off-target tissue binding of inebilizumab, a single dose IV biodistribution study was conducted in Fischer-344 rats (ONC551-0012). The rat was selected as the relevant species for off-target binding, as a comparable staining pattern were seen between rat and human tissue in the MI-0007 study above. Staining of rare cells within the seminiferous tubules of the testes indicated a potential for off-target tissue binding of inebilizumab, leading to the conduct of a testicular toxicity study in rats (08-2087). A GLP compliant testicular toxicity study was then conducted in rats with five repeat-doses of inebilizumab administered IV at dose of 0, 2.5 and 25 mg/kg (08-2087). No test-related effect on weight, macroscopic or histopathological findings were seen in the testes or epididymites of the treated rats, indicating no *in vivo* testicular toxicity at the tested doses. The results are considered reliable, as the dosing period covered a minimum of 3 seminiferous epithelial cycles and the high dose of 25 mg/kg caused distribution to the testes in the biodistribution study.

The translational value of ADA formation in animal models are limited. Nevertheless, immunogenicity and formation of ADA was assessed based on data from the 1, 3, 6-months repeat-dose studies and the 3-months SC and IV repeat-dose study but the results were only sparsely addressed in the overview and toxicology written summary. It appeared like ADA were primarily formed in the lowest dose groups (at 0.675 mg/kg and 0.5 mg/kg in the 1- and 3-months study respectively). As stated by the applicant, the ADA formation correlated with depletion and recovery kinetics of B lymphocytes in the inebilizumab treated groups, as the development of ADA is dependent upon antibody-producing B cells.

No data was presented for immunotoxicity, dependence, metabolites or impurities.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has provided an acceptable justification for not conducting a full environmental risk assessment. Since inebilizumab is an afucosylated, monoclonal antibody with effect on human CD19 B-cells, it is expected to be fully metabolised into small peptides and amino acids via catabolic pathways in the body with negligible excretion of intact, biologically active protein. In accordance to guideline (EMEA/CHMP/SWP/4447/00 corr 21*), inebilizumab is therefore considered to be of no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The binding properties, effector function and efficacy of inebilizumab were sufficiently characterised in pharmacodynamic *in vitro* and *in vivo* studies.

A series of assays identified and showed that the humanised, affinity-optimised monoclonal antibody variant 16C4 (the fucosylated form of inebilizumab) bound specifically to human CD19 approximately twice as strongly as the humanised antibody (study No ONC551-0001). The fucosylated form of inebilizumab mAb 16C4 had enhanced binding, slower dissociation, and minimal internalisation favourable for achieving antibody-dependent cellular cytotoxicity. Furthermore, a 10-fold increase in the binding of afucosylated human IgG1-Fc to the human activating Fcγ receptor, FcγRIIIA and its murine homologue, FcγRIV over the fucosylated form was demonstrated (study No ONC551-0002).

Inebilizumab mediated ADCC cytotoxicity against B lymphoma cell lines (study No ONC551-0003), normal human peripheral B cells, lymphocytic leukemia tumour cells, acute lymphoblastic leukemia tumour cells (study No ONC551-0004) and both human peripheral blood mononuclear cell differentiated plasma cells as well as freshly isolated plasma cells from human bone marrow (study No RIA551-0002). It was also demonstrated that the ADCC of inebilizumab was without activation of complement-dependent cytotoxicity (study No ONC551-0003).

The human CD19 transgenic (huCD19 Tg) mice was established as the pharmacologically relevant toxicology species. Three different *in vitro* tissue cross-reactivity studies showed inebilizumab was specific for human CD19, does not cross-react with rodent CD19 (study No ONC551-009) and has no or poor cross-reactivity with CD19 on the surface of B cells from rat (study No MI-0007), rabbit (study No RIA551-0005), baboon, rhesus monkey, African green monkey, or cynomolgus monkey (study No ONC551-0008). In study No RIA551-0005 no detectable binding of inebilizumab to IgM positive B cells from rabbit blood in three separate experiments was seen.

The *in vivo* pharmacological activity of inebilizumab was evaluated in huCD19 Tg mice as the relevant species. In study No ONC551-0010 the specific depletion and recovery of B cells in normal blood and tissues was shown in huCD19 Tg mice at single IV doses of inebilizumab (10 to 250 µg/mouse).

The pharmacological activity of inebilizumab was characterised in several *in vivo* models. Treatment with inebilizumab effectively depleted CD19+ B cells and plasma cells in EAE huCD19 Tg mice. This led to a global reduction of autoantibodies in blood and in the CNS and to significantly reduced disease scores (Chen et al, 2014 and Chen et al, 2016). Inebilizumab also effectively depleted blood and tissue B cells and splenic plasma cells in a second autoimmune mouse model (study No RIA551-0003). Sle1-human CD19 Tg mice displayed reduced total serum immunoglobulin, autoantibodies, and inflammatory mediators in this model. Some inflammatory markers in circulation were decreased and others were increased.

In a preliminary PK and PD study of inebilizumab following a single IV bolus injection at doses of 0.5, 1.0, 2.5, or 12.5 mg/kg in female human CD19 transgenic mice the C_{max} increased in a dose-dependent manner within the dose-range of 0.5 to 12.5 mg/kg, the AUC_{inf} increased in a more than dose-proportional manner at this dose range and the terminal $t_{1/2}$ increased with increasing doses. Inebilizumab treatment led to marked B-cell depletion in blood, bone marrow and spleen with different effects on B-cell recovery.

The characterisation of the immunological properties of inebilizumab including specific receptor targeting, low biodistribution to non-target tissues and low cross-reactivity justified the omission of secondary PD studies in conformity with ICH guideline S6(R1).

In accordance with the ICH guideline S7A no dedicated safety pharmacology studies were carried out since inebilizumab is a biotechnology-derived product that achieves highly specific receptor targeting. Safety pharmacology endpoints were included in the general toxicity studies.

The lack of non-clinical PD DDI studies was accepted as inebilizumab was highly specific for human CD19.

Pharmacokinetics and toxicokinetics

A sandwich enzyme-linked immunoassay method was developed and qualified for the quantification of inebilizumab in mouse serum from the PK/PD Study ONC551-0011. An electrochemiluminescent, solution-phase, bridging immunoassay that uses MSD technology (Method SOP CT050091) was developed and validated by MedImmune for the detection and titration of ADA to inebilizumab in mouse serum (MedImmune Validation Report CTVR0045).

Two assays for the measurement of inebilizumab study No CTVR-0044 (used in the pivotal toxicology study Nos 08-2083, 08-2084, 09-2153, 10-2237, AAO00141 and 62509) and detection of anti-inebilizumab antibodies study No CTVR-0045 (used in the pivotal toxicology study Nos 08-2083, 08-2084, 09-2153 and 10-2237) in mouse serum were developed and validated according to GLP.

The TK of inebilizumab in huCD19 Tg mice were assessed as an integral part in the pivotal toxicology studies (study Nos 08-2083, 08-2084, 09-2153, 10-2237, AAO00141 and 62509).

Absorption and exposure of inebilizumab were evaluated in huCD19 Tg mice following single (study No ONC551-011) and multiple IV or SC administrations (study Nos 08-2083, 08-2084, 09-2153 and 10-2237). Inebilizumab exhibited nonlinear PK following single IV administration in the 0.5 and 12.5 mg/kg dose range, consistent with the presence of an antigen sink. More than a dose-proportional increase in exposure was observed. A decrease in clearance and an increase in terminal $t_{1/2}$ were observed with increasing inebilizumab dose from 0.5 mg/kg to 12.5 mg/kg. In the 1-month repeat-dose study, systemic exposure increased more than dose-proportionally. After last dose the mean terminal $t_{1/2}$ were 7.78, 12.0 and 14.7 days for the 0.675, 3.71, and 36.6 mg/kg dose groups, respectively. In the 3-month repeat-dose study, following the first IV administration of inebilizumab to huCD19 Tg mice, nonlinear PK were described by a more than a dose-proportional increase in both $AUC_{0\text{-}7d}$ and minimum concentration on Day 8. The nonlinearity was less pronounced at steady state, consistent with B-cell depletion and the consequent loss of the antigen sink. In studies involving placental transfer, adequate exposure of fetus to inebilizumab was demonstrated by detecting inebilizumab in the serum of fetuses at levels comparable or exceeding the levels measured in the corresponding maternal animals.

In general, TK data for inebilizumab showed that exposure increased in a dose-proportional manner and was independent of sex. Immunogenicity samples were not collected from the TK groups, the impact of ADA on TK profiles and TK parameters was not analysed.

Tissue distribution of inebilizumab was carried out in the Fischer-344 rat because antigen-specific or cross-reactive binding studies previously showed that the staining pattern of human tissue panel was more similar to the staining pattern in the rat (study No MI-0007). Following a single IV injection in male and female Fischer-344 rats the tissue distribution pattern of inebilizumab demonstrated that there were no detectable membrane-bound or intracellular signal in any of the tissues examined, except for the testes (study No ONC551-0012). Due to detectable staining in the testes, the potential testicular toxicity of inebilizumab was further investigated in study No 08-2087. Fischer 344 rats were injected IV once weekly with 0, 2.5, or 25 mg/kg inebilizumab for 1 month (5 injections) and revealed no macro- or microscopic findings in the testes of treated rats and no evidence of testicular toxicity.

In studies involving placental transfer, male huCD19 Tg mice received a total of 9 weekly IV injections of inebilizumab while female huCD19 Tg mice received a total of 5 weekly IV injections of inebilizumab at the doses of 3 or 30 mg/kg. Following the first and last IV bolus administration of inebilizumab,

systemic exposure increased in an approximately dose-proportional manner in the tested range of 3 to 30 mg/kg. Fetal-to-maternal inebilizumab concentration percent ratios were 114% and 31.1% for dose groups 3 and 30 mg/kg, respectively (study No AAO00141). Following 3 and 30 mg/kg intravenous (bolus) injection of inebilizumab on Gestation Days 6, 9, 12, 15, and 18 and on Lactation Days 1, 4, 7, 10, 14, 17, and 20 maternal serum concentrations of inebilizumab were approximately dose-proportional on lactation day 21. Comparable maternal and pup serum levels of inebilizumab on Lactation Day/Postnatal Day 21 indicated inebilizumab is excreted into the milk (study No 62509).

Inebilizumab is a humanised IgG1κ mAb, which is expected to be degraded to small peptides and amino acids. In accordance with ICH S6(R1) the omission of metabolism studies of inebilizumab was accepted.

As inebilizumab is expected to be degraded to small peptides and individual amino acids the lack of excretion studies is endorsed.

Inebilizumab is a humanised mAb where the primary elimination pathway is clearance by the reticuloendothelial system. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in clearance of inebilizumab. Therefore, the potential risk of interaction between inebilizumab and other drugs was considered low and no PK DDI studies were conducted.

Toxicology

The toxicological profile of inebilizumab was characterised in two non-GLP single-dose studies (ONC551-0013 and ONC551-0014) and in three GLP compliant repeat-dose toxicity studies with once weekly IV administration of inebilizumab for 1-, 3- and 6-months (Study 08-2083, 08-2084 and 09-2153). Moreover, a GLP compliant 3-month study was conducted comparing SC and IV administration of inebilizumab (Study 10-2237). All toxicological studies were conducted in the transgenic huCD19 mouse model, as binding to human CD19 does not occur in standard toxicology models in rodents, rabbits and monkeys. With no other pharmacologically relevant animal species, this is endorsed in accordance with ICH 56(R1).

In general, inebilizumab was well tolerated in single-dose studies up to 50 mg/kg and in repeat-dose studies up to 30 mg/kg/week, supporting a general NOAEL of 30 mg/kg/week determined based on the 3- and 6-months IV repeat-dose study. A HED-based safety margin of 6.9-fold and an exposure-based safety margin of 55-fold was calculated by comparing doses and exposures at the NOAEL of 30 mg/kg/week over a 6-month treatment period in huCD19 Tg mice in the 09-2153 study and human patients. This is endorsed.

Consistent with the expected pharmacological effect of inebilizumab, B-cell depletion occurred at all doses with a dose-dependent decrease and recovery pattern. Findings were most evident at high doses and included decreases in B lymphocytes in blood, spleen and bone marrow, decreased spleen weight and histopathological examination showed inebilizumab-related findings in spleen and lymph nodes, as a reduction of follicles/germinal centres. A small number of changes unrelated to the pharmacological effect was detected in the repeat-dose studies, most of which were reversible after recovery and therefore not considered adverse. An increased incidence of bronchiolo-alveolar adenomas occurred in males receiving 30 mg/kg/week by IV administration the 3-month study comparing SC and IV administration of inebilizumab (Study 10-2237). Additionally, skin lesions were detected predominantly in the SC group, indicating an immunosuppressive effect of inebilizumab and hence, an increased general risk of infection.

In all the repeat dose toxicity studies, systemic exposures increased with the dose level. However, none of the studies included TK data for the control groups. This was justified from a 3R principle, since transgenic mice was used.

In accordance with ICH S6 (R1), no genotoxicity studies were conducted, and an acceptable weight of evidence discussion was presented, supporting that any carcinogenicity studies would most likely not add clinically relevant information under the current circumstances.

A dose-dependent treatment-related reduction in fertility index and in the number of pregnant mice per number of mice in cohabitation were seen in the GLP compliant combined male and female fertility and embryofetal development study.

In the conducted pre- and postnatal development study, no adverse effects on the F_0 dams, F_1 growth, survival, and reproductive development and performance, and F_2 fetuses were detected at any dosage level and the NOAELs was considered to be 30 mg/kg/week. However, no NOAEL could be determined for F1 development and immunotoxicity, as findings of impaired normal B-cell function were seen in the F1 generation at all doses and correlated with findings of placenta crossing and B-cell depletion in the combined fertility and embryofetal development study. This is now reflected in SmPC.

No unexpected tissue cross-reactivity of inebilizumab were seen in cryosection of human, rat (Fischer-344) and huCD19 Tg mouse tissues (MI-0007). However, in an IV biodistribution study in Fischer rats (ONC551-0012) staining of rare cells within the seminiferous tubules of the testes indicated a potential for off-target tissue binding of inebilizumab, leading to the conduct of a testicular toxicity study in rats (08-2087). Since this staining did not correlate to findings in repeat-dose studies, it is not considered clinically relevant.

In accordance to guideline (EMEA/CHMP/SWP/4447/00 corr 21*), inebilizumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, *in vitro* and *in vivo* pharmacology studies demonstrated proof of concept and mode of action. Antigenic specificity for inebilizumab was determined. The huCD19 Tg mice model was established as the relevant species. This model displayed similar binding and effector function as found in human cells and predictably demonstrated the pharmacologic effect of CD19+ B-cell depletion and recovery in the blood and tissues. Studies on secondary PD, dedicated safety pharmacology and PD DDI were omitted.

From the PK point of view, the huCD19 Tg was the most relevant species for non-clinical efficacy and safety studies. The repeat-dose studies displayed dose-proportionality and following last administration of inebilizumab, parallel terminal phases with similar clearance values and $t_{1/2}$ were observed in the dose range of 3.0 to 36.6 mg/kg for both male and female huCD19 Tg mice. ADA were negligible. Inebilizumab was only distributed in the testes. Placental transfer was shown by detecting inebilizumab in the serum of fetuses at levels comparable or exceeding the levels measured in the corresponding maternal animals. No studies on metabolism, excretion and drug interactions were conducted.

Overall, the toxicology programme revealed no major concerns. Findings of B-cell depletions in single- and repeat-dose studies were consistent with the expected pharmacological effect of inebilizumab. Reproductive and developmental toxicity studies showed a dose-dependent treatment-related reduction in fertility index, B cell depletion in fetuses and impaired B-cell function in the F1 generation of treated animals. Additionally, a decrease in T-cell dependent antibody response was noted in the pre- and postnatal development study. An *in vivo* study of testicular toxicity in rats, revealed no evidence of toxicity at the tested doses.

Based on the non-clinical data presented by the applicant regarding PD, PK and toxicology, the application could be approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant 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**

Table 2: Clinical studies included in this submission

Study ID Design	Diagnosis of Enrolled Subjects	Test Product Dosage regimen, Route of Administration, and Duration of treatment	Number of Subjects	Study Objectives
Phase 1 Safety, Tolerability, PK, and PD				
MI-CP200 Phase 1, randomized, double-blind, placebo-controlled study	Subjects with SSc who had at least moderate skin thickening in an area suitable for repeat biopsy	Cohort 1: 0.1 mg/kg single IV inebilizumab or placebo Cohort 2: 0.3 mg/kg single IV inebilizumab or placebo Cohort 3: 1.0 mg/kg single IV inebilizumab or Placebo Cohort 4: 3.0 mg/kg single IV inebilizumab or Placebo Cohort 5: 10.0 mg/kg single IV inebilizumab or placebo Randomized period: Single dose + 84 days follow-up	28 randomized Cohort 1 (n = 1) Cohort 2 (n = 4) Cohort 3 (n = 6) Cohort 4 (n = 6) Cohort 5 (n = 7) Placebo (n = 4)	Evaluate the safety and tolerability of escalating single IV doses of inebilizumab in adult subjects with SSc who had at least moderate skin thickening in an area suitable for repeat biopsy.
CD-IA-MEDI-551-1102 Phase 1, multicenter, multinational, randomized, blinded, placebo-controlled, dose-escalation study	Subjects with relapsing forms of MS	Fixed IV dose on Day 1 and Day 15: Cohort 1: 30 mg IV inebilizumab or placebo Cohort 2: 100 mg IV inebilizumab or placebo Cohort 5: 600 mg IV inebilizumab or placebo Single SC dose: Cohort 3: 60 mg SC inebilizumab placebo Cohort 4: 300 mg SC inebilizumab or placebo Treatment/ follow-up period: 169 days	28 subjects randomized IV: Cohort 1 (n = 5 [a]) Cohort 2 (n = 4 [a]) Cohort 5 (n = 6) Placebo (n = 5) SC: Cohort 3 (n=3) Cohort 4 (n = 3) Placebo (n = 2)	Evaluate the safety and tolerability of ascending IV and SC doses of inebilizumab in adult subjects with relapsing forms of MS.

Phase 2/3 Efficacy and Safety				
CD-IA-MEDI-551-1155 A multicenter, multinational, randomized, double-blind, placebo-controlled study with an open-label extension	Adults with active NMOSD	Randomized-controlled period: 300 mg IV inebilizumab or placebo on Day 1 and Day 15 (3:1 ratio) Open-label period: 300 mg IV inebilizumab on OLP Day 1, blind 300 mg IV inebilizumab (or placebo) on OLP Day 15, then 300 mg IV inebilizumab Q26W thereafter RCP (197 days) OLP (minimum 1 year, maximum of 3 years from date of last subject into the OLP)	231 randomized inebilizumab, n = 175 (174 treated) Placebo, n = 56	Compare the efficacy of inebilizumab versus placebo in reducing the risk of an NMOSD attack in subjects with NMOSD.

AQP4-IgG = aquaporin-4-antibody; IV = intravenous, NMOSD = neuromyelitis optica spectrum disorders; OLP= open-label period; P = placebo; PD = pharmacodynamic, PK = pharmacokinetic, Q26W = once every 26 weeks; RCP = randomised, controlled period; SC = subcutaneous.
a In Study 1102, 6 subjects were randomised inebilizumab 30 mg to Cohort 1, but one subject received 100 mg instead of 30 mg.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Inebilizumab (formerly known as MEDI-551) is being developed for the treatment of NMOSD. Inebilizumab is a humanised, affinity optimised, afucosylated immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds to the B cell specific surface antigen CD19 resulting in the depletion of CD19+ B cells, plasmablasts and some plasma cells.

No dedicated human PK studies were conducted for inebilizumab. The clinical pharmacology programme assessed the PK, PD, and immunogenicity of inebilizumab in two completed phase 1 studies (CP200 and 1102, conducted in subjects with scleroderma and multiple sclerosis, respectively), and in one phase 2/3 global randomised prospective placebo-controlled study in subjects with NMOSD (Study CD-IA-MEDI-551-1155 [Study 1155]) (Table 7). Population PK characteristics were assessed based on pooled data from all 3 studies and exposure-response characteristics were assessed using data from NMOSD Study 1155. The population PK (popPK) dataset contained 1617 measurable PK samples from 213 subjects (IV administration).

Dose rationale

The recommended dosing regimen of inebilizumab is a fixed dose of 300 mg administered as an IV infusion on treatment day 1 and day 15, and thereafter one dose of 300 mg every 6 months. The 300 mg fixed dose was selected for study in NMOSD subjects to achieve and maintain persistent depletion of peripheral B cells for 28 weeks. The second dose of inebilizumab, administered 2 weeks later, was timed to deplete the newly recirculated B cells out of the lymphoid tissues.

The applicant notes that the selected dose of 300 mg resides on the efficacy plateau.

Analytical methods

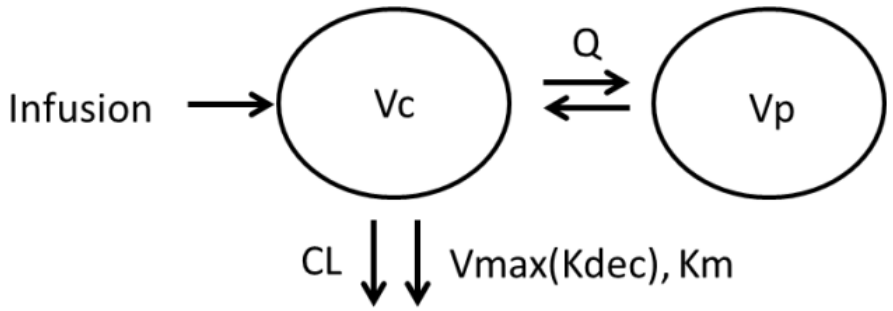
A stepwise enzyme-linked immunosorbent assay method was used to quantitate the PK inebilizumab concentration in human serum samples. The ADA method is a bridging assay format measured on the Meso Scale Discovery electrochemiluminescence technology platform. The CD20+ B cell count in peripheral blood was measured as an exploratory PD marker using a validated flow cytometric,

fluorescence-activated cell sorting method. In general, the assays were considered adequately documented. Presence of ADAs was shown to impact the quantification of inebilizumab resulting in lower concentrations. The drug tolerance of the ADA screening and confirmatory assay were acceptable. Many of the samples positive for ADAs against inebilizumab came from placebo treated patients or were pre-treatment samples. Measurement of CD20+B cell count was used as an alternative approach to assess for presence of functionally neutralizing antibodies.

Population PK modelling

Three datasets (IV data only, combined IV and SC data and SC data only) with data from studies CP200, 1102 and 1155 were used in the population analyses. The popPK dataset of IV administration contained 1617 measurable PK samples from 213 subjects. The final IV PK model was a 2-compartment model with parallel non-specific linear clearance and Michaelis-Menten nonlinear clearance that decreases with time. Effect of body weight was included on disposition parameters with estimation of scaling exponents. The allometric scaling factors of weight was estimated to 0.39 and 0.4 for volume of distribution in the central compartment (Vc) and volume of distribution in the peripheral compartment (Vp) and to 0.57 and 0.84 for clearance (CL) and Q (inter-compartmental clearance), respectively.

Figure 1: PK model of intravenously administered inebilizumab



CL=clearance; Vc =Volume of distribution in the central compartment; Q=inter-compartmental clearance; Vp= volume of distribution in the peripheral compartment; Vmax= maximum velocity of Michaelis-Menten equation; K_{dec}= first=order rate constant describing the decrease of Vmax over time; Km= concentration to achieve the half of Vmax.

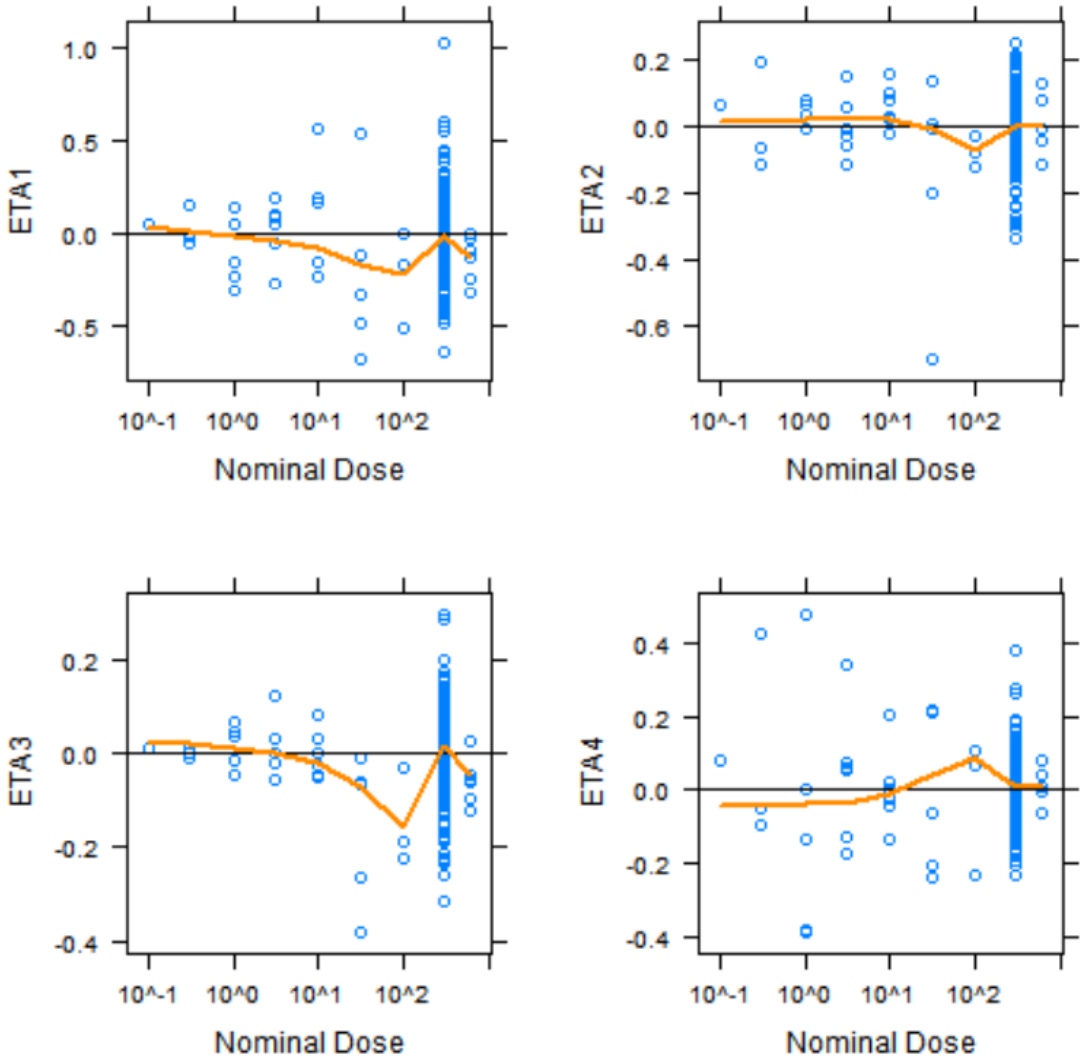
The final parameters were estimated with good precision (all relative standard error <30%) and interindividual variability with coefficient of variation <30%. The IIV of Vp and maximum velocity of Michaelis-Menten equation (V_{max}) were both estimated with poor precision and high shrinkage suggesting data do not inform the estimated distribution of these parameters. The final IV PK model was evaluated by bootstrapping (n=1000), goodness-of-fit plots and prediction-corrected Visual Predictive Check. None of the diagnostics indicated trends of misspecification and the model could adequately describe the observed data.

Table 3: Parameter estimates of final IV PK model (Run 922) of inebilizumab in adult subjects with NMOSD

Parameter	Estimate	RSE (%)	IIV (CV%)	RSE (%)	Shrinkage (%)
CL (mL/d)	188.22	2.2	27	25	8.2
Weight on CL [a]	0.57	15.8	NA	NA	NA
V_c (mL)	2946.39	1.4	17	30	27.4
Weight on V_c [a]	0.39	22.4	NA	NA	NA
Q (mL/d)	363.23	6.0	NA	NA	NA
Weight on Q [a]	0.84	21.1	NA	NA	NA
V_p (mL)	2569.43	2.8	16	45	38.8
Weight on V_p [a]	0.40	27.9	NA	NA	NA
V_{max} (µg/d)	832.50	5.3	30	61	61.2
Study CP200 on V_{max} (%)	209.91	19.5	NA	NA	NA
K_{dec} (d^{-1})	0.00294	55.1	NA	NA	NA
K_m (µg/mL)	5.89	25.5	NA	NA	NA
Proportional ERR (%CV)	21.78	4.6	NA	NA	12.1

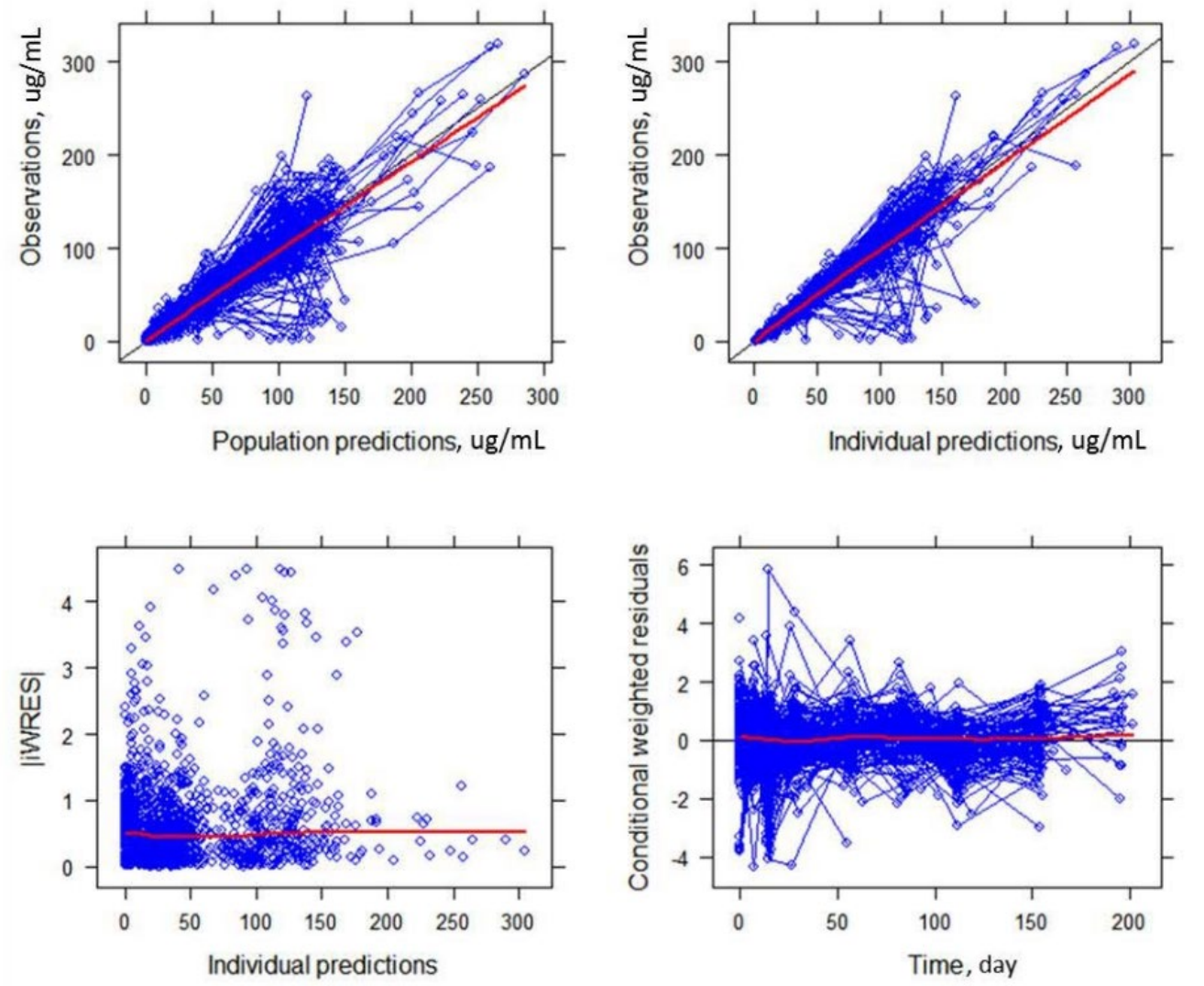
CL = clearance; CV = coefficient of variation; ERR = error; IIV = interindividual variability; IV = intravenous; K_{dec} = first-order rate constant for decrease in Vmax; Km = concentration corresponding to half of Vmax; NA = not available; Q = intercompartmental clearance; RSE = relative standard error in percent; Vc = volume of distribution in the central compartment; Vmax = maximum velocity of the saturable clearance process; Vp = volume of distribution in the peripheral compartment
RSE were obtained from asymptotic SE in NONMEM and % RSE was calculated by (SE/final parameter estimate)*100.
The condition number is 158.97

Figure 2: ETAs vs. nominal dose plots of the final IV PK model (Run 922)



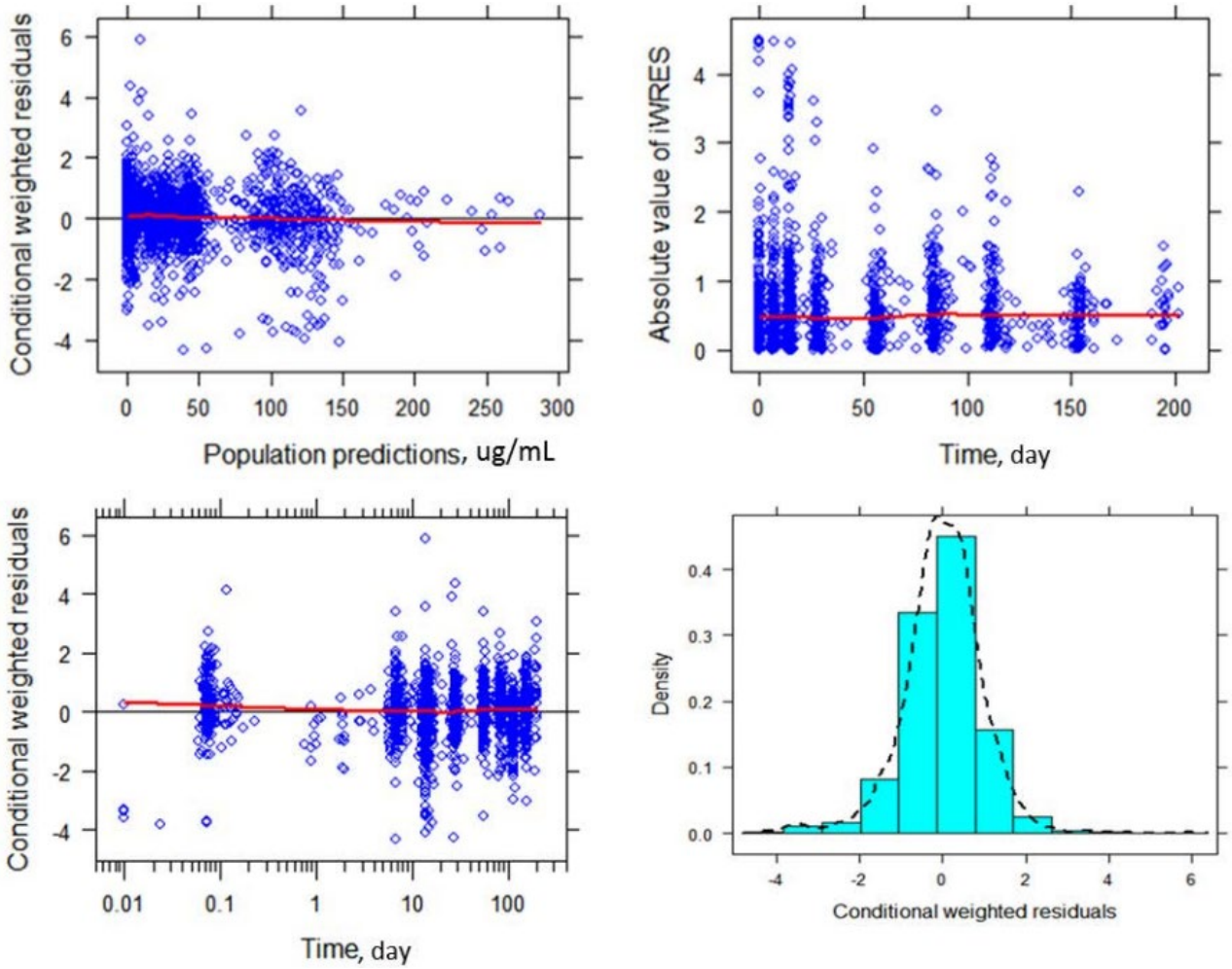
ETA1 = IIV on CL; ETA2 = IIV on Vc; ETA3 = IIV on Vp; ETA4 = IIV on V_{max}; IIV = interindividual variability. The black line represents horizontal line crossing the y axis at value of zero. The orange line represents the loess smoother. The nominal doses were 0.1, 0.3, 1, 3, 10 mg/kg and 30, 100, 300, 600 mg whose numerical part was used as Nominal Dose in the x axis.

Figure 3: Standard goodness of fit plots of final IV model (Run 922)



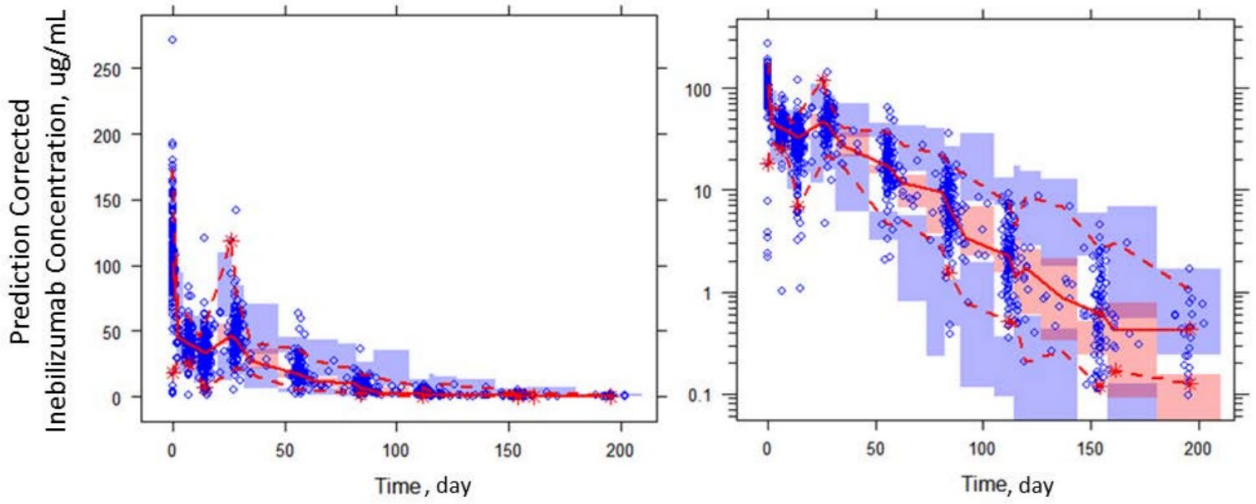
IV = intravenous; |iWRES| = absolute individual weighted residuals. "Observations" are inebilizumab concentrations. "Population predictions" are the concentrations predicted for individual's observations based on typical (population) values of the pharmacokinetic parameters, whereas "Individual predictions" are the concentrations predicted for individual's observations based on individual values of pharmacokinetic parameters. All the concentrations are in ug/mL unit. The circles are the pairs of observations and predictions or weighted residuals. The red solid lines are loess smoothing lines.

Figure 4: Diagnostic plots of weighted residuals (run 922)



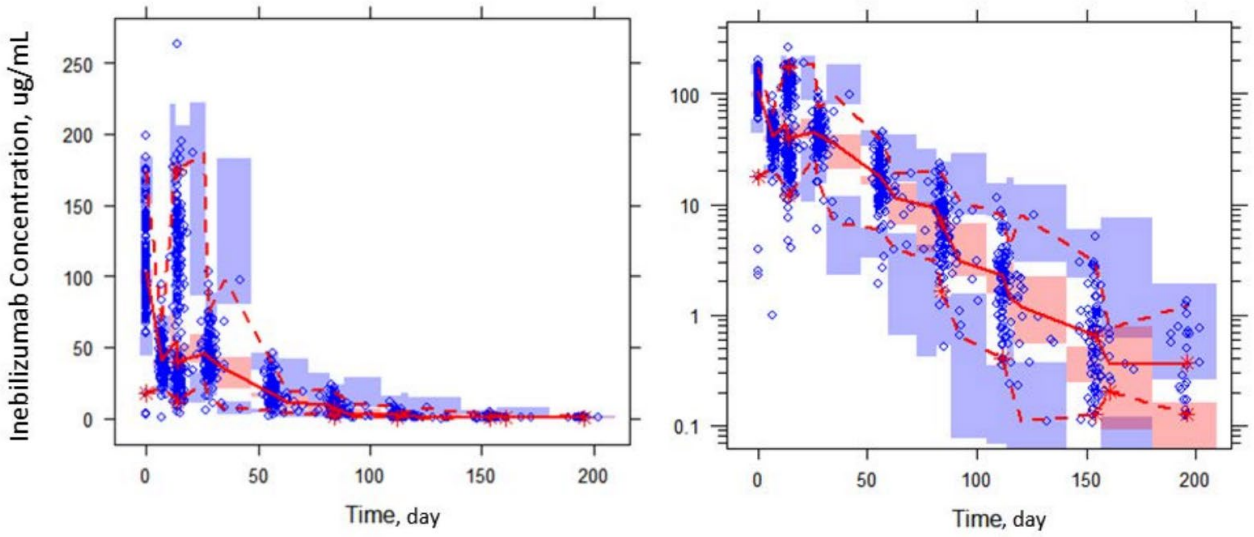
The red solid lines indicate loess smooth lines. "Population predictions" are the concentrations predicted for individual's observations based on typical (population) values of the pharmacokinetic parameters.

Figure 5: Prediction-corrected visual predictive check plot (in linear and log scale, Run 922)



The blue circle represents the observed concentration. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations. The shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.

Figure 6: Visual predictive check plot of Study 1155 (in linear and log scale, Run 922)



The blue circle represents the observed concentration. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations. The shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.

After the final IV PK model was developed, the initially excluded PK data from the 6 multiple sclerosis subjects (Study 1102) who received inebilizumab subcutaneously were combined with the IV PK data to characterise the first order absorption rate constant and absolute bioavailability via SC injection. Data were too sparse for reliable estimations.

Table 4: Parameter estimates of the final SC PK model (Run 987)

Parameter	Estimate	RSE (%)	IIV (CV%)	RSE (%)	Shrinkage (%)
Absorption rate constant (d^{-1})	0.17	13	NA	NA	NA
Bioavailability	0.81	11	98	98	14.3

CV = coefficient of variation; d = day; IIV = interindividual variability; NA = not available; PK = pharmacokinetic; RSE = relative standard error; SC = subcutaneous. RSE were obtained from asymptotic SE in NONMEM and % RSE was calculated by (SE/final parameter estimate)*100. . The condition number is 2.7

Absorption

The product is intended for IV administration and the bioavailability is therefore 100% and C_{max} is reached at the end of infusion.

Reported PK data observed in the target population dosed with the intended 300 mg regimen (study 1155) are presented in Table 5.

Table 5: Summary of Inebilizumab PK parameters in RCP by AQP4-IgG status

AQP4-IgG Status	Dose 1			Dose 2			Overall			
	PK Parameter									
	T_{max} (d)	C_{max} (µg/mL)	AUC_{0-14d} (µg·d/mL)	T_{max} (d)	C_{max} (µg/mL)	AUC_{0-14d} (µg·d/mL)	$AUC_{inf,cum}$ (µg·d/mL)	CL (mL/d)	V_{ss} (mL)	$t_{½}$ (d)
AQP4-IgG Sero+	N = 160	N = 160	N=155	N=156	N=156	N=152	N=127	N=127	N=127	N=127
	0.07 (0.07 – 7.00)	96.8 (38.1)	660 (31.9)	0.07 (0.07 – 14.00)	107 (45.5)	956 (39.9)	2950 (35.1)	203 (35.1)	4230 (27.8)	17.8 (25.2)
AQP4-IgG Sero-	N = 13	N = 13	N = 12	N = 12	N = 12	N = 12	N = 10	N = 10	N = 10	N = 10
	0.07 (0.07 – 7.00)	109 (26.6)	761 (18.7)	0.07 (0.07 – 14.00)	119 (45.3)	1110 (35.2)	3310 (21.9)	181 (21.9)	4090 (21.6)	21.1 (45.2)
AQP4-IgG Combined	N = 173	N = 173	N = 167	N = 168	N = 168	N = 164	N = 137	N = 137	N = 137	N = 137
	0.07 (0.07 – 7.00)	97.7 (37.4)	667 (31.3)	0.07 (0.07 – 14.00)	108 (45.4)	967 (39.6)	2980 (34.3)	202 (34.3)	4210 (27.3)	18.0 (27.2)

AQP4-IgG sero-= seronegative aquaporin-4 autoantibodies; AQP4-IgG sero+= seropositive aquaporin-4 autoantibodies; AUC_{0-14d} = area under the concentration-time curve from Time 0 (dosing) to 14 days postdose; $AUC_{inf,cum}$= cumulative area under the concentration-time curve from Time 0 of Dose 1 to infinity; C_{max}= maximum observed concentration; CL=systemic clearance, CV%=percent coefficient of variation; N= sample size; NA=not applicable; RCP=randomised-controlled period; $t_{1/2}$=terminal elimination half-time; t_{max} = time to the maximum concentration (C_{max}); Vss = steady-state volume of distribution.
Parameters are presented as geometric mean (geometric CV%) except t_{max} which is presented as median (Min-Max). All PK parameters and descriptive statistics are rounded to 3 significant figures except t_{max} (rounded to 2 decimal places) and geometric CV% (rounded to 1 decimal place).

The difference in total sample size reported between the 2 doses and overall PK parameters is primarily due to subjects with insufficient data in the terminal phase to estimate parameters.

The Drug Substance included process changes from a pilot Process (used on nonclinical toxicology), Process 1 (used on nonclinical toxicology and clinical), Process 2 (used on nonclinical toxicology and clinical) to a Process 3 (commercial). This also resulted in Drug Product changes that were supported by analytical comparability and demonstrated that the commercial Drug Product is comparable to the clinical Drug Products that have been used throughout clinical development. No *in vivo* studies were performed with the commercial Drug Product.

Distribution

Based on population PK analysis, the estimated typical central and peripheral volume of distribution were 2.95L and 2.57L, respectively. The interindividual variability of distribution volumes was low (≤17% coefficient of variation). The distribution volumes increased with body weight.

Elimination

From population PK analysis, the estimated systemic clearance of the first-order elimination pathway was 0.19 L/day and the $t_{1/2}$ was 18 days.

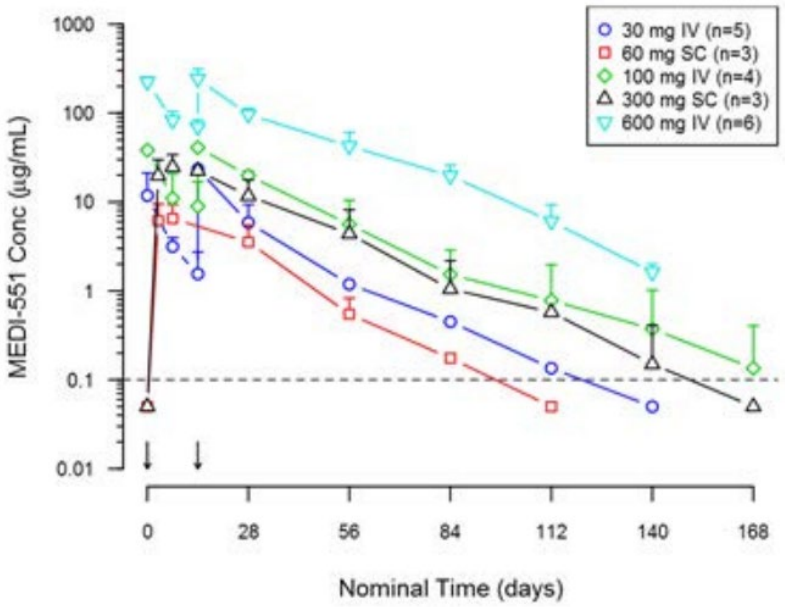
The primary elimination pathways for mAbs like inebilizumab are degradation by the reticuloendothelial system (like endogenous IgG) or by target-mediated elimination. At the therapeutic dose level, the nonlinear CD19-mediated elimination pathway is considered to be saturated.

Dose proportionality

Following a single IV administration (study CP200), inebilizumab exhibited nonlinear PK in the dose range investigated (0.1-10.0 mg/kg). The C_{max} of inebilizumab demonstrated a dose-proportional increase, while area under the concentration-time curve from dosing to last measurable timepoint (AUClast) and AUCinf increased more than dose-proportionally.

In study 1102, the PK of inebilizumab after two IV administrations was dose-proportional in the 30-600 mg range (Figure 7).

Figure 7: Mean serum concentration-time profiles of Inebilizumab in adult subjects with relapsing forms of multiple sclerosis following IV (x2) or SC administration (Study 1102)

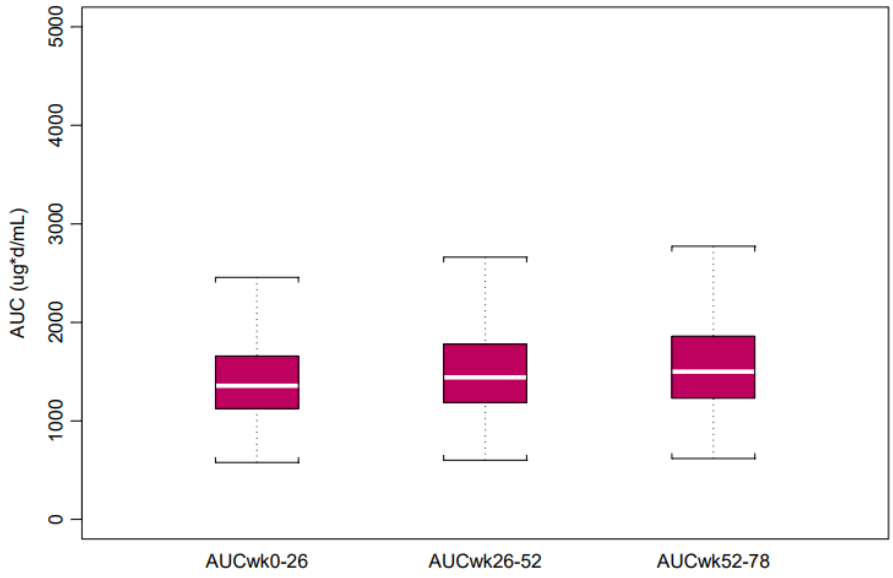


IV= intravenous; LLOQ= lower limit of quantitation; MEDI-551 = inebilizumab; MS = multiple sclerosis; SC = subcutaneous. Data below LLOQ (0.1 µg/mL; as shown by dashed line) are plotted at ½ LLOQ for illustrative purposes only. Error bars represent standard deviations. Arrows indicate dosing events (IV on Days 1 and 15 and SC on Day 1).

Time dependencies

Simulations of the impact of a time-dependent target-mediated CL on inebilizumab PK exposure indicate that the exposure is expected to be very similar after the first, second, and third administration.

Figure 8: Boxplot of AUC for the simulated Q26W Inebilizumab PK



AUC = area under the serum concentration-time curve; NMOSD = neuromyelitis optica spectrum disorders, PK = pharmacokinetic; Q26W = once every 26 weeks; wk = week. To facilitate visual assessment, Day 15 dose was omitted; 1000 subjects generated with resampled actual body weight of NMOSD subjects in Study 1155 received 300 mg inebilizumab Q26W.

Intra- and inter-individual variability

Inter-individual variability was estimated for CL, V_c, and V_p in the final popPK model (Table 3). The interindividual variability in the selected PK parameters estimated in the final popPK model varied between 16% and 27%.

Pharmacokinetics in target population

Inebilizumab PK was evaluated in both the target population and in two small studies with patients with scleroderma and multiple sclerosis. Although other patient populations contribute to the popPK analysis, the results are not expected to significantly deviate from what would be seen in a pure NMOSD population.

Special populations

Subject baseline characteristics of the three studies are provided in Table 6.

Table 6: Descriptive statistics of baseline categorical and continuous covariates

	Study CP200	Study 1102	Study 1155	Total
	N = 24	N = 15	N = 174	N = 213
Sex, n (%)				
Male	7 (29.2)	6 (40)	15 (8.6)	28 (13.1)
Female	17 (70.8)	9 (60)	159 (91.4)	185 (86.9)
Race, n (%)				
White	20 (83.3)	13 (86.7)	92 (52.9)	125 (58.7)
Black	3 (12.5)	1 (6.7)	15 (8.6)	19 (8.9)
Asian	0	0	39 (22.4)	39 (18.3)
American Indian or Alaskan	0	0	14 (8)	14 (6.6)
Other	1 (4.2)	1 (6.7)	14 (8)	16 (7.5)
Anti-Drug Antibody, n (%)				
Positive	4 (16.7)	0	17 (9.8)	21 (9.9)
Negative	20 (83.3)	15 (100)	157 (90.2)	192 (90.1)
Age (year)				
Mean (SD)	48.1 (8.91)	44.2 (9.86)	43.0 (11.6)	43.7 (11.3)
Median	48.5	44.0	43.0	44.0
Range	31.0-64.0	28.0-60.0	18.0-73.0	18.0-73.0

	Study CP200	Study 1102	Study 1155	Total
	N = 24	N = 15	N = 174	N = 213
Weight (kg)				
Mean (SD)	73.6 (17.7)	78.3 (21.9)	68.3 (17.4)	69.6 (17.9)
Median	73.2	72.0	65.0	66.2
Range	41.1-114	54.0-122	38.0-148	38.0-148
BMI (kg/m²)				
Mean (SD)	26.3 (5.91)	26.7 (5.90)	25.2 (5.50)	25.4 (5.57)
Median	26.8	26.0	24.5	24.7
Range	15.7-37.9	19.8-38.6	15.6-52.8	15.6-52.8
Total Bilirubin (µmol/L)				
Mean (SD)	4.56 (2.35)	9.13 (3.78)	8.20 (5.23)	7.86 (5.03)
Median	4.28	8.00	7.00	7.00
Range	1.71-12.0	4.00-17.0	3.00-40.0	1.71-40.0
Alkaline Phosphatase (U/L)				
Mean (SD)	74.1 (20.6)	79.7 (28.8)	67.0 (25.5)	68.7 (25.4)
Median	73.5	90.0	63.0	66.0
Range	36.0-118	33.0-129	26.0-188	26.0-188
Aspartate Transaminase (U/L)				
Mean (SD)	22.1 (8.37)	20.5 (6.74)	22.4 (18.9)	22.3 (17.4)
Median	21.0	21.0	19.0	19.0
Range	9.00-53.0	12.0-33.0	7.00-164	7.00-164
Creatinine Clearance (mL/min)				
Mean (SD)	129 (55.1)	126 (47.4)	119 (39.7)	121 (42.2)
Median	122	108	110	110
Range	51.5-282	84.1-245	50.9-247	50.9-282
Estimated Glomerular Filtration Rate (mL/min/1.73 m²)				
Mean (SD)	113 (50.7)	96.1 (19.6)	103 (26.5)	103 (29.9)
Median	107	93.1	97.0	96.6
Range	42.8-292	67.6-128	56.9-226	42.8-292
CD20 (cells/µL)				
Mean (SD)	161 (143)	187 (66.6)	205 (129)	198 (128)
Median	108	182	183	174
Range	22.0-624	93.4-319	6.28-676	6.28-676

N, n = number of subjects; SD = standard deviation

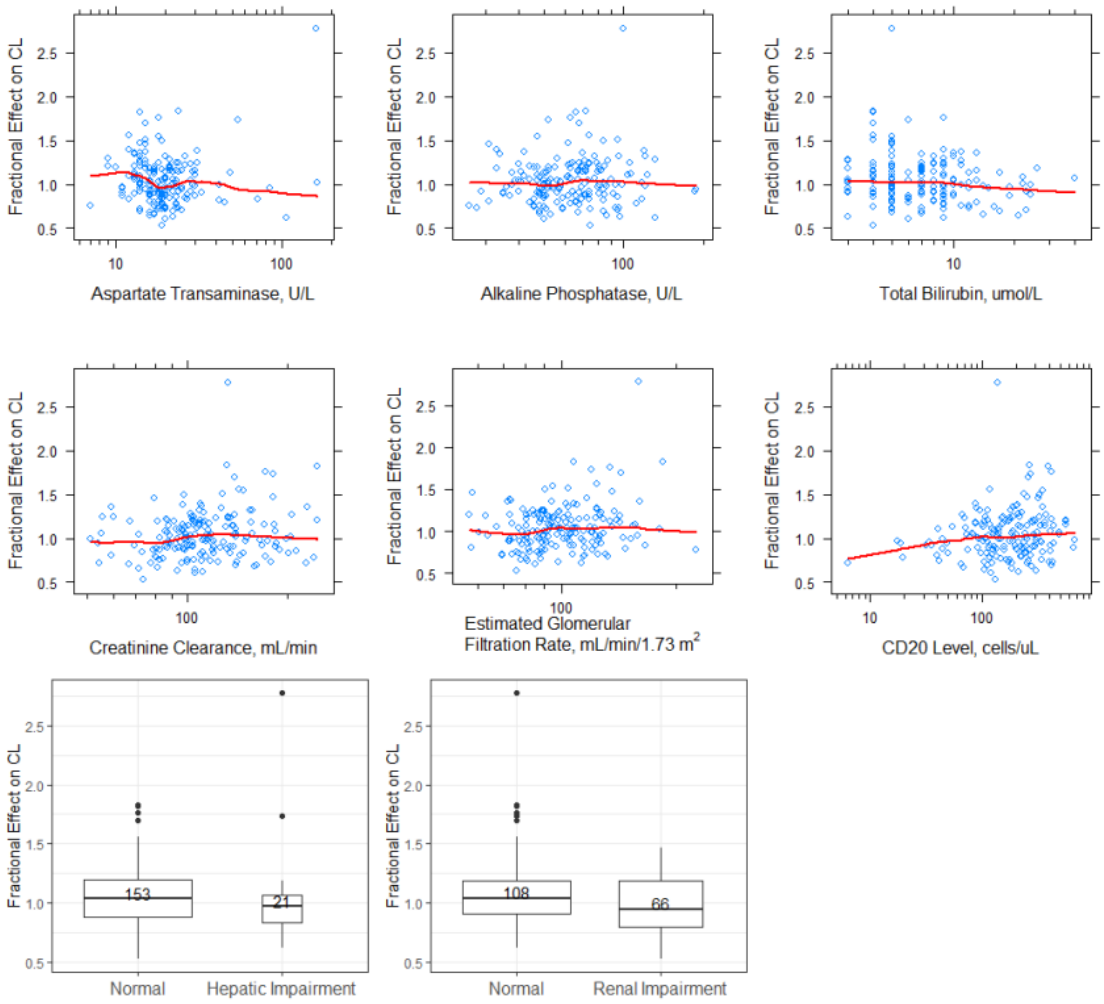
Impaired renal function

The pop PK analysis did not indicate any impact of creatinine clearance/eGFR on CL of inebilizumab (Figure 9). However, data are sparse comprising 63 subjects with mild and only 3 with moderate impairment, and no subjects with creatinine clearance below 50 ml/min.

Impaired hepatic function

The pop PK analysis did not indicate any impact of hepatic impairment on inebilizumab CL (Figure 10). However, data are sparse comprising 19 subjects with mild, 2 subjects with moderate, and no subjects with severe impairment.

Figure 9: Inebilizumab CL was not affected by hepatic function, renal function and baseline B-cell count



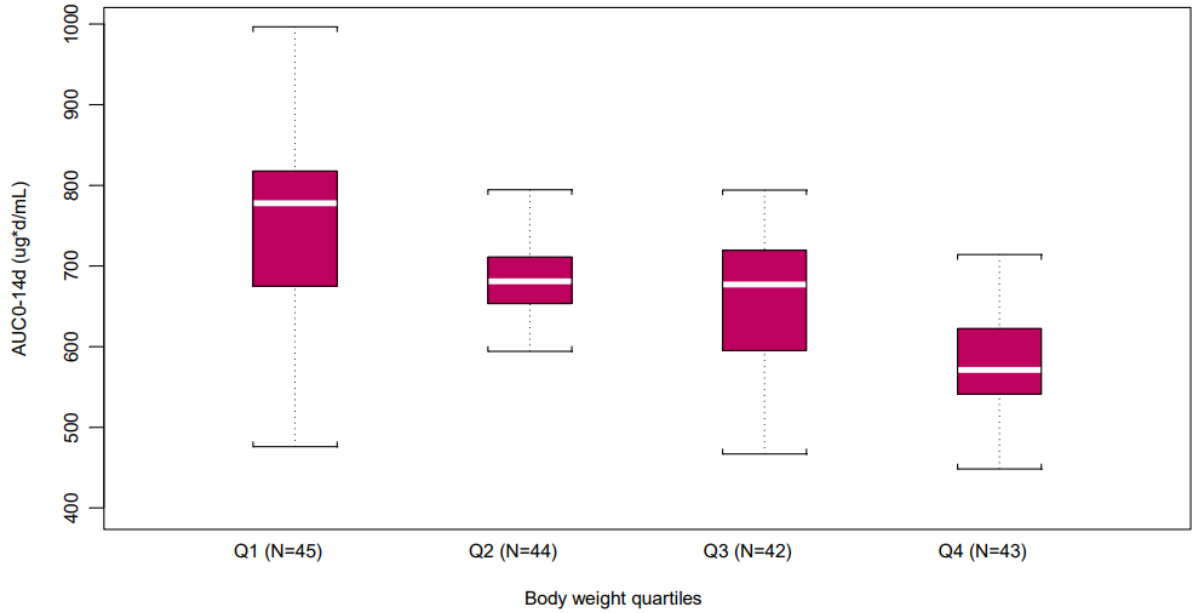
CL = clearance; IIV = interindividual variability. The horizontal curves in scatter plots are loess smooth lines. Hepatic impairment (HI) was defined as normal if total bilirubin (TB) and aspartate transaminase (AST) are ≤ Upper Normal Limit (UNL); mild HI if TB ≤ UNL and AST > UNL or TB > 1 to 1.5 times of UNL and any AST values; moderate HI if TB > 1.5 to 3 times of UNL and any AST values, when UNL of TB and AST are 17.1 µmol/L and 40 U/L, respectively. The HI group consists of 19 subjects with mild HI and 2 subjects with moderate HI. Due to the
small number in the moderate HI group, the subjects of mild and moderate HI groups were combined for plotting.
Renal Impairment (RI) was defined as normal if estimated glomerular filtration rate (eGFR) is ≥ 90 mL/min/1.73m2; mild if eGFR is 60 to 89 mL/min/1.73 m2; moderate if eGFR is 30 to 59 mL/min/1.73 m2. The RI group consists of 63 subjects with mild RI and 3 subjects with moderate RI. Due to the small number in the moderate RI group, the subjects of mild and moderate RI groups were combined for plotting.
The number in each box is the number of subjects. The lower and upper hinges correspond to the first and third quartiles (interquartile range: IQR), while the line inside in the box is the median of the distribution. The upper whisker extends from the hinge to the largest value no further than 1.5 x IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 x IQR of the hinge. Data beyond the end of the whiskers are called "outlying" points and are plotted individually as solid circles. Boxes are drawn with widths proportional to the square-roots of the number of observations in the groups.

Weight

As for other therapeutic mAbs, inebilizumab CL and distribution volumes increased with body weight. The observed range in weight was 38-148 kg.

PK exposure is lower in subjects with heavier body weight (Q4) compared with the rest of the subjects (Figure 10).

Figure 10: Boxplot of first dose AUC0-14d by body weight quartiles (Study 1155)

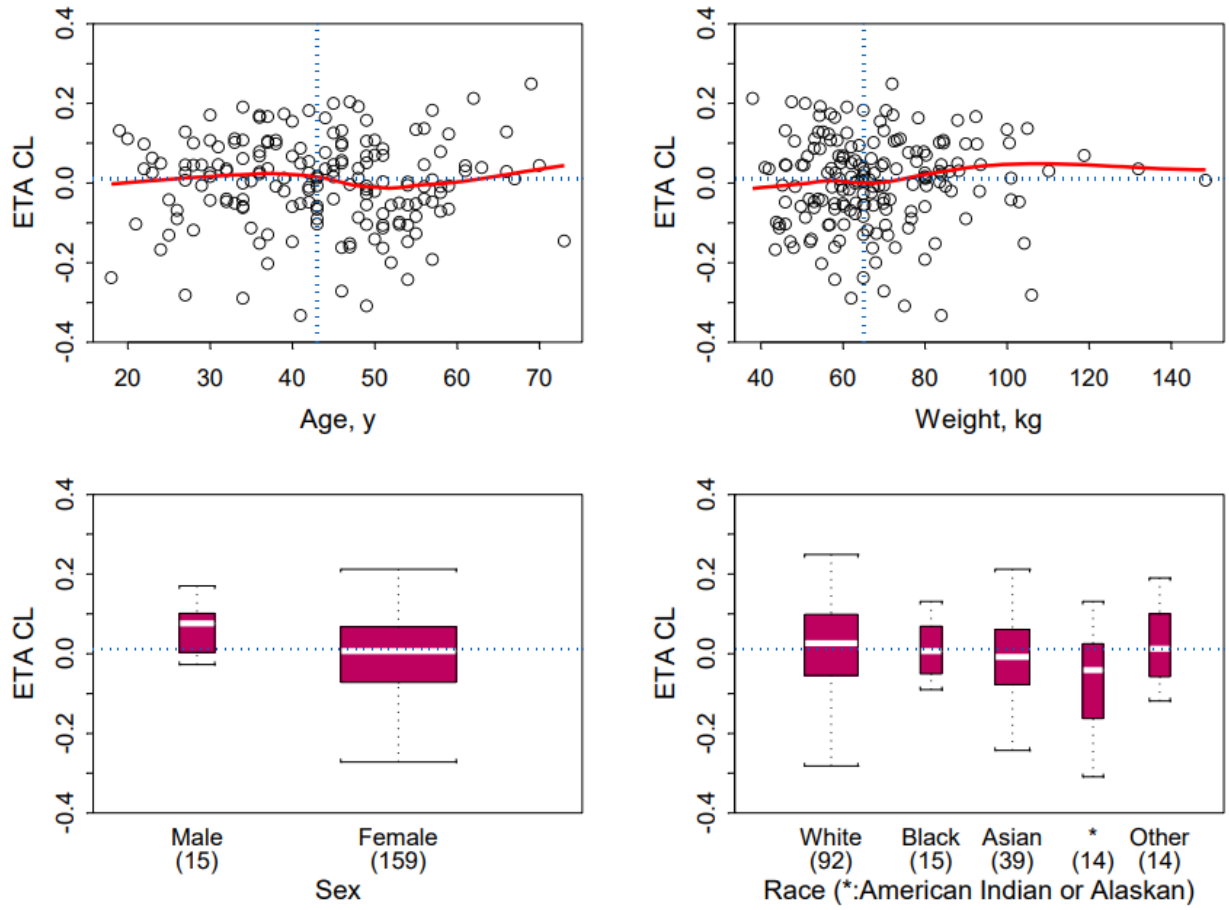


$AUC_{0\text{-}14d}$ = area under the serum concentration-time curve from time 0 to 14 days postdose; Q = quartile.

Gender, race, and age

Based on population PK analysis, neither gender, race, nor age affected inebilizumab clearance (Figure 11). Inebilizumab has not been studied in adolescents or children.

Figure 11: Fractional effect of inebilizumab clearance by age, weight, gender and race (Study 1155)



CL = clearance; ETA = interindividual variability.

Pharmacokinetic interaction studies

Formal DDI studies have not been conducted for inebilizumab.

Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the CL of inebilizumab. 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 NMOSD (paracetamol, diphenhydramine, prednisolone, and methylprednisolone) had no impact on inebilizumab CL.

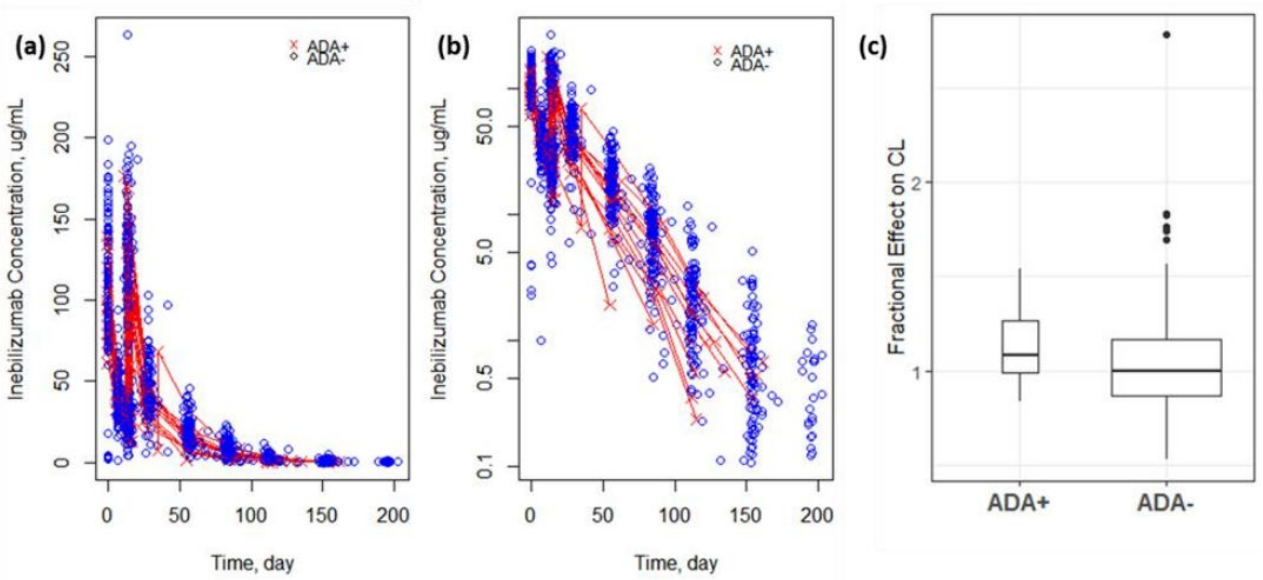
As with other B-cell depleting drugs, concomitant usage of inebilizumab and other IST may result in an increased risk of infection.

Immunogenicity

In study 1155, during the RCP, the ADA prevalence (at any time including baseline) for inebilizumab-treated subjects was 9.8% (17/174), while the prevalence for placebo subjects was 14.3% (8/56).

Although the CL of inebilizumab in ADA-positive subjects appeared higher than that in ADA-negative subjects, population analysis showed no statistically significant effect of the presence of ADA on CL (Figure 12).

Figure 12: Comparison of PK profiles between ADA-positive and ADA-negative subjects in Study 1155



ADA+ = anti-drug antibody positive; ADA- = anti-drug antibody negative; CL = clearance; PK = pharmacokinetic. The first and the second plots are in linear and log scale y-axis. The data from the ADA+ subjects are connected with lines. For the boxplot: the lower and upper hinges correspond to the first and third quartiles (interquartile: IQR), while the line inside in the box is the median of the distribution. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are called "outlying" points and are plotted individually as solid circles. Boxes are drawn with widths proportional to the square-roots of the number of observations in the groups.

In study CP200, ADAs against inebilizumab were detected in 4 out of 24 subjects (16.7%), which is considered a high ratio, and all four subjects had lower exposure to inebilizumab after single dosing. It is noted that no apparent impact on B-cell depletion was observed in the ADA-positive subjects following a single dose of inebilizumab.

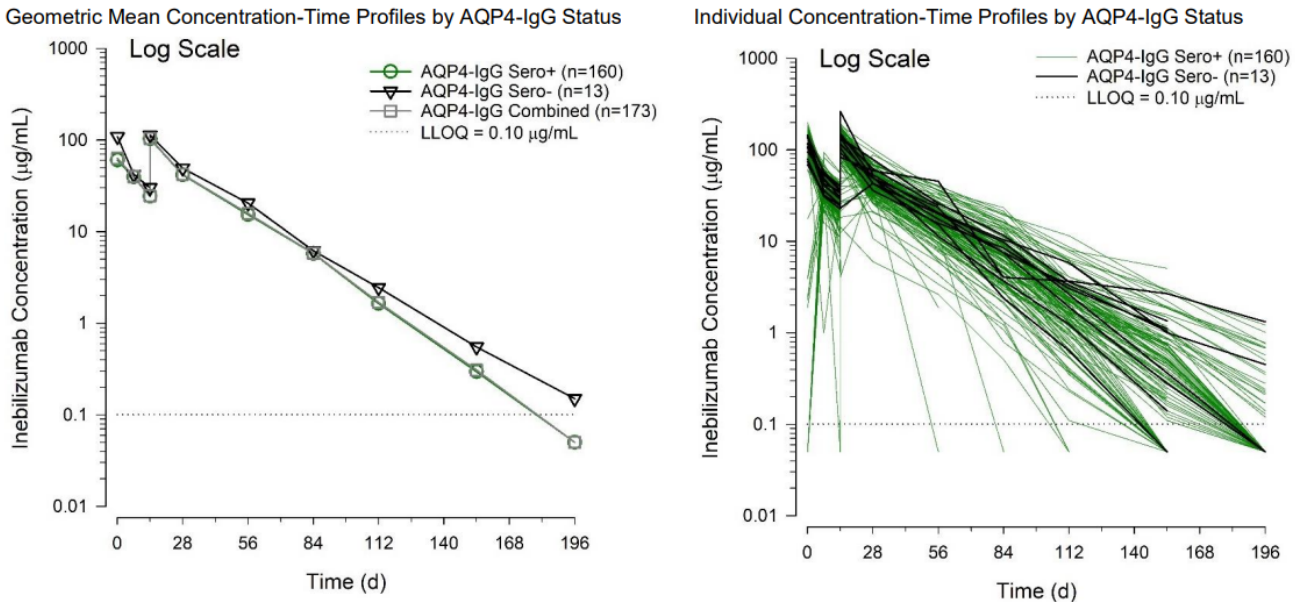
The popPK model that accounts for time-varying ADA status effect on clearance did not show any significant impact.

AQP4-IgG status

In study 1155, a difference in exposure between AQP4-IgG seronegative and seropositive subjects is noticed 84 days after first exposure. The difference is not considered clinically meaningful. The indication is restricted to AQP4-IgG seropositive subjects.

The concentration-time profiles by AQP4-IgG status are presented in Figure 13 and PK parameters are summarised in Table 5.

Figure 13: Geometric mean and individual serum concentration-time profiles of inebilizumab by AQP4-IgG status in adult subjects with NMOSD following Two IV infusions in the randomised-controlled period (Study 1155)



AQP4-IgG = aquaporin-4 autoantibodies; d = day; IV = intravenous; LLOQ = lower limit of quantitation; n = sample size; NMOSD = neuromyelitis optica spectrum disorder; sero- = seronegative; sero+ = seropositive. The AQP4-IgG Seropositive and AQP4-IgG Combined populations had comparable geometric mean concentration-time profiles; therefore, on the semi-log plot, the 2 curves are almost fully overlapping.

2.6.2.2. Pharmacodynamics

Inebilizumab is a humanised, affinity-optimised, afucosylated immunoglobulin G1 kappa (IgG1κ) mAb that binds to the B cell-specific surface antigen CD19, resulting in the depletion of B cells, including plasmablasts and some plasma cells.

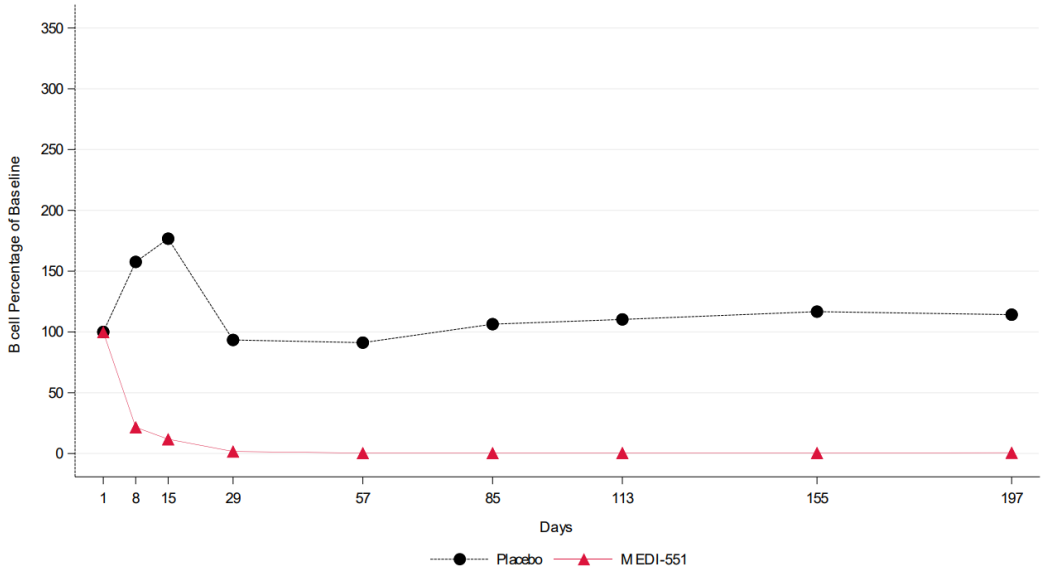
The primary PD endpoint was change from baseline in CD20-positive B-cells.

Assessment of an exposure-efficacy (E-E) relationship was conducted using AC-determined NMOSD attack as efficacy parameter. Assessment of an exposure-safety (E-S) relationship has not been provided.

Depletion of B-cells

In study 1155, following treatment with inebilizumab, blood CD20+ B-cell counts were profoundly decreased during the 28-week randomised-controlled period (RCP). For B-cell counts, assays for CD20+ B-cells were used because the presence of inebilizumab interferes with the recognition of cell surface CD19 in the CD19 assay. CD20+ B-cells were significantly reduced 8 days after the initial infusion and remained below the lower limit of normal in 100% of inebilizumab-treated subjects at 4 weeks and 94% of subjects at 28 weeks after initial treatment. CD20+ B-cell counts were not significantly different between any RCP timepoints in the placebo group (Figure 14).

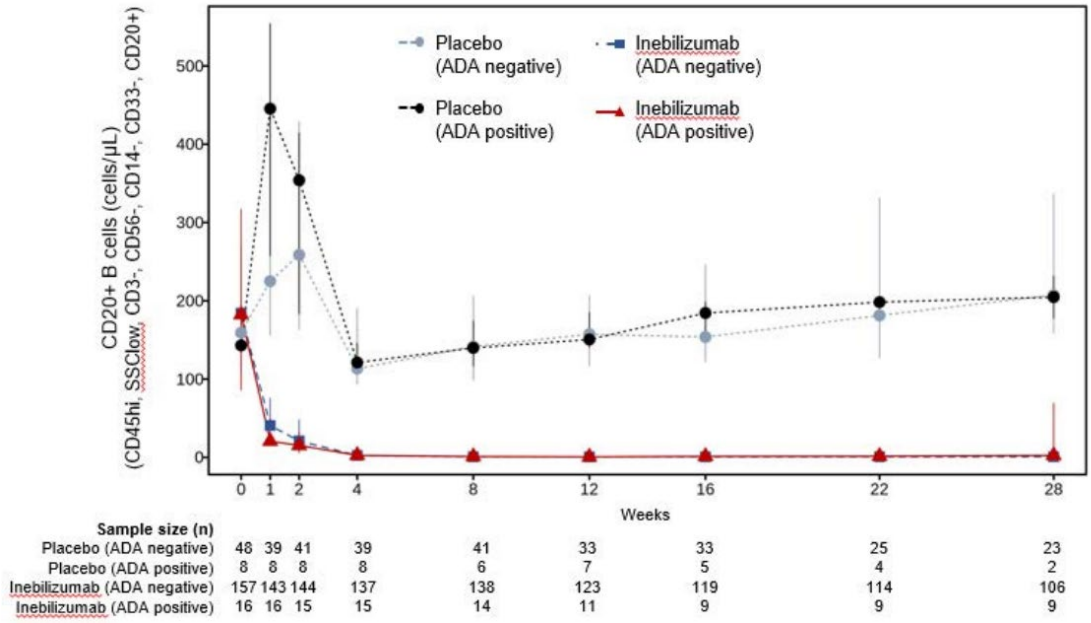
Figure 14: Median values for CD20 B-cell count as percentage of baseline over time, randomised-controlled period (ITT Population) (Study 1155)



ITT = intent-to-treat; MEDI-551 = inebilizumab.
Median blood CD20+ B-cell count as a percentage of baseline over time in inebilizumab and placebo-treated subjects plotted on a linear scale

Inebilizumab produces a profound depletion of the CD20-positive B-cells, and this effect is not influenced by ADA status. Depletion of B-cells stratified by ADA status in study 1155 is depicted in Figure 15**.**

Figure 15: Peripheral blood median absolute CD20 B-cell count in inebilizumab and placebo-treated subjects in RCP by ADA status



ADA = anti-drug antibody; n = sample size. Error bars represent the 25% and 75% percentile of each ADA group. CD20 counts between ADA positive and ADA negative inebilizumab-treated subjects were compared at each timepoint using a Mann-Whitney U test. No statistically significant differences ($p < 0.05$) were observed.

It is reported by the applicant that CD19 is expressed on a wider lineage of B cells, compared to CD20, and that AQP4 autoantibodies originates from a subpopulation of CD19-positive and CD20-negative B cells. In all of the performed studies, B-cell counts were assessed using assays for CD20+ B cells because the presence of inebilizumab interferes with the recognition of cell surface CD19 in the CD19 assay.

Relationship between plasma concentration and effect

Exploratory exposure-response (E-R) analyses were conducted investigating the relationship between inebilizumab exposure and endpoints of efficacy by means of Cox proportional hazard models or logistic regression models. Kaplan-Meier plots and Forest plots were used to display the results of the analyses. No model diagnostics were provided. The effect of body weight and ADA status on efficacy measures was also evaluated.

Efficacy exposure-response analyses

The relationships between PK exposure and the primary efficacy endpoint (AC-determined NMOSD attack) and key secondary efficacy endpoints were evaluated. Three PK metrics, namely $AUC_{0\text{-}14d}$ following the first dose, AUCcumulative, and the CL of the first-order elimination pathway, were obtained from the population PK modelling (Table 7).

Table 7: Summary statistics of model-predicted individual PK exposures.

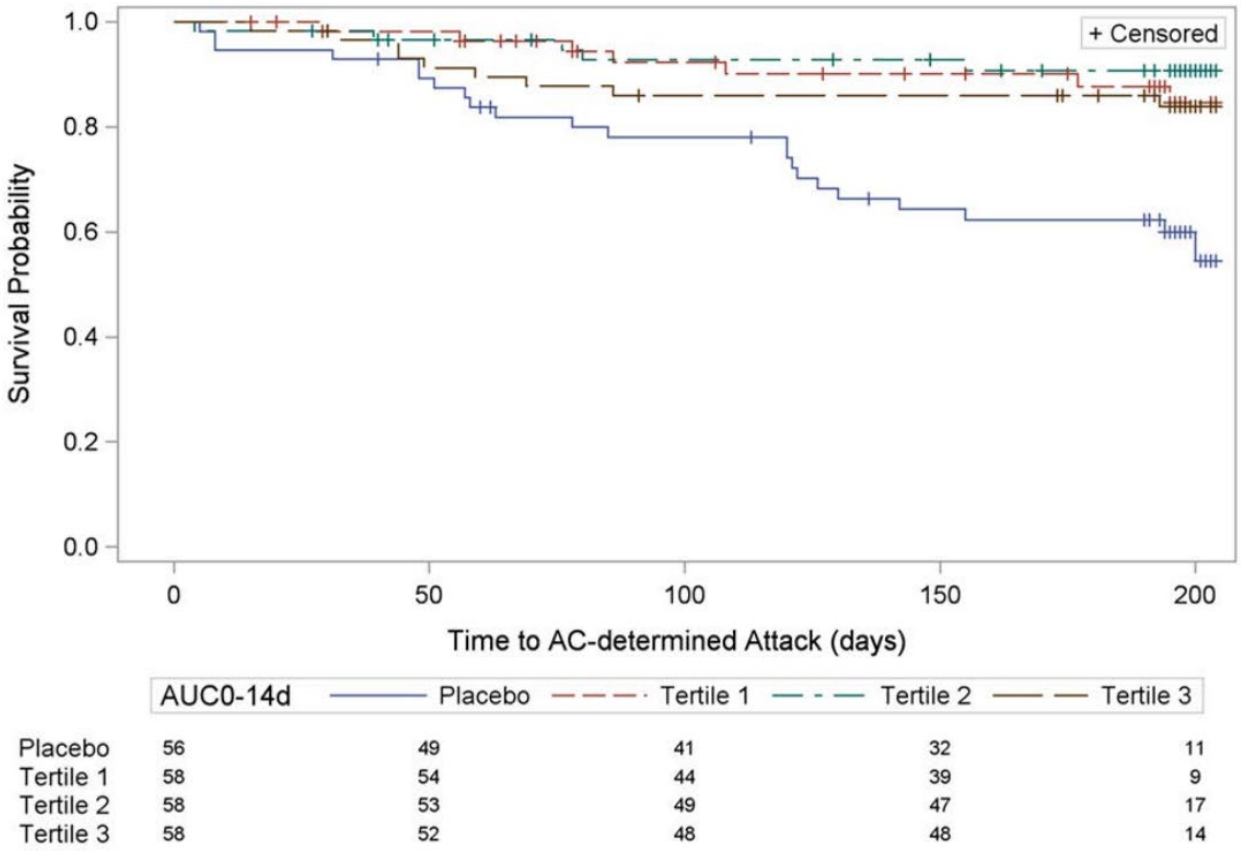
Exposure Metric		n	Mean	Standard Deviation	Median	Minimum - Maximum
$AUC_{0\text{-}14d}$ (µg·d/mL)	Overall	174	676.2	105.2	675.5	397.2 - 996.6
	Tertile 1	58	564.1	52.1	568.3	397.2 - 635.1
	Tertile 2	58	673.6	20.5	675.5	636.1 - 706.2
	Tertile 3	58	791.0	65.2	778.7	708.2 - 996.6
$AUC_{cumulative}$ (µg·d/mL)	Overall	174	2696.7	956.2	2766.2	7.0 – 5605.6
	Tertile 1	58	1694.8	623.3	1884.1	7.0 – 2382.0
	Tertile 2	58	2717.2	205.6	2766.2	2358.2 – 3027.3
	Tertile 3	58	3678.1	585.2	3559.2	3028.9 – 5605.6
CL (mL/d)	Overall	174	198.9	59.8	190.2	91.0 - 424.9
	Tertile 1	58	143.6	19.4	146.1	91.0 - 172.7
	Tertile 2	58	188.4	9.9	190.2	173.7 - 208.7
	Tertile 3	58	264.7	52.4	251.7	209.5 - 424.9
Body Weight (kg)	Overall	173	68.4	17.4	65.0	38.0 - 148.4
	Q1	42	49.7	4.7	50.7	38.0 - 56.5
	Q2 & Q3	87	65.6	5.7	65.0	56.8 – 78.0
	Q4	44	91.7	14.6	86.2	78.0 – 148.4

$AUC_{0\text{-}14d}$ = area under the concentration time curve from time 0 to 14 days postdose; $AUC_{0\text{-}14d}$ Tertile 1= inebilizumab-treated subjects with low $AUC_{0\text{-}14d}$; $AUC_{0\text{-}14d}$ Tertile 2 = inebilizumab-treated subjects with medium $AUC_{0\text{-}14d}$; $AUC_{0\text{-}14d}$ Tertile 3 = inebilizumab-treated subjects with high $AUC_{0\text{-}14d}$; AUCcumulative = cumulative area under the concentration time curve from time 0 of Dose 1 to the last measurable concentration in RCP; $AUC_{cumulative}$ Tertile 1 = inebilizumab-treated subjects with low $AUC_{cumulative}$; $AUC_{cumulative}$ Tertile 2 = inebilizumab-treated subjects with medium $AUC_{cumulative}$; $AUC_{cumulative}$ Tertile 3= 300mg inebilizumab-treated subjects with high AUCcumulative; CL = systemic clearance; NA = not applicable; Q1 = inebilizumab-treated subjects with lowest quartile body weight; Q2 & Q3 = inebilizumab-treated subjects with interquartile range (2nd and 3rd Quartile) of body weight; Q4 = inebilizumab-treated subjects with large quartile of body weight. For an unbiased assessment of the PK exposure-response relationship, population PK model estimated individual CL was utilised as a surrogate of overall PK exposure AUC_{inf}. Subjects in the Tertile 3 for clearance represent subjects with the lowest AUC (Tertile 1) for $AUC_{cumulative}$ and $AUC_{0\text{-}14d}$ while subjects in the Tertile 1 for clearance represent subjects with the highest AUC (Tertile 3) for $AUC_{cumulative}$ and $AUC_{0\text{-}14d}$

Primary endpoint

The Kaplan-Meier plot of AC-determined NMOSD attack during the RCP in placebo and inebilizumab-treated subjects with low (first tertile), middle (second tertile), and high (third tertile) $AUC_{0\text{-}14d}$ is shown in Figure 16. The AUC following the first dose was selected for E-R assessment since steady-state PK data were unavailable. Per protocol, subjects who experienced an AC-determined NMOSD attack exited the RCP and had the option to enrol into the OLP to initiate or continue to receive inebilizumab treatment, resulting in incomplete PK profiles following the second dose in those who discontinued treatment in the RCP.

Figure 16: Kaplan-Meier (Survival) plot for time to AC-determined NMOSD attack during the RCP in subjects with low, medium, and high $AUC_{0\text{-}14d}$



AC = Adjudication Committee; $AUC_{0\text{-}14d}$ = area under the concentration-time curve from Time 0 to 14 days postdose; NMOSD = neuromyelitis optica spectrum disorder; RCP = randomised, controlled period; Tertile 1 = 300mg inebilizumab-treated subjects with low $AUC_{0\text{-}14d}$; Tertile 2 = 300mg inebilizumab-treated subjects with medium $AUC_{0\text{-}14d}$; Tertile 3 = 300mg inebilizumab-treated subjects with high $AUC_{0\text{-}14d}$ The numbers under the legend represent the corresponding number of subjects for placebo, Tertile 1, Tertile 2 and Tertile 3 at the X axis time to AC-determined attack (days). The hazard ratio and 95% confidence interval were 0.289 (0.123 – 0.679) for $AUC_{0\text{-}14d}$ Tertile 1, 0.189 (0.072 – 0.501) for $AUC_{0\text{-}14d}$ Tertile 2, and 0.341 (0.157 – 0.741) for $AUC_{0\text{-}14d}$ Tertile 3.

There was no apparent relationship between the hazard ratio for the primary endpoint with $AUC_{0\text{-}14d}$ (Figure 16), suggesting the 300 mg dose of inebilizumab resides at the efficacy plateau. In fact, the efficacy was slightly lower in subjects with high AUC0-14d, likely due to random variability across subgroups.

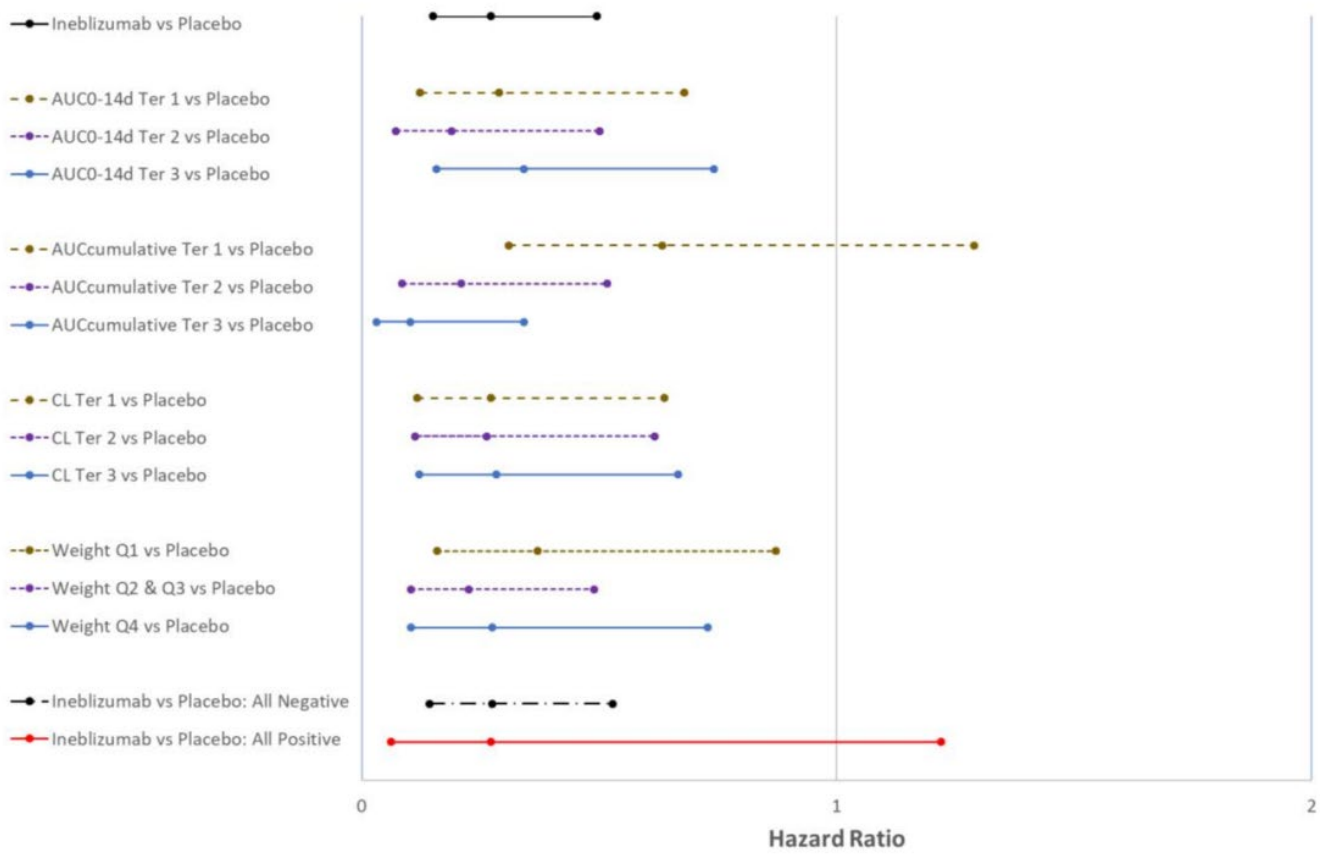
Exposure: The protocol allowed those who experienced an AC-determined NMOSD attack to leave the RCP and enter the OLP, resulting in lower $AUC_{cumulative}$ in such subjects. For an unbiased assessment, population PK model-estimated individual CL was utilised as a surrogate of overall PK exposure (AUC_{inf}): subjects with slow, medium, and fast CL correspond to the high, medium, and low AUC_{inf}, respectively. Among subjects in the inebilizumab group during the RCP, there was essentially no impact of CL on AC-determined NMOSD attack (Figure 17). The similarity in efficacy outcome in subjects with different CL

confirmed that the 300 mg dose of inebilizumab resides at the efficacy plateau of lowering NMOSD attack probability, i.e., PK variability across subjects had no impact on the therapeutic efficacy outcome.

Body Weight: Reduction in the risk of AC-determined NMOSD attack with inebilizumab compared to placebo during the RCP was observed in subjects across different body weight groups. With the 300 mg dose, there were no clear trends in efficacy across the subjects with different quartiles of body weight (Figure 18 and Figure 18).

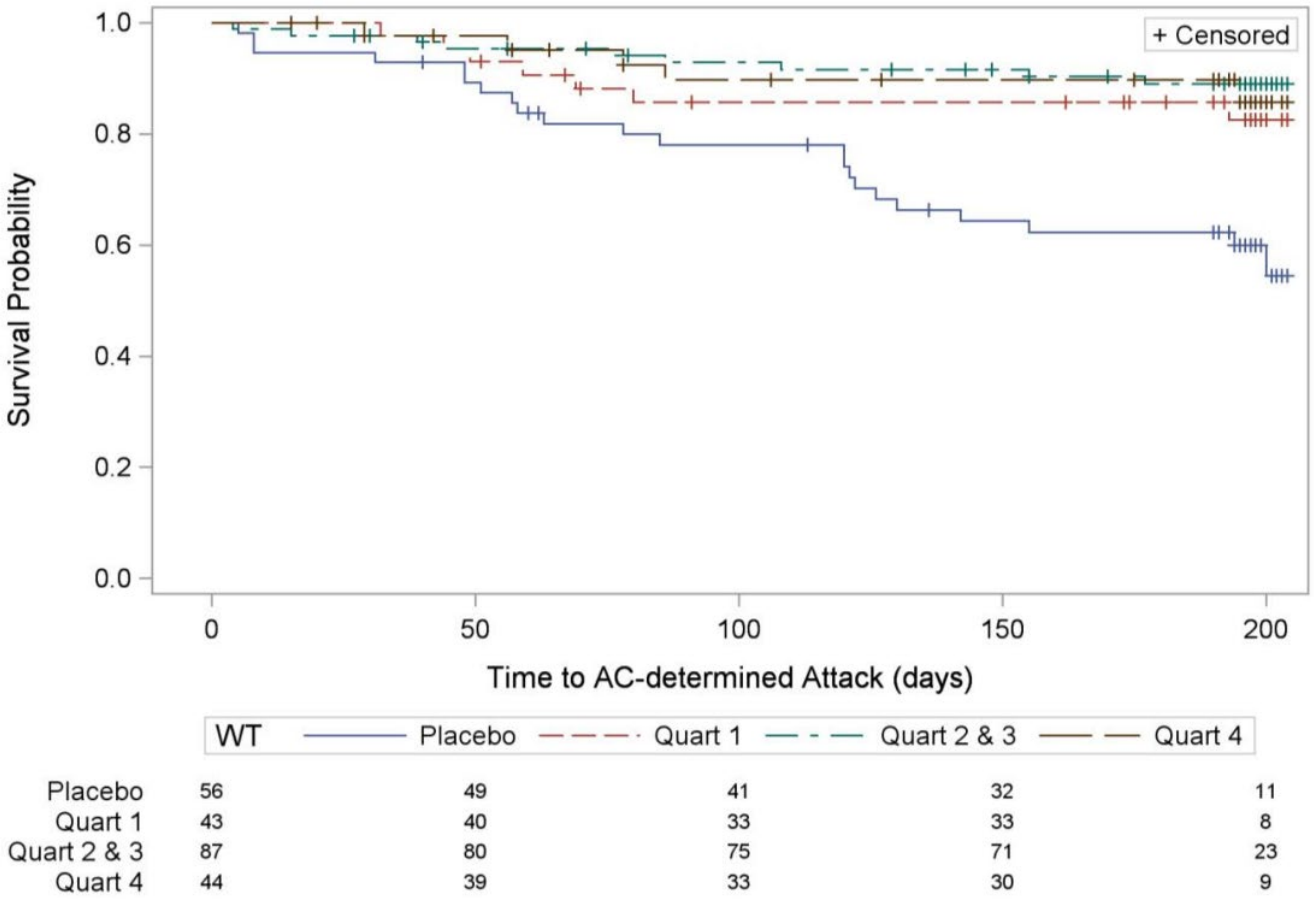
ADA: The presence of ADA had no significant effect on the risk of AC-determined NMOSD attacks in subjects with NMOSD (Figure 17).

Figure 17: Forest plot of risk of AC-determined NMOSD attack by exposure, clearance, weight, and ADA subgroups during the RCP



ADA = anti-drug antibodies; $AUC_{0\text{-}14d}$ = area under the concentration-time curve from Time 0 to 14 days postdose; $AUC_{0\text{-}14d}$ Ter 1= inebilizumab-treated subjects with low $AUC_{0\text{-}14d}$; $AUC_{0\text{-}14d}$ Ter 2 = inebilizumab-treated subjects with medium AUC0-14d; $AUC_{0\text{-}14d}$ Ter3 = inebilizumab-treated subjects with high AUC0-14d; $AUC_{cumulative}$ = cumulative area under the concentration-time curve from Time 0 of Dose 1 to the last measurable concentration in RCP; $AUC_{cumulative}$ Ter 1 = inebilizumab-treated subjects with low $AUC_{cumulative}$; $AUC_{cumulative}$ Ter 2 = inebilizumab-treated subjects with medium $AUC_{cumulative}$; $AUC_{cumulative}$ Ter 3 = 300mg inebilizumab-treated subjects with high $AUC_{cumulative}$; CL = systemic clearance; CL Ter 1 = inebilizumab-treated subjects with low CL; CL Ter 2 = inebilizumab-treated subjects with medium CL; CL Ter 3 = 300mg inebilizumab-treated subjects with high CL; EDSS = Expanded Disability Status Scale; NMOSD = neuromyelitis optica spectrum disorder; RCP = randomised, controlled period; Weight Q1 = inebilizumab-treated subjects with lowest quartile body weight; Weight Q2 & Q3 = inebilizumab-treated subjects with interquartile range (2nd and 3rd Quartile) of body weight; Weight Q4 = inebilizumab-treated subjects with large quartile of body weight. All Negative = only subjects who were determined ADA negative; All Positive = only subjects who were determined ADA positive. Odds ratio and 95% CI < 1 supports treatment with inebilizumab was better than placebo.

Figure 18: Kaplan-Meier (Survival) plot for time to AC-determined NMOSD attack during the RCP in subjects with low, medium and high body weight



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

Quart = quartile; Quart 1= inebilizumab treated subjects with lowest quartile body weight; Quart 2 & 3 = inebilizumab-treated subjects with interquartile range (2nd and 3rd Quartile) of body weight; Quart 4 = inebilizumab-treated subjects with large quartile of body weight. The numbers under the legend represent the corresponding number of subjects for placebo, Quartile 1, Quartile 2 and 3 and Quartile 4 at the X axis time to AC-determined Attack (days). The hazard ratio and 95% confidence interval were 0.371 (0.158 – 0.872) for body weight Quartile 1, 0.225 (0.103 - 0.489) for body weight Quartile 2 and 3, and 0.275 (0.104 - 0.728) for Quartile 4

Key Secondary Endpoints

A nominally significant improvement with inebilizumab compared with placebo was demonstrated for 3 of the 4 key secondary endpoints: worsening from baseline to the last visit of the RCP in EDSS, cumulative total active MRI lesions during the RCP, and number of NMOSD-related in-patient hospitalisations during the RCP. There was no effect of inebilizumab treatment on the secondary endpoint of change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart at the last visit during the RCP.

No relationship between exposure, CL, weight, and ADA status of inebilizumab and secondary endpoints was demonstrated.

Safety exposure-response analysis

Infusion-related reactions are an identified risk of inebilizumab. Hypersensitivity reactions (including anaphylaxis and serious skin reactions), immune complex disease (vasculitis, nephritis), cytopenia, serious infections (including viral reactivation and opportunistic infections), and progressive multifocal leukoencephalopathy (PML) are potential risks of inebilizumab. These events were assessed as adverse events of special interest (AESI) in study 1155.

Inebilizumab-treated subjects were split into 4 quartiles based on PK exposure (first dose $AUC_{0\text{-}14d}$) (Table 8). The quartiles were then compared by frequency of treatment-emergent serious adverse events (SAEs). Quartile 1 is the group with highest exposure. After receiving the first dose, more patients in quartile 1 had SAEs but the number of patients with SAEs is small and no clear exposure related trend is observed. In conclusion, no apparent exposure-safety relationship has been demonstrated.

Table 8: Subjects with TESAEs after receiving inebilizumab by quartile per PK exposure (Study 1155)

PK exposure quartile	AQP4-IgG sero+ n/N (%) n = 161	AQP4-IgG sero- n/N (%) n = 13	Total n/N (%) n = 174
1	12 / 42 (28.6%)	1 / 2 (50.0%)	13 / 44 (29.5%)
2	1 / 42 (2.4%)	0 / 1 (0.0%)	1 / 43 (2.3%)
3	3 / 36 (8.3%)	2 / 7 (28.6%)	5 / 43 (11.6%)
4	8 / 41 (19.5%)	0 / 3 (0.0%)	8 / 44 (18.2%)

AQP4-IgG = autoantibodies against aquaporin-4; n = number of subjects; N = number of subjects in group; PK = pharmacokinetic; sero+ = seropositive; sero- = seronegative; TESAEs = treatment-emergent serious adverse events

2.6.3. Discussion on clinical pharmacology

Inebilizumab is being developed for the treatment of NMOSD. Inebilizumab is a humanised, affinity optimised, afucosylated immunoglobulin G1 kappa (IgG1κ) mAb that binds to the B cell specific surface antigen CD19 resulting in the depletion of CD19 positive (CD19+) B cells, plasmablasts and some plasma cells.

No dedicated human PK studies were conducted for inebilizumab. The clinical pharmacology programme assessed the PK, PD, and immunogenicity of inebilizumab in two completed phase 1 studies (subjects with scleroderma and multiple sclerosis), and in one phase 2/3 randomised prospective placebo-controlled study in subjects with NMOSD. PopPK characteristics were assessed based on pooled data from all 3 studies and exposure-response characteristics were assessed using data from NMOSD Study 1155. The popPK dataset contained 1,617 measurable PK samples from 213 subjects (IV administration).

The bioanalysis of inebilizumab is considered adequately documented. Presence of ADAs may impact the quantification of inebilizumab in study samples. Drug tolerance of the ADA assay was acceptable. Several samples that tested positive for ADAs against inebilizumab came from placebo treated patients or were pre-treatment samples.

The population kinetics for inebilizumab IV was described by a 2-compartment model with parallel non-specific linear clearance and Michaelis-Menten nonlinear clearance that decreases with time. Body weight was the only covariate included. The allometric scaling factors of weight effect on distribution parameters were estimated and deviated from the typical values. A model for SC administration (n=6 SC, n=213 IV) was developed in an attempt to characterise the bioavailability and ka, however, data were too sparse for reliable estimations.

Due to the PD effect of the substance no dedicated human PK studies in healthy subjects were performed. The effect of renal or hepatic impairment was not formally tested in dedicated clinical trials, and no interaction studies has been undertaken.

The recommended dosing regimen of inebilizumab is a fixed dose of 300 mg administered as an IV infusion on treatment Day 1 and Day 15, and thereafter one dose of 300 mg every 6 months.

The product is intended for IV administration and the bioavailability is therefore 100% and C_{max} is reached at the end of infusion. Overall volume of distribution is estimated to be approximately 6 L. The reported values of clearance and $t_{1/2}$ of 0.19 L/day and 18 days, respectively, are typical for mAbs. At the therapeutic dose level, a saturation of the CD19-mediated elimination pathway is expected.

The primary elimination pathways for mAbs like inebilizumab are degradation by the reticuloendothelial system (like endogenous IgG) or by target-mediated elimination. Metabolites are amino acids and small peptides that are recycled into the protein metabolism.

Based on study CP200 and 1102, with one and two IV administrations, respectively, dose-proportionality of AUC is uncertain due to diverging results. C_{max} seems to exhibit dose-proportionality. Simulations of the impact of a time-dependent target-mediated CL on inebilizumab PK exposure indicate that the exposure is expected to be very similar after the first, second, and third administration.

As to special populations, popPK analyses found no impact of age, gender, race, renal impairment, or hepatic impairment on inebilizumab clearance.

No renal or hepatic impairment studies have been conducted. The popPK analysis did not indicate any impact of renal or hepatic impairment on CL of inebilizumab. However, data are sparse and no subjects with severely impaired renal or hepatic function were evaluated. Given the elimination pathways of the drug product, an effect of impaired renal or hepatic function on the exposure of inebilizumab is not expected.

No clinical DDI studies have been conducted. In the popPK analysis, co-medication with paracetamol, methylprednisolone, diphenhydramine, or prednisolone did not seem to influence the CL of inebilizumab. As with other B-cell depleting drugs, concomitant usage of inebilizumab and other immunosuppressant drugs may result in an increased risk of infection.

The primary PD endpoint was change from baseline in CD20-positive B-cells. In all three studies in the clinical pharmacology programme, inebilizumab treatment led to a major reduction in peripheral CD20-positive B-cell counts.

No secondary PD biomarkers of inebilizumab effects have been evaluated.

In study 1155, the incidence of AC-determined NMOSD attacks (primary efficacy endpoint) was lower in all exposure subgroups compared to placebo. No exposure-efficacy relationship was demonstrated. The body weight range was 38 kg to 148 kg. As weight is a significant covariate of Vd and clearance, effect of weight was tested on response and presented in Kaplan Meier plots. The results did not indicate any impact of weight on efficacy (time to onset of AC-Determined NMOSD Attack), and the proposed fixed dose (300 mg) seems acceptable.

There is no indication of an impact on the primary endpoint (AC-determined NMOSD attacks) between ADA-positive and ADA-negative subjects receiving inebilizumab.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology programme consists of three clinical studies and popPK/PD analyses. Considering the nature of the product (mAb), the pharmacology package is considered adequate and the proposed dosing of inebilizumab seems appropriate.

2.6.5. Clinical efficacy

The evidence of the efficacy of Uplizna (inebilizumab) is based on data from the double-blind (DB) part (completed) of one phase 2/3 clinical trial, i.e. Study CD-IA-MEDI-551-1155 (Study 1155). Maintenance of the effect is based on available results from the ongoing open label period (OLP) of the study and is limited to an updated analysis of annualised Adjudication Committee (AC)-determined NMOSD relapse rate (ARR). OLP will continue for a maximum of 3 years after the last subject enrolled.

2.6.5.1. Dose response studies

No dose-response study has been conducted. Dose finding was performed in Phase I trials (SAD and MAD studies) in Scleroderma and Relapsing MS patients.

In the phase 1 study in scleroderma (Study MI-CP200), inebilizumab was administered as an IV infusion at single doses up to 10 mg/kg, or placebo was administered.

In the phase 1 study in relapsing multiple sclerosis (Study 1102), inebilizumab was administered as a single fixed IV course (30, 100, or 600 mg) on Day 1 and Day 15, or a single SC dose (60 or 300 mg), or placebo was administered.

All subjects were monitored over a 24-week period. Any subject whose B-cell count had not returned to baseline, or lower limit of normal value, was asked to return to the study site every month for 3 months and every 3 months thereafter until the B-cell count returned to baseline or lower limit of normal value.

Based on PK and B-cell PD data from Study CP200, a fixed dose of 300 mg inebilizumab given on Day 1 and Day 15 was predicted to fully deplete peripheral blood B cells to undetectable levels and maintain B-cell suppression for 28 weeks, thereby sustaining B cell depletion for the duration of the RCP. In theory, an initial dose of inebilizumab will deplete the peripheral blood B cells; however, additional B cells will then recirculate out of the lymphoid tissues. The second dose of inebilizumab on Day 15 was timed to deplete the newly recirculated B cells from the peripheral blood. This dose regimen was supported by clinical data from other B-cell depleting mAbs, where IV dosing on Day 1 and Day 15 provided optimal B-cell depletion in both blood and tissues (Huffstutter et al, 2011; Hauser et al, 2008; Bar-Or et al, 2008; Kappos et al, 2011).

2.6.5.2. Main study

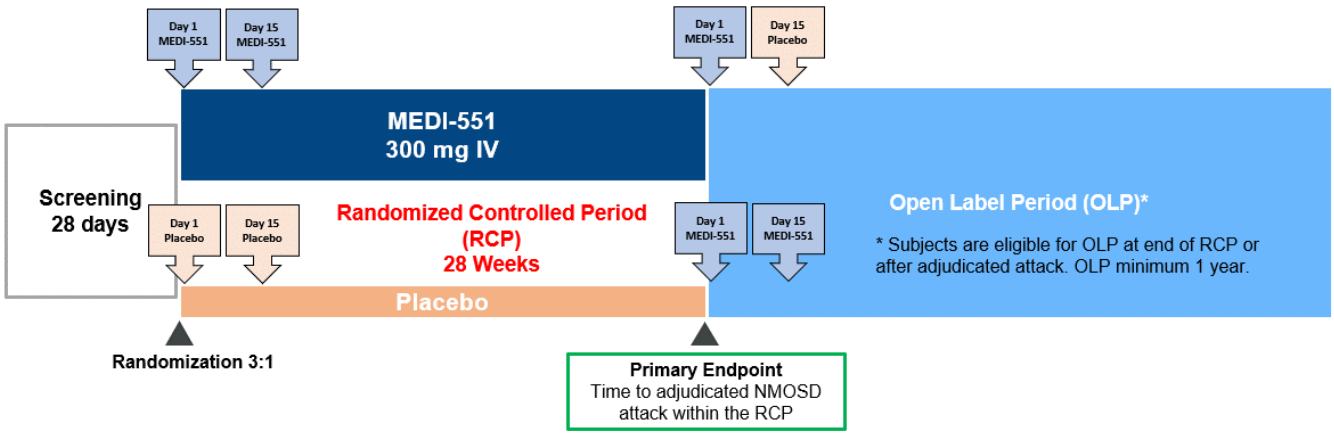
A Double-masked, Placebo-controlled Study with Open-label Period to Evaluate the Efficacy and Safety of MEDI-551 in Adult Subjects with Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders

Methods

The design of the pivotal trial is a multicentre, multinational, randomised, DB, placebo-controlled, parallel group confirmatory trial. The study had screening (28 days), randomised controlled (up to 197 days), open label (minimum of one year and a maximum of 3 years after the last subject enters) and safety follow up (minimum 52 weeks) periods.

Study RCP duration was variable for subjects. Subjects who experienced an AC-determined attack in the RCP, or who completed the Day197 visit without an attack, exited the RCP and had the option to enrol into the OLP and initiate or continue treatment with inebilizumab. Subjects in whom an attack was not confirmed by the AC continued in the RCP until Day 197 (or until another attack occurred and was determined to be an NMOSD attack by the AC).

Figure 19: Study flow diagram



IV = intravenous; MEDI-551 = inebilizumab; NMOSD = neuromyelitis optica spectrum disorders; OLP = open-label Period; RCP = randomised-controlled period.

- **Study Participants**

Main inclusion criteria:

Eligible patients in Study 1155 were adults (18 years and older) with an EDSS score ≤ 7.5 (≤ 8.0 if the Investigator and medical monitor agreed that the subject was reasonably able to participate in the study), a diagnosis of NMOSD at the time of screening, and a documented history of ≥ 1 NMOSD attacks that required rescue therapy in the previous year or ≥ 2 NMOSD attacks that required rescue therapy in the preceding 2 years.

Subjects who had a relapse immediately prior to screening must have had at least 4 weeks in which their relapse symptoms were stable or improving prior to randomisation.

AQP4-IgG seropositive and seronegative subjects (as tested and verified by the central laboratory only) were enrolled in the study. The study was designed to include a ratio of seropositive to seronegative that represents the reported ratio in the literature (approximately 80% subjects who are AQP4-IgG seropositive and 20% of subjects who are AQP4-IgG seronegative). Subjects who are AQP4-IgG seronegative, where the diagnosis of NMOSD is less clear, needed to meet the clinical criteria for NMOSD according to Wingerchuk et al 2006 by the determination of independent Eligibility Committee.

The NMOSD diagnostic criteria were updated in 2015, after enrolment for the study had already begun and the protocol was not amended regarding this change. As it turned out, the protocol criteria for AQP4-IgG seropositive subjects were consistent with the 2015 IPND diagnostic criteria for NMOSD, and as such, the protocol-defined study population was representative of the population defined by the new criteria.

Main exclusion criteria:

The use of background IST while on trial was not permitted.

A comprehensive set of exclusion criteria addressed concomitant or previous therapy (rituximab or any experimental B-cell depleting agent within last 6 months, alemtuzumab, total lymphoid irradiation, bone marrow transplant, T-cell vaccination therapy, intravenous immune globulin (IVIG), natalizumab, cyclosporin, methotrexate, mitoxantrone, cyclophosphamide, tocilizumab, eculizumab), drug or food allergy, autoimmune diseases, any concomitant disease that required steroid treatment within the 6 months prior to screening, AQP4-IgG seronegative subjects with a brain MRI abnormality that met the diagnostic criteria for multiple sclerosis, vaccination history, immune status, infection status and risk, malignancy risk, general safety, laboratory criteria, B cell counts, and CD19+ B cell counts below the lower limit of normal (LLN) according to the central laboratory.

- **Treatments**

During RCP, a fixed dose of 300 mg inebilizumab was given on Day 1 and Day 15. A placebo-comparator treatment arm was chosen for the conduct of this study.

Inebilizumab and placebo were provided in 10mL vials which were stored at 2ºC to 8ºC and were not frozen or shaken. The investigational product (IP) was diluted into a 250 mL 0.9% sodium chloride IV infusion bag for administration.

No background IST for treatment of NMSOD were permitted. A 2-week course of oral corticosteroids (prednisone 20 mg/day or equivalent oral glucocorticoid) (plus a 1-week taper) was given to all subjects following the first administration of IP in the RCP only. The rationale was to provide prophylaxis against an NMOSD attack for the period wherein the PD effect of inebilizumab was not expected and when increase rate of attack has been reported with other B-cell depletion therapy (e.g. during first month of therapy with rituximab). Based on PK/PD data, a period of approximately 2-4 weeks is required for maximal B cell depletion to occur.

During the OLP, a fixed dose of 300 mg inebilizumab administered on OLP Day 1 and then every 26 weeks was predicted to fully deplete peripheral blood B cells to undetectable levels and maintain B-cell suppression for the dose interval of the OLP.

During both the RCP and OLP, all subjects were premedicated with IV methylprednisolone (80-125 mg or equivalent glucocorticoid), oral diphenhydramine (25-50 mg or equivalent antihistamine), and oral paracetamol (acetaminophen; 500-650 mg) prior to IP administration to reduce the risk of infusion-related reactions.

Due to the potential severity of NMOSD attacks and their debilitating nature, rescue therapy was initiated as needed for NMOSD attacks at the discretion of the site Investigator. Treatment of an attack was preferably initiated after completion of the attack assessments and the determination as to whether the protocol attack criteria were met. However, the Investigator could initiate rescue therapy at any time before full assessment was completed. Rescue therapy was given as directed by the investigator and may have included IV corticosteroids, IVIG, and/or plasma exchange.

- **Objectives**

Primary Objective:

To compare the efficacy of inebilizumab versus placebo in reducing the risk of an NMOSD attack in subjects with NMOSD.

Secondary Objectives:

To compare the efficacy of inebilizumab versus placebo on the

1) reduction of EDSS worsening in subjects with NMOSD;

2) change from baseline of low-contrast visual acuity score in subjects with NMOSD;

3) reduction of the cumulative active MRI lesion count (new Gd-enhancing or new/enlarging T2);

4) reduction of NMOSD-related in-patient hospitalisations in subjects with NMOSD.

Additional secondary objectives were to:

- characterise the long-term efficacy of inebilizumab by means of annualised attack rate;
- evaluate the safety and tolerability of a single course of inebilizumab in subjects with NMOSD in the RCP and repeated doses of inebilizumab in the OLP; and
- characterise the PK profile and immunogenicity of inebilizumab in NMOSD subjects.

- **Outcomes/endpoints**

Primary efficacy endpoint:

The primary efficacy endpoint was time (days) from Day 1 to onset of an AC-determined NMOSD attack on or before Day 197.

For the primary analysis, only AC-determined attacks were used.

The NMOSD attack criteria were developed and used in this study. The definition of an NMOSD attack is the presence of a new symptom(s) or worsening of an existing symptom(s) related to NMOSD that meets at least one of the protocol-defined criteria for an attack (Table 14).

Subjects with new or worsening symptom(s) of a potential NMOSD attack were evaluated at an assessment visit at the clinical site by the investigator as soon as possible, but within 72 hours of the report. The data from these procedures was provided to the AC to conduct the adjudication. Only attacks that occurred in the RCP or OLP underwent an assessment visit; attacks that occurred during the screening period, safety follow-up period (SFP), or during an interval between the end of RCP and Day 1 of OLP did not undergo an assessment visit, but were instead recorded as adverse events (AEs).

Table 9: Protocol-defined criteria for an NMOSD attack

Example Symptoms of an NMOSD Attack [a]	Attack Type [b]	Protocol-defined Attack Criteria
Blurred vision Loss of vision Eye pain	ON	1. > 15-character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in a previously affected eye and no other ophthalmological explanation 2. ≥ 2-step drop [c] in CF to NLP from last visit as measured in a previously affected eye and no other ophthalmological explanation 3. ≥ 7 character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye 4. ≥ 7 character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye 5. ≥ 5 character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye 6. ≥ 5 character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye 7. ≥ 1-step drop [d] in CF to NLP from last visit as measured in a previously affected eye AND a new RAPD in affected eye 8. ≥ 1-step drop [d] in CF to NLP from last visit as measured in a previously affected eye AND loss of a previously documented RAPD in fellow eye 9. ≥ 7 character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve [f] 10. ≥ 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve [f] 11. ≥ 1-step drop [d] in CF to NLP from last visit as measured in a previously affected eye **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve [f]
Deep or radicular pain Extremity paraesthesia Weakness Sphincter dysfunction Lhermitte's sign (not in isolation)	Myelitis [e]	12. ≥ 2-point worsening in 1 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit 13. ≥ 1-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more 14. ≥ 1-point worsening in 2 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit when the last visit score was 1 or greater AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord 15. ≥ 0.5-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more **AND** a new GD-enhancing or new/enlarging T2 MRI lesion in the spinal cord

Example Symptoms of an NMOSD Attack [a]	Attack Type [b]	Protocol-defined Attack Criteria
Nausea Intractable vomiting Intractable hiccups Other neurological signs [g]	Brainstem	16. Isolated (not present at last visit) intractable nausea, vomiting, and/or hiccups lasting for greater than 48 hours AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem 17. ≥ 2-point worsening in 1 or more of the relevant (brainstem, cerebellar) FSS compared to last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem
Encephalopathy Hypothalamic dysfunction	Brain	18. ≥ 2-point worsening in 1 or more of the relevant (cerebral, sensory, pyramidal) FSS (with a score of 3 or more at the current visit) compared to last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brain consistent with the clinical presentation

CF = counting fingers; EDSS = Expanded Disability Severity Score; FSS = Functional System Scores; Gd = gadolinium; HM = hand motion; LP = light perception; MRI = magnetic resonance imaging; NLP = no light perception; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; RAPD = relative afferent pupillary defect.
a The symptoms listed are examples and are not inclusive of all NMOSD symptoms.
b Four major areas of the body may be affected by an attack: the optic nerve, resulting in ON; the spinal cord, resulting in myelitis; the brainstem, resulting in a number of outcomes; and the brain.
c At least 2-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to HM, LP, or NLP; CF to LP or NLP; HM to NLP.
d At least 1-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to CF, HM, LP, or NLP; CF to HM or LP or NLP; HM to LP or NLP; LP to NLP.
e Note: A 1-point change in a single FSS without a change in the EDSS, with or without a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord, is not considered a clinically significant change and will not count as an attack per this protocol.
f Lesions seen in the optic chiasm also count toward these criteria.
g Other neurological signs may include: double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, or other cranial nerve abnormality.

Key secondary endpoints:

1. Worsening from baseline in EDSS at last visit during the RCP. A subject will be considered to have a worsening in overall EDSS score if one of the following criteria is met:

   a. Worsening of 2 or more points in EDSS score for subjects with baseline score of 0.
   b. Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5.
   c. Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more.

2. Change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart, at last visit during the RCP.

3. Cumulative total active MRI lesions (new Gd-enhancing or new/enlarging T2) during the RCP.

4. Number of NMO/NMOSD-related in-patient hospitalisations. In-patient hospitalisation is defined as more than an overnight stay. Hospitalisations for the administration of NMO-related medications or procedures only were not counted when measuring this variable.

Other secondary endpoints:

ARR (total number of AC-determined NMO/NMOSD attacks normalised by person-years) during any exposure to inebilizumab.

Exploratory endpoints:

Assessment of NMOSD attack severity, NMOSD attack recovery, Modified Rankin Scale, Pain Numeric Rating Scale, SF-36 Health Survey, healthcare resource utilisation, additional ophthalmology assessments.

- **Sample size**

This study was planned to detect a target relative reduction of 60% (HR of 0.4) in risk for time from Day 1 to onset of an AC-determined NMOSD attack on or before Day 197 with at least 90% power and α = 0.05 (two-sided). A total of 67 AC-determined NMOSD attacks were required for the ITT population. If the seropositive cohort had 80% of the attacks, the study had approximately 82% power to detect the target relative reduction of 60%. A blinded review of the attack rate for the first 78 subjects to complete the RCP, and a simulation based on these subjects indicated a > 90% probability of achieving the required 67 AC-determined attacks with 252 subjects. The number of Japanese subjects was determined primarily by feasibility and did not depend on a minimum number of NMOSD attacks observed from Japanese subjects.

- **Randomisation and Blinding (masking)**

Following a screening period of up to 28 days, eligible patients were randomised and dosed in a 3:1 ratio (IV inebilizumab 300 mg on Day 1 and on Day 15, or matching placebo). Subjects were stratified by AQP4-IgG serostatus at screening, then further stratified by Japan versus Non-Japan region. The stratification ratio was anticipated to be approximately 80:20 with higher allocation to the seropositive cohort.

Subjects, Investigators, and Sponsor staff were blinded to treatment assignments. The procedures for administering blinded IP were followed throughout the RCP as well as on OLP Day 15 to ensure RCP treatment assignments remained blinded after subjects entered the OLP. At the time of the CSR (15 May 2019), subjects and Investigators remained blinded to subjects' RCP treatment assignments.

Study personnel responsible for evaluating the key efficacy endpoints (EDSS, ophthalmology data, and MRI) were not otherwise involved in the care of the subject. This was done to reduce the risk that knowledge of other study data (e.g AEs) might bias their evaluations. The EDSS and ophthalmology raters also conducted their assessments without access to prior evaluation results to further reduce the potential for bias.

An independent data monitoring committee (IDMC) for this study was charged per protocol with providing oversight of safety, conducting the futility analysis, and monitoring the process and function of the AC.

- **Statistical methods**

Analysis Populations

Intent-to-treat (ITT) population was defined as all subjects who were randomised into the study, received at least one dose of IP, and which included both AQP4-IgG seropositive and seronegative subjects. Efficacy results were analysed based on both the AQP4-IgG seropositive population and total ITT population.

Analysis of primary endpoint

The primary hypothesis for this study was that by depleting CD19+ B cells including plasmablasts and some plasma cells, inebilizumab would be effective in reducing the risk of NMOSD attack compared to placebo, thus effectively reducing the risk of irreversible disability caused by such attacks.

The planned data cut-off date for the primary analysis was when the last subject completed the discontinuation visit following the 67th AC-determined NMOSD attack, or after all subjects have completed the RCP if 67 AC-determined attacks did not occur, or when the last subject completed the discontinuation visit following discontinuation of enrolment upon recommendation of the IDMC based on evidence of efficacy and safety.

For the AQP4-IgG seropositive cohort, the treatment effect for the primary endpoint was assessed using the Cox proportional hazards model (CPHM) with treatment indicator (inebilizumab or placebo) as an explanatory factor; whereas for the ITT population, the model also included serostatus as an additional explanatory factor. The hazard ratio (HR) of inebilizumab versus placebo was estimated together with its associated 95% confidence intervals (CIs).

Only AC-determined attacks with an assessment visit scheduled within 120 hours (5 days) of reporting symptoms and all assessments completed within 10 days of an assessment Visit, were included in the primary analysis. Other AC-determined attacks that were not included in primary analysis were included in other supportive analyses. Missing baseline evaluations or data for primary analysis were not imputed and were considered missing.

Multiple sensitivity analyses (8 predefined) assess the robustness of the primary endpoint:

1. Analysis using the CPHM with following baseline characteristics and treatment as explanatory variables: number of prior NMOSD relapses, baseline EDSS score.

2. Analysis similar to primary analysis (attacks from all strata) based on unanimous adjudicated attacks (all 3 adjudicators agree) as events, remaining subjects will be considered as censored.

3. Analysis similar to primary analysis (attacks from all strata) including subjects who prematurely discontinue the RCP without experiencing an AC-determined attack as treatment failures (events); remaining subjects will be considered as censored.

4. Analysis similar to primary analysis (attacks from all strata) including safety SFP data for subjects who prematurely discontinue the RCP without experiencing an AC-determined attack. Attack data from the SFP up to 204 days after the subject's initial randomisation will be used in the analysis for subjects who prematurely discontinue the RCP. If the subject did not have an attack in the SFP before or on Day 204, then they will be censored at Day 204.

5. Analysis similar to primary analysis (attacks from all strata) based on only clinical criteria (ie excluding attacks that require MRI-dependent criteria); remaining subjects will be considered as censored.

6. The impact of the loss of attacks outside of the attack assessment windows in the primary analysis will be evaluated. The AC-determined attacks falling into different attack assessment windows will be analysed similarly to primary analysis.

- Attacks regardless of attack assessment window;
- Attacks with an Assessment Visit scheduled within 72 hours (3 days) of reporting symptoms and all assessments done within 5 days of an Assessment Visit;
- Attacks with an Assessment Visit scheduled within 72 hours (3 days) of reporting symptoms, regardless whether all assessments are done within 5 days of an Assessment Visit.

7. The impact of attacks with onset before the full PD effect of inebilizumab has been reached will be evaluated. Subjects with AC-determined attacks with onset on or before Day 15 will be censored at the time of the attack.

8. Analysis similar to primary analysis including AC-determined attacks up to and including 27Jan2017; remaining subjects will be censored on 27Jan2017 (the appropriate firewalled Sponsor contact, but not the study team, received a recommendation from IDMC to stop enrolment and conclude the RCP of the study on 27Jan2017.

Per the US FDA's request, sensitivity analysis on relapses as reported by subjects was conducted as well. The compliance with the study medication for both treatment arms and its impact on the primary and key secondary study outcomes were investigated. The applicant also evaluated the impact on key study results of study sites with Investigators who disclosed financial interests.

Analysis of secondary endpoints

The analyses for the key secondary endpoints for the AQP4-IgG seropositive subjects were as follows:

• EDSS worsening: Treatment effect for secondary efficacy endpoint based on EDSS worsening was assessed using a logistic regression model with treatment and baseline EDSS as explanatory variables. The percentage of subjects meeting the endpoint, odds ratios (OR), p value, and 95% CIs of the ORs are presented.

• Low-contrast visual acuity: The treatment effect for the low-contrast visual acuity measured by change from baseline in low-contrast Landolt C Broken Rings Chart binocular scores was assessed using an analysis of covariance model using treatment and baseline Landolt C Broken Rings Chart binocular score as explanatory variables.

• MRI lesions and in-patient hospitalisations: The treatment effect for the secondary efficacy endpoints based on the cumulative number of active MRI lesions and number of NMOSD-related in-patient hospitalisations was tested using Negative Binomial regression with treatment as an explanatory variable.

Similar analyses were performed for the ITT population by extending the above-mentioned models to include an indicator variable for serostatus.

Missing values of the secondary efficacy endpoints due to dropout or missing data were to be handled as follows:

1. For worsening from baseline in EDSS endpoint, missing values will be considered as 'worsening' according to non-responder imputation rule.

2. For low-contrast visual acuity endpoint, the last non-missing value will be considered for analysis.

Type I error control and multiplicity

The primary endpoint was to be tested first at $\alpha = 0.05$ for the AQP4-IgG seropositive cohort and, if significant, was to be tested in the overall ITT population at $\alpha = 0.05$. If the primary endpoint was statistically significant in the ITT population, the secondary endpoints were tested. The same sequential testing strategy was used within each of 4 individual key secondary endpoints. However, the secondary endpoints were not hierarchically ordered. Based on 2 populations of interest (seropositive and ITT populations) and one primary, four key secondary endpoints, 10 null hypotheses of no treatment effect were tested.

The multiplicity adjustment strategy based on Bonferroni-based chain procedure. Each secondary hypothesis was initially tested based on the Bonferroni method at $\alpha = 0.05/4 = 0.0125$. If the null hypothesis for a particular secondary endpoint was rejected across both the seropositive and the ITT populations, the Type I error saved was to be propagated equally to other non-rejected sets of secondary null hypotheses. The testing procedure was to be repeated until all null hypotheses were rejected or no further null hypothesis could be rejected.

Subgroup analyses

Sex (male vs female), baseline EDSS (< 5 vs ≥ 5), number of prior NMOSD relapses (< 2 vs ≥ 2), disease duration category (< 5 years vs ≥ 5 years), AQP4-IgG serostatus (positive vs negative) as determined at screening were the five subgroup analyses were performed for the ITT population on the efficacy endpoints. Per the US FDA's request, subgroup analyses by race, site region, and previous treatment for the prevention of NMO attacks on the primary endpoint were performed.

Interim analyses

An unblinded interim analysis was planned for a futility assessment by the IDMC when approximately 34 (50% of the total planned AC-determined) NMOSD attacks occurred the study. The futility analysis was performed per protocol by the IDMC with unblinded data on 14 November 2017, and the study was found not futile (Cree et al 2019, appendix).

A blinded review of the attack rate for the first 78 subjects to complete the RCP was used to modify sample size in protocol/SAP amendments.

Results

- **Participant flow**

Despite planned target population size of 67 AC-determined attacks with 252 subjects, on 07 Sep 2018, the applicant received a recommendation from the IDMC to stop enrollment and to close the RCP as efficacy was established and there was no justification to continue to expose patients to the placebo arm where risk for attack is higher with no background treatment. All subjects in the RCP at that time were given the option to enter the open-label treatment arm. At that point, 231 patients were enrolled with 230 treated, and 42 AC-determined NMOSD attacks had occurred in the RCP (one additional AC-determined NMOSD attack occurred before DCO for a total of 43 AC-determined NMOSD attacks in the RCP). The Sponsor remained blinded until after database lock.

A total of 231 subjects were randomised to treatment (213 AQP4-IgG seropositive and 18 seronegative). 230 subjects were included in ITT analyses.

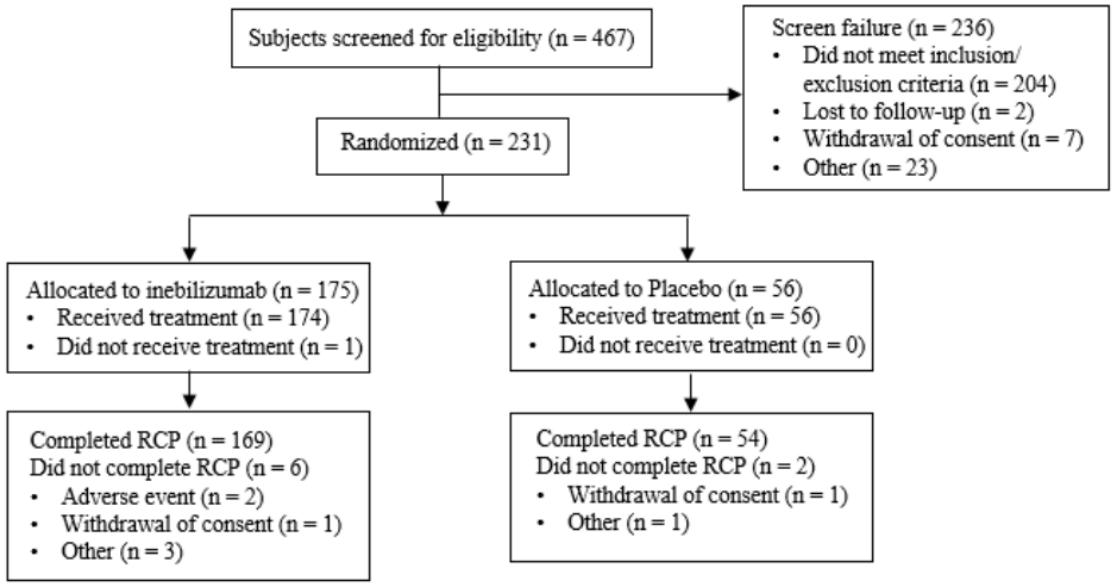
Overall, 223 subjects (97.0%) completed the RCP and 213 subjects (90.4% for placebo and 95.7% for inebilizumab) entered the OLP. The rates of withdrawal during RCP were 3.8% for placebo and 2.5% for inebilizumab, while these rates were 17% for placebo/inebilizumab and 20.8% for inebilizumab/inebilizumab during OLP.

The number of subjects randomised from each site was low: one site randomised 10 subjects, 10 sites each randomised between 6 and 9 subjects, and the remaining 71 sites each randomised < 6 subjects.

Other reasons for withdrawal during RCP included (n=3 from inebilizumab arm) disallowed concomitant treatment need, incorrect randomisation, NMO attack after randomisation but before dosing, and (n=1 in placebo arm) patient decision to continue with safety follow up instead of RCP procedures.

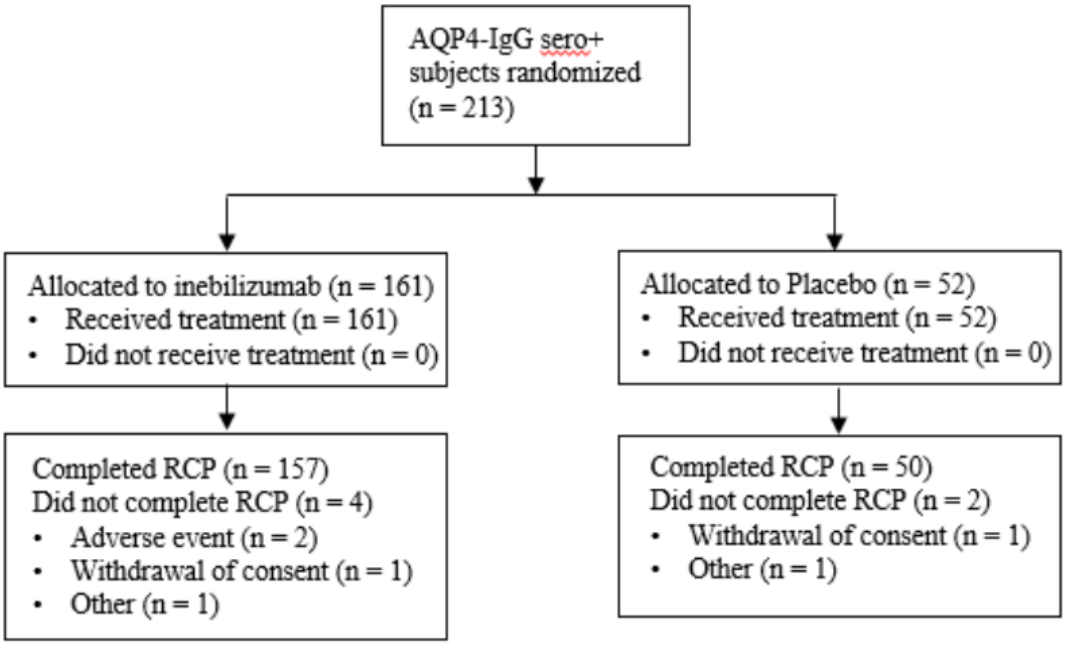
The reasons for withdrawal during OLP included 14 withdrawals of consent, 3 AEs, 3 deaths, 1 lost to follow up and 21 due to other reasons.

Figure 20: Subject disposition, randomised-controlled period (all subjects randomised)



RCP = randomised-controlled period.

Figure 21: Subject disposition, randomised-controlled period (AQP4-IgG seropositive subjects)



AQP4-IgG = autoantibodies against aquaporin-4; RCP = randomised-controlled period; sero+ = seropositive

- **Recruitment**

Duration: first patient enrolled on 06 Jan 2015; last RCP visit for the last subject occurred on 26 Oct 2018; database lock for RCP was 18 Dec 2018; the CSR was dated 15 May 2019.

Study centres: 82 sites in 24 countries

- **Conduct of the study**

Statistical Analysis Plan (SAP)

The original SAP was not submitted, there were 4 subsequent versions: 31 Oct 2016, 27 Feb 2017, 12 Sep 2018, and a final version dated 18 Oct 2018. The numerous amendments to the SAP are predominantly minor; however, the changes also touch upon handling of outcome variables and blinded sample size.

Protocol amendments

There were 6 protocol amendments in this study: 01 Jul 2014 (before first patient was enrolled), 10 Dec 2015, 18 Oct 2016, 08 Mar 2017, 16 Jul 2018, 11 Oct 2018.

Protocol amendment no. 2 included some changes in response to SA from the EMA. Protocol amendment no. 4 included the removal of the sample size reassessment (as agreed with the FDA) and the inclusion of clear guidance that stopping enrolment is event driven and based on the occurrence of 67 AC-determined NMOSD attacks or when 252 subjects have been enrolled, whichever occurs first. Finally, Protocol amendment no. 6 included changes to the protocol based on the recommendations from the IDMC, based on evidence of efficacy and safety, to stop study enrolment and allow subjects in the RCP at that time the option to enter the OLP.

- **Baseline data**

Subjects had a mean age (range) of 42.9 years (18-74 years), and the majority were female with proportionally more males among the AQP4-IgG seronegative subjects (47.1%, 8/17) than among the AQP4-IgG seropositive subjects (6.1%, 13/213); the majority of subjects were white (52.2%) (Table 10).

Table 10: Demographics (ITT population)

	AQP4-IgG sero+ N = 213			AQP4-IgG sero- N = 17			Total N = 230		
	Placebo N = 52	Inebilizumab N = 161	Overall N = 213	Placebo N = 4	Inebilizumab N = 13	Overall N = 17	Placebo N = 56	Inebilizumab N = 174	Overall N = 230
Age (years)									
n	52	161	213	4	13	17	56	174	230
Mean	42.4	43.2	43.0	44.8	40.8	41.7	42.6	43.0	42.9
SD	14.3	11.6	12.3	7.7	11.4	10.6	13.9	11.6	12.2
Median	43.0	43.0	43.0	42.0	44.0	43.0	42.5	43.0	43.0
(Min, Max)	(18, 74)	(18, 73)	(18, 74)	(39, 56)	(22, 55)	(22, 56)	(18, 74)	(18, 73)	(18, 74)
Age Category									
n	52	161	213	4	13	17	56	174	230
< 65	48 (92.3%)	155 (96.3%)	203 (95.3%)	4 (100%)	13 (100%)	17 (100%)	52 (92.9%)	168 (96.6%)	220 (95.7%)
≥ 65	4 (7.7%)	6 (3.7%)	10 (4.7%)	0	0	0	4 (7.1%)	6 (3.4%)	10 (4.3%)
Sex									
n	52	161	213	4	13	17	56	174	230
Male	3 (5.8%)	10 (6.2%)	13 (6.1%)	3 (75.0%)	5 (38.5%)	8 (47.1%)	6 (10.7%)	15 (8.6%)	21 (9.1%)
Female	49 (94.2%)	151 (93.8%)	200 (93.9%)	1 (25.0%)	8 (61.5%)	9 (52.9%)	50 (89.3%)	159 (91.4%)	209 (90.9%)
Race [a]									
n	52	161	213	4	13	17	56	174	230
American Indian or Alaskan Native [b]	5 (9.6%)	11 (6.8%)	16 (7.5%)	0	3 (23.1%)	3 (17.6%)	5 (8.9%)	14 (8.0%)	19 (8.3%)
Asian	8 (15.4%)	37 (23.0%)	45 (21.1%)	0	2 (15.4%)	2 (11.8%)	8 (14.3%)	39 (22.4%)	47 (20.4%)
Black or African American	5 (9.6%)	14 (8.7%)	19 (8.9%)	0	1 (7.7%)	1 (5.9%)	5 (8.9%)	15 (8.6%)	20 (8.7%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
White	24 (46.2%)	86 (53.4%)	110 (51.6%)	4 (100%)	6 (46.2%)	10 (58.8%)	28 (50.0%)	92 (52.9%)	120 (52.2%)
Other	10 (19.2%)	12 (7.5%)	22 (10.3%)	0	1 (7.7%)	1 (5.9%)	10 (17.9%)	13 (7.5%)	23 (10.0%)
Multiple Categories Checked	0	1 (0.6%)	1 (0.5%)	0	0	0	0	1 (0.6%)	1 (0.4%)
Ethnicity									
n	52	161	213	4	13	17	56	174	230
Hispanic or Latino	15 (28.8%)	25 (15.5%)	40 (18.8%)	0	3 (23.1%)	3 (17.6%)	15 (26.8%)	28 (16.1%)	43 (18.7%)
Not Hispanic or Latino	37 (71.2%)	136 (84.5%)	173 (81.2%)	4 (100%)	10 (76.9%)	14 (82.4%)	41 (73.2%)	146 (83.9%)	187 (81.3%)
Body Mass Index(kg/m^2)									
n	52	159	211	4	13	17	56	172	228
Mean	27.300	25.286	25.783	23.415	24.422	24.185	27.022	25.221	25.663
SD	6.904	5.642	6.023	1.170	3.554	3.150	6.730	5.509	5.868
Median	25.100	24.610	24.650	23.135	25.990	23.380	24.750	24.615	24.635
(Min, Max)	(18.36, 44.48)	(15.60, 52.83)	(15.60, 52.83)	(22.34, 25.05)	(18.52, 29.39)	(18.52, 29.39)	(18.36, 44.48)	(15.60, 52.83)	(15.60, 52.83)
Region US vs. Non-US									
n	52	161	213	4	13	17	56	174	230
US	11 (21.2%)	27 (16.8%)	38 (17.8%)	1 (25.0%)	2 (15.4%)	3 (17.6%)	12 (21.4%)	29 (16.7%)	41 (17.8%)
Non-US	41 (78.8%)	134 (83.2%)	175 (82.2%)	3 (75.0%)	11 (84.6%)	14 (82.4%)	44 (78.6%)	145 (83.3%)	189 (82.2%)

Mean baseline EDSS was 3.9 for the ITT population, with variability noted for AQP4-IgG seronegative subjects likely due to small numbers of subjects (n = 17 total) (Table 11).

Most subjects (82.6%) in the ITT population were diagnosed with NMOSD within 5 years prior to study Day 1; the mean disease duration was 2.49 years prior to Day 1. Most subjects (83.0%) had experienced ≥ 2 relapses prior to enrolment (

Table 12).

The Eligibility Committee rejected about two thirds of the AQP4-IgG seronegative subjects who were referred for review and enrolment confirmation. This high rate of rejection underscores the uncertainty of diagnosis of NMOSD in AQP4-IgG seronegative subjects and led to the enrolment of fewer of these subjects into the study. The study design did not enforce the enrolment of 20% AQP4-IgG seronegative subjects, but rather allowed for open enrolment with the assumption that the ratio between AQP4-IgG seronegative and seropositive subjects would represent the reported ratio (20/80%).

Table 11: Summary of baseline characteristics (ITT population)

	AQP4-IgG sero+ N = 213			AQP4-IgG sero- N = 17			Total N = 230		
	Placebo N = 52	Inebilizumab N = 161	Overall N = 213	Placebo N = 4	Inebilizumab N = 13	Overall N = 17	Placebo N = 56	Inebilizumab N = 174	Overall N = 230
EDSS									
n	52	161	213	4	13	17	56	174	230
Mean	4.35	3.81	3.94	2.13	3.85	3.44	4.19	3.81	3.90
SD	1.63	1.77	1.75	0.85	2.30	2.16	1.68	1.81	1.78
Median	4.00	3.50	3.50	2.25	4.00	3.50	4.00	3.50	3.50
(Min, Max)	(1.0, 8.0)	(0.0, 8.0)	(0.0, 8.0)	(1.0, 3.0)	(0.0, 7.5)	(0.0, 7.5)	(1.0, 8.0)	(0.0, 8.0)	(0.0, 8.0)
EDSS category									
n	52	161	213	4	13	17	56	174	230
0	0	2 (1.2%)	2 (0.9%)	0	2 (15.4%)	2 (11.8%)	0	4 (2.3%)	4 (1.7%)
1-5	36 (69.2%)	122 (75.8%)	158 (74.2%)	4 (100%)	7 (53.8%)	11 (64.7%)	40 (71.4%)	129 (74.1%)	169 (73.5%)
> 5	16 (30.8%)	37 (23.0%)	53 (24.9%)	0	4 (30.8%)	4 (23.5%)	16 (28.6%)	41 (23.6%)	57 (24.8%)
Low-contrast visual acuity score [a]									
Binocular									
n	52	161	213	4	13	17	56	174	230
Mean	19.3	23.1	22.2	22.5	28.5	27.1	19.6	23.5	22.5
SD	15.7	16.4	16.3	15.8	20.2	19.0	15.6	16.7	16.5
Median	20.0	25.0	25.0	27.0	39.0	34.0	21.0	26.5	25.0
(Min, Max)	(0, 55)	(0, 57)	(0, 57)	(0, 36)	(0, 55)	(0, 55)	(0, 55)	(0, 57)	(0, 57)
High-contrast visual acuity score [a]									
Binocular									
n	52	161	213	4	13	17	56	174	230
Mean	40.6	47.8	46.0	48.0	51.1	50.4	41.2	48.0	46.3
SD	23.3	16.9	18.9	16.4	15.3	15.1	22.8	16.8	18.6
Median	49.5	54.0	53.0	52.5	55.0	55.0	49.5	54.0	53.5
(Min, Max)	(0, 70)	(0, 70)	(0, 70)	(26, 61)	(7, 70)	(7, 70)	(0, 70)	(0, 70)	(0, 70)
Total number of Gd-enhancing lesions									
Overall									
n	52	161	213	4	13	17	56	174	230
Mean	0.8	1.2	1.1	1.0	0.5	0.6	0.9	1.2	1.1
SD	0.9	1.2	1.1	1.4	0.8	0.9	0.9	1.2	1.1
Median	1.0	1.0	1.0	0.5	0.0	0.0	1.0	1.0	1.0
(Min, Max)	(0, 4)	(0, 5)	(0, 5)	(0, 3)	(0, 2)	(0, 3)	(0, 4)	(0, 5)	(0, 5)

Table 12: Disease history (ITT population)

	AQP4-IgG sero+ N = 213			AQP4-IgG sero- N = 17			Total N = 230		
	Placebo N = 52	MEDI551 N = 161	Overall N = 213	Placebo N = 4	MEDI551 N = 13	Overall N = 17	Placebo N = 56	MEDI551 N = 174	Overall N = 230
Type of original diagnosis									
NMO	42 (80.8%)	139 (86.3%)	181 (85.0%)	3 (75.0%)	10 (76.9%)	13 (76.5%)	45 (80.4%)	149 (85.6%)	194 (84.3%)
NMOSD	10 (19.2%)	22 (13.7%)	32 (15.0%)	1 (25.0%)	3 (23.1%)	4 (23.5%)	11 (19.6%)	25 (14.4%)	36 (15.7%)
Age at diagnosis									
n	52	161	213	4	13	17	56	174	230
Mean	40.0	41.2	40.9	44.5	40.0	41.1	40.3	41.1	40.9
SD	14.9	12.1	12.8	7.2	11.0	10.2	14.5	12.0	12.6
Median	40.5	42.0	41.0	42.0	43.0	43.0	41.0	42.0	41.5
(Min, Max)	(15, 74)	(17, 70)	(15, 74)	(39, 55)	(22, 55)	(22, 55)	(15, 74)	(17, 70)	(15, 74)
Prior AQP4-IgG testing									
Yes	51 (98.1%)	152 (94.4%)	203 (95.3%)	4 (100%)	10 (76.9%)	14 (82.4%)	55 (98.2%)	162 (93.1%)	217 (94.3%)
Seropositive	50 (98.0%)	146 (96.1%)	196 (96.6%)	0	2 (20.0%)	2 (14.3%)	50 (90.9%)	148 (91.4%)	198 (91.2%)
Seronegative	1 (2.0%)	6 (3.9%)	7 (3.4%)	4 (100%)	8 (80.0%)	12 (85.7%)	5 (9.1%)	14 (8.6%)	19 (8.8%)
No	1 (1.9%)	9 (5.6%)	10 (4.7%)	0	3 (23.1%)	3 (17.6%)	1 (1.8%)	12 (6.9%)	13 (5.7%)
Age at 1st relapse									
n	52	161	213	4	13	17	56	174	230
Mean	37.8	38.6	38.4	44.5	37.1	38.8	38.3	38.5	38.4
SD	15.6	12.1	13.0	7.2	10.5	10.2	15.2	12.0	12.8
Median	36.5	37.0	37.0	42.0	38.0	41.0	38.5	37.0	37.0
(Min, Max)	(5, 73)	(16, 70)	(5, 73)	(39, 55)	(22, 52)	(22, 55)	(5, 73)	(16, 70)	(5, 73)
Disease duration (years)[a]									
n	52	161	213	4	13	17	56	174	230
Mean	2.92	2.49	2.59	0.78	1.37	1.23	2.77	2.41	2.49
SD	3.54	3.39	3.42	0.66	1.59	1.43	3.45	3.30	3.33
Median	1.67	1.10	1.13	0.57	0.91	0.87	1.38	1.06	1.10
(Min, Max)	(0.2, 16.9)	(0.1, 22.2)	(0.1, 22.2)	(0.3, 1.7)	(0.2, 5.5)	(0.2, 5.5)	(0.2, 16.9)	(0.1, 22.2)	(0.1, 22.2)
Disease duration category									
<5 years	42 (80.8%)	132 (82.0%)	174 (81.7%)	4 (100%)	12 (92.3%)	16 (94.1%)	46 (82.1%)	144 (82.8%)	190 (82.6%)
>=5 years	10 (19.2%)	29 (18.0%)	39 (18.3%)	0	1 (7.7%)	1 (5.9%)	10 (17.9%)	30 (17.2%)	40 (17.4%)
Type of 1st relapse									
Optic neuritis (ON)	25 (48.1%)	82 (50.9%)	107 (50.2%)	2 (50.0%)	6 (46.2%)	8 (47.1%)	27 (48.2%)	88 (50.6%)	115 (50.0%)
Myelitis	26 (50.0%)	85 (52.8%)	111 (52.1%)	2 (50.0%)	8 (61.5%)	10 (58.8%)	28 (50.0%)	93 (53.4%)	121 (52.6%)
Brain/Brainstem	11 (21.2%)	15 (9.3%)	26 (12.2%)	2 (50.0%)	2 (15.4%)	4 (23.5%)	13 (23.2%)	17 (9.8%)	30 (13.0%)
Type of most recent relapse									
Optic neuritis (ON)	19 (36.5%)	77 (47.8%)	96 (45.1%)	2 (50.0%)	8 (61.5%)	10 (58.8%)	21 (37.5%)	85 (48.9%)	106 (46.1%)
Myelitis	32 (61.5%)	94 (58.4%)	126 (59.2%)	2 (50.0%)	5 (38.5%)	7 (41.2%)	34 (60.7%)	99 (56.9%)	133 (57.8%)
Brain/Brainstem	8 (15.4%)	6 (3.7%)	14 (6.6%)	2 (50.0%)	2 (15.4%)	4 (23.5%)	10 (17.9%)	8 (4.6%)	18 (7.8%)
Number of relapses category									
1	13 (25.0%)	24 (14.9%)	37 (17.4%)	1 (25.0%)	1 (7.7%)	2 (11.8%)	14 (25.0%)	25 (14.4%)	39 (17.0%)
2	9 (17.3%)	36 (22.4%)	45 (21.1%)	2 (50.0%)	3 (23.1%)	5 (29.4%)	11 (19.6%)	39 (22.4%)	50 (21.7%)
3	5 (9.6%)	27 (16.8%)	32 (15.0%)	1 (25.0%)	2 (15.4%)	3 (17.6%)	6 (10.7%)	29 (16.7%)	35 (15.2%)
4	8 (15.4%)	19 (11.8%)	27 (12.7%)	0	2 (15.4%)	2 (11.8%)	8 (14.3%)	21 (12.1%)	29 (12.6%)
5	4 (7.7%)	14 (8.7%)	18 (8.5%)	0	2 (15.4%)	2 (11.8%)	4 (7.1%)	16 (9.2%)	20 (8.7%)
6	2 (3.8%)	13 (8.1%)	15 (7.0%)	0	2 (15.4%)	2 (11.8%)	2 (3.6%)	15 (8.6%)	17 (7.4%)
7	4 (7.7%)	8 (5.0%)	12 (5.6%)	0	0	0	4 (7.1%)	8 (4.6%)	12 (5.2%)
8	1 (1.9%)	7 (4.3%)	8 (3.8%)	0	0	0	1 (1.8%)	7 (4.0%)	8 (3.5%)
9	1 (1.9%)	1 (0.6%)	2 (0.9%)	0	0	0	1 (1.8%)	1 (0.6%)	2 (0.9%)
10	2 (3.8%)	3 (1.9%)	5 (2.3%)	0	0	0	2 (3.6%)	3 (1.7%)	5 (2.2%)
>10	3 (5.8%)	9 (5.6%)	12 (5.6%)	0	1 (7.7%)	1 (5.9%)	3 (5.4%)	10 (5.7%)	13 (5.7%)
<2	13 (25.0%)	24 (14.9%)	37 (17.4%)	1 (25.0%)	1 (7.7%)	2 (11.8%)	14 (25.0%)	25 (14.4%)	39 (17.0%)
>=2	39 (75.0%)	137 (85.1%)	176 (82.6%)	3 (75.0%)	12 (92.3%)	15 (88.2%)	42 (75.0%)	149 (85.6%)	191 (83.0%)

Myelitis									
n	41	131	172	3	12	15	44	143	187
Mean	5.47	4.71	4.89	0.57	3.60	2.99	5.14	4.62	4.74
SD	5.74	5.68	5.68	0.28	4.17	3.90	5.68	5.56	5.58
Median	3.57	2.55	2.71	0.55	2.26	1.14	3.10	2.55	2.61
(Min, Max)	(0.2, 26.1)	(0.1, 27.4)	(0.1, 27.4)	(0.3, 0.9)	(0.3, 14.6)	(0.3, 14.6)	(0.2, 26.1)	(0.1, 27.4)	(0.1, 27.4)
Brain/Brainstem									
n	17	31	48	2	3	5	19	34	53
Mean	5.99	4.53	5.05	1.23	3.18	2.40	5.49	4.41	4.80
SD	6.79	4.58	5.44	0.52	4.26	3.21	6.58	4.51	5.30
Median	3.16	2.70	2.88	1.23	1.04	1.04	2.93	2.47	2.70
(Min, Max)	(0.2, 23.2)	(0.4, 17.3)	(0.2, 23.2)	(0.9, 1.6)	(0.4, 8.1)	(0.4, 8.1)	(0.2, 23.2)	(0.4, 17.3)	(0.2, 23.2)
ARR[c] prior to 1st IP administration	0.86	0.84	0.84	2.29	1.07	1.15	0.88	0.85	0.86
ARR prior to 1st IP administration per subject									
n	52	161	213	4	13	17	56	174	230
Mean	1.456	1.682	1.627	3.006	2.263	2.438	1.567	1.726	1.687
SD	1.360	1.490	1.459	2.144	1.896	1.914	1.459	1.525	1.508
Median	1.198	1.172	1.172	2.722	1.585	1.585	1.238	1.195	1.220
(Min, Max)	(0.24, 8.91)	(0.11, 9.61)	(0.11, 9.61)	(1.16, 5.42)	(0.32, 6.41)	(0.32, 6.41)	(0.24, 8.91)	(0.11, 9.61)	(0.11, 9.61)

- **Numbers analysed**

Efficacy results were analysed based on both the AQP4-IgG seropositive population and total ITT population. 230 subjects total were included in ITT analyses, 213 AQP4-IgG seropositive (161 on inebilizumab).

One randomised subject, AQP4-IgG seronegative, was excluded from both the efficacy analyses (ITT population) and the safety analyses (As-treated population). The subject was randomised to receive inebilizumab and had an NMOSD attack prior to dosing, resulting in discontinuation from the RCP.

- **Outcomes and estimation**

Primary endpoint:

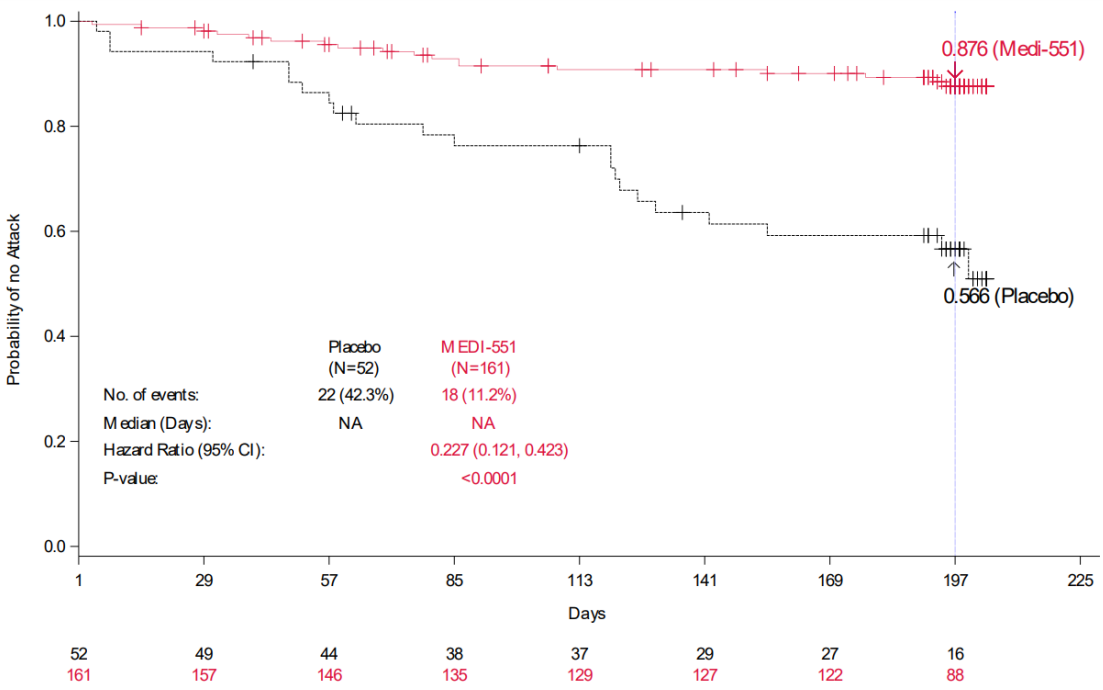
The data presented are based on the primary analysis conducted on the basis of the DB RCP in pivotal study.

Table 13: Primary analysis of time to adjudication committee-determined NMOSD attack, randomised-controlled period (ITT population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Number of subjects with an attack	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
Number of censored subjects	30 (57.7%)	143 (88.8%)	4 (100%)	10 (76.9%)	34 (60.7%)	153 (87.9%)
Hazard ratio[a]		0.227		NA		0.272
95% CI [a]		(0.1214 , 0.4232)		(NA , NA)		(0.1496 , 0.4961)
p-value [a]		<0.0001		0.9977		<0.0001

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; NA = not applicable; ITT = Intent-to-treat; sero- = seronegative; sero+ = seropositive.
a Based on Cox regression method, with placebo as the reference group

Figure 22: Kaplan-Meier plot for time to adjudication committee-determined NMOSD Attack, randomised controlled period (ITT population, AQP4-IgG seropositive subjects)



AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; MEDI-551 = inebilizumab; NA = not applicable.

Sensitivity analyses are presented in Table 19. Sensitivity analyses were consistent with the primary analysis in the sense that the HR estimates were all below 1.00 and all sensitivity analyses reached significance (<0.05).

Table 14: Summary of results for the sensitivity analyses, randomised-controlled period (ITT population) (Study 1155).

Sensitivity analysis variable(s)	AQP4-IgG sero+ N = 213			Total N = 230		
	Hazard ratio [a]	95% CI [a]	p-value [a]	Hazard ratio[a]	95% CI [a]	p-value [a]
Adjusted by Number of Historical NMOSD Acute Relapses and Baseline EDSS Score	0.228	(0.1207, 0.4297)	<0.0001	0.266	(0.1452, 0.4885)	<0.0001
Time to AC-determined Attack – Unanimous Decision Only	0.248	(0.1261, 0.4861)	<0.0001	0.248	(0.1261, 0.4861)	<0.0001
Including Subjects Who Prematurely Discontinued the RCP Without Experiencing an NMOSD Attack	0.275	(0.1522, 0.4976)	<0.0001	0.338	(0.1911, 0.5967)	0.0002
Based on Clinical Criteria only	0.231	(0.1188, 0.4504)	<0.0001	0.267	(0.1397, 0.5090)	<0.0001
Time to AC-determined attack or rescue therapy	0.285	(0.1626, 0.5000)	<0.0001	0.327	(0.1911, 0.5583)	<0.0001
Time to Investigator - determined NMOSD Attack	0.262	(0.1456, 0.4700)	<0.0001	0.323	(0.1842, 0.5679)	<0.0001
Including Attacks from the SFU up to Day 204 for Subjects Who Prematurely Discontinued the RCP	0.227	(0.1214, 0.4232)	<0.0001	0.272	(0.1496, 0.4961)	<0.0001
Subjects with AC-determined attacks before or on Day 15 are censored at the time of the attack	0.229	(0.1175, 0.4455)	<0.0001	0.282	(0.1493, 0.5343)	0.0001
Time to Subject-reported NMOSD Attacks	0.354	(0.2069, 0.6066)	0.0002	0.393	(0.2345, 0.6599)	0.0004

AQP4-IgG = autoantibodies against aquaporin-4; AC = Adjudication Committee; CI = confidence interval; EDSS = Expanded Disability Status Scale; N = number of subjects; NMOSD = neuromyelitis optica spectrum disorders; RCP = randomised-controlled period; sero+ = seropositive; SFP = safety follow-up period.
a Based on Cox regression method, with placebo as the reference group.

Table 15 summarises the degree of agreement between the AC and Investigator decisions whether potential NMOSD attacks in the RCP met protocol-defined attack criteria. The kappa statistic for agreement between Investigator and AC decisions was 0.6859, indicating moderate agreement. There were 64 possible relapse events adjudicated by the AC, 36 in the group treated with inebilizumab (20.7%) and 28 in the placebo group (50%). The investigator-determined clinical events were 34 in the group treated with inebilizumab and 25 in the placebo group. AC confirmed 21 attacks in the group treated with inebilizumab and 21 in the placebo group.

Table 15: Relationship between investigator and AC attack determinations

		Adjudication Committee		Total
		Attack	Non-attack	
Investigator	Attack	43	8	51
	Non-attack	0	13	13
	Total	43	21	64

Key secondary endpoints:

1. Worsening in EDSS score from baseline to last visit of the RCP occurred in a lower proportion of subjects in the inebilizumab group than the placebo group among AQP4-IgG seropositive subjects (Table 16 and Table 17).

Table 16: Worsening from baseline in EDSS using a logistic regression model, randomised-controlled period (ITT population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Worsening [a] from baseline in EDSS at last visit [b]	18/52 (34.6%)	25/161 (15.5%)	1/4 (25.0%)	2/13 (15.4%)	19/56 (33.9%)	27/174 (15.5%)
Odds ratio [c]		0.371		0.911		0.370
95% CI of Odds ratio [c]		(0.1807, 0.7633)		(0.0528, 15.7083)		(0.1850, 0.7389)
p-value [c]		0.0070		0.9487		0.0049

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; EDSS = Expanded Disability Status Scale; ITT = intent-to-treat sero+ = seropositive; sero- = seronegative.
a A subject was considered to have a worsening in EDSS score if one of the following criteria was met: (1) Worsening of 2 or more points in EDSS score for subjects with baseline score of 0; (2) Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5; (3) Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more.
b Subjects with missing data are imputed as 'worsening'. Denominator represents the total number of subjects in each group with baseline.
c Odds ratio, its 95% CI, and p-value are estimated by logistic regression model, using non-responder imputation, i.e., missing values will be considered as 'worsening'.

Table 17: Worsening from baseline in EDSS by visit for randomised-controlled period (ITT population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	MEDI551 N = 161	Placebo N = 4	MEDI551 N = 13	Placebo N = 56	MEDI551 N = 174
Week 12[a]	15/52 (28.8%)	29/159 (18.2%)	2/4 (50.0%)	2/13 (15.4%)	17/56 (30.4%)	31/172 (18.0%)
Week 28[a]	4/29 (13.8%)	11/124 (8.9%)	1/4 (25.0%)	0/8 (0%)	5/33 (15.2%)	11/132 (8.3%)
Last visit [b]	18/52 (34.6%)	25/161 (15.5%)	1/4 (25.0%)	2/13 (15.4%)	19/56 (33.9%)	27/174 (15.5%)

2. Low-contrast visual acuity binocular score (measured by low-contrast Landolt C Broken Rings Chart) change from baseline to the last visit of the RCP was similar in the inebilizumab and placebo groups (Table 18).

Table 18: Analysis of change from baseline in low contrast visual acuity binocular score at last visit using analyses of covariance model (randomised-controlled period)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	MEDI551 N = 161	Placebo N = 4	MEDI551 N = 13	Placebo N = 56	MEDI551 N = 174
n	52	158	4	13	56	171
Observed mean (SE)	0.846 (1.405)	0.481 (0.486)	1.000 (1.958)	2.462 (1.914)	0.857 (1.310)	0.632 (0.472)
LSMEAN (SE)[a]	0.600 (0.999)	0.562 (0.572)	0.262 (2.929)	2.689 (1.616)	1.442 (1.217)	1.576 (0.935)
LSMEAN difference (SE)[a]		-0.038 (1.153)		2.427 (3.3570)		0.134 (1.096)
95% CI[a]		(-2.3122, 2.2357)		(-4.7721, 9.6263)		(-2.0254, 2.2941)
p-value[a]		0.9736		0.4815		0.9026

LSMEAN, LSMEAN difference its 95% CI and p-value are estimated by using an analysis of Covariance model, using last non-missing low-contrast visual acuity.

3. Cumulative total active MRI lesions (new Gd-enhancing or new/enlarging T2) during the RCP (Table 19). In the RCP, 45.3% of inebilizumab subjects had new Gd-enhancing MRI lesions (placebo 59.6%), and 21.7% of inebilizumab subjects had new/enlarging T2 MRI lesions (placebo 40.4%) among AQP4-IgG seropositive subjects. New Gd-enhancing lesions were most common in the optic nerve, followed by spinal cord and brain; no new Gd-enhancing lesions were seen in the brainstem. New/enlarging T2 lesions were most common in the spinal cord, followed by optic nerve, brain, and brainstem.

Table 19: Analysis of cumulative number of active mri lesions using negative binomial regression model, randomised-controlled period (ITT Population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Cumulative number of active MRI lesions						
n	31	74	1	5	32	79
Mean	2.3	1.7	4.0	1.4	2.3	1.6
SD	1.3	1.0	NA	0.9	1.3	1.0
Median	2.0	1.0	4.0	1.0	2.0	1.0
(Min, Max)	(1, 5)	(1, 6)	(4, 4)	(1, 3)	(1, 5)	(1, 6)
Rate ratio[a]		0.568		0.538		0.566
95% CI		(0.3851, 0.8363)		(0.0818, 3.5462)		(0.3866, 0.8279)
p-value		0.0042		0.5198		0.0034

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; MRI = magnetic resonance imaging; SD = standard deviation; sero- = seronegative; sero+ = seropositive.
a Rate ratio reduction in cumulative number of active MRI lesions. Rate ratio analysis is based on the entire population, not just those who had an event. Treatment effect and its 95% CI , and p-value are estimated from the negative binomial regression

Upon query, the annualised rates of MRI lesions (cumulative number of active MRI lesions, new Gd-enhancing T1 lesions, new/enlarging T2 MRI lesions) in the RCP and OLP are presented in Table 20.

Table 20: Annualised rate of MRI lesions (Study 1155)

	Active MRI lesion	New Gd-enhancing T1 lesion	New/enlarging T2 lesion
RCP			
Placebo (n = 56)	3.64	3.46	2.11
Inebilizumab (n = 174)	1.63	1.55	0.94
OLP			
Placebo/Inebilizumab (n = 51)	1.13	0.92	0.50
Inebilizumab/inebilizumab (n = 165)	0.83	0.62	0.59
Subjects with ≥ 1 dose of inebilizumab (n = 225)	1.00	0.79	0.63

MRI = magnetic resonance imaging; OLP = open-label period; RCP = randomised-controlled period.

Treatment with inebilizumab reduced the number of NMO/NMOSD-related in-patient hospitalisations compared to treatment with placebo. In-patient hospitalisation is defined as more than an overnight stay (Table 21).

Table 21: Analysis of number of NMOSD-related in-patient hospitalisations using negative binomial regression model, randomised-controlled period (ITT Population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Cumulative number of NMOSD-related in-patient hospitalizations						
n	7	8	1	2	8	10
Mean	1.4	1.0	1.0	1.0	1.4	1.0
SD	0.8	0	NA	0	0.7	0
Median	1.0	1.0	1.0	1.0	1.0	1.0
(Min, Max)	(1, 3)	(1, 1)	(1, 1)	(1, 1)	(1, 3)	(1, 1)
Rate ratio [a]		0.258		0.615		0.286
95% CI		(0.0904, 0.7384)		(0.0558, 6.7866)		(0.1105, 0.7411)
p-value		0.0115		0.6918		0.0100

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorders; SD = standard deviation; sero- = seronegative; sero+ = seropositive.
a Rate ratio reduction in number of NMOSD-related in-patient hospitalisations. Rate ratio analysis is based on the entire population, not just those who had an event. Treatment effect and its 95% CI , and p-value are estimated from the negative binomial regression.

- **Ancillary analyses**

Multiplicity adjustment:

A multiplicity adjustment was performed for the analyses of the primary and key secondary efficacy endpoints. The adjusted p-values remained < 0.05 for all endpoints except for change from baseline in low-contrast visual acuity binocular score at last visit.

Persistence of efficacy:

ARR (total number of AC-determined NMO/NMOSD attacks normalised by person-years) during any exposure to inebilizumab, as of the primary date of cut-off of 26 Oct2 018, was calculated for evaluating persistence of efficacy (Table 22).

Table 22: Annualised adjudication committee-determined NMOSD attack rate (any inebilizumab population)

	AQP4-IgG sero+ N = 208	AQP4-IgG sero- N = 17	Total N = 225
Number of AC-determined attack	42	3	45
Total person-year [a]	323.595	34.152	357.747
Annualized attack rate [b]	0.13	0.088	0.126

AC = Adjudication Committee; AQP4-IgG = autoantibodies against aquaporin-4; SFP = safety follow-up period; sero- = seronegative; sero+ = seropositive.
a Total person-years will be calculated as the sum of the person-years for individual subject. Person-year for individual subject is defined as (Date of last day before SFP - 1st inebilizumab dose date +1)/365.25.
b Annualised attack rate is defined as total number of AC-determined attacks divided by total person-years.

At the time of the Day 120 safety update (date of cut-off 06 Jun 2019), an updated analysis of annualised AC-determined NMOSD attack rate was performed (Table 23).

Table 23: Annualised adjudication committee-determined NMOSD attack rate at 120-day safety updated (any inebilizumab population)

	AQP4-IgG sero+ N = 208	AQP4-IgG sero- N = 17	Total N = 225
Number of AC-determined attack	51	3	54
Total person-year [a]	432.96	43.31	476.27
Annualized attack rate (95% CI) [b]	0.118 (0.088, 0.155)	0.069 (0.014, 0.202)	0.113 (0.085, 0.148)

AC = Adjudication Committee; AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; N = number of subjects; NMOSD = neuromyelitis optica spectrum disorders; sero- = seronegative; sero+ = seropositive; SFP = safety follow-up period
a Total person-years were calculated as the sum of the person-years for individual subject. Person-year for individual subject is defined as (Date of last day before SFP - 1st inebilizumab dose date +1)/365.25.
b Annualised attack rate is defined as total number of AC-determined attacks divided by total person-years. 95% CI is calculated using exact Poisson confidence interval.

NMOSD Attacks by Domain

Table 24 summarises the AC-determined NMOSD attacks by domain. All of the 43 AC-determined NMOSD attacks involved myelitis and/or ON. Less than 5% of attacks involved the brainstem, and both of these also included either ON or myelitis. No AC-determined attacks affected the brain.

Table 24: Summary of AC-determined NMOSD attacks by domain during the RCP (ITT population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Overall AC-determined attacks	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
By domain [a]						
Brainstem	2	0	0	0	2	0
Myelitis	14	11	0	2	14	13
ON	10	8	0	2	10	10
Attacks in 2 domains						
Brainstem and myelitis	1	0	0	0	1	0
Brainstem and ON	1	0	0	0	1	0
Myelitis and ON	2	1	0	1	2	2

AQP4-IgG = autoantibodies against aquaporin-4; ITT = intent-to-treat; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; RCP = randomised-controlled period; sero+ = seropositive; sero- = seronegative.
a Subjects with an attack in > 1 domain may be counted in multiple domain categories. Categorisation by domain was determined by concordance of AC members Source: Data on file.

Severity of attacks:

Severity was assessed using an exploratory scale (opticospinal impairment scale) based on the degree of neurological worsening since the prior assessment (Table 25). Similar results were obtained using a second exploratory scale based on severity by attack criteria.

Table 25: AC-determined NMOSD attacks based on severity according to the OSI, RCP (ITT population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
AC-determined attacks	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
Overall attack severity grade						
Major	10 (45.5%)	6 (33.3%)	0	0	10 (45.5%)	6 (28.6%)
Minor	12 (54.5%)	12 (66.7%)	0	3 (100%)	12 (54.5%)	15 (71.4%)

AQP4-IgG = autoantibodies against aquaporin-4; ITT = intent-to-treat; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; OSI = opticospinal impairment scale; RCP = randomised-controlled period; sero+ = seropositive; sero- = seronegative.

Analysis of Attack Recovery:

Thirteen subjects with RCP attacks in the inebilizumab group and 17 in the placebo group had attack follow-up data within 35 days (Table 26).

Table 26: AC-determined NMOSD attacks by recovery grades, RCP (ITT population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
AC-determined attack	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
Attack recovery grade						
Major	2 (9.1%)	2 (11.1%)	0	0	2 (9.1%) [a]	2 (9.5%) [b]
Minor	6 (27.3%)	5 (27.8%)	0	0	6 (27.3%) [a]	5 (23.8%) [b]
No recovery	9 (40.9%)	4 (22.2%)	0	2 (66.7%)	9 (40.9%) [a]	6 (28.6%) [b]

AC = Adjudication Committee; AQP4-IgG = autoantibodies against aquaporin-4; ITT = intent-to-treat; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; RCP = randomised-controlled period; sero+ = seropositive; sero- = seronegative.
a In the placebo group, the number of subjects for whom recovery data was collected was 17. Using this as a denominator to calculate percentages yields the following: Major, 11.8%; Minor, 35.5%; No recovery, 52.9%.
b In the inebilizumab group, the number of subjects for whom recovery data was collected was 13. Using this as a denominator to calculate percentages yields the following: Major, 15.4%; Minor, 38.5%; No recovery, 46.2%.

Exploratory Analyses of Modified Rankin Scale:

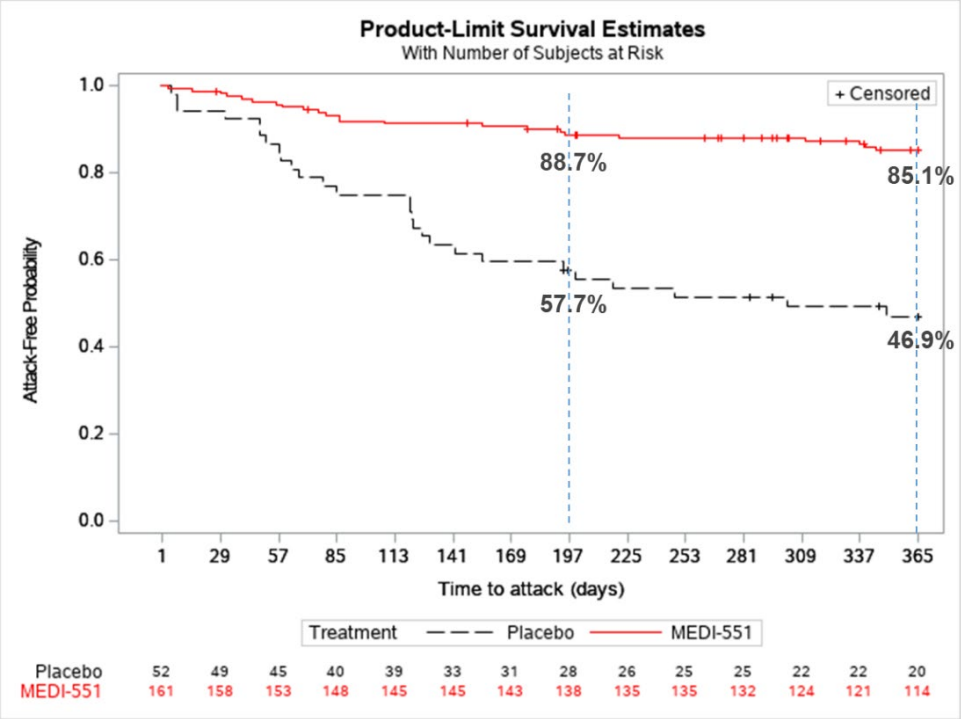
AQP4-IgG seropositive subjects who received inebilizumab were 74.2% more likely to report less disability compared to placebo subjects. In 52.8% of possible pairs of inebilizumab and placebo subjects, inebilizumab subjects had a better outcome than the placebo subjects at the last visit. In 25.7% of pairs, placebo subjects had a better outcome and in 21.5% of pairs, inebilizumab subjects were tied with placebo subjects. This leads to Wilcoxon-Mann-Whitney odds of 1.742 (p = 0.0014).

Exploratory Analyses of Time to First NMSOD Attack in the RCP and OLP and During the OLP:

Survival probability estimates at Day 197 were 88.7% and 87.7% for the AQP4-IgG seropositive and ITT populations, respectively. Corresponding estimates at Day 365 of the OLP were 85.1% and 84.4%, respectively.

In the analysis of time to first AC-determined OLP attack, subjects who received placebo during the RCP displayed a similar survival curve in the OLP to that seen in the inebilizumab subjects in the RCP (Figure 23).

Figure 23: Time to first AC-determined attack (randomised-controlled period + open label period) (AQP4-IgG seropositive population)

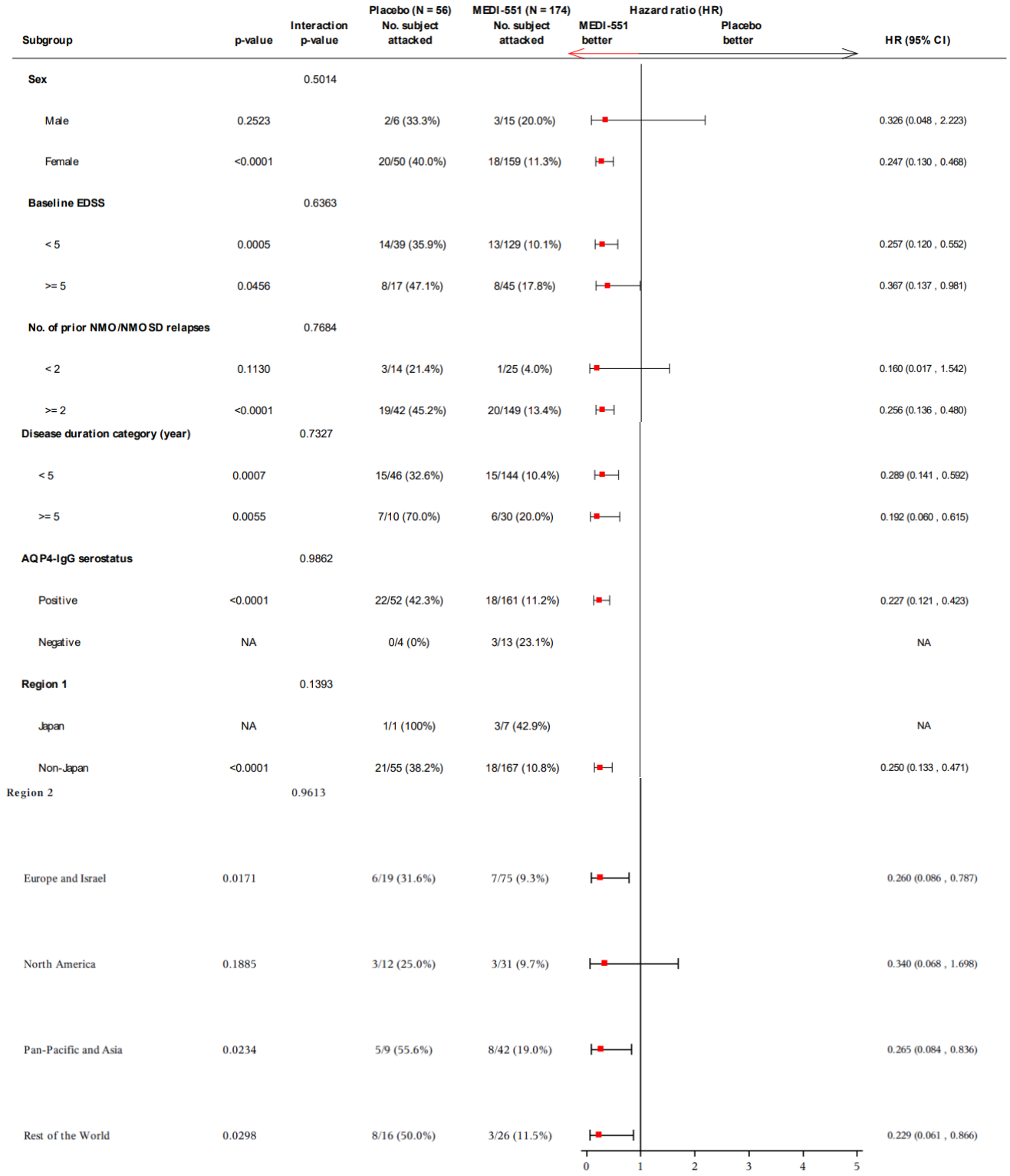


AC = Adjudication Committee; AQP4-IgG = autoantibodies to aquaporin-4; MEDI-551 = inebilizumab.

Subpopulation:

The primary endpoint, time to AC-determined NMOSD attack was evaluated in prespecified subgroups within the total ITT population including sex, baseline EDSS, number of prior NMOSD relapses, disease duration category, AQP4-IgG serostatus, and region (Japan/Non-Japan) (Figure 24).

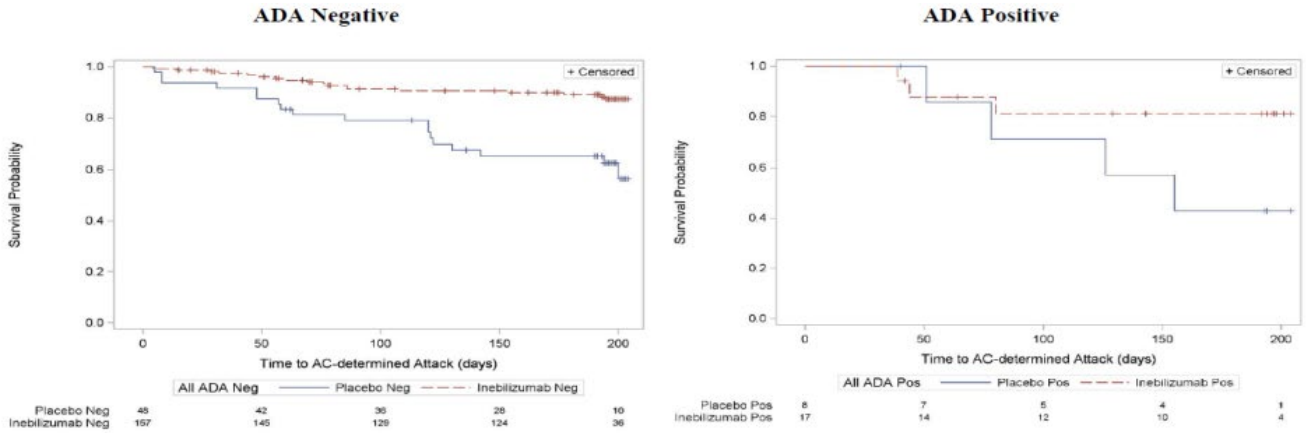
Figure 24: Forest Plot for subgroup analysis of time to adjudication committee-determined attack, randomised-controlled period (ITT population)



AQP4-IgG = autoantibodies against aquaporin-4; HR = hazard ratio; CI = confidence interval; EDSS = Expanded Disability Status Scale; MEDI-551 = inebilizumab; N = number of subjects; NA = not applicable; NMO/NMOSD = neuromyelitis optica spectrum disorders.

Immunogenicity:

Figure 25: Kaplan-Meier plot for time to ac-determined NMOSD attack during the RCP in by ADA status



ADA= anti-drug antibody (immunogenicity); inebilizumab Pos = inebilizumab treated subjects with ADA positive results in the RCP; inebilizumab Neg= inebilizumab treated subjects with ADA negative results in the RCP; Placebo Pos = Placebo ADA positive subjects; Placebo Neg= Placebo ADA negative subjects.
The numbers under the legend represent the corresponding number of subjects for placebo and inebilizumab at the X axis time to AD-determined Attacks (days).
The hazard ratio and 95% confidence interval were 0.272 (0.061-1.220) for all inebilizumab ADA positive versus all placebo ADA positive and 0.274 (0.143-0.528) for all inebilizumab ADA negative versus all placebo ADA negative.

In subgroup analysis for the primary endpoint, there was no difference in the HRs (0.274 and 0.272) obtained from evaluation of all ADA-positive subjects (inebilizumab versus placebo) and all ADA-negative subjects (inebilizumab versus placebo), respectively.

Neutralizing antibodies were not tested.

Table 27: Summary of ADA Response to Inebilizumab (ITT Population)

	RCP Only (N = 230)		Any Inebilizumab Population [a]
	Placebo N = 56	Inebilizumab N = 174	Overall N = 225
Any ADA result (n)	56	174	225
ADA positive at any time including baseline (prevalence)	8 (14.3%)	17 (9.8%)	30 (13.3%)
Median of maximum titer	200	100	100
Minimum, maximum	50, 1600	50, 400	50, 1600
Baseline and ≥ 1 Post-baseline ADA result	56	171	213
ADA positive at baseline and not detected post-baseline	0	5 (2.9%)	8 (3.8%)
ADA positive post-baseline and positive at baseline	4 (7.1%)	7 (4.1%)	11 (5.2%)
ADA positive post-baseline and not detected (or missing) at baseline	4 (7.1%)	5 (2.9%)	10 (4.7%)
Median of maximum titer	850	100	75
Minimum, maximum	50, 1600	50, 400	50, 400
Persistent Positive [b]	7 (12.5%)	7 (4.1%)	15 (7.0%)
Median of maximum titer	200	100	200
Minimum, maximum	100, 1600	50, 400	50, 400
Transient Positive [c]	1 (1.8%)	5 (2.9%)	6 (2.8%)
Median of maximum titer	50	50	50
Minimum, maximum	50, 50	50, 100	50, 400
Treatment-boosted ADA [d]	0	0	2 (0.9%)
Treatment-emergent ADA [e] (incidence)	4 (7.1%)	5 (2.9%)	12 (5.6%)
Median of maximum titer	850	100	150
Minimum, maximum	50, 1600	50, 400	50, 400

ADA= anti-drug antibody; ITT = intent-to-treat; N = sample size; RCP = randomised-controlled period.
a Subjects who received at least one dose of inebilizumab (either in RCP or OLP); within this population baseline, particularly with respect to placebo subjects, is defined as any timepoint prior to treatment with inebilizumab. b Persistent positive is defined as positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment; assessed in all ADA positive subjects.
c Transient positive is defined as negative at last post-baseline assessment and positive at only one postbaseline assessment or at ≥ 2 post-baseline assessments (with <16 weeks between first and last positive); assessed in all ADA positive subjects)
d Defined as baseline ADA titre that was boosted to a 4-fold or higher level following drug administration.
e Defined as subjects who have treatment-induced ADA (post-baseline positive only) and/or treatment boosted ADA

- **Summary of main efficacy results**

The following tables summarise 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 28: Summary of efficacy for trial CD-IA-MEDI-551-1155

Title: A DOUBLE-MASKED, PLACEBO-CONTROLLED STUDY WITH OPEN LABEL PERIOD TO EVALUATE THE EFFICACY AND SAFETY OF MEDI-551 IN ADULT SUBJECTS WITH NEUROMYELITIS OPTICA AND NEUROMYELITIS OPTICA SPECTRUM DISORDERS			
Study identifier	CD-IA-MEDI-551-1155 EudraCT number: 2014-000253-36		
Design	Study CD-IA-MEDI-551-1155 (Study 1155) is a multicentre, multinational, randomised, double-blind, placebo-controlled study with an open-label extension period to evaluate the efficacy and safety of IV inebilizumab in adult patients with AQP4-IgG seropositive or seronegative NMOSD. Eligible patients were randomised and dosed in a 3:1 ratio (intravenous [IV] inebilizumab 300 mg on Day 1 and on Day 15, or matching placebo). Background immunosuppressive therapy was not permitted. Subjects were followed for a 197-day period (the randomised controlled-period, RCP) for new or worsening symptom(s) of a potential NMOSD attack. The Investigator evaluated all subjects with new or worsening symptom(s) of an attack at an attack Assessment Visit at the clinical site. An independent and blinded Adjudication Committee (AC) of 3 expert NMOSD physicians evaluated all possible NMOSD attacks. The unblinded IDMC performed evaluations of safety and clinical outcome data at specified regular intervals throughout the study. Subjects who experienced an AC-determined attack in the RCP, or who completed the Day 197 visit without an attack, exited the RCP and had the option to enrol into an OLP and initiate or continue treatment with inebilizumab in a manner that did not unblind their RCP treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		197 ± 7 days 28 days A minimum of one year and a maximum of 3 years after the last subject enters the open label period.
Hypothesis	Superiority to placebo		
Treatments groups	Inebilizumab (MEDI551)		MEDI551. 197±days, 175
	Placebo (PBO)		PBO. 197± days, 56
Endpoints and definitions	Primary endpoint	Attack	The primary efficacy endpoint time (days) from Day 1 to onset of an AC-determined NMOSD attack on or before Day 197.
	Secondary endpoint	EDSS	Worsening from baseline in EDSS at last visit during the RCP.
	Secondary endpoint	Visual Acuity	Change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart, at last visit during the RCP.
	Secondary endpoint	MRI	Cumulative total active MRI lesions (new Gd-enhancing or new/enlarging T2) during the RCP.
	Secondary endpoint	Hospitalisations	Number of NMOSD-related in-patient hospitalisations.
Database lock	18 December 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All efficacy results were analysed based on first the AQP4-IgG seropositive population and then total intent-to-treat (ITT) population. Intent to treat: Subjects randomised and who received any IP. At time of an AC-determined attack in the RCP, or completion of the Day 197 visit without an attack or withdraw early from the RCP.		

Descriptive statistics and estimate variability	Treatment group	AQP4-IgG sero+ MEDI551	AQP4-IgG sero+ PBO	MEDI551	PBO
	Number of subjects	161	52	174	56
	Attack (Number [%] of subjects with attack)	18 (11.2%)	22 (42.3%)	21 (12.1%)	22 (39.3%)
	EDSS (Number [%] of subjects with EDSS worsening from baseline)	25 (15.9%)	18 (34.6%)	27 (15.5%)	19 (33.9%)
	Visual Acuity (LS mean)	0.562	0.600	1.576	1.442
	Standard error	0.572	0.999	0.935	1.217
	MRI (Number of subjects with, and mean number of active MRI lesions)	74, 1.7	31, 2.3	79, 1.6	32, 2.3
	Standard deviation	1.0	1.3	1.0	1.3
	Hospitalisations (Number of subjects with, and mean number of hospitalisations)	8, 1.0	7, 1.4	10, 1.0	8, 1.4
	Standard deviation	0	0.8	0	0.7

Effect estimate per comparison	Primary endpoint Attack	Comparison groups	AQP4-IgG sero+ MEDI551 vs PBO	MEDI551 vs PBO
		Hazard ratio	0.227	0.272
		95% confidence interval	(0.1214, 0.4232)	(0.1496, 0.4961)
		P-value from Cox regression model	<.0001	< 0.0001
	Secondary endpoint EDSS	Comparison groups	AQP4-IgG sero+ MEDI551 vs PBO	MEDI551 vs PBO
		Odds ratio	0.371	0.370
		95% confidence interval	(0.1807, 0.7633)	(0.1850, 0.7389)
		Nominal P-value from logistic regression model	0.0070	0.0049
	Secondary endpoint Visual Acuity	Comparison groups	AQP4-IgG sero+ MEDI551 vs PBO	MEDI551 vs PBO
		LS mean difference	-0.038 (1.153)	0.134
		95% confidence interval	(-2.3122, 2.2357)	(-2.0254, 2.2941)
		Nominal P-value from ANCOVA	0.9736	0.9026

	Secondary endpoint MRI	Comparison groups	AQP4-IgG sero+ MEDI551 vs PBO	MEDI551 vs PBO
		Rate ratio	0.568	0.566
		95% confidence interval	(0.3851, 0.8363)	(0.3866, 0.8279)
		Nominal P-value from negative binomial regression model	0.0042	0.0034
	Secondary endpoint Hospitalisations	Comparison groups	AQP4-IgG sero+ MEDI551 vs PBO	MEDI551 vs PBO
		Rate ratio	0.258	0.286
		95% confidence interval	(0.0904, 0.7384)	(0.1105, 0.7411)
		Nominal P-value from negative binomial regression model	0.0115	0.0100
Notes	After multiplicity comparison adjustment, the effects comparing MEDI551 vs PBO in AQP4-IgG seropositive population and ITT population are statistically significant for primary endpoint and nominally significant for the secondary endpoints presented above except for visual acuity.			

2.6.5.3. Clinical studies in special populations

The effects of renal or hepatic impairment on the PK of inebilizumab have not been formally studied. Subjects had an age range of 18-74 years at baseline.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	10/230	0	0
Non Controlled Trials	NA	NA	NA

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

NA

2.6.5.5. Supportive study

NA

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

No dose-response study has been conducted. Dose finding was performed in Phase I trials (SAD and MAD studies) in scleroderma and Relapsing MS patients. The 300 mg fixed dose of inebilizumab administered IV on Days 1 and 15 was selected for study in NMOSD subjects to achieve and maintain persistent depletion of peripheral B cells for 28 weeks.

The design of the pivotal trial is a multicentre, multinational, randomised, DB, placebo-controlled, parallel group confirmatory trial. The study consisted of screening (28 days), randomised controlled (up to 197 days), open label (minimum of one year and a maximum of 3 years after the last subject enters) and safety follow up (minimum 52 weeks) periods. The study was overseen by an IDMC and an AC.

Study RCP duration was variable for subjects. Subjects who experienced an AC-determined attack in the RCP, or who completed the Day197 visit without an attack, exited the RCP and had the option to enrol into the OLP (open label period) and initiate or continue treatment with inebilizumab (still ongoing in 2019). Subjects in whom an attack was not confirmed by the AC continued in the RCP until Day 197 (or until another attack occurred and was determined to be an NMOSD attack by the AC).

The use of background IST while on trial is not permitted and no active comparator is used. Rescue therapy was initiated as needed for NMOSD attacks at the discretion of the site Investigator and may have included IV corticosteroids, IVIG, and/or plasma exchange. The CHMP did not initially endorse conducting a pure (no background IST allowed) placebo-controlled trial for Inebilizumab (EMEA/H/SA/2664/1/2013/III). This aspect was further revised in a follow up SA (EMEA/H/SA/2664/1/FU/1/2015/II) and the conduction of a placebo-controlled trial without IST as standard of care was only regarded appropriate considering included measures to mitigate placebo exposure (e.g. unequal randomisation; use of a time-to-event outcome; limiting the time on placebo in a given patient to a maximum of 6.5 months). These conditions were met in current design. There were no EU approved treatment options at the time of study design, so no comparison to an active comparator is acceptable. It should be noted that other treatments currently approved (eculizumab and satralizumab) for NMOSD were studied as an add-on to background IST, although one of two pivotal studies for satralizumab was also placebo-controlled without IST. Overall, the study design is considered acceptable. However, due to no IST use in the background, the applicant was required to discuss potential interactions with other IST or treatments for acute management of attacks and amelioration of persistent symptoms, instructions for starting treatment with inebilizumab and switching from or to other treatments used in standard of care. The applicant added a dedicated subsection in section 4.4 of the SmPC: "Prior treatment with immunosuppressive therapies" where the relevant information is included, and the concerns are addressed in the risk management plan (RMP).

The inclusion criteria are specific for NMOSD, enriched the population for patients with active and relapsing disease, and together with exclusion criteria they can generally be considered to define a relevant patient population, with a caveat due to inclusion of AQP4-IgG seronegative patients.

Eligible patients in Study 1155 were adults (18 years and older) with an EDSS score ≤ 7.5 (≤ 8.0 if the subject was reasonably able to participate in the study), a diagnosis of NMOSD at the time of screening, and a documented history of ≥ 1 NMOSD attacks that required rescue therapy in the previous year or ≥ 2 NMOSD attacks that required rescue therapy in the preceding 2 years. Enrolment of patients only with active and relapsing disease is understandable and acceptable due to desired minimum exposure to placebo and short time in RCT.

Both treatment naïve and previously treated patients were enrolled, however, patients were excluded if previously treated with IST within an interval specified for each such therapy. A comprehensive set of exclusion criteria addressed concomitant therapy, autoimmune diseases or any concomitant disease that required steroid treatment within the 6 months prior to screening, vaccination history, immune status, infection status and risk, malignancy risk, general safety, laboratory criteria, B cell counts, CD19+ B cell counts, but were not limited to these.

The study was designed to include both AQP4-IgG seropositive and seronegative patients (expected ratio was the reported ratio in the literature, 80-90% of all subjects are AQP4-IgG seropositive). Subjects who are AQP4-IgG seronegative, where the diagnosis of NMOSD is less clear, needed to meet the clinical criteria for NMOSD according to Wingerchuk et al 2006 by the determination of Independent Eligibility Committee. The CHMP showed some concerns on the inclusion of AQP4-IgG seronegative patients due to paucity of scientific evidence supporting the background scientific rationale, potential negative impact for the assessment derived from the inclusion of a heterogeneous group (differences from AQP4-IgG seropositive patients, differences within seronegative group), and the study not being powered for

assessing the efficacy of inebilizumab in AQP4-IgG seronegative patients based on sample size considerations and the analysis plan presented by the applicant (EMEA/H/SA/2664/1/2013/III).

The NMOSD diagnostic criteria were updated in 2015, after enrolment for the study had already begun and the protocol was not amended regarding this change. As it turned out, the protocol criteria for AQP4-IgG seropositive subjects were consistent with the 2015 IPND diagnostic criteria for NMOSD, and as such, the protocol-defined study population was representative of the population defined by the new criteria.

As no background IST for treatment of NMSOD were permitted, a 2-week course of oral corticosteroids (prednisone 20 mg/day or equivalent oral glucocorticoid) (plus a 1-week taper) was given to all subjects following the first administration of IP in the RCP only. The rationale was to provide prophylaxis against an NMOSD attack for the period where the PD effect of inebilizumab was not expected (approximately 2-4 weeks) and when increase rate of attack has been reported with other B-cell depletion therapy (e.g. during first month of therapy with rituximab). The applicant informed that the 2-week course of oral corticosteroids (plus a 1-week taper) was not further pursued for patients entering the OLP after receiving placebo as they have not recently discontinued an IST. The SmPC is updated accordingly to inform physicians of this course of therapy for patients starting inebilizumab treatment in clinical trials.

The primary efficacy endpoint was time to onset of an AC-determined NMOSD attack. It is considered appropriate choice as a time to event endpoint helping to minimise the risk of placebo exposure. The definition for the criteria of the clinical endpoint is detailed by the protocol, and the events were adjudicated centrally by an independent committee as advisable. Of note, the CHMP recommended using investigator-confirmed attacks for the primary analyses and conducting sensitivity analyses using the adjudicated cases. However, all pivotal trials for inebilizumab, eculizumab and satralizumab used adjudicated events (relapses) for primary endpoint.

The selected key secondary endpoints were worsening from baseline in EDSS at last visit during the RCP, change from baseline in low-contrast visual acuity binocular score at last visit during the RCP, cumulative total active MRI lesions (new Gd-enhancing or new/enlarging T2) during the RCP, number of NMO/NMOSD-related in-patient hospitalisations. It may be questioned whether the proposed and endorsed hierarchical order of key secondary endpoints was taken into account in the submitted application as there seems to be many changes on study endpoints and statistical analysis plan on the way. ARR (total number of AC-determined NMOSD attacks normalised by person-years) during any exposure to inebilizumab was chosen to evaluate maintenance of efficacy over OLP. Although secondary endpoints are relevant in the clinical use to evaluate disability or severity of attacks and disease activity at patient level, they are not established methods to measure treatment effect on NMOSD.

According to testing hierarchy in SAP, the primary endpoint was to be tested first at $\alpha = 0.05$ for the AQP4-IgG seropositive cohort and, if significant, was to be tested in the overall ITT population at $\alpha = 0.05$. If the primary endpoint was statistically significant in the ITT population, each secondary endpoint was tested with the same sequential testing strategy but without a hierarchical order in between different endpoint. This strategy is acceptable but could be questioned in the following cases:

1. Amendment 6 implicitly plans a stop of the trial for efficacy on IDMC recommendation before reaching the 67 final events, this early stop is not accounted for in the proposed multiplicity procedure for controlling the overall type-one error. Several looks in the data of a trial need a reallocation of the type-one error through interim and final analyses of the primary and key secondary endpoints. As justification why the interim step was not accounted for in the multiplicity adjustment process, the applicant informed that they did not plan interim looks at efficacy, but it was performed by the IDMC. The explanation of not being aware of the process is not acceptable. After accounting for the multiplicity adjustment, the p-values for the primary efficacy endpoint were < 0.0001 for both the ITT population and AQP4-seropositive patients. Thus, issue is not pursued.

2. Tests on key secondary endpoints are not powered on expected clinical effects, any statistically significant test on these endpoints should be supported by relevant clinical benefit. Therefore, the secondary endpoints are only briefly described in SmPC.

Efficacy data and additional analyses

Despite planned target population size of 67 AC-determined attacks with 252 subjects, on 07 Sep 2018, the applicant received a recommendation from the IDMC to stop enrolment as efficacy was established and there was no justification to continue to expose patients to the placebo arm where risk for attack is higher with no background treatment. At that point, 231 subjects were randomised to treatment (213 AQP4-IgG seropositive and 18 seronegative) at 82 participating sites in 24 countries. 230 patients and 43 AC-determined NMOSD attacks were included in ITT analyses. Overall, 223 subjects (97.0%) completed the RCP and 213 subjects entered the OLP. The percent of screening failure (236/457 51.6%) in this study was high. 46/230 (20%) patients reported an important protocol deviation. Overall, 223 subjects (97.0%) completed the RCP and 213 subjects (90.4% for placebo and 95.7% for inebilizumab) entered the OLP. The rates of withdrawal during RCP were 3.8% for placebo and 2.5% for inebilizumab, while these rates were 17% for placebo/inebilizumab and 20.8% for inebilizumab/inebilizumab during OLP.

Overall, study population at baseline reflects the intended indication for AQP4-IgG seropositive NMOSD and illuminates further the challenges around diagnosis and treatment of seronegative population despite "expected" similar phenotype. Subjects had a mean age (range) of 42.9 years (18-74 years), 4.3% of the patients were at or above the age of 65, the majority were female (90.9%) and of white race (52.2%) with 40.9% enrolled in Europe-Israel region.

Baseline disease characteristics in AQP4-IgG seropositive subgroup were suitable with slightly more disability in placebo group compared to inebilizumab group with higher mean EDSS (4.35 vs 3.81), higher percentage of patients in EDSS category >5 (30.8% vs 23%), but slightly less disease activity with higher number of patients with less than 2 relapses (25% vs 15%) and less mean number of Gd enhancing lesions (0.8 vs 1.2). Distribution of involvement as ON, myelitis or brainstem, and ARR prior to treatment in the study was well balanced. Slight differences between placebo and active groups in AQP4-IgG seropositive subset are not expected to have significant impact on the primary endpoint and key secondary endpoints.

The number of AQP4- IgG seronegative patients was too low for formal statistical testing. This has been partly affected by the uncertainty of diagnosis for AQP4-IgG seronegative subjects (too many rejected by AC). AQP4-IgG seronegative subgroup showed imbalances in demographics and baseline disease characteristics due to very small numbers. Specifically, the mean disease duration is significantly different in AQP4-IgG seronegative group as 1.2 years (0.2 to 5.5 years) (in comparison to 2.5 years (0.1 to 22.2 years) in AQP4-IgG seropositive group), with more significant brain/brainstem involvement and a smaller number of relapses concentrated in a shorter time period. Two out of 17 seronegative patients (1 out of 4 seronegative placebo subgroup patients) had only 1 attack at baseline. Placebo treated patients in AQP4-IgG seronegative group showed baseline differences (only 0.78 years disease duration, maximum 3 attacks, 50% brain/brainstem involvement, 2.29 ARR prior to IP administration) which could be one of the reasons for observed difference in results from AQP4-IgG seropositive group. Due to very short time frame in the RCP and possibly different etiological mechanisms involved in AQP4-IgG seronegative NMOSD, it is impossible to know if the seronegative patients would have had attacks if they were followed longer without inebilizumab treatment. Limited data suggest that seronegative NMOSD might have higher likelihood to be monophasic or to have fewer relapses. Overall, AQP4-IgG seronegative group is considered as a significantly different group at baseline with very small numbers, no place in testing hierarchy, no attacks observed in placebo subgroup during study period, and no observed therapy benefit.

As such, the applicant was requested to restrict the indication for AQP4-IgG seropositive patients. The proposed indication for inebilizumab was changed as "indicated as monotherapy for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive" after resolution of major objections raised on the indication wording on inclusion of endpoints and AQP4-IgG seronegative patients and intended use as "monotherapy".

The efficacy of inebilizumab in reducing risk of attacks in AQP4-IgG seropositive population is confirmed. In the AQP4-IgG-seropositive subgroup, 18 (11%) of 161 participants receiving inebilizumab had an attack compared with 22 (42%) of 52 participants receiving placebo (HR 0.227 [95% CI 0.121–0.423]; p <0.0001). The number needed to treat was 3.23 (95% CI 2.72–4.54) (Cree et al 2019). This is considered clinically meaningful change. The HR of AC-determined attacks with inebilizumab treatment relative to placebo was 0.272 (95% CI: 0.1496, 0.4691) for the total ITT population (p < 0.0001). The significant result for ITT group is considered to be driven by strong results from seropositive group which constitutes 93% of ITT population.

Sensitivity analyses were consistent with the primary analysis in the sense that the HR estimates were all below 1.00 and all sensitivity analyses reached significance (<0.05). Sensitivity analyses of primary analysis address most of the concerns around the study conduct (potential unblinding, determination of attacks, discontinuations) or heterogeneity of study population.

There were 64 possible relapse events adjudicated by the AC, 36 in the group treated with inebilizumab (20.7%) and 28 in the placebo group (50%). Of the 64 potential attacks assessed in the RCP of the study, the Investigator determined that 51 (80%) met attack criteria and 13 (20%) did not. In contrast, the AC determined that 43 potential attacks (67%) met attack criteria and 21 (33%) did not. Twenty-one of the 36 (58.3%) events in the inebilizumab group were confirmed by the AC; 22 of the 28 (79%) in the placebo group were confirmed by the AC. Despite higher rate of AC-confirmed relapses in the placebo treatment group which could introduce bias, sensitivity analyses of primary endpoint included analyses with all investigator determined or patient reported attacks which supported results with primary endpoint analysis. The issue is not pursued. All of the 43 AC-determined NMOSD attacks involved myelitis and/or ON. Less than 5% of attacks involved the brainstem, and both of these also included either ON or myelitis. No AC-determined attacks affected the brain.

Three of four key secondary endpoints showed nominally significant results but their clinical significance was questioned due to methodological concerns and their uncertain predictive value on treatment effect.

Changes from baseline in low-contrast visual binocular acuity did not differ between inebilizumab and placebo recipients. The overall effect of inebilizumab treatment on existing or cumulating disability of optic neuritis attacks is unclear, though it should be kept in mind that clinical manifestations of optic neuritis are devastating, frequently permanent and lead to blindness and that episodes of optic neuritis are more frequently unilateral while the low-contrast visual acuity was tested binocularly.

At the end of the RCP, significantly fewer inebilizumab than placebo recipients in the AQP4-IgG seropositive [16% vs. 35% (ORs=0.371; p = 0.007)] and overall ITT [16% vs. 34% (ORs=0.370; p=0.0049)] populations had worsening on the EDSS. There should be some caution with interpretation of this result as EDSS is highly correlated with presence of a recent attack. On the positive side, exploratory analysis with modified Rankin Scale was supportive (AQP4-IgG seropositive subjects who received inebilizumab were 74.2% more likely to report less disability compared to placebo subjects) and severity of attacks in AQP4-IgG seropositive population were reduced from 45.5% to 33.3% major attacks with inebilizumab use. The sustainability of results in longer term follow up is unknown.

The cumulative number of active MRI lesions, new Gd-enhancing MRI lesions, new/enlarging T2 MRI lesions decreased with inebilizumab treatment compared to the placebo. In the RCP, 45.3% of inebilizumab subjects had new Gd-enhancing MRI lesions (placebo 59.6%), and 21.7% of inebilizumab subjects had new/enlarging T2 MRI lesions (placebo 40.4%) among AQP4-IgG seropositive subjects. New Gd-enhancing lesions were most common in the optic nerve, followed by spinal cord and brain; no new Gd-enhancing lesions were seen in the brainstem. New/enlarging T2 lesions were most common in the spinal cord, followed by optic nerve, brain, and brainstem. The annualised rates of MRI lesions (cumulative number of active MRI lesions, new Gd-enhancing T1 lesions, new/enlarging T2 MRI lesions) in RCP and OLP were presented upon query and the analyses are supportive of the primary endpoint.

Treatment with inebilizumab reduced the number of in-patient hospitalisations compared to treatment with placebo in RCP. The rate ratio between the groups was 0.258 (95% CI:0.0904, 0.7384; p = 0.0115) among AQP4-IgG seropositive subjects.

A multiplicity adjustment performed for the analyses of the primary and key secondary efficacy endpoints revealed significant results for all except for change in low-contrast visual acuity.

Persistence of efficacy was evaluated through ARR (total number of AC-determined NMO/NMOSD attacks normalised by person-years) during any exposure to inebilizumab. Across the RCP and OLP, as of the primary DCO of 26Oct2018, the annualised AC-determined NMOSD attack rate in any AQP4-IgG seropositive subject treated with inebilizumab was 0.13. Updated annualised AC-determined NMOSD attack rate in the same subgroup at the time of the Day 120 safety update (date of cut-off 06 Jun 2019) was 0.118 (0.088-0.155). Effect of inebilizumab treatment seen on time to first AC-determined attack during RCP was sustained throughout the OLP, as measured by numerically similar survival estimates at Day 365 of the OLP (85.1%) compared with those seen on Day 197 of the RCP (88.7%) in the AQP4-IgG seropositive population. Due to open label design, the results have to be considered cautiously.

The rhythm of administration was mainly based on experience with rituximab in MS. B cell data show persistent depletion in 94% of cases at 28 weeks on Inebilizumab treatment. Further data with memory B lymphocytes counts under Inebilizumab treatment should be provided to confirm the maintenance of biologic effect in this study. A follow-up study for monitoring of the B cell memory is planned.

Subgroup analyses of the primary endpoint were performed across the prespecified subgroups related to demographics and baseline disease characteristics (sex, race, baseline EDSS, number of prior NMOSD relapses, disease duration, AQP4-IgG serostatus, region [Japan/Non-Japan], site region, and previous treatment for the prevention of NMOSD attacks. There were no significant interaction p-values for any of these subgroup analyses. *Post hoc* analysis based on patient´s age and additional information on older subjects are requested and reviewed, however are limited and it is reflected in SmPC. The "Europe" analysis (n=94) proposed in the overview does not correspond to the EU population involved in the trial (n=56). Further analyses confirm that the treatment effect in the EU subgroup is consistent with the primary analysis: in the AQP4-IgG-seropositive subgroup, 5/40 (12,5%) patients receiving Inebilizumab had an attack compared with 3/10 (30%) patients receiving placebo (HR 0,361 [95% CI 0,086–1,516]; p =0,1640). This point estimate shows more than 60% reduction risk of attacks under Inebilizumab treatment as compared to the placebo response, which is in line with the 79% and 77% and reduction risks respectively in the non-EU population (HR=0.205) and overall seropositive population (HR=0.227).For the endpoint of low-contrast visual acuity, inebilizumab was nominally better in the subgroup with < 2 prior NMOSD relapses compared with ≥ 2 prior relapses (nominal p = 0.0129; interaction p = 0.0019), in Japan compared with non-Japan (nominal p = 0.0026; interaction p = 0.0317), and in subjects who had not received prior NMOSD medications (nominal p = 0.0251; interaction p = 0.0090). The results should be interpreted with caution given the small number of subjects and insignificant key secondary endpoint of low-contrast visual acuity. However, nominally

better results for patients with less than 2 relapses might be in line with clinical thinking that frequently and permanently diminished visual acuity would not improve with effective relapse control.

There were concerns around immunogenicity subgroup results (e.g. validity of the ADA assay, interaction of ADAs with the quantification of inebilizumab in real-life study samples or clearance of inebilizumab, lack of testing for neutralizing antibodies in ADA positive samples and their clinical impact). Observed dominance of pre-existing and treatment-boosted antibodies make it questionable that current ADA assay results could be of any use at all in clinical evaluation in this dossier or in real life. The applicant argues that any association between neutralizing antibodies and risk of attacks could be evaluated by B-cell count as the more reproducible, sensitive, and actionable evaluation of any clinical impact. Due to mechanism of action and demonstrated overlap of results on comparison of PK, PD, and efficacy by ADA status, the argument is acceptable. In case of any clinical suspicion for loss of efficacy due to immunogenicity, the clinician should follow B-cell counts as a direct measure of clinical impact. In section 5.1 of the SmPC, a summary of immunogenicity data (in terms of incidence, subtypes of ADA and impact on PK, safety, B-cell kinetics) is provided.

2.6.7. Conclusions on the clinical efficacy

The efficacy of inebilizumab in reducing risk of attacks in AQP4-IgG seropositive NMOSD population as monotherapy is confirmed. AQP4-IgG seronegative group is considered as significantly different group at baseline with very small numbers and no observed therapeutic benefit.

The use of inebilizumab (Anti-CD19 mAb) in this condition is based on direct depletion of CD19+ B cells which could be effective in reducing the risk for NMOSD attack by depleting plasmablasts producing AQP4-IgG.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In the pivotal phase 2/3 Study 1155, the populations for safety analyses are:

- As-treated population: Subjects who received any IP (either inebilizumab or placebo) were included in the As-treated population and analysed according to treatment received. Specifically, subjects randomised to inebilizumab who received all placebo doses were included in the placebo group; conversely, subjects randomised to placebo who received at least one dose of inebilizumab were included in the active treatment group.
- Any Inebilizumab population: Subjects who received at least one dose of inebilizumab (either in the RCP or OLP).
- Open-label population: Subjects who received at least one dose of inebilizumab during the OLP. These subjects had baseline data from the RCP.
- Non-OLP population: Subset of the As-treated population who did not roll over to OLP.

For this submission, safety data from the entire Study 1155 is provided (database lock date: 18 Dec 2020). The last RCP visit for the last subject occurred on 26 Oct 2018. For the entire study, date of final subject visit was 06 Nov 2020.

A total of 225 adult patients with NMOSD (Study 1155), 24 adult subjects with scleroderma (Study CP200), and 21 subjects with MS (Study 1102) were treated with inebilizumab in these studies. Besides deaths, only safety data pertaining to the pivotal Study 1155 are presented in the Clinical Safety part of the Overview.

Across the RCP and the OLP of Study 1155, 225 subjects have received one or more doses of inebilizumab; 174 of these patients received active treatment during the RCP, while the remainder were initially randomised to placebo before receiving active treatment during the open-label study period. The median duration of inebilizumab in the overall Any inebilizumab population was 1178.0 days and the total inebilizumab exposure was 730.4 person-years.

The extent of exposure in the RCP was calculated as last RCP dose date minus 1st RCP dose date + 60 days, the latter representing 5 half-lives of inebilizumab; similarly, extent of exposure in the Any Inebilizumab Population was calculated from the date of the last OLP dose (excluding placebo dose at Day 15) minus first dose date plus 60 days. Since the B-cell depleting effect of inebilizumab is in the order of 6 months, the applicant's methodology regarding calculation of exposure time may be considered conservative.

Overall, considering the rarity of NMOSD, the safety database is deemed sufficient to support MAA for inebilizumab.

Among the inebilizumab groups and placebo groups, demographic and baseline disease characteristics were generally well balanced. In the ITT population (which comprised the same subject populations as the As-treated Population), the mean age was 42.9 years with a small proportion above the age of 65 years (4.3%). Of the total population, 90.9% were female. However, the ratio of female to male was different between the AQP4-IgG seropositive and seronegative subjects, 93.9% versus 6.1%, and 52.9% versus 47.1%, respectively. With Europe representing approximately 40% of patients recruited and White race further constituting >50% of the ITT population, the geographical and racial distribution of study subjects would not appear to represent any clear limitations to extrapolating the safety results to European patients.

2.6.8.2. Adverse events

Overview of Adverse Events

During the RCP, the majority of subjects had at least one treatment emergent adverse events (TEAE) (

Table 29). In the total As-treated population, similar proportions of subjects experienced TEAEs in the inebilizumab group (73.0%) and the placebo group (73.2%). There were no deaths during the RCP. The proportions of subjects with at least one treatment-emergent serious adverse events (TESAE) and/or ≥ Grade 3 TEAE were similar between the inebilizumab group (10.9%) and the placebo group (16.1%). During the RCP, in the total As-treated population, the incidence rate of TEAEs per 100 person-years was 620.23 in the inebilizumab group and 662.63 in the placebo group. In the OLP, the incidence rate of TEAEs per 100 person-years was 227.86 in the inebilizumab/inebilizumab group and 278.51 in the placebo/inebilizumab group.

In the inebilizumab group, 2 subjects had a TEAE resulting in discontinuation of IP and 4 subjects had a TEAE leading to dose interruption. There were no TEAEs resulting in treatment interruption or discontinuation in the placebo group.

Table 29: Overall Summary of Treatment-emergent Adverse Events, Randomised-controlled Period (As-treated Population)

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
Subjects [a] with:	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
At least one TEAE	37 (71.2%)	119 (73.9%)	4 (100%)	8 (61.5%)	41 (73.2%)	127 (73.0%)
At least one IP-related TEAE	13 (25.0%)	40 (24.8%)	1 (25.0%)	2 (15.4%)	14 (25.0%)	42 (24.1%)
At least one TEAE of ≥ Grade 3 severity [b]	7 (13.5%)	14 (8.7%)	0	1 (7.7%)	7 (12.5%)	15 (8.6%)
Death (Grade 5 severity [b])	0	0	0	0	0	0
At least one TESAE [c]	6 (11.5%)	7 (4.3%)	0	2 (15.4%)	6 (10.7%)	9 (5.2%)
At least one TESAE [c] and/or ≥ Grade 3 severity [b] TEAE	9 (17.3%)	16 (9.9%)	0	3 (23.1%)	9 (16.1%)	19 (10.9%)
At least one IP related TESAE [c]	0	1 (0.6%)	0	0	0	1 (0.6%)
At least one TEAE leading to discontinuation of IP	0	2 (1.2%)	0	0	0	2 (1.1%)
At least one TEAE leading to dose interruption	0	4 (2.5%)	0	0	0	4 (2.3%)

AQP4-IgG = autoantibodies to aquaporin-4; IP = investigational product; N = number of subjects; sero- = seronegative; sero+ = seropositive; TEAE = treatment-emergent adverse event; TESAE = treatment emergent serious adverse event.
a Subjects are counted once for each category regardless of the number of events.
b Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal. Ç
c Serious adverse event criteria: death, life-threatening, required in-patient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

In the OLP, 61 of 216 subjects (28.2%) had at least one TESAE and/or ≥ Grade 3 TEAE, 5 subjects had a TEAE resulting in discontinuation, and 7 subjects had a TEAE resulting in dose interruption (

Table 30). During the OLP, there were 3 fatal TEAEs (

Table 30).

Table 30: Overall summary of treatment-emergent adverse events (open-label period and any inebilizumab population)

Subjects[a] with:	Open-label Period (Open-label Population)						Any Inebilizumab Population		
	AQP4-IgG sero+ N = 201		AQP4-IgG sero- N = 15		Total N = 216		AQP4-IgG sero+ N = 208	AQP4-IgG sero- N = 17	Total N = 225
	Placebo/ Inebilizumab N = 47	Inebilizumab/ Inebilizumab N = 154	Placebo/ Inebilizumab N = 4	Inebilizumab/ Inebilizumab N = 11	Placebo/ Inebilizumab N = 51	Inebilizumab/ Inebilizumab N = 165			
At least one TEAE	41 (87.2%)	133 (86.4%)	4 (100%)	11 (100%)	45 (88.2%)	144 (87.3%)	192 (92.3%)	16 (94.1%)	208 (92.4%)
At least one IP related TEAE	18 (38.3%)	44 (28.6%)	1 (25.0%)	5 (45.5%)	19 (37.3%)	49 (29.7%)	82 (39.4%)	7 (41.2%)	89 (39.6%)
At least one TEAE of ≥ Grade 3 severity [b]	15 (31.9%)	30 (19.5%)	1 (25.0%)	1 (9.1%)	16 (31.4%)	31 (18.8%)	53 (25.5%)	2 (11.8%)	55 (24.4%)
Death (Grade 5 severity [b])	1 (2.1%)	2 (1.3%)	0	0	1 (2.0%)	2 (1.2%)	3 (1.4%)	0	3 (1.3%)
At least one TESAE [c]	17 (36.2%)	21 (13.6%)	2 (50.0%)	1 (9.1%)	19 (37.3%)	22 (13.3%)	41 (19.7%)	5 (29.4%)	46 (20.4%)
At least one TESAE [c] and/or ≥ Grade 3 severity [b] event	19 (40.4%)	39 (25.3%)	2 (50.0%)	1 (9.1%)	21 (41.2%)	40 (24.2%)	65 (31.3%)	5 (29.4%)	70 (31.1%)
At least one IP related TESAE [c]	4 (8.5%)	5 (3.2%)	0	0	4 (7.8%)	5 (3.0%)	10 (4.8%)	0	10 (4.4%)
At least one TEAE leading to discontinuation of IP	1 (2.1%)	3 (1.9%)	0	1 (9.1%)	1 (2.0%)	4 (2.4%)	6 (2.9%)	1 (5.9%)	7 (3.1%)
At least one TEAE leading to dose interruption	2 (4.3%)	3 (1.9%)	1 (25.0%)	1 (9.1%)	3 (5.9%)	4 (2.4%)	8 (3.8%)	2 (11.8%)	10 (4.4%)

AQP4-IgG = autoantibodies to aquaporin-4; IP = investigational product; N = number of subjects; sero- = seronegative; sero+ = seropositive; TEAE = treatment-emergent adverse event; TESAE = treatment emergent serious adverse event.
a Subjects are counted once for each category regardless of the number of events.
b Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal. Ç
c Serious adverse event criteria: death, life-threatening, required in-patient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

Overall, similar TEAE profiles were observed in the AQP4-IgG seropositive and total As-treated population. There were too few subjects in the seronegative population to draw conclusions based on any apparent imbalances.

Common Adverse Events

The most common AEs associated with inebilizumab were urinary tract infections, joint pain and other pain-related preferred terms (PTs): In the RCP, there were higher proportions of patients treated with inebilizumab vs placebo reporting the AEs urinary tract infection (11.5% vs. 8.9%), arthralgia (10.3% vs. 5.4%) and back pain (7.5% vs. 3.6%). The reason for the higher rate of arthralgia is unclear. The proportion of subjects for whom arthralgia was reported during the OLP was 10.3% for the inebilizumab/inebilizumab subjects and 19.3% for the placebo/inebilizumab subjects. No patient discontinued Study 1155 due to arthralgia or other pain-related symptoms.

In addition, falls (4.6% vs. 1.8%), the sensory symptoms dysaesthesia (1.7% vs. 0%), hypoaesthesia (3.4% vs. 1.8%) and paraesthesia (2.3% vs. 0%), eye pain (2.3% vs. 1.8%) and blurred vision (1.7% vs. 0%) were more common in subjects treated with inebilizumab vs. placebo. These AEs were not considered treatment-related by the investigators and may be associated with NMOSD.

Apart from relatively few events of diarrhoea (n=20 (8.9%), nausea n= 16 (7.1%)) and constipation (n=14 (6.2%)) within the gastrointestinal disorders SOC, the most common AEs in the Any Inebilizumab Population (Table 32) were overall similar to those described during the RCP.

No significant differences in incidence of AEs or any new obvious safety signals were apparent when limiting the analysis to AQP4-IgG-seropositive subjects.

Table 31: Treatment-emergent adverse events (≥ 5% in total inebilizumab group) by system organ class and preferred term, randomised-controlled period (As-treated population)

System Organ Class[a] Preferred Term (MedDRA version 23.1)	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Subjects with at least one TEAE with ≥ 5% in Total Inebilizumab group	37 (71.2%)	119 (73.9%)	4 (100%)	8 (61.5%)	41 (73.2%)	127 (73.0%)
Infections and infestations						
Nasopharyngitis	6 (11.5%)	12 (7.5%)	0	1 (7.7%)	6 (10.7%)	13 (7.5%)
Urinary tract infection	5 (9.6%)	18 (11.2%)	0	2 (15.4%)	5 (8.9%)	20 (11.5%)
Injury, poisoning and procedural complications						
Infusion-related reaction	5 (9.6%)	15 (9.3%)	1 (25.0%)	1 (7.7%)	6 (10.7%)	16 (9.2%)
Musculoskeletal and connective tissue disorders						
Arthralgia	3 (5.8%)	17 (10.6%)	0	1 (7.7%)	3 (5.4%)	18 (10.3%)
Back pain	2 (3.8%)	11 (6.8%)	0	2 (15.4%)	2 (3.6%)	13 (7.5%)
Nervous system disorders						
Headache	4 (7.7%)	14 (8.7%)	0	0	4 (7.1%)	14 (8.0%)

AQP4-IgG = autoantibodies against aquaporin-4; MedDRA = Medical Dictionary for Regulatory Activities; sero+ = seropositive; sero- = seronegative; TEAE = treatment-emergent adverse event.
a Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.

Table 32: Treatment-emergent adverse events (⩾ 5% in total inebilizumab group) by system organ class and preferred term (any inebilizumab population)

System Organ Class [a] Preferred Term (MedDRA version 23.1)	AQP4-IgG sero+ N = 208	AQP4-IgG sero- N = 17	Total N = 225
Subjects with at least one TEAE with ≥ 5% in Total Inebilizumab group	192 (92.3%)	16 (94.1%)	208 (92.4%)
Blood and lymphatic system disorders			
Anaemia	13 (6.3%)	0	13 (5.8%)
Eye disorders			
Eye pain	11 (5.3%)	1 (5.9%)	12 (5.3%)
Gastrointestinal disorders			
Constipation	14 (6.7%)	0	14 (6.2%)
Diarrhoea	17 (8.2%)	3 (17.6%)	20 (8.9%)
Nausea	15 (7.2%)	1 (5.9%)	16 (7.1%)
General disorders and administration site conditions			
Fatigue	13 (6.3%)	1 (5.9%)	14 (6.2%)
Infections and infestations			
Bronchitis	13 (6.3%)	2 (11.8%)	15 (6.7%)
Influenza	20 (9.6%)	0	20 (8.9%)
Nasopharyngitis	44 (21.2%)	3 (17.6%)	47 (20.9%)
Upper respiratory tract infection	35 (16.8%)	0	35 (15.6%)
Urinary tract infection	56 (26.9%)	3 (17.6%)	59 (26.2%)
Injury, poisoning and procedural complications			
Fall	12 (5.8%)	1 (5.9%)	13 (5.8%)
Infusion-related reaction	27 (13.0%)	2 (11.8%)	29 (12.9%)
Musculoskeletal and connective tissue disorders			
Arthralgia	36 (17.3%)	3 (17.6%)	39 (17.3%)
Back pain	26 (12.5%)	5 (29.4%)	31 (13.8%)
Pain in extremity	14 (6.7%)	2 (11.8%)	16 (7.1%)
Nervous system disorders			
Headache	33 (15.9%)	1 (5.9%)	34 (15.1%)
Hypoaesthesia	12 (5.8%)	1 (5.9%)	13 (5.8%)
Paraesthesia	13 (6.3%)	1 (5.9%)	14 (6.2%)
Psychiatric disorders			
Insomnia	12 (5.8%)	3 (17.6%)	15 (6.7%)
Respiratory, thoracic and mediastinal disorders			
Cough	20 (9.6%)	1 (5.9%)	21 (9.3%)

AQP4-IgG = autoantibodies against aquaporin-4; MedDRA = Medical Dictionary for Regulatory Activities; sero+ = seropositive; sero- = seronegative; TEAE = treatment-emergent adverse event.
a Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.

Table 33: Treatment-emergent adverse events (≥ 2% in total MEDI-551 group) by system organ class and preferred term (randomised-controlled period) as-treated population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
System Organ Class[a] Preferred Term (MedDRA version 23.1)	Placebo N = 52	MEDI551 N = 161	Placebo N = 4	MEDI551 N = 13	Placebo N = 56	MEDI551 N = 174
Subjects with at least one event occuring in ≥2% subjects in Any MEDI-551 Group [b]	23 (44.2%)	82 (50.9%)	0	8 (61.5%)	23 (41.1%)	90 (51.7%)
Blood and lymphatic system disorders	0	6 (3.7%)	0	0	0	6 (3.4%)
Lymphopenia	0	3 (1.9%)	0	0	0	3 (1.7%)
Neutropenia	0	4 (2.5%)	0	0	0	4 (2.3%)
Endocrine disorders	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Hyperthyroidism	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Eye disorders	1 (1.9%)	6 (3.7%)	0	1 (7.7%)	1 (1.8%)	7 (4.0%)
Eye inflammation	0	0	0	1 (7.7%)	0	1 (0.6%)
Eye pain	1 (1.9%)	4 (2.5%)	0	0	1 (1.8%)	4 (2.3%)
Vision blurred	0	2 (1.2%)	0	1 (7.7%)	0	3 (1.7%)
Gastrointestinal disorders	3 (5.8%)	7 (4.3%)	0	1 (7.7%)	3 (5.4%)	8 (4.6%)
Diarrhoea	3 (5.8%)	7 (4.3%)	0	1 (7.7%)	3 (5.4%)	8 (4.6%)
General disorders and administration site conditions	1 (1.9%)	7 (4.3%)	0	1 (7.7%)	1 (1.8%)	8 (4.6%)
Fatigue	1 (1.9%)	4 (2.5%)	0	0	1 (1.8%)	4 (2.3%)
Non-cardiac chest pain	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Peripheral swelling	0	3 (1.9%)	0	0	0	3 (1.7%)
Immune system disorders	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Seasonal allergy	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Infections and infestations	10 (19.2%)	47 (29.2%)	0	3 (23.1%)	10 (17.9%)	50 (28.7%)
Bacteriuria	0	0	0	1 (7.7%)	0	1 (0.6%)
Cystitis	0	4 (2.5%)	0	1 (7.7%)	0	5 (2.9%)
Hordeolum	0	3 (1.9%)	0	0	0	3 (1.7%)
Nasopharyngitis	6 (11.5%)	12 (7.5%)	0	1 (7.7%)	6 (10.7%)	13 (7.5%)
Pharyngitis	0	3 (1.9%)	0	0	0	3 (1.7%)
Respiratory tract infection viral	0	3 (1.9%)	0	0	0	3 (1.7%)
Rhinitis	0	3 (1.9%)	0	0	0	3 (1.7%)
Sinusitis	0	3 (1.9%)	0	0	0	3 (1.7%)
Urinary tract infection	5 (9.6%)	18 (11.2%)	0	2 (15.4%)	5 (8.9%)	20 (11.5%)
Injury, poisoning and procedural complications	1 (1.9%)	7 (4.3%)	0	1 (7.7%)	1 (1.8%)	8 (4.6%)
Fall	1 (1.9%)	7 (4.3%)	0	1 (7.7%)	1 (1.8%)	8 (4.6%)
Skin laceration	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Investigations	0	0	0	1 (7.7%)	0	1 (0.6%)
Crystal urine present	0	0	0	1 (7.7%)	0	1 (0.6%)
Metabolism and nutrition disorders	1 (1.9%)	0	0	1 (7.7%)	1 (1.8%)	1 (0.6%)
Hypertriglyceridaemia	1 (1.9%)	0	0	1 (7.7%)	1 (1.8%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	5 (9.6%)	25 (15.5%)	0	2 (15.4%)	5 (8.9%)	27 (15.5%)
Arthralgia	3 (5.8%)	17 (10.6%)	0	1 (7.7%)	3 (5.4%)	18 (10.3%)
Back pain	2 (3.8%)	11 (6.8%)	0	2 (15.4%)	2 (3.6%)	13 (7.5%)
Flank pain	0	0	0	1 (7.7%)	0	1 (0.6%)
Muscular weakness	0	3 (1.9%)	0	0	0	3 (1.7%)
Nervous system disorders	5 (9.6%)	20 (12.4%)	0	2 (15.4%)	5 (8.9%)	22 (12.6%)
Dysaesthesia	0	3 (1.9%)	0	0	0	3 (1.7%)
Epilepsy	0	0	0	1 (7.7%)	0	1 (0.6%)
Headache	4 (7.7%)	14 (8.7%)	0	0	4 (7.1%)	14 (8.0%)
Hypoaesthesia	1 (1.9%)	5 (3.1%)	0	1 (7.7%)	1 (1.8%)	6 (3.4%)
Paraesthesia	0	4 (2.5%)	0	0	0	4 (2.3%)

Psychiatric disorders	1 (1.9%)	3 (1.9%)	0	1 (7.7%)	1 (1.8%)	4 (2.3%)
Insomnia	1 (1.9%)	3 (1.9%)	0	1 (7.7%)	1 (1.8%)	4 (2.3%)
Renal and urinary disorders	0	4 (2.5%)	0	1 (7.7%)	0	5 (2.9%)
Leukocyturia	0	1 (0.6%)	0	1 (7.7%)	0	2 (1.1%)
Nocturia	0	3 (1.9%)	0	0	0	3 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	4 (2.5%)	0	0	1 (1.8%)	4 (2.3%)
Oropharyngeal pain	1 (1.9%)	4 (2.5%)	0	0	1 (1.8%)	4 (2.3%)
Skin and subcutaneous tissue disorders	0	4 (2.5%)	0	1 (7.7%)	0	5 (2.9%)
Hyperhidrosis	0	0	0	1 (7.7%)	0	1 (0.6%)
Rash	0	4 (2.5%)	0	0	0	4 (2.3%)

a Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.
b Treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo)

Adverse Events by Severity

Most TEAEs reported during the RCP and OLP were mild or moderate in severity.

Overall, during the RCP, patients treated with inebilizumab experienced fewer Grade 3 TEAEs than patients treated with placebo (8.0% vs. 12.5%), including in the SOC of Infections and Infestations, the SOC under which Grade 3 TEAEs were most frequently reported (n=3 (5.4%) and n=4 (2.3%) in the placebo and inebilizumab group, respectively). The only Grade 3 TEAEs occurring in more than 1 inebilizumab-treated subject during the RCP were 2 cases each of urinary tract infection and hypertension.

There were 9 subjects with life-threatening (Grade 4) TEAEs in the study. During the RCP, 1 subject in inebilizumab group had Grade 4 atypical pneumonia, which resulted in treatment discontinuation. The subject was first hospitalised on study day 18, i.e. when the maximal PD effect of inebilizumab had likely not occurred. CBC revealed lymphocyte and absolute neutrophil counts within the reference range. The sponsor considered that the event was possibly related to study drug, however, possible risk factors contributing to the event included a history of pulmonary tuberculosis and prior treatment with mycophenolate mofetil within 30 days of AE onset.

In total, 8 subjects experienced Grade 4 TEAEs during the OLP (4 in the inebilizumab/inebilizumab group and 4 in the placebo/inebilizumab group). Among these, 1 subject in the inebilizumab/inebilizumab group had Grade 4 respiratory failure. This TEAE involved a 47-year-old female patient initially randomised to the inebilizumab group who was hospitalised on multiple occasions for treatment of opportunistic respiratory infections, with administered treatments including IV immunoglobulin. There would appear to be ample indication that this life-threatening TEAE was likely related to treatment with inebilizumab, and that immunosuppression resulting in potentially life-threatening infections is a serious concern, even during relatively short duration of treatment.

The patient with 4 TEAEs reported with Grade 4 severity (CNS infection, NMOSD, probable PML, and post-cardiac arrest syndrome) is discussed in "*Serious Adverse Events and Deaths*" below. PTs of Grade 4 TEAEs observed during the OLP for the remaining 6 subjects are listed below; all were assessed as not related to inebilizumab by Investigator and Sponsor.

- Grade 4 Urinary tract infection, Pneumonia, Uraemic encephalopathy, Pickwickian syndrome, Rhabdomyolysis, Sleep apnea syndrome, Acute respiratory failure, and Acute kidney injury.
- Grade 4 Heroin overdose.
- Grade 4 Back pain and Muscular weakness.
- Grade 4 Perforated appendicitis.
- Grade 4 Acute cholecystitis.
- Grade 4 Bacteraemia.

Table 34: Summary of treatment-emergent adverse events by highest severity, randomised-controlled period (as-treated population)

	Highest Severity[a]	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
		Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Subjects with at least one TEAE	Grade 1	14 (26.9%)	59 (36.6%)	4 (100%)	3 (23.1%)	18 (32.1%)	62 (35.6%)
	Grade 2	16 (30.8%)	46 (28.6%)	0	4 (30.8%)	16 (28.6%)	50 (28.7%)
	Grade 3	7 (13.5%)	13 (8.1%)	0	1 (7.7%)	7 (12.5%)	14 (8.0%)
	Grade 4	0	1 (0.6%)	0	0	0	1 (0.6%)

AQP4-IgG = autoantibodies against aquaporin-4; sero+ = seropositive; sero- = seronegative; TEAE = treatment-emergent adverse event.
a Grade 1= Mild, Grade 2=Moderate, Grade 3= Severe, Grade 4= Life-threatening, Grade 5= Fatal. Severity grade displays if there is an occurrence in at least one group.

Table 35: Summary of treatment-emergent adverse events highest severity, open-label period (open-label population)

	Highest Severity[a]	AQP4-IgG sero+ N = 201		AQP4-IgG sero- N = 15		Total N = 216	
		Placebo/ Inebilizumab N = 47	Inebilizumab/ Inebilizumab N = 154	Placebo/ Inebilizumab N = 4	Inebilizumab/ Inebilizumab N = 11	Placebo/ Inebilizumab N = 51	Inebilizumab / Inebilizumab N = 165
Subjects with at least one TEAE	Grade 1	8 (17.0%)	42 (27.3%)	1 (25.0%)	5 (45.5%)	9 (17.6%)	47 (28.5%)
	Grade 2	18 (38.3%)	61 (39.6%)	2 (50.0%)	5 (45.5%)	20 (39.2%)	66 (40.0%)
	Grade 3	11 (23.4%)	25 (16.2%)	0	0	11 (21.6%)	25 (15.2%)
	Grade 4	3 (6.4%)	3 (1.9%)	1 (25.0%)	1 (9.1%)	4 (7.8%)	4 (2.4%)
	Grade 5	1 (2.1%)	2 (1.3%)	0	0	1 (2.0%)	2 (1.2%)

AQP4-IgG = autoantibodies against aquaporin-4; sero+ = seropositive; sero- = seronegative; TEAE = treatment-emergent adverse event.
a Grade 1= Mild, Grade 2=Moderate, Grade 3= Severe, Grade 4= Life-threatening, Grade 5= Fatal. Severity grade displays if there is an occurrence in at least one group.

Adverse Events of Special Interest

During the RCP, infusion-related reactions were more common in the placebo group compared to the inebilizumab treatment arm (10.7% vs. 9.2%). The most common infusion-related reaction symptoms observed in the Any Inebilizumab population were headache (n =7, 3.1%) and nausea (n = 5, 2.2%). In the OLP, infusion-related reactions were less frequent in the inebilizumab/inebilizumab group than in the placebo/inebilizumab group. Throughout Study 1155, there were no anaphylactic or other serious allergic events related to infusion, with all infusion-related reactions rated Grade 1 or Grade 2, including one Grade 2 infusion-related reaction (migraine) that was serious and required hospitalisation of the patient.

Infections overall were reported in a similar percentage of patients in both treatment groups during the RCP (39.1% in the inebilizumab total group and 41.1% in the placebo group). Also, patients treated with inebilizumab experienced fewer serious infections compared to placebo (1.1% vs. 3.6%). According to the originally submitted CSR of Study 1155 dated 15 May 2019 (which formed the basis for the day 80

critical assessment reports), during the RCP, opportunistic infections were recorded in a lower proportion of subjects treated with inebilizumab (2.9%) compared to placebo (10.7%); conversely, in the open-label period, opportunistic infections occurred more frequently in the inebilizumab/inebilizumab group compared to placebo/inebilizumab-treated subjects (10.9% vs. 5.9%). According to the updated CSR (dated 09 Jun 2021) submitted together with the applicant's *MAA Day 120 Clinical Responses*, during the RCP there were no occurrences of opportunistic infection, and during the OLP there were 2 opportunistic infections, both occurring in inebilizumab-treated subjects. The difference in observed frequency of opportunistic infections between the primary analysis (database lock Dec 2018) and the final analysis (database lock Dec 2020) is due to up-versioning of MedDRA between the initial and final analyses. The initial analysis was based on the Opportunistic Infection SMQ from MedDRA version 21.0. The final analysis was based on the "narrow" terms in the Opportunistic Infection SMQ from MedDRA version 23.0. This resulted in some preferred terms (in particular herpes zoster, influenza, and oral herpes) no longer being tabulated as opportunistic infections and accounts for the apparent reduction in opportunistic infection frequency; these preferred terms are now categorised in the SOC "Infections." Based on the initial submission's information, while the data overall does not demonstrate any clear trend regarding opportunistic infections, the noted between-group difference during the OLP could indicate that treatment with inebilizumab over the longer term might indeed increase such risk. As previously discussed, one TEAE of Grade 4 respiratory failure during the OLP was reported for a patient in the inebilizumab/inebilizumab group who was hospitalised on multiple occasions for treatment of opportunistic respiratory infections.

There was one case of "probable PML" (verbatim term)/"progressive multifocal leukoencephalopathy" (PT) reported in the OLP, which was associated with a fatal TESAE of pneumonia. This case is presented in the section "*Serious adverse events and deaths*" below.

Of note, 2 cases of COVID-19 were reported during the OLP of study 1155 (including one fatal case of COVID-19 pneumonia and 3 events related to COVID-19 have been reported in post-marketing surveillance data up to 30Apr2021). The applicant indicates that SARS-CoV-2 immunisation status of the 5 COVID-19 cases is not known and that based on the dates of occurrence relative to COVID-19 vaccine availability, vaccination of these patients was unlikely.

The applicant agrees that data is needed on vaccine responses in patients receiving inebilizumab. COVID-19 vaccine responses are being measured in the ongoing kidney transplant desensitisation study (VIB0551.P2.S1) and will be measured in the long-term follow-up of NMOSD patients.

During the OLP, one subject had a serious adverse event of "colon cancer stage III". The size and duration of the randomised controlled period and the open label follow-up extension are too limited to adequately assess long-term risks of secondary malignancies (and opportunistic infections).

Table 36: Treatment-emergent adverse events of special interest by category, randomised-controlled period (as-treated population)

Category [a]	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Subjects with at least one TEAE of special interest	26 (50.0%)	79 (49.1%)	1 (25.0%)	4 (30.8%)	27 (48.2%)	83 (47.7%)
Infusion-related reaction	5 (9.6%)	15 (9.3%)	1 (25.0%)	1 (7.7%)	6 (10.7%)	16 (9.2%)
Anaphylactic reaction	0	0	0	0	0	0
Hypersensitivity	0	0	0	0	0	0
Infections	23 (44.2%)	65 (40.4%)	0	3 (23.1%)	23 (41.1%)	68 (39.1%)
Hepatic function abnormality	2 (3.8%)	8 (5.0%)	0	0	2 (3.6%)	8 (4.6%)
Cytopenia	0	8 (5.0%)	0	0	0	8 (4.6%)
Opportunistic infections	0	0	0	0	0	0
PML	0	0	0	0	0	0

AQP4-IgG = autoantibodies against aquaporin-4; PML = progressive multifocal leukoencephalopathy; sero+ = seropositive; sero- = seronegative; TEAE = treatment-emergent adverse event
a Subjects are counted once for each System Organ Class and Preferred Term regardless of the number of events.

Table 37: Treatment-emergent adverse events of special interest by category, open-label period (open-label population)

Category [a]	AQP4-IgG sero+ N = 201		AQP4-IgG sero- N = 15		Total N = 216	
	Placebo/ Inebilizumab N = 47	Inebilizumab/ Inebilizumab N = 154	Placebo/ Inebilizumab N = 4	Inebilizumab / Inebilizumab N = 11	Placebo/ Inebilizumab N = 51	Inebilizumab / Inebilizumab N = 165
Subjects with at least one TEAE of special interest	40 (85.1%)	110 (71.4%)	2 (50.0%)	9 (81.8%)	42 (82.4%)	119 (72.1%)
Infusion-related reaction	6 (12.8%)	8 (5.2%)	0	2 (18.2%)	6 (11.8%)	10 (6.1%)
Anaphylactic reaction	0	0	0	0	0	0
Hypersensitivity	0	2 (1.3%)	0	0	0	2 (1.2%)
Infections	39 (83.0%)	105 (68.2%)	2 (50.0%)	8 (72.7%)	41 (80.4%)	113 (68.5%)
Hepatic function Abnormality	3 (6.4%)	6 (3.9%)	0	0	3 (5.9%)	6 (3.6%)
Cytopenia	3 (6.4%)	4 (2.6%)	0	0	3 (5.9%)	4 (2.4%)
Opportunistic infections	0	2 (1.3%)	0	0	0	2 (1.2%)
PML [b]	0	1 (0.6%)	0	0	0	1 (0.6%)

AQP4-IgG = autoantibodies against aquaporin-4; NMOSD = neuromyelitis optica spectrum disorders; PML = progressive multifocal leukoencephalopathy; sero+ = seropositive; sero- = seronegative; TEAE = treatment-emergent adverse event.
a Subjects are counted once for each category regardless of the number of events.
b One case of "probable PML" (verbatim term)/ "progressivee multifocal leukoencephalopathy" (preferred term) was reported. A definitive diagnosis could not be established, but the differential diagnosis included PML, acute disseminated encephalomyelitis, or atypical NMOSD attack.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

There was a total of 5 deaths reported in the two phase 1 and one phase 2/3 studies of inebilizumab.

During the pivotal Study 1155, there were no deaths during the RCP and 3 deaths during the OLP. One of these cases involved a patient (age 30-40 years) with longstanding NMOSD and significant baseline disability who was initially randomised to placebo. The applicant's assessment that this death was not related to inebilizumab is considered reasonable, as the clinical picture suggested a new NMOSD-related proximal CNS lesion affecting respiratory function as likely cause of the subject's rather sudden demise: a protocol-defined relapse occurred two days prior to death, during which the subject experienced increased extremity weakness and new bladder/bowel dysfunction. The second death was a patient (age 60-70 years) randomised to inebilizumab who after several months of treatment was hospitalised with lesions consistent with PML, with differential diagnoses including acute disseminated encephalomyelitis and atypical NMOSD relapse. JC virus testing results were discrepant. While a definite diagnosis of the CNS lesions could not be established, this case of potential PML together with the fact that other B-cell-depleting therapies have been associated with risk of PML support an SmPC warning for PML and other opportunistic infections. The third death involved a subject who was randomised to inebilizumab and subsequently entered the OLP. The subject died as a result of viral pneumonia due to coronavirus disease 2019 (COVID-19). Both Investigator and Sponsor assessed this event as not related to inebilizumab.

There would appear to be no indication that the two deaths in the phase 1 study programme were related to treatment with the IP.

Other Serious Adverse Events

During the RCP, 15 subjects had at least TESAE: 9 subjects (5.2%) in the inebilizumab group and 6 subjects (10.7%) in the placebo group. There was no predominant event by PT and there were no overall trends observed by SOC. However, with regards to hepatobiliary disorders, 3 TESAEs (PTs: cholangitis acute, cholecystitis acute and hepatic function abnormal) were reported in the inebilizumab-treated group versus none in the placebo group during the RCP. TESAEs within the Infections and infestations SOC were reported for 2 patients (1.1%) treated with inebilizumab ("atypical pneumonia" and "urinary tract infection") and for two subjects (3.6%) in the placebo group (PTs: "meningitis viral", "pneumonia" and "septic shock"). During the RCP, 2 subjects in the inebilizumab-arm also experienced hepatobiliary SAE ("cholangitis acute", "cholecystitis acute", as per above) which could have been included in the basket of isolated single events involving serious infections. Nonetheless, there was no difference in the incidence of serious infections between active and placebo treatment groups. Two of the TESAEs within the active treatment group ("Neuromyelitis optica spectrum disorder" and "myelitis transverse", the latter reported as non-infectious) were likely due to the disease under study.

During the OLP, in total 41 subjects (19.0%) had at least one TESAE. Among these, 23 subjects had serious infections, including 8 subjects with urinary tract infection and 6 subjects with pneumonia, two of which resulted in death (including one case of COVID-19 pneumonia), two cases of appendicitis as well as single cases of bacteraemia, bronchiolitis, cellulitis, COVID-19, chorioretinitis, Hepatitis A, influenza, intervertebral discitis, neuroborreliosis, osteomyelitis, "possible PML", pyelonephritis chronic, renal abscess, sinusitis, subcutaneous abscess, and herpes zoster. The TESAEs of bronchiolitis, cellulitis, herpes zoster, influenza, sinusitis, and subcutaneous abscess were reported as related to IP, as was a case of sepsis. TESAEs of seizures and acute kidney injury were also reported.

2.6.8.4. Laboratory findings

Laboratory Values Over Time

No clinically meaningful trends were identified in the average changes from baseline during the RCP or OLP in haematologic variables of haemoglobin, haematocrit, eosinophils, eosinophils/leukocytes (%), basophils, basophils/leukocytes (%), erythrocytes, mean corpuscular haemoglobin concentration, mean corpuscular volume, and platelets.

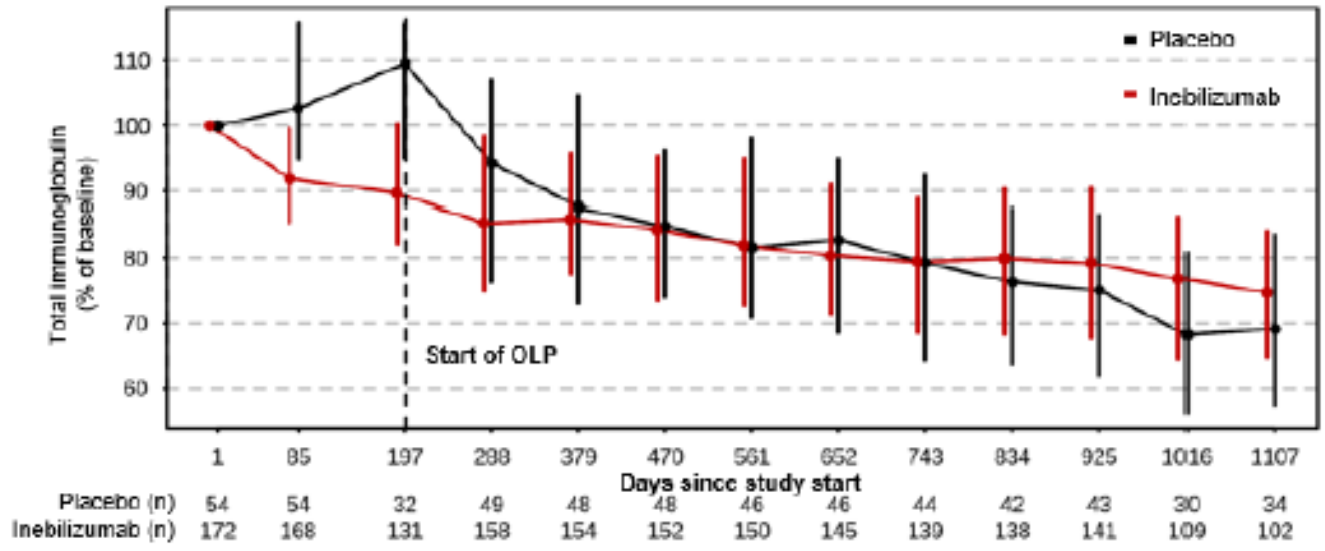
During the RCP overall, lymphocyte counts were lower in the inebilizumab group than the placebo group, which is consistent with the mechanism of action of the drug. With longer-term exposure during the OLP, the lymphocyte levels trended back to the baseline level.

Neutrophil levels were elevated in both treatment groups at Weeks 1 and 2, likely reflecting an effect from corticosteroids. Neutrophil levels returned to the baseline level at Week 4. Mean percent change from baseline at Week 28 in neutrophil levels was similar between the treatment groups (0.87% for inebilizumab, 1.14% placebo). During the OLP, there was no trend for neutrophil counts.

No clinically meaningful trends were identified in the average changes from baseline in albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, cholesterol, creatinine, gamma glutamyl transferase, magnesium, potassium, sodium, triglycerides, urate, or glucose.

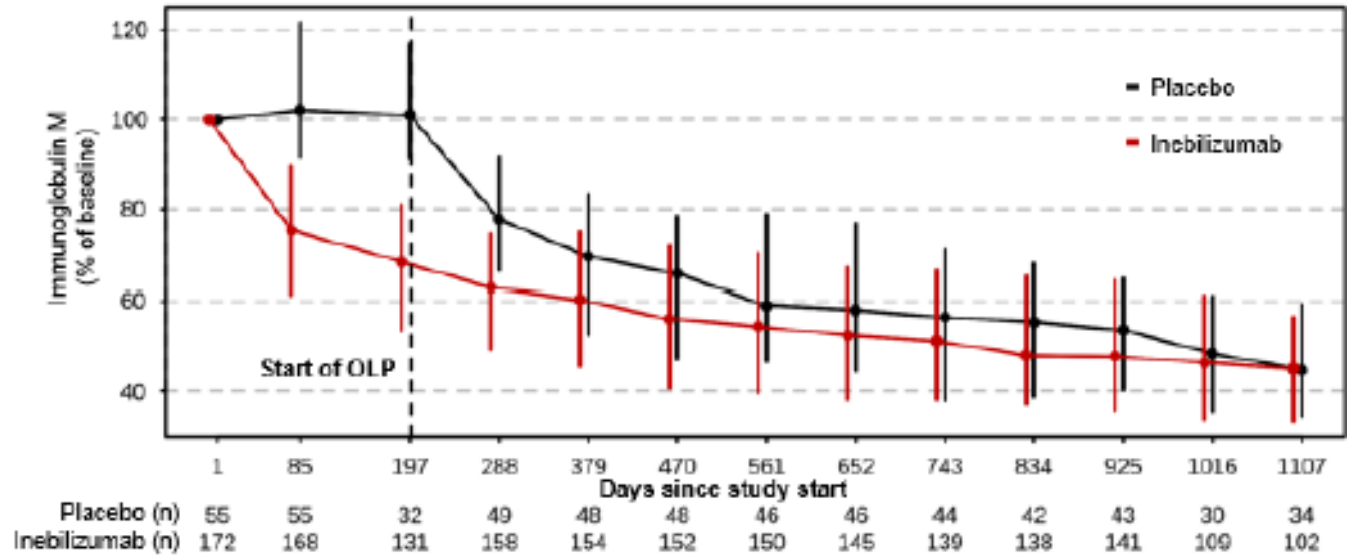
Immunoglobulin results by visit in the RCP and OLP are provided for total Ig (Figure 26) and for IgM (Figure 27).

Figure 26: Median percent of baseline in total immunoglobulin levels (Study 1155)



OLP = open-label period

Figure 27: Median percent of baseline in IgM levels (Study 1155)



IgM = immunoglobulin M; OLP = open-label period

During the OLP, Ig levels generally trended lower over time. Of note are the following:

- In the subjects receiving inebilizumab from the start of the RCP, the median percent of baseline in total Ig levels at OLP Week 0 was approximately 90%, decreasing to 70-75% of baseline by Study Day 1107 in all inebilizumab-treated subjects, including placebo-randomised subjects receiving inebilizumab in the OLP.
- Ig subtypes followed the same overall decreasing trend as total Ig levels with IgE showing the greatest median percentage change from baseline levels at Study Day 1107 (-78%). IgA and IgM levels decreased to approximately 58% and 45%, respectively, of baseline by Study Day 1107.
- The change in IgG levels was more gradual and was consistent with total Ig.

This progressive decrease in serum immunoglobins, which did not appear to reach a clear plateau, is a substantial concern as it may over time lead to increased risk of serious and/or opportunistic infections. The level of immunoglobulins should be monitored prior to initiating treatment, during treatment and after discontinuation of treatment until B-cell repletion as per SmPC wordings.

Anti-tetanus toxoid IgG was measured to evaluate the effect on inebilizumab on vaccine-generated antibody titres. Tetanus vaccine titres were tested at Day 1 for all subjects. Subjects with a negative result did not continue to be tested; subjects who tested positive were tested at protocol specified timepoints (RCP: W0 and W28; OLP: W13, W26, W52 and every 26 weeks thereafter).

Results were available for 91 inebilizumab and 25 placebo treated subjects at RCP Week 28. Median percent change from baseline was 6.82% for inebilizumab and -5.10% for placebo. During the OLP, for the group originally randomised to inebilizumab, the median percent change from baseline in titre at OLP Week 52 was 15.82% (n=118), at OLP Week 104 was 7.78% (n=109), and at OLP Week 156 was -1.01% (n=65). In contrast, for the group originally randomised to placebo, the median percent change from baseline in titre at OLP Week 52 was -0.11% (n=40), at OLP Week 104 was -8.85% (n=32), and at OLP Week 156 was -13.48% (n=19).

Regarding the apparent decrease from baseline in median vaccine titres in the placebo/inebilizumab group during the OLP, the applicant indicated that this decrease was apparent at most of the OLP time points with some variation in median values, and concludes that the significance of this effect is not clear and may be related to the relatively small number of subjects in the placebo/inebilizumab subgroup as the OLP progressed.

In conclusion, vaccine titre results for subjects treated with inebilizumab/inebilizumab indicate no reduction in tetanus vaccine titres after 3.5 years of treatment, while results for subjects of the placebo/inebilizumab group are more equivocal. In this regard, the fact that no sentence indicating the proportion of patients with positive antibody titres against the tetanus toxin when compared to baseline after treatment with inebilizumab has been added in section 4.5, is supported.

Individual Subject Changes

During the RCP, a higher proportion of subjects in the inebilizumab group had at least a 2-grade worsening from baseline compared to the placebo group in the following laboratory parameters:

- Leukocytes: inebilizumab 6.4% versus placebo 1.8%
- Lymphocytes (decreased): inebilizumab 20.2% versus placebo 8.9%
- Neutrophils: inebilizumab 5.8% versus placebo 0%.

By analysis of laboratory results in the RCP, a neutrophil level of 1.0 to 1.5 × 10^9/L was observed in 6.9% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. A neutrophil level of 0.5 to 1.0 × 10_9/L was observed in 1.7% of inebilizumab-treated patients versus 0% of placebo-treated patients. Neutropenia was generally transient, and no subject with laboratory-defined Grade 2 or higher neutropenia experienced a serious infection.

Of 9 reports of neutropenia, the time to onset for 8 events occurred at least 4 weeks after the previous dose (range, 34 to 291 days; mean, 151 days) and the duration ranged from 7 to 109 days (mean, 35 days). The majority of the events were mild to moderate in severity and 9 events resolved. The applicant added "late onset neutropenia" to the tabulated list of adverse reactions in section 4.8 of the SmPC, which is supported. A dedicated paragraph has been added to section 4.4 of the SmPC, with measurements of blood neutrophils to be recommended in patients with signs and symptoms of infection, in agreement with SmPC of other B-cell depleting therapies.

No other clinically meaningful trends were observed.

Individual Clinically Significant Abnormalities

Grade 2 leukopenia was numerically more common in the inebilizumab group (3.3% inebilizumab, 0% placebo at RCP Week 28).

There were no Grade 3 or higher leukopenia events.

Neutropenia reported as AE was numerically more common in the inebilizumab group, though overall rates were low: 1.7% vs 0% in placebo for ≥ Grade 3 events during the RCP; 1.9% vs. 0% for ≥ Grade 3 events in the inebilizumab/inebilizumab group compared to placebo/inebilizumab-treated subjects during the OLP. No cases of Grade 4-5 neutropenia were reported. Neutropenia lead to discontinuation of inebilizumab in one patient following study day 576. The subject had previously experienced two cases of mild influenza, which began on study day 375 and study day 438. No other episodes of infection were reported for this patient. Reduced neutrophil counts have been reported for other B-cell depleting monoclonal antibodies and may be a class effect.

There were no cases that fulfilled the Hy's criteria for hepatic injury

2.6.8.5. Safety in special populations

Intrinsic and Extrinsic Factors

Fewer American Indian or Alaskan Native subjects reported TEAEs (inebilizumab group 35.7% versus 73.0% in total population; placebo group 40.0% versus 73.2% in the total population). Within the inebilizumab group, at least one TEAE was reported in a higher proportion of the subgroup with prior NMOSD treatment than the subgroup without prior NMOSD treatment (80.9% versus 57.6%). No other notable subgroup differences were present when analyzed by sex, race, geographic region, or previous treatment; however, some subgroups had too few subjects to draw conclusions regarding potential imbalances. A popPK analysis indicated that there was no significant effect of sex, age, or race on inebilizumab clearance.

The number of patients >65 years of age in the pivotal Study 1155 was limited to n=10.

No formal clinical studies have been conducted to investigate the effect of renal or hepatic impairment on inebilizumab.

Use in Pregnancy and Lactation

While pregnancy or lactation constituted exclusion criteria in the clinical study programme, pregnancies occurred in 3 inebilizumab-treated patients. All 3 children were delivered with no abnormalities or health problems reported.

Immunoglobulins are known to cross the placenta, and lymphocytopenia have been reported in infants exposed in utero to maternal treatment with other B-cell depleting antibodies. There was a reduction in huCD19+ B cells in the fetal livers of progeny of dosed mice, suggesting inebilizumab crosses the placenta and depletes B cells. In a study evaluating the reproductive process in huCD19 transgenic mice, inebilizumab appeared to be associated with reduced number of pregnancies without apparent adverse effects on fetal development. However, offspring from both inebilizumab dose levels tested displayed diminished antibody response to functional testing after B-cells had repopulated.

Considered the above and the fact that women of reproductive age make up a substantial proportion of patients with NMOSD a Pregnancy Registry has been requested.

2.6.8.6. Immunological events

Rates of TEAEs, including infusion-related reactions, did not differ based on ADA status. Concerns on the validity of the ADA assay were discussed and the arguments provided by the applicant were considered acceptable (clinical efficacy discussion).

No clinical data has established a link between B cell depletion and development or worsening of autoimmune diseases.

2.6.8.7. Safety related to drug-drug interactions and other interactions

The risk of PK DDI involving inebilizumab as either victim or perpetrator is considered low.

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

2.6.8.8. Discontinuation due to adverse events

During the RCP, 2 subjects had TEAEs resulting in permanent discontinuation of the IP. Both subjects were in the inebilizumab group: 1 subject had atypical pneumonia and the other subject had worsening of myasthenia gravis. During the OLP, 5 subjects had TEAEs leading to permanent discontinuation; these TEAEs were neutropenia, steroid withdrawal syndrome, hepatic steatosis, pneumonia, liver function test increased, and breast cancer female.

Overall, the rates of discontinuation due to AE during the RCP and OLP were low. However, these low rates should be viewed in context of the short time of treatment during the RCP (up to 197 days), including the RCP's time-to-event design, together with the relatively limited duration of the OLP.

During the OLP, an imbalance in discontinuations due to "Withdrawal of consent" was observed between groups of AQP4-IgG seropositive subjects (n = 13 for inebilizumab/inebilizumab vs. n = 0 for placebo/inebilizumab). The applicant has clarified that in no case did the investigator provide a reason underlying such withdrawals. While this between-group difference is unexplained, the unequal randomisation (3:1 inebilizumab versus placebo) must be acknowledged. Further, the lack of any clear imbalance between groups in overall withdrawals during the OLP (17% for placebo/inebilizumab and 20.8% for inebilizumab/inebilizumab) and the fact that "AE" was available to the investigator as a reason for subject withdrawal offer some level of reassurance.

2.6.8.9. Post marketing experience

On June 11, 2020, the US FDA approved inebilizumab (Uplizna) for treatment of NMOSD in adult patients who are AQP4 antibody positive. The applicant provided a summary of requested post-marketing data (11 Jun 2020 – 30 Apr 2021). Fifty-two (52) spontaneous case reports are mentioned for a total of 165 events. Among these events, 9 were considered serious and 156 were considered non-serious. Narratives for these 9 SAEs were provided by the applicant but were however not considered very informative due to the lack of details and missing information. (These 9 SAEs including 5 cases with limited information or due to underlying NMOSD (gait inability, monoplegia, NMOSD, blindness and NMOSD) and 3 SAEs related to Covid-19 infections). The risk of increased susceptibility to infection is already described in section 4.4 of the SmPC and is considered appropriate.

2.6.9. Discussion on clinical safety

Clinical Studies Contributing to the Safety Evaluation

The safety assessment of inebilizumab is mainly based on data from the randomised controlled period and the OLP of a single pivotal phase 2/3 trial (CD-IA-MEDI-551-1155 [Study 1155]). In addition, data from two small, single-dose phase 1 studies, one in patients with scleroderma (Study MI-CP200 [Study CP200]) and one in subjects with relapsing forms of MS (Study CD-IA-MEDI-551-1102 [Study 1102]) are briefly summarised.

Safety Population and Exposure

Patients recruited into the pivotal clinical Study 1155 covered a broad spectrum of NMOSD disease severity at baseline, both naïve and previously treated patients were included. Background immunosuppressive therapy was not permitted. Among 230 subjects randomised and treated during the RCP (56 subjects received placebo), only 17 (including 4 placebo-treated subjects) were seronegative for the antiAQP4-lgG antibody. The ratio of female to male was different between the AQP4-IgG seropositive and seronegative subjects, 93.9% versus 6.1%, and 52.9% versus 47.1%, respectively. Otherwise, demographic and baseline disease characteristics did not differ notably in regard to safety

risks by AQP4-IgG status and were overall well-balanced between treatment groups. The number of patients >65 years of age in Study 1155 was limited to n=10.

The total exposure among 174 patients treated with inebilizumab during the RCP (duration up to 197 days) in Study 1155 was 82.55 person-years. Across the RCP and the OLP, 225 subjects received one or more doses of inebilizumab, with 87.6% of the subjects in the Any Inebilizumab population having received IP for > 548 days. As of end of study, the total person years of inebilizumab exposure was 730.36, and 204 subjects (189 AQP4-IgG-seropositive) had been treated with inebilizumab for ⩾366 days.

In conclusion, the number of patients exposed to inebilizumab in the pivotal Study 1155 is rather small but exceeds the minimum of 100 subjects exposed to IP for at least one year recommended by ICH E1 guidance. Furthermore, the applicant's analysis of exposure time can be considered conservative: exposure time calculations were based on last dose date plus 60 days (to reflect approximately 5 $t_{1/2}$ of IP), however inebilizumab is predicted to maintain B-cell suppression for 28 weeks.

Disposition

Two patients (3.6%) in the placebo group and 6 patients (3.4%) in the inebilizumab arm did not complete the RCP. Of the 6 subjects in the inebilizumab group who withdrew from the RCP, 2 discontinued due to AEs: 1 subject with worsening of myasthenia gravis and 1 subject with atypical pneumonia. During the OLP, 5 subjects had TEAEs leading to permanent discontinuation; these TEAEs were neutropenia, steroid withdrawal syndrome, hepatic steatosis, pneumonia, liver function test increased, and breast cancer female. These discontinuations due to TEAE do not raise specific concerns, since each TEAE that resulted in permanent discontinuation of IP was experienced by one subject. During the OLP, an imbalance in discontinuations due to "Withdrawal of consent" was observed between groups of AQP4-IgG seropositive subjects (n = 13 for inebilizumab/inebilizumab vs. n = 0 for placebo/inebilizumab). The applicant has clarified that in no case did the investigator provide a reason underlying such withdrawals. While this between-group difference is unexplained, the unequal randomisation (3:1 inebilizumab versus placebo) is acknowledged. Further, the lack of any clear imbalance between groups in overall withdrawals during the OLP (17% for placebo/inebilizumab and 20.8% for inebilizumab/inebilizumab) and the fact that "AE" was available to the investigator as a reason for subject withdrawal offer some level of reassurance.

Overview of Adverse Events

Adverse events were analysed in terms of percentage incidence in standard frequency tables. During the RCP, the majority of subjects had at least one TEAE. In the total As-treated population, similar proportions of subjects experienced TEAEs in the inebilizumab group (73.0%) and the placebo group (73.2%). In general, during the RCP, patients treated with inebilizumab had proportionately fewer severe and serious AEs compared to placebo-treated subjects, and the majority of AEs were mild or moderate.

During the OLP, the incidence rate of TEAEs per 100 person-years was 227.86 in the inebilizumab/inebilizumab group and 278.51 in the placebo/inebilizumab group.

Common Adverse Events

The most common AEs associated with inebilizumab were urinary tract infections, joint pain and other pain-related PTs: In the RCP, there were higher proportions of patients treated with inebilizumab vs placebo reporting the AEs urinary tract infection (11.5% vs. 8.9%), arthralgia (10.3% vs. 5.4%) and back pain (7.5% vs. 3.6%). The explanation for the potentially higher rate of joint pain and back pain with inebilizumab is unknown. Of note, an even higher rate of arthralgia (> 15%) has been reported for another NMOSD therapy (satralizumab (Enspryng)) with a different mechanism of action (interleukin-6 receptor antagonism). No patient discontinued Study 1155 due to arthralgia or other pain-related symptoms. The opposite finding in use of analgesics during the RCP – reported by 67.9% in the placebo

group vs. 50.6% of subjects randomised to inebilizumab – offers some further level of reassurance.

Conversely, lower rates of several AEs potentially associated with NMOSD (pain in extremity, pruritus, vomiting) were observed in the inebilizumab group compared with placebo.

No significant differences in incidence of AEs or any new obvious safety signals were apparent when limiting the analysis to AQP4-IgG-seropositive subjects.

Apart from relatively few events of diarrhoea (n=20 (8.9%), nausea (n=16(7.1%)) and constipation (n=14 (6.2%)) within the gastrointestinal disorders SOC, the most common AEs in the Any Inebilizumab Population were overall similar to those described during the RCP.

AEs involving infusion-related reaction, hypersensitivity, infections and cytopenia are among adverse events of special interest discussed below.

Treatment-emergent serious adverse events

During the RCP, 15 subjects had at least one TESAE: 9 subjects (5.2%) in the inebilizumab group and 6 subjects (10.7%) in the placebo group. There was no predominant event by PT and there were no trends observed by SOC. During the OLP, 41 subjects had at least one TESAE; 23 subjects had TESAEs in the SOC of Infections and infestations, including 8 subjects with urinary tract infections and 4 subjects with pneumonia.

Across both treatment periods, few subjects receiving inebilizumab had TEAEs leading to permanent discontinuation of IP: 2 subjects in the RCP (one with atypical pneumonia and one with myasthenia gravis) and 5 subjects in the OLP (neutropenia, steroid withdrawal syndrome, hepatic steatosis, pneumonia, liver function test increased, and breast cancer female).

Adverse Events of Special Interest

Infections

Infections overall were reported in a similar percentage of patients in both treatment groups during the RCP (39.1% in the inebilizumab total group and 41.1% in the placebo group). Serious infections were reported in 2 subjects (3.6%) in the placebo group and 2 subjects (1.1%) in the inebilizumab group. According to the originally submitted CSR of Study 1155 dated 15May2019 (which formed the basis for the day 80 critical assessment reports), during the RCP, opportunistic infections were recorded in a lower proportion of subjects treated with inebilizumab (2.9%) compared to placebo (10.7%); conversely, in the open-label period, opportunistic infections occurred more frequently in the inebilizumab/inebilizumab group compared to placebo/inebilizumab-treated subjects (10.9% vs. 5.9%). According to the updated CSR (dated 09Jun2021) submitted together with the applicant's MAA Day 120 Clinical Responses, during the RCP there were no occurrences of opportunistic infection, and during the OLP there were 2 opportunistic infections, both occurring in inebilizumab-treated subjects. The difference in observed frequency of opportunistic infections between the primary analysis (database lock Dec 2018) and the final analysis (database lock Dec 2020) is due to up-versioning of MedDRA between the initial and final analyses. The initial analysis was based on the Opportunistic Infection SMQ from MedDRA version 21.0. The final analysis was based on the "narrow" terms in the Opportunistic Infection SMQ from MedDRA version 23.0. This resulted in some preferred terms (in particular herpes zoster, influenza, and oral herpes) no longer being tabulated as opportunistic infections and accounts for the apparent reduction in opportunistic infection frequency; these preferred terms are now categorised in the SOC "Infections." Based on the initial submission's information, while the data overall does not demonstrate any clear trend regarding opportunistic infections, the noted between-group difference during the OLP could indicate that treatment with inebilizumab over the longer term might indeed increase such risk. As previously discussed, one TEAE of Grade 4 respiratory failure during the OLP was reported for a patient

in the inebilizumab/inebilizumab group who was hospitalised on multiple occasions for treatment of opportunistic respiratory infections.

Information concerning the mechanism of the risk of infection, need for monitoring and discontinuation in case of infections is reflected in section 4.4. of the SmPC.

There were 7 subjects with life-threatening (Grade 4) TEAEs in Study 1155 involving infections, with these subjects including one patient who subsequently died following onset of new brain lesions involving possible PML. These events are discussed below (see "Adverse Events by Severity").

The SmPC includes a dedicated section for PML in section 4.4.

Of note, 2 cases of COVID-19 were reported during the OLP of study 1155 (including one fatal case of COVID-19 pneumonia and 3 events related to COVID-19 have been reported in post-marketing surveillance data up to 30Apr2021. The SARS-CoV-2 immunisation status of these 5 COVID-19 cases is not known, but based on the dates of occurrence relative to vaccine availability it is likely that these patients had not been vaccinated. The Sponsor agrees that data is needed on vaccine responses in patients receiving inebilizumab. COVID-19 vaccine responses are being measured in the ongoing kidney transplant desensitisation study (VIB0551.P2.S1) and will be measured in the long-term follow-up of NMOSD patients.

In conclusion, while the data overall does not demonstrate any clear trend regarding risk of opportunistic or other serious infections, inebilizumab was associated with a small number of life-threatening infections, and longer-term treatment might well increase such risk. (See related discussion below regarding progressive decrease in serum immunoglobulins). Due to exclusion criteria, mechanism of action for inebilizumab and observed safety profile, severe active infection including active chronic infections such as hepatitis B and tuberculosis, history of PML and severely immunocompromised state have been added to the SmPC's list of contraindications.

Infusion-related Reactions

During the RCP, infusion-related reactions were more common in the placebo group compared to the inebilizumab treatment arm (9.2% vs. 10.7%). The placebo treatment had the same excipients as the active IP.

Throughout Study 1155, there were no anaphylactic or other serious allergic events related to infusion, with all infusion-related reactions rated Grade 1 or Grade 2. Only one infusion-related reaction was recorded as a serious AE, with this event in the OLP involving a case of migraine with debut during an infusion necessitating a single night's hospitalisation beginning two days post-infusion. Overall, the data suggests that infusion of inebilizumab following appropriate pre-medication (IV methylprednisolone (or equivalent glucocorticoid), oral diphenhydramine (or equivalent antihistamine) and oral paracetamol) appears to be well-tolerated. Specific guidance in the event an infusion-related reaction occurs is provided in section 4.4 of the SmPC. Considering the protein nature of the product, its mechanism of action and the fact that the applicant considers hypersensitivity reactions as an important potential risk in the RMP, a warning on hypersensitivity reactions has been added in section 4.4 of the SmPC. The applicant has listed infusion-related reactions with a frequency of "very common" in section 4.8 of the SmPC.

Haematology and coagulation

During the RCP, a higher proportion of subjects in the inebilizumab group had at least a 2-grade worsening from baseline compared to the placebo group in the following laboratory parameters:

- Leukocytes: inebilizumab 6.4% versus placebo 1.8%
- Lymphocytes (decreased): inebilizumab 20.2% versus placebo 8.9%
- Neutrophils: inebilizumab 5.8% versus placebo 0%.

Since neutropenia and lymphopenia are associated with an increased risk of infection and that inebilizumab is intended for chronic administration, the risk of neutropenia and lymphopenia is identified in section 4.4 of the SmPC and measurements of blood neutrophils and lymphocytes are recommended prior to initiation of treatment with inebilizumab, regularly during treatment and upon signs of infections. Since neutropenia and late neutropenia have been reported for B-cell depleting therapies, a dedicated paragraph has been added to section 4.4 of the SmPC, with measurements of blood neutrophils to be recommended in patients with signs and symptoms of infection. Lymphopenia and decreased lymphocyte count events are consistent with the mechanism of action of B-cell depletion. Neutropenia has been observed with other B-cell depleting monoclonal antibodies and may be a class effect.

Neutropenia was generally transient, and no subject with laboratory-defined Grade 2 or higher neutropenia experienced a serious infection. Grade 3 neutropenia occurred in 3 subjects (all treated with inebilizumab) during the RCP and in 1 subject (in the inebilizumab/inebilizumab group) during the OLP. Neutropenia lead to discontinuation of inebilizumab in one patient (during the OLP). No cases of Grade 4 neutropenia were reported.

Malignancies

One subject had a TESAE of "colon cancer stage III" (PT), which was the first malignancy in the study for a subject treated with inebilizumab. The size and duration of the RCP (up to 197 days) and the open label follow-up extension (continuing for a maximum of 3 years after the last subject was randomised) are too limited to adequately assess long-term risks of secondary malignancies (and opportunistic infections). Of note, ocrelizumab, which targets CD20-expressing B cells, has been associated with a (statistically non-significant) increase in malignancies (driven by breast cancer) relative to placebo- and interferon beta-1a- comparators (Ocrevus EPAR). In this context, the facts that inebilizumab depletes an even wider of B-lymphocytes compared to ocrelizumab would appear to represent cause for concern. Language regarding malignancy has been provided in Section 4.4 of the SmPC although a risk of malignancy has not been clearly established with inebilizumab or other B-cell-depleting agents. Active malignancies are included among the SmPC's list of contraindications. Long-term monitoring for risk of secondary cancers will be implemented in the RMP.

Adverse Events by Severity

During the RCP, patients treated with inebilizumab experienced fewer Grade 3 TEAEs than patients treated with placebo (8.0% vs. 12.5%), including in the SOC of Infections and Infestations, the SOC under which Grade 3 TEAEs were most frequently reported (n=4 (2.3%) and n=3 (5.4%) in the inebilizumab and placebo group, respectively). The only Grade 3 TEAEs occurring in more than 1 inebilizumab-treated subject during the RCP were 2 cases each of urinary tract infection and hypertension.

During the RCP and OLP, there were 9 subjects with life-threatening (Grade 4) TEAEs in Study 1155. One subject (in the inebilizumab group) had Grade 4 atypical pneumonia within the first month of treatment, which resulted in discontinuation (possible risk factors contributing to the event included a history of pulmonary tuberculosis and prior treatment with mycophenolate mofetil within 30 days of AE onset). During the OLP, 8 subjects experienced Grade 4 TEAEs. Among these, 6 subjects had Grade 4 TEAEs within or related to the Infections and infestations SOC: 1 subject (placebo/inebilizumab group) had Grade 4 cholecystitis acute, 1 subject (placebo/inebilizumab group) had Grade 4 perforated appendicitis, 1 subject (placebo/inebilizumab group) had Grade 4 urinary tract infection and pneumonia among multiple events with Grade 4 severity, 1 subject in the inebilizumab/inebilizumab group had Grade 4 respiratory failure, this following persistent opportunistic bacterial, viral and mycotic respiratory infections, 1 subject (inebilizumab/inebilizumab group) had Grade 4 bacteremia, and 1 subject (inebilizumab/inebilizumab group) had 4 Grade 4 TEAEs, which were CNS infection, NMOSD, probable PML, and post-cardiac arrest syndrome. The events CNS infection, NMOSD, and PML were the differential diagnosis for the single event of new brain lesions observed and are not separate events; this subject also experienced a fatal TEAE of pneumonia.

No fatal (Grade 5) TEAEs occurred during the RCP. During the OLP, there were 3 fatal TESAEs. One of these deaths involved a patient (60-70 years) who developed new brain lesions consistent with, but not conclusively confirmed as, PML, with differential diagnoses including acute disseminated encephalomyelitis and atypical NMOSD relapse. While a definite diagnosis of the CNS lesions could not be established, this case of potential PML together with the fact that other B-cell-depleting therapies have been associated with risk of PML support an SmPC warning for PML and other opportunistic infections. The second fatality was in a patient (30-40 years) with longstanding NMOSD and significant baseline disability who likely developed a new NMOSD-related proximal CNS lesion leading to respiratory failure. The applicant's assessment that the latter death was not related to inebilizumab is considered reasonable. The third death involved a subject who was randomised to inebilizumab and subsequently entered the OLP. The subject died as a result of viral pneumonia due to coronavirus disease 2019 (COVID-19). Both Investigator and Sponsor assessed this event as not related to inebilizumab.

On June 11, 2020, the US FDA approved inebilizumab (Uplizna) for treatment of NMOSD in adult patients who are AQP4 antibody positive. The applicant provided a summary of requested post-marketing data (11 Jun 2020 – 30 Apr 2021). Fifty-two (52) spontaneous case reports are mentioned for a total of 165 events. Among these events, 9 were considered serious and 156 were considered non-serious. Narratives for these 9 SAEs, while characterised by lack of detail, did not identify new significant safety data (said narratives included 5 cases of events likely related to the underlying disease and 3 cases related to Covid-19 infections).

Adverse Events by Subgroups

Subgroup analyses performed by the applicant did not uncover any noteworthy difference in AE incidence by gender, anti-drug antibody status, race or geographic region. However, the small numbers of subjects within certain subgroups limit interpretation of the comparisons. Likewise, there were no obvious differences in incidence of TESAEs during the RCP or OLP by AQP4-IgG status; again, the limited number of subjects in the anti-AQP4 lgG seronegative group together with low number of events within individual SOCs limit comparisons.

Other Safety Concerns

In Study 1155, by the end of the RCP, total immunoglobulins decreased by approximately 10% in subjects treated with inebilizumab. Within each class of Ig, the largest reductions during the RCP in inebilizumab-treated subjects was for IgE and IgM (median percent change from baseline of -35% and -32%, respectively). The decrease in Ig over time continued in the OLP: in subjects receiving inebilizumab from the start of the RCP, the median percent change in total Ig and IgG levels was -

12.42% and -8.88%, respectively, at OLP Week 0, declining to -39.19% and -28.64%, respectively, at OLP Week156. This progressive decrease in serum immunoglobins, which did not appear to reach a clear plateau, is a substantial concern as it may over time lead to increased risk of serious and/or opportunistic infections. The applicant provided an analysis on the association of reduced levels of immunoglobulins and occurrence of infections in inebilizumab-treated patients. Results indicate that there was no statistically significant association between infection rate and worst level of IgG ($p = 0.7576$), IgM ($p = 0.3354$), or IgA ($p = 0.3154$). Given the limited data, the applicant concluded that data do not rule out such an association. 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. The study data are not sufficient to permit determination of the timing of B-cell repletion; this is reflected by text in SmPC section 4.4. In view of the generally limited number of subjects and the relatively short duration of treatment in Study 1155, the applicant is committed to conduct 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.

While pregnancy or lactation constituted exclusion criteria in the study programme, pregnancies occurred in 3 inebilizumab-treated patients. All 3 children were delivered with no abnormalities or health problems reported. In the SmPC, a period of 6 months for use of effective contraception following the last administration of inebilizumab is recommended. Based on experience with other B-cell depleting antibodies, section 4.6 of the SmPC includes information relating to the potential risk of fetal B-cell depletion and monitoring following in utero exposure to inebilizumab, including that vaccinations with live virus vaccines such as BCG vaccine should be postponed until the infant's B-cell count has recovered. Considering that women of reproductive age make up a substantial proportion of patients with NMOSD, a pregnancy registry has been requested.

2.6.10. Conclusions on the clinical safety

The amount of exposure to inebilizumab in the pivotal phase 2/3 Study 1155 is considered adequate to inform a B/R assessment.

Inebilizumab causes prolonged depletion of CD19 positive (CD19+) B cells, plasmablasts and some plasma cells via both antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis mechanisms. The most common AEs associated with inebilizumab were urinary tract infections, joint pain and other pain-related PTs and were apparently manageable conditions, with few subjects discontinuing due to adverse event. In line with the safety profile described for other B-cell depleting therapies, the primary risk associated with inebilizumab is likely infections. Although Study 1155 did not demonstrate an increased incidence of infections in inebilizumab-treated subjects compared to placebo, the relatively small number of subjects and short treatment duration confer significant uncertainty, and in inebilizumab-treated subjects, several cases of Grade 4 AEs related to infections as well as a single death involving possible PML were reported. In particular, inebilizumab was associated with a progressive decrease in serum immunoglobulins, which did not appear to reach a clear plateau. This is a substantial concern as it may over time lead to increased risk of serious and/or opportunistic infections. Inebilizumab's long-term effects on serum immunoglobulins and on associated risk of infection are considered to necessitate further surveillance post-marketing. Furthermore, long-term monitoring for risk of secondary cancers will be implemented in the RMP. Considering that women of reproductive age make up a substantial proportion of patients with NMOSD and that pregnancies occurred in 3 inebilizumab-treated subjects, a post-authorisation pregnancy registry has been requested.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 38: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infusion reaction. • Neutropenia.
Important potential risks	• 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.
Missing information	• Safety in patients > 65 years. • Use during pregnancy and lactation. • Patients concomitantly receiving other immunosuppressive agents.

2.7.2. Pharmacovigilance plan

Table 39: Summary of ongoing and planned additional pharmacovigilance activities

Study/ Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3: Required additional pharmacovigilance activities				
An Observational Pregnancy Safety Study in Women with NMOSD Exposed to UPLIZNA® Planned	The registry is conducted to better characterise 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 neuromyelitis optica spectrum disorder (NMOSD), 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, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.	Exposure during pregnancy and lactation. Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women.	Protocol submission by	October 2021
			Interim updates	Each PSUR
			Interim study report	July 2026
			Final report	July 2033
CorEvitas SPHERES (Synergy of Prospective Health &	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	• Infusion reaction • Serious infections, viral reactivation, and opportunistic infections	First Patient In:	June 2021

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Experimental Research for Emerging Solutions) Registry for Neuromyelitis Optica Spectrum Disorder (NMOSD) Ongoing	systematically evaluate the burden for patients with this disease and to describe treatment utilisation patterns. AEs 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	• PML • Malignancy • Use during pregnancy and lactation • Patients concomitantly receiving other immunosuppressive agents • Safety in patients >65 years	Interim updates	Each PSUR
			Final study report:	December 2028
Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) Treated With inebilizumab in Europe Planned	Describe the characteristics (including demographics, disease burden, selected comorbidities and concomitant medication use) of NMOSD patients who initiate treatment with inebilizumab To assess treatment and drug utilisation patterns of NMOSD patients who initiate treatment with inebilizumab Observe clinical and treatment outcomes by estimating the occurrence of events of interest including infusion related reactions, serious infections including PML, and malignancy.	• Infusion reaction • Serious infections, viral reactivation, and opportunistic infections • PML • Malignancy • Patients concomitantly receiving other immunosuppressive agents • Safety in patients >65 years	Protocol submission	March 2022
			Interim updates	Each PSUR
			Final study report	December 2026
A safety study of NMOSD patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study Planned	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 reaction • Serious infections, viral reactivation, and opportunistic infections • PML • Malignancy • Use during pregnancy and lactation • Patients concomitantly receiving other immunosuppressive agents • Safety in patients >65 years	Protocol submission	March 2022
			Interim updates	Each PSUR
			Final Study Report	August 2028

2.7.3. Risk minimisation measures

Table 40: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk 1: Infusion reaction	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4, Section 4.8, Section 5.1. PL Section 2 and Section 4. Recommendations for proper administration in SmPC Section 4.2 and Section 4.4. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** SPHERES Real-World Observational Study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: prescription only. **Additional risk minimisation measures:** None	Post-Authorisation Safety Study
Important identified risk 2: Neutropenia	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 PL Section 4 Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risk 1: Serious infections, viral reactivation, and opportunistic infections	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3,4.4, 4.5 and 4.8. PL Section 2, Section 4. Recommendations for infection assessment before administration in SmPC Section 4.2. Clinical setting: IV product that can only be administered in an infusion centre or hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** SPHERES Real-World Observational Study Post-Authorisation Safety Study
Important potential risk 2: PML	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2, Section 4 Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire. **Additional pharmacovigilance activities:** SPHERES Real-World Observational Study Post-Authorisation Safety Study
Important potential risk 3: Malignancy	**Routine risk minimisation measures:** SmPC Sections 4.3 and 4.4. PL Section 2 Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** SPHERES. Real-World Observational Study Post-Authorisation Safety Study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk 4: Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.6, and 5.3. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Pregnancy Registry.
Missing information 1: Safety in patients > 65 years	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** SPHERES Real-World Observational Study Post-Authorisation Safety Study
Missing information 2: Use during pregnancy and lactation	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.6. PL Section 2. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Pregnancy Registry SPHERES Real-World Observational Study
Patients concomitantly receiving other immunosuppressive agents	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.5 PL Section 2. Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. Legal status: prescription only. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** SPHERES Real-World Observational Study Post-Authorisation Safety Study

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 05 May 2010. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Uplizna (inebilizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, chronic, autoimmune, inflammatory, disorder of the CNS with a worldwide prevalence of 0.5-10/100,000. The disease is characterised by attacks of predominantly ON and longitudinally extensive transverse myelitis, and, less frequently, affecting the brain and brainstem. Cases clinically diagnosed as NMOSD may include AQP4-IgG seropositive and AQP4-IgG seronegative

Up to 90% of patients with NMOSD have relapsing episodes of ON and myelitis rather than following a monophasic course. A second attack occurs within 1 year of onset in 60% of AQP4-IgG seropositive patients and within 3 years in 90% of patients. Attacks can be severe and result in blindness, paralysis,

and even death due to neurogenic respiratory failure. There are cases of monophasic NMOSD but the criteria that accurately predict long-term adherence to a monophasic course cannot currently be defined. An interval longer than 4 weeks between index attacks indicates relapsing disease (Wingerchuk et al, 2015).

3.1.2. Available therapies and unmet medical need

Patients who are AQP4-IgG seropositive should be assumed to be at risk for relapse indefinitely and preventive treatment should be considered, even in the setting of a prolonged clinical remission (Wingerchuk et al, 2015).

Current treatments for NMOSD are aimed at prevention of attacks, acute management of attacks, and amelioration of persistent symptoms. High-dose steroids and plasmapheresis are generally used for the acute management of attacks. Symptomatic treatments are used to address symptoms, which can include general and neuropathic pain (e.g, anti-epileptics, anti-spasmodics, anti-depressants, or analgesics), bowel (e.g, laxatives), bladder (e.g, bethanechol), and fatigue and depression (e.g, psychotherapy or medication) disorders. Patients with NMOSD have been treated prophylactically for attack prevention with off-label immunosuppressants such as azathioprine, mycophenolate mofetil, daily prednisone, or rituximab. Since 2019 to the date of this report, two new therapies have been authorised in EU for the treatment of APQ4-IgG seropositive NMOSD patients.

Results of uncontrolled studies with rituximab (anti-CD20) provide low level evidence for utility of B-cell depletion as a means of preventing attacks in NMOSD. B-cell analysis of rituximab failures revealed the presence of CD19+/CD20- plasmablasts, which supports the need for a more comprehensive B cell-depleting therapy than rituximab for effective treatment of this disease. CD19 is expressed on a wider lineage of B cells, from pro-B to plasmablasts and some plasma cells, compared to CD20. It is therefore conceivable that direct depletion of CD19+ B cells could be more effective in reducing the risk for NMOSD attack by more effectively depleting plasmablasts producing AQP4-IgG, being the hypothesis tested for inebilizumab.

After the first dose, inebilizumab is administered once every 6 months which makes the posology very convenient for the patients. Therefore, there is a still medical need in this very severe and rare disease, in particular with regards to preventing relapse with a convenient posology. This is also supported by patients who were consulted by EMA through Eurordis (a non-profit alliance of rare disease patient organisations).

3.1.3. Main clinical studies

The main evidence of the efficacy submitted is a single phase 2/3 multicentre, randomised, DB, placebo-controlled study comparing 300 mg iv inebilizumab or placebo (without any background IST) in previously treated or *de-novo* adult patients with NMOSD who have an EDSS score ≤ 7.5 (≤ 8.0 if able to participate in the study) and a relapsing active course of disease (≥ 1 relapse in the prior year, or ≥ 2 in the prior 2 years, that required rescue therapy) (Study CD-IA-MEDI-551-1155, Study 1155). The RCP duration was maximum 6.5 months.

The primary objective was to compare the efficacy of Inebilizumab versus placebo in reducing the risk of an NMOSD attack in subjects with NMOSD. The primary endpoint was defined as time to onset of an AC- determined NMOSD attack on or before Day 197.

230 NMOSD patients were randomised, 213 patients were AQP4-IgG positive (161 in Inebilizumab arm and 52 in placebo arm) and 17 were AQP4-IgG seronegative (13 in Inebilizumab arm and 4 in placebo arm).

Maintenance of the effect is based on available results from the ongoing open label period of the study and is limited to an updated analysis of AC-determined ARR.

3.2. Favourable effects

Primary Endpoint:

In the AQP4-IgG-seropositive subgroup, 18 (11%) of 161 participants receiving inebilizumab had an attack compared with 22 (42%) of 52 participants receiving placebo (HR 0.227 [95% CI 0.121–0.423]; p <0.0001) representing a 77.3 % reduction in the risk of relapse. For ITT population (AQP4-IgG-seropositive and seronegative), the HR of AC-determined attacks with inebilizumab treatment relative to placebo was 0.272 (95% CI: 0.1496, 0.4691) (p < 0.0001). Sensitivity analyses were consistent with the primary analysis in the sense that the HR estimates were all below 1.00 and all sensitivity analyses reached significance (<0.05).

Key secondary endpoints:

Three of four key secondary endpoints showed nominally significant results.

At the end of the RCP, significantly fewer inebilizumab than placebo recipients in the AQP4-IgG seropositive [16% vs. 35% (odds ratio 0.371; p = 0.007)] and overall ITT [16% vs. 34% (odds ratio 0.370; p=0.0049)] populations had worsening on the EDSS.

The cumulative number of active MRI lesions, new Gd-enhancing MRI lesions, new/enlarging T2 MRI lesions decreased with inebilizumab treatment compared to the placebo in both AQP4-IgG seropositive subjects (rate ratio 0.568 [95% CI: 0.3851, 0.8363]; p = 0.0042) and ITT population (rate ratio 0.566 [95% CI: 0.3866, 0.8279]; p = 0.0034). In the RCP, 45.3% of inebilizumab subjects had new Gd-enhancing MRI lesions (placebo 59.6%), and 21.7% of inebilizumab subjects had new/enlarging T2 MRI lesions (placebo 40.4%) among AQP4-IgG seropositive subjects. New Gd-enhancing lesions were most common in the optic nerve, followed by spinal cord and brain; no new Gd-enhancing lesions were seen in the brainstem. New/enlarging T2 lesions were most common in the spinal cord, followed by optic nerve, brain, and brainstem.

Treatment with inebilizumab reduced the number of in-patient hospitalisations compared to treatment with placebo in RCP in both AQP4-IgG seropositive subjects (rate ratio 0.258 [95% CI: 0.0904, 0.7384]; p = 0.0115) and total ITT population (rate ratio 0.286 [95% CI: 0.1105, 0.7411]; p = 0.0100).

A multiplicity adjustment performed for the analyses of the key secondary efficacy endpoints revealed significant results for all except for change in low-contrast visual acuity.

Across the RCP and OLP the AC-determined ARR in any AQP4-IgG seropositive subject treated with inebilizumab was 0.13, and in any subject treated with inebilizumab was 0.126. Updated AC-determined ARR in the AQP4-IgG seropositive subgroup at the time of the Day 120 safety update (date of cut-off 06 Jun 2019) was 0.118 (0.088-0.155). This shows maintenance of ARR over time in OLP. Supportively, survival estimate in the AQP4-IgG seropositive population at Day 197 of the RCP was 88.7%, followed by 85.1% on Day 365 of the OLP.

Exploratory analysis with modified Rankin scale was supportive of EDSS findings (AQP4-IgG seropositive subjects who received inebilizumab were 74.2% more likely to report less disability compared to placebo subjects) and severity of attacks in AQP4-IgG seropositive population were reduced from 45.5% to 33.3% major attacks with inebilizumab use.

3.3. Uncertainties and limitations about favourable effects

There are limitations of the study design with potential impact on favourable effects. The use of background IST while on trial was not permitted and no active comparator was used. Consequently, there are concerns about the potential interactions with other IST or treatments for acute management of attacks and amelioration of persistent symptoms, instructions for starting treatment with inebilizumab and switching from or to other treatments used in standard of care. As such, a dedicated subsection was added in section 4.4 of the SmPC: "Prior treatment with immunosuppressive therapies" where the relevant information is included. Additionally, the concerns are addressed in the RMP. Additionally, the applicant was requested to specify in the wording of the indication (section 4.1) that inebilizumab is to be used as a monotherapy.

The significant result for primary analysis of ITT group is driven by strong results from seropositive group which constitutes 93% of ITT population. The study was not powered for assessing the efficacy of inebilizumab in AQP4-IgG seronegative patients, the number of AQP4- IgG seronegative patients enrolled was too low for formal statistical testing (7% of enrolled patients, 4 in the placebo arm and 13 in the Inebilizumab arm), they were not included in testing hierarchy and they showed imbalances in demographics and baseline disease characteristics. No attacks were observed in placebo subgroup AQP4-IgG seronegative group, and there is no observed therapy benefit. Due to very short time frame in the RCP and possibly different etiological mechanisms involved in AQP4-IgG seronegative NMOSD, it is impossible to know if the seronegative patients would have had attacks if they were followed longer without inebilizumab treatment. Treatment effect in AQP4-IgG seronegative patients is unknown. Consequently, the applicant was requested to narrow the indication to adult NMOSD patients with AQP4-IgG.

The primary efficacy endpoint was set as time to onset of an AC-determined NMOSD attack, and not investigator-confirmed attacks reflecting actual clinical practise and decision making and as advised in the SA (EMEA/H/SA/2664/1/2013/III). Nevertheless, all pivotal trials for inebilizumab, eculizumab and satralizumab used adjudicated events (relapses) for primary endpoint and the sensitivity analysis using investigator-determined NMOSD attack showed similar results.

Although secondary endpoints are chosen as relevant tools in the clinic to evaluate disability or severity of attacks and disease activity at patient level, they are not developed or validated for NMOSD, they are not established methods to measure treatment effect on NMOSD and there are methodological concerns (e.g. missing data being imputed as attacks, timing of EDSS evaluation around attacks), high correlation with presence of a recent attack and uncertain independent predictive value on treatment effect from primary endpoint. The clinical significance of results for EDSS and MRI related endpoints are questionable.

For the endpoint of low-contrast binocular visual acuity, inebilizumab was nominally better in the subgroup with < 2 prior NMOSD relapses compared with ≥ 2 prior relapses (nominal p=0.0129; interaction p=0.0019), and in subjects who had not received prior NMOSD medications (nominal p=0.0251; interaction p=0.0090). The results should be interpreted with caution given the small number of subjects and the fact that low contrast visual acuity was measured binocularly while the majority of optic neuritis episodes in NMOSD are unilateral.

B cell data > 28 weeks effect are missing.

3.4. Unfavourable effects

The profile of inebilizumab is consistent with its mechanism of action (anti-CD19 monoclonal antibody leading to B-cell depletion) and other B-cell depleting therapies (anti-CD20) with reported cases of infusion-related reactions, infections, neutropenia, lymphopenia and decreases in immunoglobulins.

Urinary tract infection is a very common and respiratory tract infection, infusion-related reactions, arthralgia, back pain, lymphopenia and neutropenia are common adverse reactions with inebilizumab. ADR reported at higher proportions (≥5%) with inebilizumab than with placebo were urinary tract infection (11.5% vs. 8.9%), arthralgia (9.8% vs. 3.6%) and back pain (7.5% vs. 3.6%). Patients treated with inebilizumab had a similar overall risk of TEAEs and had proportionately fewer severe and SAEs compared to placebo-treated subjects. Two subjects in the inebilizumab group had a TEAE resulting in discontinuation of IP vs. no such subjects in the placebo group.

During the RCP, infections overall were reported in a similar percentage of patients in both treatment groups (37.9% in the inebilizumab and 41.1% in the placebo total groups) and patients treated with inebilizumab experienced fewer serious infections compared to placebo (1.7% vs. 3.6%). In the OLP, the proportion of infections was important in both placebo/inebilizumab treated patients (70.6%, 36 subjects) and inebilizumab/inebilizumab treated patients (53.9%, 89 patients). Among these, serious infections represented 17.6% of placebo/inebilizumab patients (n=9) and 4.8% of inebilizumab/inebilizumab treated patients (n=8). Also, opportunistic infections – as per analysis based on the Opportunistic Infection SMQ from MedDRA version 21.0 - occurred more frequently in the inebilizumab/inebilizumab group compared to placebo/inebilizumab-treated subjects (10.9% vs. 5.9%).

There were 4 subjects with life-threatening (Grade 4) TEAEs, all involving infections, during the OLP, including one patient who subsequently died following onset of new brain lesions involving possible PML.

By the end of the RCP, total immunoglobulins decreased by approximately 10% in subjects treated with inebilizumab. The decrease in immunoglobulins over time continued in the open-label extension period: in subjects receiving inebilizumab from the start of the RCP, the median percent change in total Ig and IgG levels was -12.42% and -8.88%, respectively, at OLP Week 0, declining to -40.12% and -36.12%, respectively, at OLP Week 143. Furthermore, inebilizumab was associated with reduced neutrophil counts.

3.5. Uncertainties and limitations about unfavourable effects

There is currently a limited safety database with 225 patients treated with at least one dose of inebilizumab in the pivotal phase 2/3 Study 1155. As of the date of cut-off of 06 Jun2019, 177 subjects (162 AQP4-IgG-seropositive) and 53 subjects (45 AQP4-IgG-seropositive) had been treated with inebilizumab for ≥366 days and ≥1094 days, respectively.

Regarding the death of the patient with probable PML, the cause of the patient's brain lesions could not be established with certainty and the differential diagnosis of the patient's brain lesions included PML, acute disseminated encephalomyelitis and atypical NMOSD relapse. Nevertheless, the SmPC includes a dedicated section for PML in section 4.4. and PML has been included in the RMP as an important potential risk.

The proportion of patients with infections and opportunistic infections was similar between placebo and inebilizumab-treated patients during the RCP. However, the RCP was of short duration (6 months) and the number of patients exposed was limited. 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, a risk of infections (including opportunistic infections) cannot be excluded for patients receiving long-term treatment. A dedicated

section has been 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.

Given the very limited long-term safety data at current stage, the potential impact of treatment with inebilizumab on the development of malignancies is unknown. During the OLP, one subject had a TESAE of "colon cancer stage III". Again, the short duration of the study and limited long-term safety data precludes a firm assessment of the risk. A dedicated section has been 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 several populations, including elderly patients as only 6 patients above 65 years were treated with inebilizumab, in patients concomitantly receiving other immunosuppressive medications and in pregnant or lactating women. Specific sections have been included in SmPC (section 4.2 for elderly; SmPC 4.4 for pregnancy; SmPC 4.5 concomitant use of IST) and all these groups are included as missing information in the RMP.

3.6. Effects Table

Table 41: Effects table for inebilizumab and NMOSD AQP4-IgG positive (data cut-off: 18 December 2018)

Effect	Short Description	Unit	AQP4-IgG sero+, MEDI551 vs PBO	ITT, MEDI551 vs PBO	Uncertainties/ Strength of evidence	References
Favourable Effects						
Attack	Time to onset of an AC-determined NMOSD attack	Hazard ratio (95% CI)	0.227 (0.121, 0.423)	0.272 (0.150, 0.496)	P < 0.0001 from CPHM. NNT at Day 197 (95% CI), 3.23 (2.72, 4.54)	Study 1155, RCP
EDSS	Worsening from baseline in EDSS at last visit during the RCP	Odds ratio (95% CI)	0.371 (0.181, 0.763)	0.370 (0.185, 0.7389)	Nominal P = 0.0070 and P= 0.0049 from logistic regression model. Directly correlated with recent attacks. Clinical significance is questionable	Study 1155, RCP
Visual Acuity	Change from baseline in low-contrast visual acuity binocular score at last visit during the RCP	Least squares mean difference (95% CI)	-0.038 (1.153) (-2.3122, 2.2357)	0.134 (1.096) (-2.0254, 2.2941)	Nominal P= 0.9736 and P= 0.9026 from ANCOVA. Might be impacted by floor effect due to accumulated optic nerve disability.	Study 1155, RCP
MRI	Cumulative number of active MRI lesions (new Gd-enhancing or new/enlarging T2) during the RCP	Rate ratio (95% CI)	0.568 (0.385, 0.836)	0.566 (0.387, 0.828)	Nominal P= 0.0042 and P= 0.0034 from negative binomial regression model. Different type/stage of pathologies are combined by different type of scans. Directly correlated with recent attacks. Clinical significance is questionable	Study 1155, RCP
Hospitalisations	Cumulative number of NMOSD-related in-patient hospitalisation	Rate ratio (95% CI)	0.258 (0.090, 0.738)	0.286 (0.111, 0.741)	Nominal P= 0.0115 and P= 0.0100 from negative binomial regression model. Excluding hospitalisations for infusion of IP.	Study 1155, RCP
Unfavourable Effects						

Effect	Short Description	Unit	AQP4-IgG sero+, MEDI551 vs PBO	ITT, MEDI551 vs PBO	Uncertainties/ Strength of evidence	References
Infections	Infection or infestations (SOC)	%	39.1% vs. 44.2%	37.9% vs. 41.1%	Short duration of RCP (up to 197 days). Over time, progressively lower Ig levels may well be associated with increased risk of infections.	Study 1155, RCP
Reduction in IgG	Results are median percent change from baseline at Week 28	%	-7% vs. 9%	-7% vs. 9%	Identified risk	Study 1155, RCP
Reduction in IgM	Results are median percent change from baseline at Week 28	%	-31% vs. 2%	-32% vs. 1%	Identified risk	Study 1155, RCP
Neutropenia	Blood and lymphatic system disorders	%	2.5% vs. 0%	2.3% vs. 0%	Identified risk	Study 1155, RCP
Infusion-related reaction	Definition unclear from CSR. No cases of anaphylactic reaction or hyper-sensitivity	%	9.3% vs. 9.6%	9.2% vs. 10.7%	Identified risk (IP was administered to subjects following pre-medication with IV glucocorticoid, oral antihistamine and oral paracetamol).	Study 1155, RCP
Arthralgia	Musculoskeletal and connective tissue disorders	%	9.9% vs. 3.8%	9.8% vs. 3.6%	Biological mechanism unclear	Study 1155, RCP
Back pain	Musculoskeletal and connective tissue disorders	%	6.8% vs. 3.8%	7.5% vs. 3.6%	Biological mechanism unclear	Study 1155, RCP

Abbreviations: NMOSD=neuromyelitis optica spectrum disorders; CI=confidence intervals; CPHM=Cox Proportional Hazard Model; RCP=randomised-controlled period; EDSS=expanded disability status scale; MRI=magnetic resonance imaging.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy package presented in this application establish the effectiveness of inebilizumab as monotherapy for the treatment of NMOSD in adult patients who are AQP4-IgG seropositive. Reduced (AC-adjudicated) relapse frequency for AQP4-IgG seropositive patients is a highly statistically significant outcome and is supported by sensitivity analyses. As relapses in patients with NMOSD can cause serious, permanent disability and can even be fatal, preventing relapses and reducing the frequency of relapses is a clinically meaningful outcome for patients with NMOSD, which is supported by the significant decrease in hospitalisation need.

The significant result for primary analysis of ITT group is considered to be driven by strong results from seropositive group which constitutes 93% of ITT population.

Background scientific evidence suggests that pathogenic AQP4-IgG is produced by B-lineage cells, specifically a subpopulation of CD19-positive CD20-negative B cells showing morphological and phenotypical properties of plasmablasts. This is supportive evidence for efficacy of inebilizumab in AQP4-IgG seropositive patients. Even using the most reliable assays, there are subsets of subjects who do not test seropositive for AQP4-IgG who may still present with NMOSD phenotype; however, different

etiological mechanisms may be involved in AQP4-IgG seronegative NMOSD. Arising evidence shows that seronegative NMOSD might have a different pathogenic mechanism and a subset of this group, NMOSD phenotype with MOG-IgG, may be a distinct entity (MOG antibody disease). Due to very short time frame in the RCP and possibly different etiological mechanisms involved in AQP4-IgG seronegative NMOSD, it is difficult to know if the seronegative patients (with or without inebilizumab treatment) would have had more attacks if they were followed longer, but due to very heterogenous pathology and low number of patients evaluated this is not considered very likely. In conclusion, there was no evidence of a clinical benefit for AQP4-IgG seronegative patients with inebilizumab treatment. As such, the indication has been restricted to adult patients with NMOSD with AQP4-IgG seropositive.

There are limitations of the study design and conduct with potential impact on favourable effects.

First of all, the primary efficacy endpoint was set as time to onset of an AC-determined NMOSD attack, and not investigator-confirmed attacks reflecting actual clinical practise and decision making. This is a concern on its own, however, due to significant results with sensitivity analysis of the primary endpoint for investigator or patient reported attacks, there is scientific support for reassurance.

Secondly, the use of background IST while on trial was not permitted, rescue treatments were limited, and no active comparator was used. Up to 90% of patients with NMOSD have relapsing episodes. The monophasic NMOSD exits as clinical entity but the criteria that accurately predict long-term adherence to a monophasic course cannot currently be defined. So, it is highly recommended to start effective treatments to prevent attacks as soon as the NMOSD diagnosis is reached and monoclonal treatments in use (such as eculizumab, satralizumab) are used as first line therapy by key experts for NMOSD. Due to pivotal study design and conduct, there is no experience with inebilizumab with switching from or to or concomitant use with other IST used in standard of care for NMOSD. Sufficient instructions should be provided to clinicians covering or mitigating these concerns, and it is necessary to support current evidence with long term exposure and efficacy-safety data.

Thirdly, the secondary endpoints were chosen from relevant tools in the clinic to evaluate disability or severity of attacks and disease activity at patient level but they are not developed or validated for NMOSD, they are not established methods to measure treatment effect for NMOSD and there are methodological concerns. EDSS is highly correlated with presence of a recent attack, so even in relapsing multiple sclerosis where EDSS use is established, disability is evaluated by 3 or preferably 6 months cumulative disability measures, instead of simple comparison of study end EDSS to baseline. Similarly, MRI has different scans for evaluating active inflammation or subacute/chronic damage, and they are typically assessed separately with some measures to take attack periods into account. The clinical significance of results for EDSS and MRI related endpoints are questionable on their own, mainly due to very high correlation with attacks and very short study period. It should be noted that exploratory endpoints such as mRS, attack severity, attack recovery, and decrease in number of attacks under treatment despite presence of active inflammation in MRI are supportive of the primary outcome of the study. The results for hospitalisation, modified Rankin scale, attack recovery could also be considered as supportive of positive functional clinical outcome despite lack of significant direct measures of functionality or quality of life. The results from the binocular low contrast visual acuity are difficult to interpreted as discussed above.

There are serious identified and potential risks with inebilizumab therapy which appear to be manageable with labeling and monitoring. Some of the most common AEs related to pain were noted in another NMOSD development programme and raise the possibility of a non-specific effect of effective therapies of unclear significance and aetiology. Otherwise, the identified risks are consistent with other approved therapies that deplete B-cells used in other indications such as multiple sclerosis and haematologic malignancies. 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 warranted and it has

been included in the RMP. Need for monitoring of the level of immunoglobulins at the beginning, during, and after discontinuation of inebilizumab until B-cell repletion as well as median time to B-cell repletion have been implemented in the SmPC. Although two deaths that occurred in the pivotal study were not clearly directly attributable to therapy, PML was included in the differential diagnosis for one of the cases with inconclusive results. Due to exclusion criteria, mechanism of action for inebilizumab and observed safety profile, severe active infection including active chronic infections such as hepatitis B and tuberculosis, history of PML and severely immunocompromised state are added to the SmPC's list of contraindications. The overall safety profile of inebilizumab is acceptable for the treatment of NMOSD, a serious, disabling, potentially fatal disease.

3.7.2. Balance of benefits and risks

A clinically relevant effect on the reduction of attacks has been well demonstrated in a study population consisting mainly of AQP4-IgG seropositive adult patients. Overall, from the analysis of safety data, no major safety issues were reported for inebilizumab in NMOSD patients. The safety profile of inebilizumab was consistent with its mechanism of action, in line with known anti-CD20 therapies and the identified risks could be manageable. The balance of benefits and risks in the proposed indication is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Uplizna is positive, subject to the conditions stated in section 'Recommendations'

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that inebilizumab is not similar to eculizumab and satralizumab within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Uplizna is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) 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:

- What is inebilizumab and how does it work
- What is neuromyelitis optica spectrum disorders (NMOSD)
- Information that inebilizumab treatment may increase the risk of 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that inebilizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.