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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imaavy

International non-proprietary name: nipocalimab

Procedure No. EMEA/H/C/006379/0000

Note

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



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List of abbreviations

AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
AECI	adverse event of clinical interest
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC _(tau,ss)	area under the serum concentration versus time curve (over the dose interval at steady state)
BLQ	below limit of quantification
BMI	body mass index
CAIA	collagen antibody-induced arthritis
C _{ei}	end of infusion serum concentrations
CFB	change from baseline
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	serum clearance
C _{max}	maximum observed serum concentration
CNS	central Nervous System
COVID-19	coronavirus 2019
CR	copy reference
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV(D)	cardiovascular (disease)
DB	double-blind
DDI	Drug-Drug Interaction
EAC	Event Adjudication Committee
EC ₅₀	half maximal effective concentration
ECLIA	electrochemiluminescence immunoassay
ECG	electrocardiogram
eCRF	electronic case report form
EFD	embryo-fetal development phase
ELISA	enzyme-linked immunosorbent assay
ePPND	enhanced pre- and postnatal development
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EOP	End of Phase
E-R	exposure-response
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
GD	gestation day
gMG	generalized Myasthenia Gravis
GOF	goodness of fit
HAECs	human aortic endothelial cells
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HLH	Hemophagocytic Lymphohistiocytosis
HV	healthy volunteers

IC ₅₀	half-maximal inhibitory concentration
ICE	intercurrent event
IgE	immunoglobulin E
IgG	immunoglobulin G
IgG1 λ	immunoglobulin G1 lambda
IIV	inter-individual variability
ITP	immune thrombocytopenia
IRR	infusion-related reactions
ISR	infusion-site reactions
IST	immunosuppressants
IV	intravenous
IVIg	intravenous immunoglobulin
J2R	jump to reference
KD	equilibrium dissociation constant
KLH	keyhole limpet hemocyanin
LCV	Lymphocryptovirus
LDL	low-density lipoprotein
LLOQ	lower of limit of quantification
LRP4	low-density lipoprotein receptor 4
LS	least squares
LTE	long-term extension
M281	nipocalimab
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
MAD	multiple ascending dose
MAR	missing at random
MCID	minimum clinically important difference
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	myasthenia Gravis-Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	revised Myasthenia Gravis Quality of Life –15
MI	multiple imputation
MMRM	mixed effects model for repeated measures
MNAR	missing not at random
MPDs	major protocol deviations
MuSK	muscle-specific kinase
NAb	neutralizing antibody
NCA	non-compartmental analysis
Neuro-QoL	Quality of Life in Neurological Disorders
NHP	non-human primate
NK	natural killer
NOAEL	no-observed-adverse-effect-level
OLE	open-label extension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLEX	therapeutic plasma exchange
POC	proof-of-concept
PT	Preferred Term

Q2W	every 2 weeks
q4w	every 4 weeks
QTcF	corrected QT interval calculated using the Fridericia formula
QMG	Quantitative Myasthenia Gravis
QSS	quasi-Steady-State
QW	weekly
RSE	relative standard error
RO	receptor occupancy
ROW	"Rest of the world"
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCORE	systematic coronary risk estimation
SD	standard deviation
SmPC	summary of product characteristics
SOC	System Organ Class
SoC	standard of Care
TEAE	treatment-Emergent AEs
TMDD	target mediated drug disposition
TT	tetanus toxoid
$t_{1/2}$	half-life
ULN	upper limit of normal
Vp/c	volume of distribution of the central/peripheral compartment
VPC	visual predictive check
WHS	Women's Health Study
WoE	weight of evidence

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen Cilag International submitted on 13 September 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Imaavy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Imaavy is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are antibody positive (anti-acetylcholine receptor [AChR], anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor 4 [LRP4])

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 applicant's 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/0117/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0117/2020 was not yet completed as some measures were deferred.

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.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance nipocalimab 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.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 February 2021	EMA/SA/0000049032	Fernando de Andres-Trelles, Minne Casteels

The scientific advice pertained to the following clinical aspects:

Clinical:

- Adequacy of the clinical development programme, and specifically on phase 3 study design, to support the filing of a marketing authorisation application for the indication of generalized myasthenia gravis;
- Acceptability of the safety database to support the filing of a marketing authorisation application.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

Co-Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	13 September 2024
The procedure started on	3 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 December 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	6 January 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 April 2025
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
— GCP inspections at two clinical investigator sites, located in Belgium and Poland and a CRO site in the United States, between 20 January and 28 February 2025. The outcome of the inspection carried out was issued on	13 May 2025
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	26 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 June 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral	19 June 2025

explanation to be sent to the applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2025
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	3 September 2025
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 Imaavy on	18 September 2025
The CHMP adopted a report on similarity of Imaavy with Soliris, Vyvgart and Rystiggo on (see Appendix 1 on similarity)	18 September 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix 2 on NAS)	18 September 2025
A revised opinion was adopted by the CHMP on 3 November 2025 to improve consistency in the presentation of safety profile information	3 November 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for nipocalimab is: “as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are antibody positive (anti-acetylcholine receptor [AChR], anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor 4 [LRP4]).”

2.1.2. Epidemiology

MG is a rare IgG autoantibody-mediated disease. In adults, MG has a global prevalence of 15 to 25 cases per 100,000 individuals and an annual incidence of 0.8 to 1 cases per 100,000 individuals. Before age 40, women are 3 times as likely to be affected by early-onset MG as men; between the ages of 40 and 50, both genders are equally affected; and after 50 years of age, men are 1.5 times as likely to be affected as women. Juvenile (children < 18 years of age) MG has been reported at an incidence of 0.1 to 0.5 cases per 100,000 individuals per year in Europe. Approximately 10% to 15% of new cases of MG are diagnosed in the adolescent population (12 to <18 years of age). Similar to adults, among paediatric MG patients, girls are affected more often than boys. No significant regional difference was observed in incidence or prevalence of the disease when analysing all age groups in Europe, North America, Canada, Central and South America.

2.1.3. Aetiology and pathogenesis

MG is a rare, heterogeneous, neuromuscular disease characterized by fluctuating muscle weakness and fatigability due to pathogenic IgG-mediated disruption of cholinergic transmission at the neuromuscular junction. Clinical diagnosis of gMG is usually confirmed by the presence of pathogenic IgG autoantibodies. Approximately 95% of gMG patients are considered “seropositive” based on the presence of known IgG autoantibodies: of these, approximately 85% are anti-AChR positive, approximately 8% are anti-MuSK-positive, and approximately 1-2% are anti-LRP4-positive. The remaining 5-6% of patients with gMG have no known autoantibodies and are considered “seronegative”. Between 50% and 92% of paediatric gMG patients are anti-AChR positive.

2.1.4. Clinical presentation

The majority of MG cases (85%) present as gMG, which affects ocular, bulbar, proximal extremity, neck, and respiratory muscles, fluctuates during the day and worsens with fatigue, repetitive activities, heat, infection, and stress. Between 53-80% of the remaining cases, which initially present with primarily ocular symptoms, progress to gMG within two years of diagnosis. Symptoms associated with gMG have been shown to impact patients’ health-related quality of life and activities of daily living. The disease can be associated with considerable morbidity due to aspiration, an increased incidence of respiratory infections and falls, and side effects of broad, non-specific immunosuppressant therapies. In addition, respiratory muscle weakness can lead to myasthenic crisis, which can require hospitalization, mechanical ventilation, tube feeding, fast-acting immunosuppressive agents, and intensive care, and can ultimately be life threatening.

2.1.5. Management

There is no cure for gMG, and most patients require lifelong treatment. Symptomatic treatment with acetylcholinesterase inhibitors may provide some relief in mild cases of gMG. However, most gMG patients also require thymectomy and/or treatment with standard of care (SoC) therapies, including corticosteroids and/or immunosuppressive medications such as azathioprine, mycophenolate mofetil/mycophenolic acid, cyclosporine, and tacrolimus. These treatments for gMG are generally associated with slow onset of action and carry significant risks. Other therapeutic modalities aimed at removing autoantibodies, such as plasma exchange and immunoadsorption, or producing immunomodulatory effects, such as IVIg, are faster acting but are typically used for patients with myasthenic crisis.

Newer agents focused on either C5 complement (eculizumab, ravulizumab, zilucoplan) or inhibition of neonatal Fc receptor (FcRn) (e.g, efgartigimod, rozanolixizumab) have been recently approved for gMG. The use of advanced therapeutic options in gMG is associated with some challenges. Treatment with C5 inhibitors is restricted to only anti-AChR positive patients because of their mechanism of action; they also have a warning for serious meningococcal infections. The dosing approach approved for available FcRn blockers is a symptom-based, cyclic dosing regimen, which can be suboptimal in some patients with a chronic disease like gMG. Of the recently approved FcRn blockers, efgartigimod is only approved for anti-AChR positive adult gMG patients (Vyvgart SmPC) and rozanolixizumab is approved for anti-AChR positive and anti-MuSK positive adult gMG patients (Rystiggo SmPC).

gMG patients who are positive for anti-MuSK and anti-LRP4 antibodies present with more severe symptoms (such as life-threatening respiratory crisis in about one-third of the anti-MuSK population), resulting in a more significant disease burden and greater unmet medical need. The only approved advanced treatment for anti-Musk+ patients is rozanolixizumab. There remains an unmet medical need

for immunoselected treatments that are safer and faster acting than the SoC options, and provide sustained efficacy in a broad population of adult and adolescent patients with gMG.

2.2. About the product

Nipocalimab is a fully human IgG1 monoclonal antibody (mAb) that selectively binds to FcRn with high specificity and high affinity at both neutral (extracellular) and acidic pH (intracellular) resulting in the reduction of circulating IgG, including IgG autoantibodies without affecting other immunoglobulins (IgA, IgE, or IgM). In MG specifically, IgG autoantibodies impair neuromuscular transmission by binding to AChR, MuSK or LRP4, leading to a decreased transmission of the brain impulse to the muscle.

The initially proposed indication is *"as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are antibody positive (anti-acetylcholine receptor [AChR], anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor 4 [LRP4])."* The finally agreed indication is *"as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive."*

Posology is based on results from MOM-M281-004, a phase 2, dose finding study that provided PK and efficacy data to simulate a posology to be studied in the phase 3 single pivotal trial. Four dosing regimens plus placebo were studied. The recommended dose regimen in SmPC is *"an initial single dose of 30 mg/kg administered intravenously, followed by a maintenance dose of 15 mg/kg every 2 weeks thereafter"*, the same posology that was used in the pivotal phase 3 trial.

2.3. Type of application and aspects on development

This is a standard marketing authorisation application.

Studies were designed and conducted in accordance with the ICH guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 (R1) 2011), the ICH guideline on safety pharmacology studies for human pharmaceuticals (ICH S7A 2000) and the ICH guideline on nonclinical safety testing in support of development of pediatric pharmaceuticals (ICH S11 2020).

No CHMP Guideline on the treatment of gMG is currently available.

The applicant received scientific advice (see above).

2.4. Quality aspects

2.4.1. Introduction

Nipocalimab, the active substance in Imaavy, is a fully human immunoglobulin G1 (IgG1) mAb produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Imaavy is presented as a concentrate for solution for infusion in single-use glass vial with a nipocalimab strength of 185 mg/mL. Two presentations are proposed:

- One vial of 1.62 mL contains 300 mg of nipocalimab;
- One vial of 6.5 mL contains 1200 mg of nipocalimab.

Nipocalimab is formulated with arginine hydrochloride, histidine, histidine monohydrochloride monohydrate, methionine, polysorbate 80 (PS80), sucrose and water for injections.

2.4.2. Active substance

General information

Nipocalimab is a fully human IgG1(λ) mAb directed against the IgG binding site on the endogenous FcRn. Nipocalimab is engineered to be aglycosylated by introducing an Asn296-to-Ala296 mutation (N296A) in the Fc region, resulting in nipocalimab being without effector functions. Light chains (LC) and heavy chains (HC) are linked together by 4 covalent inter-chain disulfide bonds, and, in addition, there are 12 intra-chain disulfide linkages. In total, nipocalimab harbours 32 cysteines, of which no cysteine residues are unpaired.

The mode of action for nipocalimab is mediated through specific binding to the IgG binding site of FcRn. As the FcRn binding shows high affinity at both neutral (extracellular) and acidic (intracellular) pH, nipocalimab binds and blocks the FcRn mediated IgG recycling of pathogenic IgG, leading to decreased levels of pathogenic IgG.

The general information provided for nipocalimab is of sufficient detail and is found acceptable.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance is manufactured at WuXi Biologics Co., Ltd., 108 Meiliang Road, Binhu District, Wuxi, Jiangsu, 214092, China. All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

Nipocalimab active substance is manufactured using CHO expression, followed by purification and formulation.

Upstream manufacturing process

The upstream process for manufacturing of nipocalimab consists of various stages. The manufacturing is initiated by thawing a vial of the working cell bank (WCB) of the production cell line, followed by subsequent cell expansion. In the next process step, inoculation is performed where the production bioreactor contains feed medium and the production bioreactor is harvested. Further details on operating conditions for each step are provided in the dossier.

The upstream manufacturing process has been sufficiently described.

Downstream manufacturing process

The downstream manufacturing process of nipocalimab active substance consists of multiple process stages. The downstream process of nipocalimab active substance consists of multiple process steps including a capture chromatography stage followed by multiple polishing chromatography steps and a final formulation step. The formulated active substance is filtered for frozen storage.

The purpose of each of the process stages is sufficiently outlined. For chromatographic steps, column diameters, bed heights, condition for sample load, wash and elution, sample collection, and column equilibration are stated. Representative chromatograms for all chromatographic steps are provided. Filter types for filters used in the downstream process are covered in section 3.2.S.2.3. Where relevant, the hold times for respective pools are defined. Hold times are further assessed in section 3.2.S.2.5. Resin sanitisation procedures and lifetime are covered in section 3.2.S.2.5.

The downstream processing steps are sufficiently described.

Batch and scale definition

One batch of nipocalimab active substance refers to the material derived from bioreactor cultivations and subsequently purified, concentrated, and formulated. The batch numbering system is described. This is found acceptable.

Reprocessing

The applicant states that reprocessing during the active substance manufacturing process is not routinely performed. It is further stated that reprocessing may be performed during commercial-scale batch manufacturing if required during active substance manufacturing. This is found acceptable and in line with the information given in section 3.2.S.2.5.

A high-level description of the procedures for storage and shipment of active substance to the registered finished product manufacturing site is included in section 3.2.S.2.2 and are further described in section 3.2.S.2.5. This is found sufficient.

Control of materials

Raw materials

Raw materials used for cell banking (master cell bank (MCB), WCB) and manufacturing of nipocalimab active substance (i.e. cell culture, purification, and formulation) are stated. Compendial and non-compendial raw materials are listed and specifications for all non-compendial raw materials are provided. The applicant states that all compendial and non-compendial raw materials are derived from animal-free sources, which is acknowledged. Single-use cultivation bags, resins, membranes, and filters used are listed. The raw materials used are sufficiently described.

All media types used in the cell culture process are provided, and their corresponding constituents stated. Medium is used in the production of nipocalimab active substance in the preculture train and is based on Medium Powder, which is stated to be a proprietary medium, formulated by the supplier e. In addition, medium utilised is stated to be proprietary medium. Lastly, medium BM3, FM1, and FM2 are also stated to be a proprietary medium. The use of these three proprietary media components is acceptable as there is a quality agreement in place between the applicant and the suppliers to ensure that the applicant is informed about any changes in the proprietary media in order to assess potential impact on the product.

Materials of animal origin

No animal-derived materials were used in the creation of the nipocalimab manufacturing cell line. Proprietary ingredients were used in the early CHO host cell suspension adaption, data on sourcing with lot numbers, country of origin, treatment and TSE certificates of suitability or other information has been provided and is found acceptable. It is agreed that the risk of TSE is negligible. For virus risk mitigation see further below.

Source, history and generation of the cell substrate

The source of the host cell line and the creation of the production cell line, with steps through security cell bank, transfectant clone, research cell bank (RCB) and primary cell bank (PCB) is adequately described. The MCB was prepared from the WCB from expansion of the MCB. The sourcing of coding sequences and the creation of the plasmids for heavy and light chains respectively are described. Plasmid illustrations and tables outlining locations of elements with plasmid base numbers, vector elements, descriptions and sources are provided. The process to obtain monoclonality and its confirmation is presented and it is agreed that monoclonality has been demonstrated. The nucleic and amino acid coding sequences of both heavy and light chains are presented. The information provided is found in line with ICH Q5B and ICH Q5D and considered as acceptable. The associated flanking regions

inserted into the vector, up to and including the junctions of insertion, are outlined, which is acknowledged.

Preparation and testing of cell banks

The cell bank system and the preparation of the cell banks are sufficiently described for the MCB, WCB and end of production cells, including the extended. GMP storage, handling, identification and number of vials produced are presented. An end-of-production cell bank (EPCB) was prepared from cells sampled. EPCB vials were further propagated prior to extended EPCB (EEPCB) cryopreservation. Cells which reached a cumulative 57 days (44.1 PDL) at EEPCB bank preparation. This, so that the cells were cultured and tested beyond the limit of *in vitro* cell age. This is endorsed.

The cell banks were tested as according to the testing scheme of ICH Q5A and ICH Q5D. All methods of analyses are briefly described. This is endorsed. The applicant confirms that the introduction of future WCBs protocols will be managed through post-approval variation applications, which is found acceptable. In this context the applicant is reminded that the use of NGS as replacement for *in vivo* tests are encouraged in line with 3Rs and ICH Q5A (R2).

Genetic stability

The MCB, WCB and EEPCB cells were characterised for gene copy number, gross structure of transcript, gDNA and cDNA sequencing. Proper integration and stability of the plasmids were confirmed up to EEPCB. There were no detected change of integrated LC or HC genes, no changes in copy number, no gross deletions, insertions, or variants of the integrated plasmid elements observed. This is accepted.

Overall, the information in section 3.2.S.2.3 is found acceptable.

Control of critical steps and intermediates

Manufacture of the nipocalimab active substance is controlled by process parameters for each stage of the manufacturing process. Process parameters with the corresponding proven acceptable ranges (PAR) are presented in section 3.2.S.2.2. The process parameters are identified, assessed, and confirmed, followed by categorisation into either critical process parameters (CPP), or non-critical process parameters (nCPP), where CPPs have greatest potential influence on critical quality attributes (CQAs). An in-process control (IPC) is defined as a test, check, or measurement performed during the manufacturing process in order to, if necessary, make relevant adjustments to the process to ensure compliance of the intermediate, active substance, or finished product with its corresponding specification. Three distinct types IPCs are presented by the applicant, an IPC with (1) an acceptance criterion, (2) an action limits, and (3) a predefined instruction. The presented classification is found acceptable.

Tables providing summaries of the three distinct types of IPCs with the corresponding acceptance criteria, action limit, or predefined instruction are provided. This is found acceptable.

Analytical procedures for in-process control testing are stated and validated to be found fit for purpose. This is found acceptable.

Process validation and/or evaluation

Manufacturing process validation of nipocalimab active substance follows a three-step approach, including commercial-scale process validation, reduced-scale process validation, and additional validation activities. To achieve a solid understanding of the manufacturing process, combined information from both process validation and evaluation has been considered. Identification of CQAs and CPPs was achieved by criticality assessment and is presented in section 3.2.S.2.6. To control the CQAs in accordance with the predetermined CQA specification, process parameter control ranges and acceptance criteria were established for CPPs. In order to establish PARs for the commercial nipocalimab manufacturing process, reduced-scale process development studies were used. Both commercial and

reduced scale were used for process validation and evaluation studies. The presented approach for process validation is supported.

Process validation, including characterisation, of the commercial manufacturing process was performed at the commercial facility. Consecutive process validation batches were included in the study. Results from characterisation are presented in this section, and the corresponding batch data are shown in section 3.2.S.4.4. For all process validation batches, the validation acceptance criteria for both IPCs and process parameters were fulfilled with no impact to process performance or product quality. In addition, the acceptance limits for batch release were met for validation batches. This is acknowledged. In conclusion, the results from both process characterisation and batch data for the commercial lots support consistency and adequate production of nipocalimab active substance. CQAs and CPPs are assessed in 3.2.S.2.6.

Ongoing process verification

An ongoing process verification will be used with the aim to assure that the process remains in a state of control during commercial manufacture. This is endorsed. The activities to collect and analyse product and process data. The collected data will be reviewed, including analysis for trends. The ongoing process verification is briefly outlined in the dossier.

Impurity clearance

As part of the process validation, testing for product- and process-related impurities was performed after manufacturing. As part of process validation, testing for product and process-related impurities was performed after manufacturing with appropriate testing. In addition, clearance studies with impurity spiking were performed. The study design and the results obtained are found acceptable, sufficiently demonstrating that impurities can be removed to acceptably low levels.

Chromatography resin and filter lifetime

The lifetime of the resins and membranes used for affinity chromatography and two polishing chromatography steps were evaluated through resin validation studies. The resin lifetime validation study will also be verified during commercial processing. All results have met the acceptance criteria and no trends have been reported. The resin lifetime studies are found acceptable. The applicant has provided protocols for commercial manufacturing-scale verification to confirm the column performance and integrity.

Hold time study

The applicant states that the manufacturing process of nipocalimab active substance contains various process intermediates, generated during manufacturing, that may be held under controlled conditions (time, temperature, storage vessel type) prior to continued processing into active substance. A microbial hold time study was performed to confirm the established hold time limits for the media, buffer solutions and in-process pools under specified conditions, including the storage vessel type and temperature. Tryptic soy broth (TSB) was used to mimic conditions. The approach is found acceptable and the microbial hold times are found justified.

There are in-process pools that are referred to as process intermediates by the applicant. Hold times and storage conditions for process intermediates are stated. The maximum hold times are based on representative data. The approach to combine information on microbial and biochemical hold time studies is found acceptable.

Reprocessing

Reprocessing is proposed for certain manufacturing stages. The applicant performed reprocessing validation studies at reduced scale and protocols for reprocessing at commercial scale are provided. The

results are found acceptable. Protocols for reprocessing for both steps at commercial scale are provided, and reprocessing has to date also been verified at commercial scale. It is endorsed that the applicant performs reprocessing at manufacturing stage 8 and 11.

Shipping validation

Nipocalimab active substance is manufactured at WuXi Biologics Co., Ltd. in China and will be transported to Vetter Pharma-Fertigung in Germany for finished product manufacturing. The conditions for active substance shipping are adequately described, where the shipping systems must maintain the active substance. The strategy described for shipping validation is found acceptable. Brief result summaries are provided for thermal qualification, distribution testing, and shipping route verification, which is acknowledged. Overall, the information and results presented in the shipping qualification document for the active substance are found sufficient and acceptable.

Extractables and leachables study

The applicant has provided an extractables and leachables risk assessment study report, evaluating the risk for all polymeric product contact materials used for nipocalimab active substance manufacturing process. The design of the extractables and leachables study is considered sufficiently described and overall thorough. Results, calculations, and conclusions are provided in the risk assessment report. This is found acceptable. With reference to the presented results, the applicant has sufficiently demonstrated that the used polymeric product contact materials pose a minimal risk to patient safety.

To conclude, process validation and evaluation of nipocalimab active substance can be considered acceptably described once the raised issues has been properly addressed.

Manufacturing process development

Section 3.2.S.2.6 is divided into three main subsections: Process History (manufacturing history and process change, analytical development history, comparability), Process Development, and Impurity Criticality Evaluation.

Manufacturing history and process change

One site, WuXi Biologics Co., Ltd., China, has been responsible for active substance batches manufactured. Multiple main processes have been used during development. There are two versions of processes which only differs in bioreactor scale and chromatography scale. The differences between the processes have been clearly presented in a tabulated form. Two major changes were implemented during manufacturing development. In the first major change production of active substance was replaced by a cell line cell bank. Secondly, the active substance nipocalimab concentration was increased. The description of the manufacturing history is found acceptable.

Comparability

Analytical comparability studies including comparisons of batch analysis and stability data, as well as extended product characterisation were performed throughout process development to support the implementation of major changes and improvements. The attributes and parameters compared are found acceptable and in line with ICH Q5E. Data from individual batches are presented in tabular form in the dossier.

In the first comparability study, comparability between pre-change and post-change evaluated. The number of batches included in the study is considered acceptable for this stage of development. The applicant concludes from evaluation of batch release data and ICH stability data that the pre-change and post-change active substance batches demonstrated comparability. The conclusion is supported.

The following comparability exercise evaluates the comparability between subsequent processes. For this exercise, multiple process batches are used, which is acceptable. Overall, the results from release

testing, extended characterisation, forced degradation study, and long-term and accelerated stability are found comparable. A comparability report for this study, in support for the conclusion, is provided in the dossier.

The subsequent comparability exercise evaluates the comparability between active substance manufactured using different processes. For this study, multiple active substance batches for each process are included, which is acceptable. The approach for setting the statistical range/limits used for comparability assessment are explained. The active substance batches met the in-process control and release acceptance criteria. The majority of the active substance characterisation results were within the historical min-max or statistical ranges ($\pm 3SD$). For attributes that were outside the min-max and statistical ranges, an additional risk assessment was performed, and those attributes were considered to have minimal potential impact on product stability, degradation pathways, pharmacokinetics, safety, and efficacy, because they did not impact bioactivity or degradation rates, or they were within the total range of product experience in clinical development. Such examples are the presence of low levels ($<2\%$) of specific residues in heavy chain in one process, and the presence of low levels ($<3\%$) of specific peptide for one process. The conclusion by the applicant that the various processes are comparable for active substance is supported.

In conclusion, the presented results from the comparability studies support comparability between the different process versions.

It has been demonstrated that low levels of specific impurities present for nipocalimab active substance can be consistently achieved. This is acceptable.

Process characterisation and control strategy

The program described for process characterisation is considered extensive. To identify critical process parameters (CPPs) for the nipocalimab manufacturing process, an initial list of process parameters is established to identify presumptive CPPs (pCCPs) that are likely to have an impact on the active substance critical quality attributes (CQAs). The selected process parameters in the list are based on historical data, scientific knowledge, manufacturing process understanding, and experience with other antibody products. The selected pCCPs are then further evaluated followed by a final categorisation of each pCCP into either a CPP or a nCCP. The overall strategy described is found acceptable.

All reduced-scale models were adequately qualified and, thus, representative of the corresponding process stage at manufacturing scale. This is for most parts acceptable.

For the upstream and downstream processes, the study design, the parameters, ranges and results of the process characterisation are provided. The results are summarized in tabulated form. The information provided on process characterisation is found acceptable, sufficiently justifying the classification of parameters and the corresponding operating ranges (ORs) and proven acceptable ranges (PARs). Furthermore, the applicant has presented a summary of IPC results together with justifications for each corresponding acceptance criterion, action limit, and predefined instruction. The presented justification of IPC limits and instructions are found acceptable.

The applicant has presented information regarding the analytical history development, microbial control strategy, control of material attributes, quality management system, and impurity criticality evaluation. The information provided in these sections is found acceptable.

In conclusion, the applicant has properly addressed the development history of the active substance manufacturing process and properly assessed and discussed the impact regarding comparability. The process development and characterisation, including development of the control strategy, is for most parts considered adequately described and justified. The information provided in section 3.2.S.2.6 can be considered sufficiently and acceptably described.

Characterisation

Elucidation of structure and other characteristics

A comprehensive analysis of the biochemical, biophysical and biological properties of nipocalimab using a wide variety of orthogonal techniques is presented. Overall, the results show that nipocalimab has the covalent structure, post-translational modifications, and other characteristics of a typical monospecific human IgG1 antibody derived from CHO cells. Nipocalimab is engineered with a mutation in the CH2 domain, N296A, to produce a non-glycosylated Fc region without effector functions. The approach to use a broad range of state-of-the-art techniques used to address identity, higher order structure, heterogeneity pattern, biological functions and purities/impurities is acknowledged and endorsed.

Characterisation was performed on active substance produced with the commercial process. The corresponding batch has also been used to prepare the primary reference material (PRM) used in clinical and process validation, and post-validation studies. Since this process version is deemed representative for manufacturing of the active substance, the use of this batch for elucidation of structure and other characteristics of nipocalimab is acceptable.

Primary structure

Peptide mapping analysis confirmed that the amino acid sequences of light and heavy chains match the theoretical sequences. 100% sequence coverage was found including confirmation of the N296A point mutation. Peptide mapping was also used to identify and quantify amino acid modifications. The dominant post-translational modifications (PTMs) were identified. All other modifications were present at lower levels. In conclusion, it is agreed that the primary sequence is sufficiently verified and PTMs identified with one exception: according to the applicant, glycosylation was not detected due to the asparagine-to-alanine point mutation in the single consensus sequence for N-linked glycosylation in the nipocalimab molecule. Additionally, O-linked glycosylation has also been adequately addressed in this section of the dossier.

Intact mass and mass heterogeneity

Mass analysis was performed on nipocalimab for full-length (intact) protein, light chain and heavy chain, respectively. Examples of deconvoluted mass spectra and theoretical molecular weights can be found in the dossier. It is stated that identified masses were considered consistent with theoretical masses, demonstrating that nipocalimab was a correctly assembled, disulfide-bonded, aglycosylated homodimer containing 2 intact LCs with cyclised N-terminal pyro-Glu and 2 intact HCs with no C-terminal lysine (CTL). This conclusion is endorsed.

Higher order structure incl. disulfide bonds

The 16 predicted disulfide linkages formed between the 32 cysteines in nipocalimab were detected. Linkage assignment for 7 out of the 9 unique disulfide bonds were definite (each reduced peptide contained a single residue) but for 2 bonds in the hinge region (peptides containing two residues), assignment was instead performed based on homology. The presence of unpaired cysteines (free thiols) was low as determined by the Ellman's assay and their location were identified by non-reduced peptide mapping. Together, these results indicate that nipocalimab has the expected disulfide bond structure for a properly folded IgG1 antibody. This is found acceptable.

Higher-order structures were further analysed by biophysical techniques. Spectrum confirmed typical β pleated sheet secondary structures with well-defined tertiary structure as expected for an IgG1 antibody. Analysis of quaternary structure demonstrated the monomeric oligomeric state in solution. Thermal stability was addressed using differential scanning calorimetry (DSC) and spectrum showing thermal transition temperatures (Tms), typical for the unfolding of an IgG1 monomer in solution, is included in the dossier. This is found acceptable.

Purity and pattern of heterogeneity

Charge heterogeneity due to PTMs upon protein expression in mammalian cell culture was evaluated using capillary isoelectric focusing (cIEF) for detection of peaks with different isoelectric points (pIs), followed by full. cIEF of nipocalimab resulted in predominant peaks: main peak corresponding primarily to nipocalimab acidic peaks corresponding primarily to nipocalimab with basic peaks. The PTMs in the acidic and basic variants did not seem to have any significant impact on the bioactivity as measured by assays used for biological characterization. The thorough approach undertaken by the applicant to identify and characterise the nipocalimab charge variants is acknowledged.

Size heterogeneity was analysed. Identities of the aggregates and fragments have been addressed with assignments of peaks included in the dossier. Nipocalimab was shown to be predominantly monomeric in solution with a low propensity for aggregation. Importantly, no significant impact on biological activity was observed for the isolated HMW fraction as measured by the three biological assays. Characterization of active substance purity with respect to size heterogeneity is assessed as acceptable.

Biological characterisation

Biological characterisation was performed to demonstrate the mechanism of action (MOA), to assess Fab specificity and Fc functionality and evaluate functionality of product-related variants. The MOA of nipocalimab is to bind to FcRn receptor at slightly acidic to neutral pH, thereby preventing recycling of other IgGs including pathogenic IgGs. Structural data support a direct competition binding mode between nipocalimab Fab with the Fc-domain of other IgGs. The inability of nipocalimab Fc-domain to engage with the FcRn receptor was demonstrated in a set of assays in which nipocalimab failed to induce antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC). In contrast, a glycosylated version of nipocalimab did. In addition, analysis was undertaken to compare binding to Fc receptors FcγRI, FcγRIIa, and FcγRIIIa compared to an unrelated IgG. These results demonstrate that nipocalimab indeed lacks effector functions. Hence, the N296A point mutation in nipocalimab was shown to produce a non-glycosylated, effector less Fc-region. This is found acceptable.

In vitro assays were developed with representative dose-response curves presented where relevant. The binding assay was chosen as the potency assay for commercial active substance and finished product release and stability potency testing. The comparison included forced degradation samples proving the binding assay to be stability indicating. Loss of direct binding activity was confirmed as orthogonal method. This loss of binding as shown in structure-function studies. A post-translational modification CQA was identified due to direct impact on bioactivity.

The applicant has developed assays that satisfactorily reflect the MOA of nipocalimab. The choice of potency assay for release and stability testing has been well justified. This approach is endorsed.

Impurities

Presence, identity, and risk assessments of product- and process-related impurities were discussed in section 3.2.S.3.2 with references to relevant sections in the dossier.

Product-related impurities in the active substance were extensively characterised in CTD S.3.1. Molecular variants of the active substance that may impact bioactivity of nipocalimab were found. Analytical methods to test these CQAs has been developed. The characterization of the product-related impurities is found acceptable.

The process-related impurities are addressed in section 3.2.S.3.2. Procedures and acceptance criteria for the removal of these impurities are presented in section 3.2.S.2.5. Batch results presented in section 3.2.S.4.4. confirm efficient removal of all the process-related impurities. This is acceptable

The risk assessment of other process-related impurities identified in the active substance manufacturing process is described in CTD 3.2.S.2.6 Impurity critical evaluation.

Contaminants are thoroughly controlled during the manufacturing process and the capability of the active substance process for virus removal has been demonstrated in section A.2. The applicant risk assessed the active substance to present a low risk for nitrosamine impurities which is agreed to.

Overall, characterisation of nipocalimab is considered acceptable.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

The specifications for nipocalimab active substance include control of identity, purity and impurities, potency and other general tests.

The methods descriptions referred to in section 3.2.S.4.2 includes unequivocal in-house identifiers.

Omitting HCP testing in the active substance specification could be considered if certain criteria are fulfilled (see EMA Q&A 2023). The method and the validation are well described in the dossier (S.2.4). The coverage of process-specific HCP antibodies was determined. Furthermore, the applicant has demonstrated extensive knowledge and control of the manufacturing process and the presented justification of IPC limits was found acceptable in S.2.6. Extensive batch data showing consistent low levels of HCP) is available in S.4.4. The omission of HCP from the active substance specification and only test as IPC is acceptable.

Testing of polysorbate is deemed acceptable.

Analytical procedure

Some tests are stated to comply with the corresponding Ph. Eur. chapters. In addition, brief method descriptions have been provided for the endotoxin and bioburden tests. This is found acceptable.

Examples of typical chromatograms and electropherograms are provided, where applicable for most of the methods. Specific information such as type of chromatographic columns is given. Thus, the method descriptions are found acceptable.

Validation of analytical procedure

The compendial analytical procedures were verified as suitable for intended use. Verification summaries have been provided in the dossier. These include specific data for nipocalimab for the methods addressing bacterial endotoxin (interfering factors, hold time) and bioburden (recovery of microorganisms) to support the suitability of the respective method. This is found acceptable.

Validation summaries of all non-compendial methods have been provided in 3.2.P.5.3 including descriptions of validation approaches and parameters. Relevant validation parameters have been evaluated. Further, relevant calculations, acceptance criteria, description of results obtained for individual samples have been presented. The validation of the analytical procedures to control nipocalimab active substance is assessed to be acceptable.

Batch analysis

Results from batch analyses using specific process were presented, active substance process validation batches and multiple clinical active substance batches. In addition, batch analyses are included in the dossier for batches produced with earlier process versions. All results complied with the proposed

specification limits in place at the time of testing. The provided release data from the commercial process is in support of a consistent manufacture of active substance. This is found acceptable.

Justification of specification

To set the specification limits for nipocalimab active substance, the applicant has used a strategy derived from compendial guidelines, ICH Q6B, product and process knowledge, prior experience with other antibodies, statistical analysis of active substance release and stability data. Where appropriate, the final step in setting the active substance specification was aligned with the finished product release specification.

The attribute specification did not include statistical analysis due to their non-trendable attributes. The limits and acceptance criteria are found acceptable.

The acceptance criteria for tests with trendable attributes amenable for statistical analysis were set using a stepwise approach. This included trend analysis of release and stability data to determine whether data derived from patient experience could be pooled and used in the total manufacturing experience. Single or separate Bayesian posterior tolerance intervals were then calculated to justify the acceptance criteria. The approach to undertake statistical analysis of clinical and process validation batches in combination with prior knowledge is endorsed. The proposed acceptance criterion for active substance as well as finished product, is acceptable.

Reference standards of materials

Different reference standards have been used during the development of nipocalimab. The history of reference standards is adequately described in terms of batch number origin, manufacturer, date of fill, and storage conditions.

For the commercial process, a two-tiered reference standard system is used. A primary and working reference standard (material) were derived from selected active substance batches manufactured and stored at the same conditions. The qualifications of the primary and working reference standard are described and the methods used for qualification, the acceptance criteria and the obtained results are provided. Assignment of relative potency is found sufficiently described.

All acceptance criteria of the qualification methods were met. This is found acceptable.

Qualification of future primary and working reference standards has been outlined by the applicant. The current PRM will be used for future PRM and WRM qualification when the testing requires comparison to an RM. The qualification protocol includes the test and acceptance criteria as listed in the active substance release specification. These tests will be performed on independent vials unless otherwise stated vials will be sampled from across the fill (beginning, middle, and end) to represent the entire batch during qualification testing. The strategy for replacement and qualification of new standards is endorsed.

The primary reference standard is requalified for stability annually by testing for purity, charge heterogeneity, and binding potency. The results will be evaluated against the acceptance criteria. In addition, the qualified working reference standard will be routinely monitored via data generated from routine GMP testing. Trend analysis will be monitored of generated requalification data (PRM) and release and stability data (WRM) to ensure no drift of critical attributes over time. The requalification scheme is deemed acceptable.

Container closure system

The components are clearly stated. Specifications and a schematic drawing are provided. The silicone liner conforms with Ph. Eur. 3.1.9 (silicone elastomer for closure and tubing). Inspection requirements for incoming containers and closures are outlined. For example, the incoming Certificate of Analysis must contain a statement that the materials of construction meet USP Class VI. This is found acceptable.

The choice of container closure system was justified by the applicant. An evaluation of the container closure system extractable compounds resulted in no toxicological safety concerns. The applicant states that all stability samples are stored in containers representative of storage closure system. This is further assessed in section 3.2.S.7.

The information in this section is deemed acceptable and sufficient.

Stability

The proposed shelf life of nipocalimab active substance is appropriate in the bioprocess container (described in S.6) at the recommended temperature.

To support the shelf-life claim, an ongoing stability program has been designed in accordance with ICH guidelines, Q5C and Q1A. Stability data is provided for long-term conditions, accelerated conditions and stressed conditions. The quality is monitored using multiple analytical procedures with established acceptance criteria as described in active substance specification (S.4.1). The stability studies were conducted in containers of the same material as for the full-size containers. Selection of batches included clinical and PV batches. These specific primary batches were manufactured representative of the commercial manufacturing process and scale and acceptably representative of commercial scale storage. This is found acceptable. Real-time data to support the shelf-life claim has been provided from recommended storage. To date, stability data is available from -70 °C and -40 °C for 18 months for the 3 clinical batches and for 6 months for the 3 PV batches. Supporting stability data obtained from accelerated (-20 °C) and stressed (5 °C) storage conditions were also presented in support of the shelf-life claim. All available stability results met the acceptance criteria for the tested CQAs (including potency, charge heterogeneity and purity) through the proposed shelf life without any observed trends.

Furthermore, a small-scale freeze-thaw study demonstrated that the active substance met all acceptance criteria after 3 cycles. Photostability studies are addressed on a finished product level (P.8). Taken together, the design of the stability program is endorsed.

Post-approval stability protocol and stability commitment

Ongoing stability studies and post-approval stability studies will be performed according to the protocols described in the dossier. The applicant commits to continue these studies through the proposed shelf-life. This is found acceptable.

Proposed shelf-life and storage conditions

To conclude, the provided stability data support the shelf life at the recommended storage condition for nipocalimab active substance.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical Development

Nipocalimab finished product is supplied in two presentations corresponding to a concentrate for solution for infusion in glass vial (1200 mg and 300 mg) both intended for single use IV infusion after dilution in 0.9% sodium chloride (250 mL). The nominal fill volume is 6.5 mL and 1.62 mL respectively. An established PAR has been set in section 3.2.P.3.3 in order to fulfil the nominal fill volume requirement of the finished product. The qualitative and quantitative composition of each presentation is provided. The chosen excipients comply with Ph. Eur. and their function has been appropriately described.

A brief description of the container closure system has been provided: A glass vial, elastomeric closure and an aluminium seal are compliant with appropriate Ph. Eur. Monograph for primary containers and

closure. For detailed assessment of the container closure system reference is made to CTD sections P.2.4 and P.7.

Overall, the information provided is considered sufficient.

Nipocalimab is formulated with arginine hydrochloride, histidine, histidine monohydrochloride monohydrate, methionine, polysorbate 80 (PS80), sucrose and water for injections.

The qualitative and quantitative composition for the 6.5 mL presentation of a unit vial of nipocalimab concentrate for solution for infusion 1200 mg/vial (185 mg/ml).

The qualitative and quantitative composition for the 1.62 mL presentation of a unit vial of nipocalimab concentrate for solution for infusion 300 mg/vial (185 mg/ml) is presented.

Pharmaceutical development

A prospective summary of the quality characteristics of the finished product in the quality target product profile (QTPP) format is outlined in section 3.2.P.2.3.

Initial formulation studies investigated different qualitative components.

Different fine-tuning experiments were conducted and resulted in the final formulation containing the following components: L-histidine buffer at pH= 6, arginine hydrochloride, L-methionine, sucrose and polysorbate 80. These components have been thoroughly evaluated and their functions have been adequately justified.

Formulation Composition Ranges and Robustness on Stability.

The target finished product formulation was selected. This target formulation was evaluated for robustness and according to Applicant to establish the proven acceptable ranges (PARs), results provided in section P.2.2.1. The investigations performed showed the target formulation to be robust. According to Questions and Answers: Improving the understanding of normal operating ranges (NORs), PARs, active substance and normal variability of process parameters EMA/CHMP/CVMP/QWP/354895/2017 the PAR is defined as a characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (ICH Q8 R2). Even if the target composition has been shown to be robust within ranges tested, as the investigated factors are composition differences of the target components, they are not process parameters but rather material attributes. The ranges established when a design of experiments (DOE) has been performed is multifactorial, and several factors have been changed simultaneously.

Different stress factors were evaluated. A study was performed, and different quality attributes measured. However, the trend is not linear over the investigated region, but a . It indicates if concentration of PS80 becomes too low, protein aggregation will occur as a consequence of shaking. Therefore, is the most critical component of the composition over the ranges investigated during the robustness study. The functionality has also been shown. Since this study not expected to occur during ordinary production and validation studies have been performed with simulated interventions and different shear stress conditions, as long as specifications of PS80 is fulfilled the risk of aggregation is considered mitigated.

A repeated times showed no stability changes for any of the formulations. Finally, a stability study did not show any major changes between the formulations.

In summary, the composition chosen for commercial manufacturing have been shown robust and fit for the purpose operating at target concentrations. It is acknowledged that a range of concentrations for the different material attributes have been shown robust, even if the original definition of PAR according to ICH Q8 (R2) refer to process parameters.

Overages and Physicochemical and biological properties

There are no formula overages applied to the formulation of finished product. The information given on physicochemical and biological properties is found sufficient.

Manufacturing process development

The manufacturing process development activities consisted of the definition of a QTPP, identification of CQAs and characterisation of CPPs as well as corresponding PARs. Criticality of quality attributes was justified. The knowledge uncertainty categorisation of the CQAs has very low scores. However, as the general risk is justified as low in this case this is acceptable. The number of relevant CQAs is found adequate covering the expected area related to quality.

Container closure system

The development of the container closure system is sufficiently presented. The container closure system for 185 mg/ml (1200 mg/vial) finished product glass vial stopper and an aluminium seal with flip-off cap.

The finished product vial presentations and rubber stoppers are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in section P.7.

The suitability of the container closure system to protect the content from microbial contamination during storage, transportation and use of finished product has been demonstrated using long-term stability and shipping validation studies, results are provided in section P.8.1 and P.3.5.

Furthermore, the suitability of the container closure system was confirmed by the results of the extractables and leachables testing, risk assessment associated with final container closure systems.

Microbial attributes

The information given on microbiological attributes is found sufficient.

Compatibility

The in-use stability study of diluted solutions in normal saline of finished product has been shown to retain their physical, chemical and biological integrity for up to 48 hours, including 24 hours at 2-8 °C, 22 hours at 30 °C, and 2 hours at 15-25 °C. Samples were taken just after the preparation of IV bag (T0), after 24 hours of hold time at 2-8 °C in the bag followed by 22 hours of hold time in the bag at 30 °C and attached ancillaries (T46), and after 2 hours of simulated administration through ancillaries including a 0.2 micron filter at 15-25 °C (T48). In SmPC, section 6.3 is stated that if immediate administration is not possible, the diluted solution can be refrigerated for up to 24 hours at 2-8 °C, with an additional 12 hours of storage at room temperature, including infusion time, at 15 °C to 30 °C. Do not freeze.

It is agreed that the in-use stability range claimed in SmPC is experimentally justified by the in-use stability studies performed in section P.2.4.

Manufacture of the product and process controls

Manufacture

Sites in charge of manufacture and control of the finished product operate in accordance with EU GMP.

The manufacturing process of finished product includes sterile filtration, filling, stoppering and capping. Finished product units are finally visually inspected (100%).

Process steps duration and hold times in the finished product manufacturing process together with their respective hold conditions and periods have been provided. The parameters mentioned have been confirmed in the validation study in section P.3.5.

No reprocessing has been described in the dossier and is consequently not allowed for the steps up to and including filling, stoppering and capping.

For each process step the CPPs were identified and justified. These activities provide the basis for the development of process control strategy.

Process controls

Scale and Equipment Independent Mixing Design Space.

The applicant is defining a design space of factors investigated according to P.2.3 Manufacturing Process Development, section 3.4.1. These ranges were confirmed experimentally for batches by measuring composition material attribute as a measure of finished product homogeneity and by measuring selected critical quality attributes as a measure of shear impact during compounding.

The compounding mixing operation is acknowledged to be well understood and that the interpretation of design space should be limited to the compounding mixing step.

The mixing procedure of the finished product compounding unit operation investigating mixing time and mixing speed has been shown to result in a homogenous finished product and the CQAs have been shown to be within the specified limits.

Control strategy

The development of the control strategy for the finished product has been sufficiently described in section P.2.3. In summary of integrated control strategy for finished product, the critical quality attributes of the manufacturing process is controlled on five levels: (A) release specifications for raw materials (B) critical process parameter limits (C) In-process testing limits (D) release specifications for finished product (E) stability specifications for finished product, (F) Non-routine assessments and (G) Good manufacturing practices, GMP. The CPPs and IPCs for the commercial manufacturing process is provided in section P.2.3., the IPC with acceptance criteria is found in P.3.4. and in the specifications in section P.5.1.

CPPs for each unit operation of finished product manufacturing and their proven acceptable ranges are presented in Process Control Strategy Development – Critical Process Parameters. The ranges were established and described in 3.2.P.2.3 and in 3.2.P.3.5. Volumes of buffer compounding and finished product compounding, thawing times, mixing speeds and mixing times, hold times, sterile differential pressure and filtration time are tabulated with ranges which are found acceptable. During aseptic filling, the CPPs identified fulfilled established proven acceptable ranges.

The quality management system is outlined in section 3.2.S.2.6 which includes handling of future changes in production with a formal corrective actions preventive actions (CAPA) system in place. All changes to critical material attributes (CMAs), CQAs, CPPs, nCPP and IPCs will be assessed and managed through the internal change control system.

Comparability

During the development, some changes have been introduced for the manufacturing process of finished product and comparability between the processes have been evaluated in comparability studies.

All quality attributes studied in the comparability studies show a high degree of similarity with very few and minor differences noted which are not expected to have any impact on safety and efficacy.

Therefore, it can be agreed to the conclusion by the applicant that the comparability has been sufficiently demonstrated for all attributes tested and all the finished product-vial presentations included and evaluated.

Overall, the information provided on manufacturing process development for the finished product is found sufficient.

Process validation and/or evaluation

Several batches of finished product (compounding batches –batches were filled with the finished product presentations, 300 and 1200 mg/vial) were manufactured at commercial site representing worst case volumes compounding vessel. Batch analyses are provided in section P.5.4 for all PV batches. This approach covering both presentations and possible batch sizes are found acceptable.

Ranges for material attributes were investigated during formulation development and found to be robust. That study justified specification limits for material attributes like pH, PS80 and protein concentration. During manufacturing of validation batches, the IPC for pH was and at release the pH range at batch analysis for the validation batches. The batch analysis of validation batches at release of concentration of PS80 in line with the limits 0.04-0.08%. The target protein concentration is 185 mg/ml for all validation batches. Finally, the range for competitive binding assay was 89-112%. Batch release for the validation batches were found to be within pre-defined limits. This is acceptable.

PARs for CPPs were challenged during the manufacturing process development as described in section P.2.3 and during process validation. This is found acceptable.

Mixing parameter ranges were validated for the PV batches.

Aseptic manufacturing and filling, Visual inspection, Cumulative light exposure and hold times were investigated and material attributes, critical quality attributes and critical process parameters and in-process controls were found to be within predefined limits and specifications.

Some minor deviations were noted, but root causes identified and handled according to CAPA routines. It was concluded that there is no risk to the quality of the finished product solution or to patient safety. The handling of the described deviation is found acceptable.

For all filled batches, the results of IPCs and process characterization samples met the predefined acceptance criteria where applicable, and all CPPs were controlled within predefined ranges. All release results met finished product release specifications. The results demonstrate that the finished product manufacturing process as executed at the commercial manufacturing site is validated.

The applicant commits to continuing the ongoing stability study of three PV batches of each presentation (300 mg and 1200 mg), P.8.2 Post-Approval Stability Protocol and Stability Commitment. Of the PV batches only were put on stability. It is acknowledged that representative PV batches has been put on stability, and the selection process has been justified.

Validation of the aseptic filling process

Media fills were used to validate the aseptic filling process. The three latest re- are described in Media Fills section in P.3.5. Worst case scenarios (e.g. filling volumes to assure optimal head space for microbiological growth) and simulated production interventions were included in the validation of the aseptic filling process. Results for the media fills cover the total filling time. The media fill validation demonstrate that the aseptic conditions are maintained during the filling process.

Hold times of the different finished product unit operations is presented in P.3.5 Process Validation and/or Evaluation: Hold Times. Hold times, cumulative hold time and cumulative exposure to ambient light exposure during fill-finish manufacturing were included for the PV batches. This is found acceptable.

The validation of the aseptic filling process has been adequately described and fulfilled pre-defined acceptance criteria.

Filter validation

Two reports are included in the dossier: Bacterial Retention Validation Report. Filtration was performed using a 0.22µm Durapore hydrophilic membrane disc with a surface area of 3.9 cm² challenged with 2.4 10⁷ cfu/cm² of *Brevundimonas diminuta*. The provided results demonstrate that the 0.2 µm filter used are fit for the purpose and justify the use of these filters in commercial manufacturing of the finished product in line with the guideline EMA/CHMP/CVMP/QWP/850374/2015.

Transport validation

Shipping validation studies of the finished product have been performed to demonstrate that the transport at 2-8°C does not adversely impact the quality of the finished product or its packaging. The study comprised of real-time shipping and simulated mechanical handling including vibrations and falling situations. The study included the 300 mg presentation and 1200 mg finished product presentation, where half of the units were used as controls not exposed to the simulated mechanical handling.

Thermal Qualification Data Summary for Active Shipping System is supplied in P.3.5; Qualification of Active Shipping System.

The provided transport validation data are found acceptable and confirm that the quality attributes are maintained when the finished product is transported within 2-8 °C.

In conclusion, the process validation data presented in section P.3.5 demonstrate that the process is robust and performs as intended, giving a finished product which meets the quality requirements when run within the defined operating ranges.

However, a transport validation study for a finished product batch starting at the lower end of specification limit is recommended.

Excipients

All excipients comply with the Ph. Eur. requirements and are commonly used excipients in parenteral formulations for biological products. Furthermore, the finished product contains no novel excipients or excipients of human or animal origin.

This is found acceptable.

Product specification, analytical procedures, batch analysis

Specification

Specifications of the finished product include control of identity, purity and impurities, potency and other general tests.

Justification of specification

Relevant tests are included in the specifications document for the finished product in section 3.2.P.5.1 covering limits for both release and end-of-shelf life of the various attributes. Method identification numbers are missing for the in-house methods in method descriptions.

Unequivocal identifiers for in-house analytical methods are included in the method description in section P.5.2.

The proposed acceptance criteria for the general tests (, identification and microbiological tests are at large found acceptable.

Process data were statistically evaluated for quality attributes having the same formulation design, with no significant differences. A significant change in intercept was seen as expected due to changes

It has been shown that polysorbate 80 has lost most of its function as aggregation inhibitor during agitation at the lowest level and is not considered robust over the entire PAR during stressed conditions, in 3.2.P.2.2.1 Formulation Development, section P.3.2.5. This was confirmed in an agitation stress study, in 3.2.P.2.2.1, section 3.2.4 Shipping Stress Studies. Here, the amount is equal for formulated product containing polysorbate 80 compared to formulation with polysorbate added. A transportation study has been performed fulfilling the acceptance criteria in 3.2.P.3.5. Two batches were investigated (300 and 1200 mg showing after transportation. Control samples were shipped to/from the Distribution Test Lab but were not exposed to the lab simulated distribution sequence. However, the control samples were never analysed - as no atypical results were obtained. Consequently, it is not possible to conclude if PS80 content was decreased or not after transportation. This indicates that levels of PS80 during transportation has not decreased compared to levels at release. However, it is expected that no aggregation will occur.

The agitation stress study is acknowledged to be an extreme condition that maximises the interfacial stress in the vial. Even if the results fulfil specification limit criteria, the starting level is far from end-of-shelf-life limits. This increase was not seen for any of the other formulations indicating a tendency PS80 to losing its function of inhibition of particle aggregation. For an aged product batch at time it might not fulfil specification limits after an agitation stress study over 24 hours simulating shipping for critical attributes reflecting aggregation properties. It is also noted that the performed shipping validation was performed using a tentative specification used at the time of the study and not the final finished product specification.

Therefore, the applicant is recommended to perform a study using a batch with a starting level of PS80 using the final finished product specification.

The proposed commercial acceptance criteria for the 1200 mg finished product align with statistical analysis of patient experience data. The proposed commercial acceptance criteria for stability. Comparability is claimed to be fulfilled, clinically but also chemically for HMWS, even if no equivalence limits have been defined and justified. In a phase 2 study, a 2-fold higher than the maximum commercial dose was used – has been clinically qualified.

The range for batches used during justification for specification is 1.4-1.6. However, the range at release data for seven PV batches was It is justified that quality attribute is comparable and clinically qualified, but it is noted that the range obtained for batches used for justification of specification differ significantly from the range obtained for PV batches at release.

The proposed acceptance criteria are found acceptable and clinically qualified as the following quality attributes have been exposed to patients at a higher level compared to the commercial dose.

Release and stability data active substance/finished product batches (total manufacturing experience) showed no statistically significant trends in stability when stored at the recommended storage temperature, refer to 3.2.S.4. and 3.2.P.5.6. Also, the applicant argues that the observed (not statistically significant) trend slopes are not scientifically meaningful within the recommended shelf-life period of active substance and finished product. Data from stressed and accelerated storage conditions showed no obvious trends and therefore supports that these parameters are not stability indicating. It is acknowledged that, in the studies presented, were not stability indicating. This implies that the applicant, in this case, agree on protein concentration as an important quality attribute.

In conclusion, overall pH and protein concentration are considered important attributes to the overall profile of product quality. In order to ensure product quality have been included in the active substance and finished product shelf-life specification.

Analytical procedures and validation

Many tests used for release and stability testing of finished product are also used for release and stability testing of active substance. These methods and validation results are presented, discussed, and assessed in sections S.4.2 and S.4.3 and cover both active substance and finished product. The analytical procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate compendial chapters. In section P.5, the following methods have been described. Validation results have been presented, discussed, and assessed. It is agreed to that the validation studies, using predetermined acceptance criteria, have demonstrated that the analytical procedures are sufficiently robust and suitable for their intended purpose.

Characterisation of impurities

Product-related impurities and process-related impurities are described. Product-related impurities are adequately controlled. Levels are considered low and will be monitored during release testing. It has been identified, that under stressed conditions at specific PS80 levels, there is a significant increase as shown in P.2.2. However, the simulated transport validation including shear stress interventions showed no increase in HMWS. The product-related impurities are considered sufficiently addressed and in control.

Process-related impurities are controlled in line with ICH Q6B described in S.3.2. Impurities. No further process-related impurities have been introduced during finished product manufacturing.

Potential process- and product-related impurities are sufficiently addressed in section S.3.2 and S.4. It has been shown that no new product or process related impurities are generated during manufacture of the finished product.

A summary report on Leachables and extractables is provided. No leachables above reporting threshold described in ICH Q3D was observed. It is concluded that the leachable risk from the container closure systems of finished product is acceptable.

Nitrosamines

A nitrosamine risk evaluation was provided, thoroughly describing the potential risk of nitrosamine formation for both active substance and finished product and the risk mitigation steps taken. The conclusions of the risk evaluation report are fully supported, and nitrosamine formation in active substance or finished product is considered negligible.

Elemental impurities

A risk-based approach in line with the recommendation of ICH Q3D is presented. It is agreed that the residual quantity of elemental impurities is very low, and meet the requirements specified in ICH Q3D.

Batch analyses

Batch analyses data have been provided for finished product batches used in clinical trials and stability manufactured at full commercial scale.

The batch analysis data complies with the limits in the proposed finished product release specification in place at the time of manufacture and confirm process and product consistency. In conclusion, the batch data provided demonstrate reproducible manufacturing of Nipocalimab finished product.

Reference standard

The finished product Nipocalimab concentration for solution for infusion 300 mg/vial and 1200 mg/vial (185 mg/mL) is, regarding formulation and composition of the active pharmaceutical ingredient (API), identical to the nipocalimab active substance. Information on the reference standards used for release, in process controls, and stability testing of the nipocalimab finished product and active substance is provided.

Container closure system

The container closure systems of Nipocalimab concentrate for solution for infusion 300 mg/vial and 1200 mg/vial (185 mg/mL) consists of a clear Type I borosilicate glass vial, closed with a rubber stopper, and secured with an aluminium seal with flip-off cap.

Appropriate analytical procedures have been established to control the components of these primary packaging configurations. Specifications of the glass vial, the rubber stopper, and the aluminium seal with flip-off cap have been provided. Information on the suppliers of the primary packaging material has been provided. The suitability of the primary container closure components is assured by compatibility and extractables and leachables studies. Compatibility of the container-closure system with Nipocalimab finished product is demonstrated with the stability information and in the development section. The vials and stoppers follow the Ph. Eur. monographs for primary containers (Ph. Eur. 3.2.1) and closures (Ph. Eur. 3.2.9). The finished product vial is packed into an opaque, paperboard carton that shield the product from light. This is found acceptable.

The glass vial is stated to be supplied unwashed and non-sterile and the rubber stopper supplied as washed and ready-to-sterilize. Information is provided, (section P.3.5) with respect to sterilization of the glass vials and rubber stoppers and testing for sterility and bacterial endotoxins. This is found acceptable.

Stability of the product

The initially proposed shelf life for the finished product was 18 months when stored at the recommended storage condition at 2 °C to 8 °C.

Stability data

The stability program with tests and test interval is generally in line with ICH Q5C and found acceptable.

An overview of produced lots is provided with lot number, storage conditions and available data expressed in months. Stability protocols and results are presented.

Samples were tested for various attributes.

The applicant has also presented a trend analysis of stability data. The statistical analyses presented were conducted using the stability data obtained from the 1200 mg/vial finished product batches listed in Table P.8-5

The shelf-life claim for both presentations (nipocalimab finished product 1200 mg/vial and 300 mg/vial) are initially based on an ongoing stability program for development, clinical and PV batches on 1200 mg/vial data, with stability data generated. Since both finished product presentations (1200 mg/vial and 300 mg/vial) use the same source of active substance, have the same protein concentration, formulation composition and comparability has been demonstrated, the justification is acceptable.

To date, stability results for the nipocalimab finished product 1200 mg presentation have been presented for up to 18 months for clinical finished product batches at both long-term storage and for months at accelerated storage conditions. In addition, stability results for 6 months at stressed conditions is available for the clinical batches. Also, stability data for PV finished product batches is presented as well as 6 months of stability data for accelerated and stressed conditions for the PV finished product batches. The data presented provide the justification for the finished product shelf-life claim of 24 months at accelerated and stressed conditions, nipocalimab finished product 1200 mg/vial shows significant changes during stability.

For nipocalimab finished product 300 mg/ml, stability results for PV batches at long-term storage condition (5 ± 3 °C) have been presented.

Both photostability (nipocalimab finished product 1200 mg/vial) and temperature cycling (nipocalimab finished product 1200 mg/vial and 300 mg/vial) studies were performed, and the results show that nipocalimab finished product is sensitive to light and should therefore be kept in the outer carton to protect from light induced degradation, in line with the wording in section 6.4 in the SmPC. It is agreed that the results from the temperature cycling studies support the stability of finished product during potential temperature excursions that may be encountered during transportation, storage, and handling.

In-use study

The in-use stability and compatibility study confirm that the nipocalimab finished product diluted in 0.9% sodium chloride is stable and compatible with a range of polymer materials.

From a microbiological point of view, unless the method of dilution precludes the risks of microbial contaminations, the prepared diluted solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. If immediate administration is not possible, the diluted solution can be refrigerated for up to 24 hours at 2 °C to 8 °C, with an additional 12 hours of storage at room temperature, including infusion time, at 15 °C to 30 °C.

Post-approval stability protocol and stability commitment

Ongoing stability studies and post-approval stability studies will be performed according to the protocols described in the dossier. The applicant commits to continue these studies through the proposed shelf-life.

Proposed shelf-life and storage conditions

On the basis of the available data at the time of CHMP Opinion, a shelf life for the nipocalimab finished product of 24 months when stored at the recommended storage condition at 2 °C to 8 °C is acceptable. Any extension of shelf life will require the submission of a variation.

Adventitious agents

Non-viral adventitious agents

Transmissible spongiform encephalopathy (TSE) infectivity risk is excluded by the omission of animal-derived raw materials from the production process Risk assessments and certificates are provided. It is acknowledged that the risk of TSE is negligible, and the information is found sufficient

No animal-derived materials were used during the production of the active substance. Manufacturing procedures and filtration steps throughout the process minimize the risk of microbial contamination. This is endorsed.

Viral adventitious agents

Unprocessed bulk harvest testing (UBH)

ICH Q5A states that this test should be a 28-day assay with a sub-cultivation at day 14. The applicant justifies the reduced in vitro assay based on the overall viral safety program. No animal derived components are used in the production of the MCB, WCB or in product manufacturing. Raw materials are controlled, and testing requirements are established for release. The MCB and WCB have been tested using a 28-day assay. It is agreed that a 14-day assay is acceptable for the routine testing of the UBH, also considering the robust virus clearance data and process steps, including an S/D treatment.

Virus clearance

Viral clearance studies were performed. The studies have been performed using qualified models mimicking the commercial process, worst case settings were studied where applicable.

For the cell culture detection, any cytotoxic or viral infectivity interference of process buffers on the cell lines used for the virus assay was evaluated prior virus validation studies.

Various viruses were studied. The viruses were chosen to represent genomes of RNA and DNA, enveloped and non-enveloped viruses, and a wide range of families, particle sizes, and chemical resistance. This is accepted.

Chromatography parameters such as resin type, column bed height, load ratios, linear flow rates, wash volumes, peak collection start and end were defined. The chromatographic steps are of orthogonal types. Clearance results are presented for both new and cycled (end of use) resins. This was confirmed for all four viruses studied. The lowest obtained clearance value was used to calculate the overall reduction numbers as a conservative approach.

Further data on the qualified scale downs is found in section 3.2.S.2.6 and virus clearance data with cycled resin (end of use) is found in section 3.2.S.2.5 including representative chromatograms. The amount of data submitted by the applicant and the approach is endorsed.

The retrovirus-like particles (RVLP) per dose safety margin equals to 1 lipid-enveloped, this is acceptable.

In summary, the characterisation and control of the cell substrates, the use of non-animal derived materials, in-process testing and virus clearance capability of the manufacturing process provides sufficient assurance of safety regarding adventitious agents in the nipocalimab process.

Overall, adventitious agents safety is considered sufficiently assured.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The dossier is appropriately structured. No GMP issues have been found, and no inspections are deemed necessary.

The active substance manufacturing process is adequately described. Description of origin and control of cell banks and gene constructs is acceptable. Characterisation of nipocalimab was performed using an extensive panel of appropriate methods and is considered acceptable. The control of active substance is found acceptable. The provided data to support the shelf-life claim for the active substance is considered acceptable and justified.

The development and manufacture of the finished product have at large been sufficiently described and justifies the chosen formulation as well as the commercial manufacturing process. The control of the finished product has been presented in a satisfactory way. The PS80 specification limit criteria at the end of shelf-life is acceptable but needs to be further validated. For an aged product batch at time $T=0$, it might not fulfil specification limits after an agitation stress study simulating shipping for critical attributes. It is also noted that the performed shipping validation was performed using a tentative specification used at the time of the study and not the final finished product specification. Therefore, the applicant is recommended to perform a shipping validation study using a batch at the lower end of the specification limit of PS80 is required using the final finished product specification (REC).

The claimed shelf-life of 24 months when stored at the recommended storage condition at 2 °C to 8 °C is supported by real-time data.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance and intermediates is adequately

described, controlled and validated. The active substance and intermediates are well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

Overall, the quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Imaavy is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The applicant is recommended to perform a shipping validation study using a batch with a low starting level polysorbate 80 using the approved finished product specification.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical program consisted of studies to investigate primary pharmacodynamics (PD), select the pharmacologically relevant species, characterize pharmacokinetics (PK)/toxicokinetics and potential immunogenicity, and evaluate potential toxicity.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The structural, biophysical and pharmacological evaluation of nipocalimab was done using several different experimental methods including x-ray crystallography, surface plasmon resonance analysis, cell-based assays, an ex vivo human placental perfusion model and *in vivo* mouse studies.

Nipocalimab binds to the IgG binding site of human FcRn, as demonstrated by x-ray crystallography studies. The x-ray crystal structure of nipocalimab Fab with human FcRn indicates that it directly competes with IgG for binding to FcRn. It was also shown that there is no steric hindrance or allosteric modulation affecting the albumin binding site of FcRn.

Sequence comparisons of human proteins that are close relatives of FcRn protein for the nipocalimab binding epitope suggests that cross-reactivity of nipocalimab with other human proteins is unlikely. Experimental results indicates that nipocalimab is a selective antibody that does not bind to HLA-A2 despite its structural and amino acid sequence homology (~48%) to FcRn alpha chain. Human FcRn residues that form the nipocalimab binding epitope are well conserved only in cynomolgus monkey FcRn and not across other species including dog, pig, rat and guinea pig.

The binding affinity of nipocalimab to FcRn was determined using surface plasmon resonance at both pH 6.0 (representing the pH of the early endosomes) and pH 7.4 (representing pH at the cell surface).

Nipocalimab bound to human and cynomolgus monkey FcRn at pH 6.0 with an equilibrium dissociation constant (KD) of ≤ 31.7 pM, ≤ 26.2 pM for human and cynomolgus monkey, respectively, and pH 7.4 with KD of ≤ 57.8 pM, 58 pM for human and cynomolgus monkey, respectively and did not bind to mouse or rat FcRn. The cynomolgus monkey was selected as a pharmacologically relevant species for nonclinical PK, PD and toxicology assessments of nipocalimab. Apparently, binding affinity studies for another non-rodent species than non-human primates (NHP) were not conducted, which would normally be expected in order to include/exclude relevant species. However, as also addressed in a scientific advice (EMA/SA/0000049032), the lack of such assessment is accepted since the cynomolgus monkey, based on binding affinity and functional *in vitro* data, is considered an appropriate and relevant species for toxicology evaluation and studies in this species were already conducted.

Treatment of human aortic endothelial cells (HAECs) with nipocalimab resulted in concentration-dependent FcRn occupancy with an half-maximal inhibitory concentration (IC₅₀) of 0.037 µg/mL and intracellular IgG accumulation with an half maximal effective concentration (EC₅₀) of 0.034 µg/mL. No impact on albumin recycling was observed. However, dose dependent decreases in serum albumin were observed in all repeat dose toxicity studies performed in the cynomolgus monkey. Similar results were observed in HVTs where nipocalimab resulted in concentration-dependent FcRn occupancy with an IC₅₀ of 0.029 mg/mL and intracellular IgG accumulation with an EC₅₀ of 0.028 µg/mL. Concentration-dependent increases in FcRn occupancy with an IC₅₀ of 0.066 µg/mL were also observed in human monocytes.

In vivo studies were performed using humanized FcRn mice (also called Tg32 mice, which have the mouse *fcgrt* *Fc gamma receptor and transporter (mouse gene)* knock-out mutation and a transgene expressing the human Fc gamma receptor and transporter (FCGRT) human gene under the control of its own native promoter). One study in Tg32 mice investigated the effects of nipocalimab on the degradation rate of exogenously administered human IgG and its correlation with FcRn occupancy on monocytes. The results showed a dose- and time-dependent increase in the degradation rate of injected human IgG in the nipocalimab-treated groups compared to the vehicle-treated group. This increase in IgG degradation rate coincided with an observed increase in levels of FcRn occupancy, indicating that longer FcRn occupancy leads to greater degradation of injected human IgG.

The therapeutic effect of nipocalimab was investigated in two different models of autoimmune disease driven by pathogenic IgG. Improvement of the disease pathology was demonstrated in the collagen antibody-induced arthritis (CAIA) Tg32 mouse model and increasing platelet levels was shown in the immune thrombocytopenia (ITP) Tg32 mouse model.

2.5.2.2. Secondary pharmacodynamic studies

No studies were listed as secondary PD studies. Nipocalimab did not cross-react to the structural similar HLA-A2 in an enzyme-linked immunosorbent assay (ELISA)-assay. The Fc region of nipocalimab is aglycosylated to prevent effector functions and activation of the complement pathway. Cell-based assays have demonstrated that nipocalimab does not exhibit antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity activity confirming that nipocalimab has no Fc-mediated effector functions and is not expected to induce cell death or tissue damage through these mechanisms.

2.5.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies have been conducted, rather safety pharmacology endpoints (cardiovascular (CV), respiratory and central nervous system (CNS) function) were incorporated into the design of the 4-week and/or 26-week GLP toxicity studies in cynomolgus monkeys,

in accordance with the provision of the ICH guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 (R1) 2011) and the ICH guideline on safety pharmacology studies for human pharmaceuticals (ICH S7A 2020). These studies are presented and assessed in toxicology section.

2.5.2.4. Pharmacodynamic drug interactions

No interaction on the receptor level is expected for nipocalimab, except for the intentional target FcRn. Based on the mechanism of inhibition of FcRn an increased clearance of IgG -based products can be expected.

2.5.3. Pharmacokinetics

The PK profile of nipocalimab was characterized in cynomolgus monkeys following a single intravenous (IV) bolus injection. The extent of FcRn occupancy by nipocalimab and reduction of serum IgG (ie, the intended therapeutic benefit of nipocalimab) were measured in these monkey studies as well, to evaluate the relationships between serum nipocalimab concentrations, receptor occupancy (RO) and PD activity.

Appropriate bioanalytical methods used to support the GLP toxicity studies were validated for quantitation of serum nipocalimab, detection of anti-nipocalimab antibodies, including characterization of their neutralizing capacity, and determination of the extent of RO by nipocalimab in various cell types in cynomolgus monkeys.

For non-GLP studies, the bioanalytical methods using similar formats were qualified, but not fully validated.

An ELISA method was validated for determination of nipocalimab concentrations in cynomolgus monkey serum. A qualitative electrochemiluminescence method was validated for the detection of anti-drug antibody (ADAs) in cynomolgus monkey serum. A validated flow cytometry cell-based assay was used for detection of neutralising antibody (Nabs) to nipocalimab in cynomolgus monkey serum. A flow cytometry antibody panel for the assessment of RO was validated on granulocytes, monocytes, T-lymphocytes, and B-lymphocytes from cynomolgus monkey whole blood (sodium heparin) samples.

The ADA assay has a sensitivity to detect ADA positive control at 100 ng/mL with drug tolerance of ≤ 50 $\mu\text{g/mL}$. Thus, false negative results may be obtained in the ADA assay above ADA titers of 0.1 $\mu\text{g/mL}$ and above nipocalimab serum concentrations greater than 50 $\mu\text{g/mL}$.

Two single-dose IV studies with nipocalimab were conducted in cynomolgus monkeys to characterize the PK of nipocalimab and the relationships between PK, RO and PD effect (IgG suppression), with doses ranging from 0.2 – 340 mg/kg. In both studies, clearance decreased and half-life increased with increasing dose levels, and serum exposures (area under the serum concentration versus time curve (AUC)) increased in a greater than dose-proportional manner, consistent with target-mediated drug disposition.

Close relationships between nipocalimab concentrations, RO and IgG decreases induced by nipocalimab in cynomolgus monkeys were observed, which is consistent with its mode of action. PD effects measured by decreases in serum IgG were achieved and maintained for at least 1 week after single IV doses of ≥ 50 mg/kg.

Repeated weekly administrations resulted in a similar PK profile compared to single dosing. Decreased exposure levels were however observed at the lowest dose level after repeated dosing compared to single dosing in the 4- and 26-week study, most likely due to ADA formation (study 529055 and 501555). trough plasma concentrations were comparable at different timepoints at the high dose levels (100 and

306 mg/kg/day) in the 4-week study, maintaining a stable exposure until end of study (study 529060). No sex differences were observed after both single and repeated dosing.

The tissue distribution of nipocalimab was assessed in Tg32 mice and was found to be comparable with that of a human monoclonal IgG1 control antibody, and typical of that expected for a mAb.

Studies using an ex-vivo dual-perfused human placental cotyledon model demonstrated minimal maternal-to-fetal transfer of nipocalimab. In the same model the ability of nipocalimab to inhibit the maternal-fetal transfer of a representative IgG was demonstrated. Nipocalimab also effectively inhibited placental transfer of itself and there was very little drug exposures to fetuses and neonates observed in the enhanced pre- and postnatal development (ePPND) study.

No *in vitro* or *in vivo* drug metabolism or excretion studies have been conducted for nipocalimab. As an IgG-based mAb, nipocalimab is considered to be catabolized and eliminated by processes involved in the turnover and degradation of endogenous proteins. No non-clinical PK drug interaction studies were performed. A potential for reduction of exposure of IgG-based mAbs via the inhibition of FcRn-mediated IgG recycling is however identified.

Nipocalimab concentrations were not measured in milk in the ePPND study in cynomolgus monkeys, however, there are clinical data on the excretion of nipocalimab in colostrum and breast milk at low levels up to 8 days postpartum in a limited number of patients.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicology studies have been performed with nipocalimab. Acute toxicity was evaluated in the repeat dose studies. This is considered acceptable.

2.5.4.2. Repeat dose toxicity

Repeat dose toxicity was evaluated in 3 repeat dose toxicity studies in cynomolgus monkeys. The duration of the studies was 2, 4 and 26 weeks. The highest tested dose in these studies, i.e. 306 mg/kg in the 4-week study, corresponded to a 44-fold exposure margin. The method of administration was IV infusion. Pivotal GLP-compliant repeat-dose studies consisted of 4- and 26-week studies in which reversibility was evaluated for 9 and 8 weeks, respectively. Dose levels and posology were similar; 0, 20, 100, and 306/300 mg/kg weekly (QW). An additional 50 mg/kg Q2W (every two week) group was included in the 26-week study. Pivotal studies were supported by a 2-week non-GLP tolerability study (IV; QW; 10 and 300 mg/kg.)

In the 2-week study nipocalimab was given once weekly, i.e. twice (on days 1 and 8) during a 14-day period. Two doses were evaluated, namely 10 and 300 mg/kg. No unscheduled deaths nor relevant treatment dependent clinical signs were noted throughout the study. There were changes such as increased number of reticulocytes, as well as reduction in decreased red blood cell mass at days 8 and 15 that were not dose dependent. Minor decrease in albumin and globulin levels were also noted at day 8 and 15. Measurement of plasma levels of cytokines indicated a dose independent increase of IL-1RA concentrations after nipocalimab administration.

In the 4-week study nipocalimab was given once weekly at doses of 0, 20, 100 and 306 mg/kg. The study included a 9-week recovery period. The no-observed-adverse-effect-level (NOAEL) was set at 306 mg/kg based on the absence of findings in clinically relevant changes in serum clinical chemistry and histological parameters, as well as the ability of serum IgG to recover to pre-dose levels after repeated

dosing with nipocalimab. Dose dependent decreases in albumin and increases in cholesterol and triglyceride levels were observed during the treatment period. These changes did not persist and had recovered in the 306 mg/kg group by the end of the recovery period, thus showing reversibility. No histopathological findings related to treatment were observed. In addition, evaluation of safety pharmacology parameters revealed no potential effects on respiratory system, CNS or CV system.

A 26-week study was performed at doses of 0, 20, 50, 100 and 300 mg/kg with weekly administrations, except for the 50 mg/kg dose that was given twice weekly. Evaluation of safety pharmacology parameters revealed no potential effects on the CV system. Symptom-related discontinuation of nipocalimab occurred in one male (300 mg/kg) that had to be euthanized at day 20 after the second dose due to worsening of clinical signs. The findings were considered to be consistent to lymphoproliferation. The clinical findings in this animal included initially reddened staining at both femoral areas during the pre-treatment period. The findings worsened to include flaking, reddened skin over the fore and hind limbs at day 9 which subsequently spread after the second dose. At day 14 swollen lymph nodes were noted. Apart from lymphoid system findings, the pre-terminated animal showed minimal to moderate levels of mononuclear cell infiltrates in multiple non-lymphoid organs; liver, lung, salivary gland, lacrimal gland, tongue, prostate, epididymis, testes, pancreas, stomach, urinary bladder, eye (ciliary body), brain (meninges and choroid plexus), oesophagus, gallbladder, heart, and kidney.

Additional findings in treated animals included sporadic transient clinical signs such as swelling, reddening of skin, tremors, salivation, pruritus and increased scratching, deep breathing and vomiting. Symptoms occurred primarily in relation to infusion and in general resolved during the dosing day. A retrospective analysis performed in the control (0 mg/kg) and 300 mg/kg group showed that all monkeys were seropositive for Lymphocryptovirus (LCV), a LCV gamma herpes virus, prior to treatment initiation. Apparently, LCV status was not evaluated in 20-, 50- and 100 mg/kg groups.

The NOAEL in the 26-week study was set by the applicant at the highest dose used in that study of 300 mg/kg/week. The sex combined systemic exposure in this dose group corresponded to an AUC_{0-96h} of 486,000 $\mu g \cdot h/mL$ which corresponds to 20,250 $\mu g \cdot day/mL$. For estimation of safety margins, an AUC comparison of a two-week interval period was used and compared to the population simulated clinical exposure $AUC_{0-14days}$ of 918 $\mu g \cdot day/mL$ derived from the Phase III study dosing scheme. This approach resulted in a safety margin of 44x to the clinical setting.

PD effects were observed in all repeat dose toxicity studies. FcRn RO in monocytes and granulocytes was observed in all treated animals at all doses as well as reduction in IgG levels. In the 4-week and 26-week studies, reversal of RO was dose dependent with slower recovery rates observed at the highest doses. IgG did also exhibit dose dependent reduction, and recovery to baseline levels during the recovery phase of the study.

Nipocalimab-related, dose dependent decreases in albumin and increases in cholesterol levels were observed in all repeat dose toxicity studies and are considered treatment as well as dose dependent. In the 4- and 26-week study, reversibility to baseline levels were observed at the recovery period and these findings were not considered adverse since they did not have any histological correlates. In the 4-week study in week 4 of the dosing period in animals in the 306 mg/kg group, albumin decrease was x0.87 in males and x 0.79 in females relative to control. The corresponding figures in the highest dose group, i.e. 300 mg/kg, in the 26-week study at week 26 were x 0.77 and x 0.76. Values for cholesterol in the 4-week study were x 1.52 and 1.47. In the 26-week study, changes were only noted in females at week 13 (x1.4) but not at week 8 and 26. Furthermore, the changes in the 4-week and 26-week studies were dose dependent. The changes were reversible.

Nipocalimab did not have direct effects on T cells and did not inhibit T-cell dependent antibody responses after keyhole limpet hemocyanin (KLH) or tetanus toxoid (TT) immunization.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted with nipocalimab. This is considered acceptable.

2.5.4.4. Carcinogenicity

Nipocalimab is a fully human IgG1 monoclonal antibody design to bind FcRn with high affinity. It does not cross-react with rodent FcRn, precluding the conduct of traditional carcinogenicity studies. Hence, and in accordance with ICH guideline S6(R1) the applicant assessed the carcinogenic potential based on a weight of evidence (WoE) approach. Nipocalimab binds to FcRn leading to increased catabolism of circulating IgG.

Since FcRn is not a signalling molecule and does not directly contribute to mechanisms such as cell proliferation and differentiation, it is highly unlikely that nipocalimab poses any carcinogenic potential. Histopathology from repeat-dose studies showed that there were no findings of proliferative changes including no hyperplasia, preneoplasia or neoplastic changes or evidence of endocrine or hormonal perturbation. In addition, no malignancies linked to nipocalimab treatment have been identified in the clinical studies. Further, published literature and available information from of the same class of anti-FcRn drugs, does not point towards an increased carcinogenic risk.

Regarding immunosuppression nipocalimab does not affect the biosynthesis of IgG or selectively removes any specific IgGs. FcRn is not a signaling receptor and does not affect other immune cells, especially the lymphocyte T and natural killer (NK) cells. In addition, the reported antigen or immune complex presentation function of FcRn does not appear to play a major role in immune surveillance since inhibition or ablation of FcRn does not abolish T-cell dependent antibody responses.

Overall, the carcinogenic potential has been adequately addressed and it is considered that the WoE submitted by the applicant lends support to the conclusion that the carcinogenic potential of nipocalimab is unlikely.

2.5.4.5. Reproductive and developmental toxicity

No dedicated male and female rodent fertility studies have been conducted by the applicant as rodents are not pharmacologically relevant species. Histopathological evaluation of reproductive organs was performed in the 26-week repeat dose toxicity study. No findings were observed. It is noted however, that monkeys in the 26-week study were sexually immature (2-3 years of age) at study start. Based on microscopy of reproductive organs, all females across groups became sexually mature during the dosing phase or the 8-week recovery phase, whereas this applied to 33-80% of males.

For evaluation of prenatal, and postnatal development including maternal function, a 2-phase ePPND study (20091416) in pregnant cynomolgus monkeys dosed weekly with nipocalimab at dose levels of 0, 100 or 300 mg/kg from gestation day (GD)45 was conducted. The infant postnatal observation period in phase 2 was 6 months.

Overall, no maternal effects on mortality and adverse effects of maternal clinical signs, body weights, or qualitative food consumption were observed, and in general treatment with nipocalimab was well tolerated. There were no effects in fetal endpoints related to nipocalimab.

In Phase I (embryo-fetal development (EFD) phase) of the ePPND study, ADA was detected in 2/11 animals in the control group. Prior to dosing, none of the animals in the 100 mg/kg group was confirmed positive for ADA compared to 3/11 animals in the 300 mg/kg group. After dosing all animals in the 100 mg/kg group (8/8) were positive for ADA at least at one time point. In the 300 mg/kg group the

corresponding proportion of ADA positive animals was 10/11. NABs were detected in most ADA positive animals.

In phase II (prenatal and postnatal development, including maternal function) of the study gross pathology changes in placenta were reported in placentas from 2/14 animals in the 100 mg/kg/week group and 2/11 in the 300 mg/kg/week group, in all comprising ca 16% of all evaluated placentas in the nipocalimab treated groups. The pathological changes included multifocal, pale and firm areas occupying a majority of the placental area. At a microscopical level, these areas correlated with infarcts.

In the four animals exhibiting abnormal placentas the frequency of foetal losses was 3 out of 4; one stillborn in the 100 mg/kg group and two aborted fetuses in the 300 mg/kg group. This pattern indicates a dose dependent severity. Further microscopic changes were observed in the placentas of additional four animals (two in the control group, one in the 100 mg/kg group and one in the 300 mg/kg group) but were considered not to be of clinical relevance.

Concerning pregnancy and postpartum outcomes in all dose level groups, 0, 100 and 300 mg/kg/week, no difference was noted with regards to mean gestation length (158 ± 5 , 163 ± 6 and 154 ± 7 , respectively). There was a slightly higher mean gestation length in the 100 mg/kg group, although all measured timepoint were within the Testing facility historical range of 159 ± 7 days. The amount of offspring losses (combined for foetal and infant) was lower in the 100 mg/kg group (33,3%) compared with 0 and 300 mg/kg groups (38,9% for both groups). All observations were above the historical control average of 28%, but within the historical range of 0.0-42.9%. When looking only at total foetal losses, the lowest amount was in the control group (4 losses), followed by the 300 mg/kg group (5 losses) and finally the 100 mg/kg group (6 losses).

Albumin and globulin levels were decreased in both dose groups. There was also a reduction in total protein and calcium although these observations were not considered adverse since they did not have any impact on maternal conditions, histopathological changes and foetal development and viability.

Decreases in albumin and increases in cholesterol, respectively, in females in the ePPND study are considered mild. At phase I, albumin levels in the 100 mg/kg group at pre-dose were 3.74 g/dL on average. The lowest level was at GD140 (2.33 g/dL). For the high dose group (300 mg/kg) pre-dose levels had an average of 3.51 g/dL. Here the lowest level was reached at GD140 with 2.03 g/dL.

RO, IgG levels as well as the presence of ADAs and NABs were similar to what was observed in the repeat toxicity studies. In Phase I, evaluation of RO was performed in both maternal and foetal tissue. In addition, placental tissue from all dose groups were collected at C-section at GD100 and GD140 and examined with respect to RO and found to be dose dependent.

ADA and NABs were present in infants at approximately the same levels as their maternal counterparts. No circulating levels of nipocalimab was detected in infants.

2.5.4.6. Toxicokinetic data

Evaluation of the impact of ADA and NABs was performed in the repeat dose toxicity studies. In the 4-week and 26-week studies ADAs were detected in most of the sampled animals at nipocalimab serum concentrations under 50 µg/mL. In addition, most of the animals where ADA could be detected were also positive for NABs at either 1 or more time points when the serum concentrations of nipocalimab were less than 0.1 µg/mL.

In the 4-week study, at doses of 100 and 306 mg/kg/week AUC increased mostly greater than dose proportional, and maximum observed serum concentration (C_{max}) increased dose proportional. The overall exposure of nipocalimab in the two highest dose groups did not seem to be affected by NABs

since reduced levels of IgG were maintained throughout the dosing period. This was also observed in the 26-week study.

The presence of ADA and NABs did not have any impact on overall exposure since the intended PD, that is reduced levels of IgG, was maintained throughout the dosing period with nipocalimab.

2.5.4.7. Local tolerance

Three local tolerance studies in rabbits, minipigs and monkeys were performed to evaluate local tolerance employing both IV and subcutaneous injections as well as paravenous administration. Overall, the administration by various routes of administration was well tolerated in all tested species, with no observed local irritation. In addition, there were no deaths nor nipocalimab related clinical observations.

The paravenous administration route used in the local tolerance study in rabbits was used to evaluate adverse effects after potential mis-dosing outside the blood vessel.

2.5.4.8. Interspecies comparison

High dose exposure comparison derived from all *in vivo* toxicity studies, i.e. 2-, 4- and 26-week studies, immunotoxicity and ePPND phase 2 studies, yielded exposure multiples between 24-71 times for AUC and 14-23 times for C_{max}, respectively (Table 1). Human exposure data was generated via a population PK/PD exposure model from the phase 3 clinical study in patients with gMG given 15 mg/kg Q2W.

For the 26-week study the applicant suggested a NOAEL level of 300 mg/kg (see further Discussion on non-clinical aspects).

Table 1. Interspecies comparison

Species/Study ID	NOAEL (mg/kg)	AUC Steady state (µg.h/ml)	AUC _{corrected} Steady state (µg.h/ml)	C _{max} (µg/ml)	Animal:Human Exposure Multiple	
					AUC	C _{max}
		♂ + ♀	♂ + ♀	♂ + ♀		
Monkey 2-w, QW (non-GLP repeat-dose)	300	373,000 (♂ only)	746,000 (♂ only)	6,850 (♂ only)	33	15
Monkey 4-w, QW (GLP repeat-dose)	300	786,500	1,573,000	8,660	71	20
Monkey 26-w, QW (GLP repeat-dose)	300	486,000	972,000	10,225	44	24
Monkey 8-w, QW (GLP immunotox)	300	357,000	714,000	7,010	32	16
ePPND phase 2 (GLP repeat-dose)	-	264,000	528,000	6,260	24	14
Human (modelled) 15 mg/kg, Q2W (maintenance dose)	-	22,032	-	434	-	-

2.5.4.9. Immunotoxicity studies

An 8-week immunotoxicology study in cynomolgus with IV administration of nipocalimab at doses of 0, 10, 100, or 300 mg/kg showed that no alterations were recorded for immune cells throughout the study period. In addition, there were no effects on cytokine levels and phagocytosis and oxidative bursts. In addition, a reduction in anti- KLH IgG center point titers was observed and consistent with the reduced

IgG levels observed at dosing. One animal in each dosing group presented with emesis that were attributed to treatment with nipocalimab.

A cross reactivity study in adult and foetal tissues was performed in order to evaluate the potential cross reactivity of nipocalimab. A panel of 38 adult human and adult cynomolgus tissues and 14 foetal/neonatal human tissues and 33 foetal cynomolgus tissues were screened. Two concentrations of nipocalimab were used for tissue staining of cryosections; 5 and 20 µg/mL.

In human adult tissues, positive cytoplasmic staining was detected in stromal cells in the adventitia, capsule or connective tissue stroma and stromal spindle cells in placenta. Tissues that were negative included, spleen lymphocytes, lymph node, thymus and myofibers in smooth and striated muscle. Foetal and cynomolgus tissues followed in general the same staining patterns as in adults.

2.5.5. Ecotoxicity/environmental risk assessment

Nipocalimab is a recombinant mAb and due to the nature of the product is not expected to pose any risk to the environment. This is acceptable.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Nipocalimab binds to the IgG binding site of human FcRn, as demonstrated by x-ray crystallography studies. The x-ray crystal structure of nipocalimab Fab with human FcRn indicates that it directly competes with IgG for binding to FcRn. It was also shown that there is no steric hindrance or allosteric modulation affecting the albumin binding site of FcRn. Cross-reactivity of nipocalimab with other human proteins is unlikely. Nipocalimab bound to human and cynomolgus monkey FcRn at pH 6.0 and pH 7.4 with affinity in the picomolar range and did not bind to mouse or rat FcRn. The cynomolgus monkey was selected as a pharmacologically relevant species for nonclinical PK, PD and toxicology assessments of nipocalimab.

Cell-based assays using HAECs showed nipocalimab inhibited IgG recycling in a concentration-dependent manner ($IC_{50} = 29.8$ ng/mL) without affecting the albumin binding site. Dose-dependent correlation between FcRn occupancy ($IC_{50} = 37$ ng/mL) and intracellular IgG accumulation ($EC_{50} = 34$ ng/mL) was also established in HAECs. In monocytes, nipocalimab displayed concentration-dependent occupancy of FcRn ($IC_{50} = 66$ ng/mL). These results provides sufficient *in vitro* evidence of the suggested mechanism of action.

One *in vivo* study performed in the Tg32 mice showed a dose- and time-dependent increase in the degradation rate of injected human IgG which coincided with an observed increase in levels of FcRn occupancy, indicating that longer FcRn occupancy leads to greater degradation of injected human IgG. This study provides a non-clinical *in vivo* proof-of concept for the mechanism of action of nipocalimab.

The therapeutic effect of nipocalimab was investigated in two different models of autoimmune disease driven by pathogenic IgG. Improvement of the disease pathology was demonstrated in the CAIA Tg32 mouse model and increasing platelet levels was shown in the ITP Tg32 mouse model. However, important study details including the "Materials and Methods" section was missing in study report No RPT-2549. These studies can nevertheless be accepted as non-clinical *in-vivo* proof of concept for the mechanism of action of nipocalimab, although they are not disease models for myasthenia gravis. The applicant states that both "*animal models represent autoimmune diseases driven by pathogenic IgG*" which is agreed. The efficacy in gMG patients needs in anyway to be established in the clinical studies.

No studies were listed as secondary PD studies. This is endorsed since nipocalimab did not cross-react to the structural similar HLA-A2 in an ELISA-assay and did not show any Fc-mediated effector functions in cell-based assays.

Safety pharmacology endpoints of nipocalimab were incorporated in the 4- and 26-week repeat-dose toxicology studies in cynomolgus monkeys. Safety margins were considered adequate as exposure values in cynomolgus monkeys from the 4- and 26 week repeat-dose studies at the NOAEL were sufficiently in excess of the maximum human exposure. This is considered sufficient, taking into account that nipocalimab is a highly specific mAb that do not represent a novel therapeutic class. In accordance with ICH Guideline S7A safety pharmacology studies can be reduced or eliminated for this kind of products. It can be concluded that nipocalimab poses a low risk for adverse effects on the CNS, respiratory and CV systems.

No interaction on the receptor level is expected for nipocalimab, except for the intentional target FcRn. Based on the mechanism of inhibition of FcRn an increased clearance of IgG -based products can be expected.

The mechanism of action of nipocalimab is adequately described in section 5.1 of the Summary of product characteristics (SmPC).

Pharmacokinetics

The PK profile of nipocalimab was investigated following both single and repeated dose administration in cynomolgus monkeys. Dose-proportional increases in exposure were observed with C_{max} at all dose levels. Based on AUC, exposure was greater than dose-proportional at lower dose levels while it was approximately dose proportional at higher doses. This correlates with a potential target-mediated drug disposition-driven loss of exposure at lower doses. The PK profile was in general similar between single and repeated dosing and no sex differences were observed. ADAs were observed in most dosed animals after administration of nipocalimab when nipocalimab serum concentrations were less than 50 µg/mL, which tested positive for NAb and a corresponding decrease in exposure was observed. While animals in the high dose groups did not test positive for ADAs and were negative for NABs, this is assumed to be false negative results as the ADA titers exceeded 0.1 µg/mL and nipocalimab concentrations exceeded 50 µg/mL. On sampling days where samples taken from animals were exhibiting a positive ADA response, there was a tendency for serum nipocalimab concentrations to be appreciably lower or non-quantifiable compared to negative animals, especially at the lower dose levels, indicating systemic exposure to nipocalimab was impacted with a faster clearance of the test item. PD effects were however confirmed at the higher dose levels in terms of receptor occupancy and decreases in IgG levels, showing that continuous dosing at high levels adequately sustains exposure to nipocalimab. The PD and toxicity profile in monkeys are therefore not considered to have been impaired by development of ADA and NABs.

Close relationships between nipocalimab concentrations, RO and IgG decreases induced by nipocalimab in cynomolgus monkeys were observed, which is consistent with its mode of action.

A single dose distribution study confirmed a similar distribution profile between nipocalimab and a human monoclonal IgG1 control antibody with a significant fraction of both antibodies distributed primarily to the liver while exhibiting minimal accumulation in kidney or excretion in urine.

Studies using an *ex vivo* dual-perfused human placental cotyledon model demonstrated minimal maternal-to-fetal transfer of nipocalimab. In the same model, the ability of nipocalimab to inhibit the maternal-fetal transfer of a representative IgG was demonstrated. This is adequately reflected in the SmPC. Nipocalimab also effectively inhibited placental transfer of itself and there was very little drug exposures to fetuses and neonates observed in the ePPND study (20091416) in pregnant monkeys as the foetal-to-maternal ratios $\leq 1.5\%$ in the third trimester or at birth.

As nipocalimab is a protein, it is considered to be catabolized and eliminated by processes involved in the turnover and degradation of endogenous proteins yielding constituent amino acids via proteolytical degradation. It is therefore acceptable that no dedicated studies were submitted to investigate metabolism and excretion of nipocalimab as the product is biotechnologically derived and is in accordance with the guideline ICH S6. No non-clinical PK drug interaction studies were performed. A potential for reduction of exposure of IgG-based mAbs via the inhibition of FcRn-mediated IgG recycling is however identified and is adequately reflected in the SmPC.

Nipocalimab concentrations were not measured in milk in the ePPND study in cynomolgus monkeys, however, there are clinical data on the excretion of nipocalimab in colostrum and breast milk at low levels up to 8 days postpartum in a limited number of patients.

The SmPC-wordings in section 4.6 on breast-feeding was amended to reflect the potential risk following excretion of IgGs into breast milk during the first few days after birth.

Toxicology

Nipocalimab is a IgG1 monoclonal antibody directed towards FcRn, intended to reduce recycling of IgG including autoantibodies. The non-clinical safety profile of nipocalimab was evaluated following the ICH S6 guideline. This included repeat dose toxicity studies up to 6 months duration and enhanced peri-post natal development toxicity study in the cynomolgus monkey. Further studies were performed evaluating immunotoxicity in an 8-week study in cynomolgus, local tolerance and tissue cross reactivity.

In line with ICH S6, safety pharmacological endpoints covering cardiovascular safety, CNS and respiratory system, were incorporated in the GLP-compliant 4-week and 26-week repeat dose toxicity studies at doses up to 306 mg/kg/week. No nipocalimab-related changes in CV, CNS and respiratory parameters were detected and thus it can be concluded that the potential of nipocalimab to directly affect vital organ function is considered minimal.

Single dose toxicity

As per current guidelines, no dedicated single-dose toxicity studies were performed with nipocalimab but was assessed as part of the repeat-dose toxicity studies. No alerts for acute toxicity were identified.

Repeat dose toxicity studies

Pivotal GLP-compliant repeat-dose studies consisted of 4- and 26-week studies in which reversibility was evaluated for 9 and 8 weeks, respectively. Dose levels and posology were similar; 0, 20, 100, and 306/300 mg/kg QW. An additional 50 mg/kg Q2W group was included in the 26-week study. Pivotal studies were supported by a 2-week non-GLP tolerability study (IV; QW; 10 and 300 mg/kg). In accordance with ICH S6(R1), a repeat-dose toxicity study of 6 months duration is sufficient taken the potential long-term use of nipocalimab into consideration.

The following evaluations were performed across pivotal repeat-dose studies; mortality, clinical signs, body weights, body weight gains, ophthalmology, electrocardiogram (ECG), clinical pathology parameters (haematology, coagulation, clinical chemistry and urinalysis), bioanalysis, IgG, cytokine, ADA and NAb analyses, RO studies (flow cytometry), toxicokinetic parameters, gross necropsy findings, organ weights and histopathologic examinations. Neurological and respiratory examinations were evaluated in the 4-week study, and T-cell dependent antibody responses via intra-treatment KLH and post-treatment TT challenges was included in the 26-week study. Overall, the study designs are considered appropriate. Endpoints specific to later sections in the overview will be discussed under the relevant sections below.

Across studies, PD-related reductions in total serum IgG were observed supporting the claimed mechanism of action of nipocalimab. However, a trend of more pronounced decreases was observed in

females compared to males. Also, dose-dependency was claimed but did not appear convincing at least between mid- and high-dosed groups. It was demonstrated that IgG levels returned to baseline levels when treatment was terminated.

Across dose groups and studies, nipocalimab was well-tolerated and few nipocalimab-related findings were observed. In the 26-week repeat-dose toxicity study one male in the 300 mg/kg group had to be euthanized due to worsening of clinical signs after receiving two doses of the test article. The monkey showed persistent clinical signs of systemic lymphoproliferation. Retrospectively, the affected animal plus the remaining recovery animals (control and 300 mg/kg) tested positive for LCV on serology. Apparently, LCV status was not evaluated in group 2-4. Additional findings in treated animals in this study included sporadic transient clinical signs such as swelling, reddening of skin, tremors, salivation, deep breathing and vomiting. It is also noted that these findings were not observed in the 4-week study. The euthanized animal was the only non-human primate out of a total of 60 animals across toxicology studies that was euthanized. Prior to initiation of the dosing phase, this animal belonging to the high dose level 300 mg/kg group, exhibited distinct clinical observation such as high lymphocyte count and red discoloration in both femoral areas prior to initial dosing. Other animals dosed with 300 mg/kg did not exhibit any adverse clinical signs. Although a direct (FcRn) or immunogenicity related effect of nipocalimab does not seem to be the cause of clinical the clinical findings, a definitive mechanism for findings such as swelling, reddened skin and tremors in NHP are currently not identified. None of these findings have been observed in clinical trials.

The test Facility (CRL), which conducted all *in vivo* studies, reported that the prevalence of LCV infection in adult macaques is very high, ranging from 95-100%. Based on this, it is considered reasonable to assume that the majority, if not all, of the monkeys enrolled in the five repeat-dose studies with nipocalimab were seropositive. Given the pre-existing abnormalities observed in the pre-terminated animal, the near-universal seropositivity for LCV among the study population, and the known mode of action of nipocalimab, the inclusion of this particular animal in the study may be questioned. Nevertheless, the isolated nature of the findings – limited to a single animal – strongly suggest that reactivation of LCV was unlikely to be related to nipocalimab administration.

The pre-terminated animal showed minimal to moderate levels of mononuclear cell infiltrates in multiple non-lymphoid organs; liver, lung, salivary gland, lacrimal gland, tongue, prostate, epididymis, testes, pancreas, stomach, urinary bladder, eye (ciliary body), brain (meninges and choroid plexus), oesophagus, gallbladder, heart, and kidney. Of note, minimal to mild levels of mononuclear cell infiltrates in e.g. brain, liver and lungs were also observed across repeat-dose studies (≥ 20 mg/kg). The applicant provided a comprehensive evaluation and sufficiently demonstrated that mononuclear cell infiltrates may occur spontaneously in monkeys, and that, as observed with nipocalimab, foreign biologics such as monoclonal antibodies may increase the incidence and/or severity of such infiltrates. Given that nipocalimab is a humanized mAb, an immune response in monkeys of greater magnitude than expected in humans was anticipated and is acknowledged. In agreement with the applicant, organ mononuclear cell infiltrates observed in monkeys may not predict similar findings in patients; however, the clinical relevance of these findings remains uncertain. Nevertheless, because organ mononuclear cell infiltrates are a known class effect in monkeys dosed with humanized monoclonal antibodies, the findings are most likely not clinically relevant.

The magnitude of the albumin decrease and cholesterol increase, respectively, in the repeat dose toxicity studies are considered mild. The lowest albumin decrease was x 0.76 relative to control in females at 300 mg/kg in the 26 -week study. The highest increase for cholesterol was observed in the 4-week study with an increase of x 1.52 relative to control. Furthermore, the changes in the 4-week and 26-week studies were dose dependent.

In the 4- and 26-week study, reversibility to baseline levels were observed at the recovery period and these findings were not considered adverse since they did not have any clear histological correlates. It should be noted that FcRn also regulates recycling of albumin. However, it has been demonstrated that the epitope of nipocalimab does not overlap with the IgG binding site on FcRn. Furthermore, based on *in vitro* data of nipocalimab there is no indication that nipocalimab affects recycling of albumin at a cellular level. The *in vitro* study DD24006 shows that nipocalimab inhibits IgG recycling but has no effect on albumin recycling. The mechanism of action behind the changes in albumin and cholesterol levels remain to be elucidated. However, it cannot be excluded that the observed decrease in albumin, and related increase in cholesterol levels may be secondary (e.g. to an immune response towards nipocalimab). Notably, a similar pattern of changes has been observed in clinical studies. In the clinic, a long-term treatment with nipocalimab with concomitant alterations of albumin and cholesterol, might have a potential impact on cardiovascular parameters over time.

Across pivotal studies, nipocalimab (≥ 20 mg/kg) caused a decrease in total protein, albumin, globulin, albumin:globulin ratio, and AST. In addition, calcium was decreased (≥ 100 mg/kg/week) in the 26-week study and cholesterol levels increased (≥ 100 mg/kg/week) on at least one timepoint in each study. In general, the applicant considered these findings non-adverse based on the lack of relevant clinical and histopathological correlates. The patterns of decrease were non-dose-dependent and reversible upon treatment discontinuation. After immunization, the KLH-specific IgG response was not detectable at the level of total immunoglobulin measurements. The applicant explained that the expected levels of KLH-specific IgG in monkeys represent only a small fraction of total IgG, and an even smaller proportion of total immunoglobulin. The justification is accepted and based on this, nipocalimab is not expected to have any clinically meaningful impact on total globulin levels in patients, either under normal conditions or in the context of a potential infection, when administered at clinically relevant doses.

Genotoxicity

Genotoxicity studies were not conducted. Nipocalimab is a mAb which are generally not considered mutagenic as they, due to their large molecular size, strictly interact with cell membranes and are not passed to be free in cytoplasm or to the nucleus of cells. Waiving of genotoxic studies is in line with ICH S6(R1) and accepted.

Carcinogenicity

Nipocalimab is a mAb which does not cross-react with rodent FcRn, precluding the conduct of traditional carcinogenicity studies. In line with ICH guideline S6(R1) and based on a WoE approach it was concluded that nipocalimab does not pose an increased carcinogenic risk.

Developmental and reproductive toxicology

Fertility and early embryonic development

In line with ICH S6(R1), the potential effects of nipocalimab on fertility were evaluated as part of the 26-week repeat-dose study in which no treatment-related effects were observed on reproductive organ weights and histopathology. The used strategy is supported, but the monkeys used in the 26-week study were sexually immature (2-3 years of age) at study start which is not in line with the guideline. Based on microscopy of reproductive organs, all females across groups became sexually mature during the dosing phase or the 8-week recovery phase, whereas this applied to 33-80% of males. For maturing animals, the time period in a sexually mature state was unknown. No specialized fertility assessments were evaluated which is reasonable in the absence of sexually mature animals. To support the nipocalimab-specific data, publicly available information on toxicity to fertility and early embryonic development for the approved anti-FcRn compounds efgartigimod (Vyvgart) and rozanolixizumab (Rystiggo) was presented. Toxicity on fertility and early embryonic development of Efgartigimod was studied after IV treatment in rats. The rozanolixizumab procedure did not include stand-alone fertility

and early embryonic development studies and effects on fertility were evaluated as part of a 26-week subcutaneous repeat-dose study in cynomolgus monkeys where menstrual cyclicity and testicular analysis were included. In these procedures, no effects on fertility or early embryonic development were noted, and the NOAEL was established at the highest dose levels; 100 and 150 mg/kg for efgartigimod and rozanolixizumab, respectively. In the current application, the applicant concluded that no effects of nipocalimab were observed on male or female reproductive organs at doses up to 300 mg/kg. This is agreed. A WoE approach was constructed by the applicant justifying the use of sexually mature animals for the evaluation of fertility. The WoE took into consideration: 1) All female and a subset of male monkeys were sexually mature at the end of the 26-week treatment period or following the 8-week treatment-free post-dose period based on microscopic evaluation of reproductive organs, 2) four of the sexually mature males were high-dose males, 3) the duration of the study was substantially longer than the spermatogenic or ovarian cycle in cynomolgus monkeys, 4) FcRn inhibition is not involved in male or female fertility why the mode of action of nipocalimab is not associated with a risk to fertility 5) It is rare for mAbs to induce testicular or ovarian findings. In general, mAbs like nipocalimab are large proteins with high binding affinity to the target protein limiting their distribution and tissue penetration, 6) high exposure levels resulting in systemic exposure multiples ~40-fold higher than the expected clinical exposure at the recommended dose level did not result in any treatment-related effects on reproductive organ weights and histopathology.

The available evidence does not indicate any concerns regarding potential effects on fertility.

Fertility and early embryonic development (ePPND) study

A 2-phase ePPND study in pregnant cynomolgus monkeys dosed weekly with nipocalimab at dose levels of 0, 100 or 300 mg/kg from GD45 was conducted. Phase 1 included subgroups c-sectioned on GD100 and GD140. A third subgroup was dosed until natural parturition. Phase 1 infants were necropsied on BD1. In phase 2, all animals were dosed until natural parturition and infant postnatal evaluations were performed through 6-months of age. As per ICH S6(R1), using only NHP's, when appropriate, is acceptable. Also, performing one well-designed ePPND study in NHP's with dosing from GD20 to birth, rather than separate EFD and/or PPND studies, can be accepted. The late start of nipocalimab dosing on GD45 is not in accordance with current guidance and limits the opportunity to evaluate potential effects on early organogenesis. In line with the applicant's justification, dosing from GD45 is considered valid to assess the potential effects of nipocalimab on prenatal development because transfer of IgG is limited during organogenesis and increases during the foetal period through the end of gestation in both monkeys and humans.

No maternal effects on mortality and adverse effects of maternal clinical signs, body weights, or qualitative food consumption were observed, and in general treatment with nipocalimab was well tolerated. There were no direct effects observed on the foetuses and neonates in animals treated with nipocalimab.

In Phase I (EFD phase) of the ePPND study ADAs were detected in 2/11 animals in the control group. In the 100 mg/kg group and 300 mg/kg group prior to nipocalimab dosing, none of the animals in the 100 mg/kg group were positive whereas 3/11 animals in the 300 mg/kg group presented with ADA. After dosing ADAs were detected in all animals in the 100 mg/kg group (8/8) and in the 300 mg/kg group the corresponding proportion was 10/11 animals. Neutralizing antibodies NABs were detected in most ADA positive animals.

In the phase II part (ePPND) of the study gross pathology changes in placenta were reported in placentas from 2/14 animals in the 100 mg/kg/week group and 2/11 in the 300 mg/kg/week group, in all comprising ca. 16% of all evaluated placentas in the nipocalimab treated groups. The pathological changes included multifocal, pale and firm areas occupying a majority of the placental area. At a microscopical level, these areas correlated with infarcts. Placental changes were associated with foetal

loss in 3 of 4 cases. It is acknowledged that no direct effects on the fetuses and neonates were observed in animals treated with nipocalimab.

In general, in ePPND studies in cynomolgus monkeys, there is a high background incidence of embryo-foetal losses and a high degree of interstudy variability, and higher levels of background losses are associated with birth. In addition, the observed third trimester losses in phase 2 were within the incidence range of historical control data for pregnancy outcomes at the test facility (0-28.6%); third trimester foetal loss (>GD100), 27.8% [5/18] in the 100 mg/kg, 22.2% [4/18] in the 300 mg/kg, and 16.7% [3/18] in controls.

Placental findings have been observed in the test facility in other DART studies in NHPs using mAbs. In the ePPND study, all 4 affected NHPs were ADA and NAb positive, although deposition of immune complexes in the placenta could not be detected by immunohistochemistry. Although the placental effects in NHPs might be attributable to maternal immunogenicity to nipocalimab, the applicant has not been able to provide a plausible mechanistic explanation to the placental findings. Although immunogenicity findings in NHP have a limited value in predicting immunogenic responses in humans and that clinical data, so far, has not revealed any observation of placental infarctions, it cannot be excluded that other mechanisms might be related to the placental findings.

In phase II ADA and NAb were present in infants where maternal ADA was detected. Since circulating levels of nipocalimab was only detected in a one infant it is likely that the presence of ADA and NAb was transferred via breast milk. All neonates had low levels of circulating IgG levels that returned to normal levels after 24 weeks. None of the neonates in the 100 mg/kg or 300 mg/kg group exhibited serum levels of nipocalimab. In the placenta FcRn is expressed in syncytiotrophoblasts that facilitate the transport of maternal IgG to the foetal capillaries. The PD consequence therefore is the reduction of maternal IgG transfer to the foetus. As mentioned above, reduced IgG levels were noted in neonates. Although there is a normalization over time in the newborn, low levels of IgG in the newborn carries a potential risk of increased infection susceptibility that may require close monitoring of the newborn the first weeks after birth.

Maternal findings were in general comparable to findings in the pivotal repeat-dose studies, included reversible dose-related decreases in albumin, globulin, total protein and calcium levels, and injection-related reactions during or immediately after one or several administrations of nipocalimab (emesis, laboured/shallow breathing, dilated pupils, salivation, tremors, liquid feces). Maternal whole-blood RO-analysis confirmed dose-dependent binding of nipocalimab to FcRn on monocytes and granulocytes consistent with findings in the repeat-dose and immunotoxicity studies. In contrast, binding to B- and T-lymphocytes was also reported (phase 2). Nevertheless, it is considered demonstrated, that nipocalimab did not affect B- and T-cell function in monkeys across studies. Based on this, the observed B- and T-cell binding is considered unlikely to be clinically relevant.

Nipocalimab was not related to clinical signs in infants, changes in foetal/infant body weights, nursing behaviour, or infant haematology, neonatal neurobehavioral evaluations, infant organ weights, foetal/infant gross pathology or histopathology.

Nipocalimab bound to placental tissues, placental tissue leukocytes, monocytes, dendritic cells and CD45+/CDX2+ cells, and on placental trophoblast-like cells (CD45-/CDX2+) in RO-assessments. Of note, tissue RO evaluations were apparently performed with a non-validated and highly variable assay and were in general considered non-GLP compliant why the results may be indicative but of limited assessment value. Nevertheless, nipocalimab-positive placental staining was only present in maternal and not foetal placental tissue. Further, FcRn RO was not detected on foetal (GD100, GD140) or neonatal (BD1, BD14 through BD182) monocytes, granulocytes, or B- or T-cells. Summarised, this indicate in-utero protection of the foetus from exposure to maternal nipocalimab. In support of this, nipocalimab was not detected in foetal umbilicus blood samples from c-sectioned fetuses except at low levels in

4/16 fetuses. Nipocalimab serum concentrations were below the limit of quantitation in infant samples (BD14, 28, 91 and 182) except at BD91 for one male infant. However, the concentration did only marginally exceed lower limit of quantification (LLOQ), and BD14/28/182 samples from the same animal were below the LLOQ. Overall, the results support a very limited transfer of maternal nipocalimab to the foetus/neonate, if any.

Tissue immunophenotyping was not affected by nipocalimab in neither dams (placenta, spleen) nor infants (spleen, inguinal lymph nodes, thymus), and did not induce changes in maternal whole blood immunophenotyping for monocyte, granulocyte, B- and T-cell populations.

In phase 2, dose-independent reductions in serum IgG levels were observed in treated dams. Despite the lack of or very limited nipocalimab exposure in utero, infants of treated dams had significantly reduced IgG levels suggesting a depressed transplacental IgG exchange. However, infant infections or changes in clinical chemistry parameters were not observed, IgG levels were reversible and infant primary and secondary anti-KLH responses were not negatively affected.

Toxicokinetics

The discussion of toxicokinetics is included in the PK discussion.

Local tolerance

Nipocalimab was well-tolerated and did not induce signs of local toxicity at injection sites based on dermal and histopathological evaluation after single or double (1-week apart) intravenous injection of 100 mg/kg of nipocalimab (3.3 ml/kg) in the ear vein of rabbits. A single dose of 3.06 mg/kg (0.1 ml) nipocalimab administered paravenously was also locally well-tolerated with no signs of local toxicity. Dermal scoring of predefined endpoints was performed for up to 17 days after dosing.

Evaluated by histopathology, no signs of local toxicity at the injection site were observed in the 26-week pivotal repeat-dose study evaluating intravenous dosing up to 300 mg/kg QW (10 ml/kg) in cynomolgus monkeys.

Interspecies comparison

Across repeat-dose studies including immunotoxicity and ePPND phase 2 studies, high dose exposure comparisons based on AUC corrected for dose intervals in monkeys (7 days) and humans (14 days) and C_{max} provided acceptable exposure multiples between 24-71 and 14-23 times the maximum expected exposure in humans, respectively.

The suggested NOAEL in the 26-week is not supported. As nipocalimab cannot be ruled out as involved in the mechanism of systemic lymphoproliferation in the euthanised monkey in the 26-week study, the NOAEL should be lowered to 100 mg/kg providing safety margins of 10.8 and 6.7 based on AUC_{0-last} and C_{max} , respectively. This is acceptable and at this point of assessment, the risk of systemic lymphoproliferation is considered of unknown clinical relevance and covered in section 4.4 of the SmPC by intra-treatment monitoring for symptoms of infection.

Tissue cross-reactivity

In the cross-reactivity study in adult and foetal tissues no nipocalimab specific endothelial staining was observed, except in one cynomolgus monkey heart valve sample, and specific staining was in general fully cytoplasmic. This is unexpected, since FcRn is described to be highly expressed in endothelium (Latvala et al 2017, Lozano et al 2018). Of note, positive endothelial staining was observed when using an anti-CD31 antibody as positive control. Nipocalimab is claimed to bind to FcRn at both acidic (intracellular) and neutral (physiological, extracellular) pH, though importantly, the development of the product is focused on epitope recognition and not immunohistochemistry. In conclusion, due to an

apparently inadequate performance of nipocalimab as an immunohistochemistry reagent, the results of the submitted TCR study are considered of no relevance for the toxicological evaluation of nipocalimab.

Antigenicity

Nipocalimab-specific ADAs and NAbs were detected during the dosing phase in most treated animals across studies with the highest impact at low dose levels. It is agreed that ADA formation was not related to toxicity and that the interpretation of data is not compromised by the formation of ADA and therefore, and in line with ICH S6(R1), no special significance is ascribed to the observed antibody response.

Of note, all infants from treated dams in the ePPND study, except one neonate on BD1, were ADA and NAbs positive. However, these findings were not correlated to the presence of nipocalimab in serum or FcRn receptor occupancy on monocytes, granulocytes, B- or T-cells via whole blood RO-analysis, and was probably due to immunoglobulin transfer via breast milk.

Immunotoxicity

In a dedicated immunotoxicity study, it was demonstrated that nipocalimab did not target humoral or cell-mediated immunity in cynomolgus monkeys. Results of this study were supported by immune endpoints including cytokine response, immune cell population flow cytometry, and immune responses to KLH and tetanus toxoid challenges evaluated in the repeat-dose studies.

Immune system specific blood endpoints in the immunotoxicity study included: immunophenotyping, phagocytosis, oxidative burst, cytotoxic T-cell activity, NK cell activity, cytokine analysis, and primary and secondary TDARs following intra-treatment KLH and post-treatment TT immunisation.

Quantification by flow cytometry showed no nipocalimab-induced alterations in blood immunophenotyping results. These results were supported by tissue immunophenotyping results in the 26-week study showing no clear impact on immune cell population in the spleen, thymus, and inguinal lymph node when evaluating absolute percentages. However, a slight, transient, and reversible nipocalimab-induced change in relative percentages of granulocytes, monocytes and NK cell populations was observed across tissue samples but is considered of limited clinical relevance.

Receptor occupancy (RO) studies demonstrated free/unbound FcRn expression on leukocytes in the order; monocytes>granulocytes>B-lymphocytes>T-lymphocytes. Dose-dependent increases in the level of occupied/bound FcRn receptors were confirmed on monocytes and granulocytes (≥ 100 mg/kg at 4 weeks) indicating binding of the dosed nipocalimab. Of note, increased RO was not confirmed in monocyte (≥ 100 mg/kg) and granulocyte (100 mg/kg) populations in week 8. Nevertheless, reductions in serum IgG concentrations were maintained through the dosing period, and FcRn occupancy was in general reversible in a dose-dependent manner during the recovery phase. Receptor occupancy analysis in the 26-week study supports the dose-dependent binding and release of nipocalimab to/from monocytes and granulocytes. Overall, RO by nipocalimab was not observed on B- and T-lymphocytes. However, the immunotoxicity study report described increased RO to B- and T-lymphocytes (300 mg/kg) which was minimal and within normal variability relative to pre-study values.

Immune cell activity was evaluated with *in vitro* cell-based methods, fluorometry and flow cytometry. Nipocalimab did not change cytotoxic T-cell activity, NK cell cytotoxicity, or granulocyte/monocyte phagocytosis and oxidative burst. These findings are aligned with *in vitro* data showing that nipocalimab displayed no antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis or complement-dependent cytotoxicity (study RPT-2479).

Overall, the occupancy data across repeat-dose studies including immunotoxicity and ePPND studies indicate that nipocalimab bound to monocytes and granulocytes contributing to the reduced recycling and increased lysosomal degradation of IgG without affecting the immune function of these cell populations.

It is agreed with the applicant that nipocalimab did not induce clinically relevant changes in the level of a comprehensive panel of cytokines across repeat-dose studies including the immunotoxicity study. However, a trend for dose-independent nipocalimab-induced increases in IL-1RA was noted either as sporadic short-lasting or persistent long-lasting events across studies. As an inflammatory inhibitor, increased levels of IL-1RA may reduce the inflammatory response. Also, excessive IL-1RA may interfere with other biological processes e.g. wound healing and tissue repair.

Nipocalimab did not depress the humoral immune response in monkeys challenged with KLH (im/sc) twice during the treatment period measured by TDAR evaluations (studies 501555, 20104942). Anti-KLH specific IgM and IgG responses occurred across all groups, and IgG responses were dose-dependently reduced by nipocalimab (≥ 100 mg/kg) in accordance with the MoA of nipocalimab. Overall, the available data do not suggest any clinically relevant immunosuppressive effect.

Other endpoints included clinical symptoms, body weights, food consumption, gross and microscopic pathology and organ weights. Emesis (non-dose-dependent) and short-term events of swollen prepuce, face and hindlimb (10 and 100 mg/kg) were observed. The prepuce swelling resolved with Non-steroidal Anti-Inflammatory Drug. The face and hindlimb swellings resolved without treatment. The cause of swelling was not determined and was claimed non-related to nipocalimab. However, swellings were also reported in the 26-week repeat-dose study and peripheral oedema is listed as a very common clinical adverse effect in the SmPC. Therefore, it cannot be ruled out that the observed swellings in monkeys may be related to nipocalimab. Nevertheless, the reflection in the SmPC is considered sufficient.

Reversibility of the IgG reducing effect of nipocalimab was demonstrated in recovery animals challenged with tetanus toxoid (im). In agreement with the applicant, all animals showed the expected anti-tetanus IgM and IgG response which was comparable to the response in controls. However, a decelerated anti-tetanus IgM and IgG response seemed apparent in the 26-week (10 and 300 mg/kg) and immunotoxicity studies (≥ 100 mg/kg), respectively. Nevertheless, levels reached control levels within 10-14 days post immunisation why the differences are not considered of clinical concern. Headings in text table 15 in appendix 8 page 636 in the immunotoxicity study report appear wrong. Headings state #day post first tetanus immunisation. It should have been post second immunisation.

The suggested NOAEL of 300 mg/kg (highest dose level) is supported.

Dependence

The dependency potential of nipocalimab was not investigated and is therefore unknown, but based on the molecular weight, chemical structure and the WoE provided by the applicant, it is agreed that it is unlikely that nipocalimab possesses a clinically relevant dependency potential.

Studies on metabolites

No traditional metabolism studies were performed with nipocalimab, which agrees with ICH S6(R1) as nipocalimab is a protein expected to be catabolized *in vivo* into small peptides and individual amino acids.

Studies on impurities

No concern regarding impurities was identified in the quality assessment. Hence, additional studies on impurities are not warranted.

Phototoxicity studies

No data on the phototoxic potential of nipocalimab were presented in the toxicology part of the dossier. According to the ICH M3(R2) guideline, the need for phototoxicity studies should be assessed on a case-by-case basis. The ICH S6(R1) guideline does not include guidance on photosafety. According to the ICH S10 guideline, photosafety evaluation of protein pharmaceuticals does not generally apply and based on this it seems justified to omit photosafety assessment for the sought medicinal product.

Other toxicity studies

Human and monkey whole blood evaluation in reaction to nipocalimab evaluated in a GLP-compliant *in vitro* study showed no effect on haemolysis, flocculation or red blood cell morphology. The *in vitro* results correlate with *in vivo* data showing no effect of nipocalimab on haematology in the pivotal toxicology studies.

Environmental Risk Assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, nipocalimab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Nipocalimab binds to the IgG Fc binding site of FcRn with binding affinity in the picomolar range and blocks IgG recycling by directly competing with IgG. There is a low likelihood for cross-reactivity with other human proteins. Therapeutic effects have been demonstrated in mouse models representing pathogenic IgG-driven autoimmune diseases other than gMG. From a non-clinical perspective these studies are considered sufficient to demonstrate the mechanism of action and the relevance for use in the proposed indication.

The PK and TK characterizations in the single-dose PK/PD and repeat-dose toxicity studies in the cynomolgus confirmed nipocalimab exposures. Nipocalimab exhibited non-linear PK with serum exposures generally increasing in a greater than dose-proportional manner, consistent with target mediated drug disposition (TMDD). No sex differences in exposure were observed. PD effects measured by decreases in serum IgG were achieved and maintained for at least 1 week after single IV doses of ≥ 50 mg/kg.

The toxicology programme of nipocalimab was considered adequate to evaluate the toxicity profile of nipocalimab in support of marketing authorisation. The toxicity profile of nipocalimab has been thoroughly evaluated in non-clinical studies according to appropriate and current guidelines. The cynomolgus monkey were the only toxicology species used based on pharmacological relevance.

The performed studies indicate that nipocalimab is generally well tolerated and the assessment of the toxicology studies raised no major concerns.

Overall, nipocalimab is considered approvable from a non-clinical perspective.

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. Tabulated summary of all clinical studies in the clinical program of nipocalimab

Study ID	Population	Dose	Enrolled Participants
Phase 1 studies			
MOM-M281-001	Healthy adults	SAD: 0.3, 3, 10, 30, or 60 mg/kg	SAD: 34 MAD: 16
MOM-M281-007	Healthy adults	MAD: 15 or 30 mg/kg 30 mg/kg at infusion rates of 0.5 to 4 mg/kg/minute, or 60 mg/kg at infusion rate of 4 mg/kg/minute	40
MOM-M281-010	Healthy Japanese adults	10, 30, or 60 mg/kg	24
80202135EDI1001 (IV cohorts)	Healthy adults	300 or 1200 mg	16
80202135EDI1002	Healthy Chinese adults	15, 30, or 45 mg/kg	30
80202135EDI1009	Healthy adults aged 18-65, inclusive, who had not received a tetanus (eg, Tdap, Td) vaccine in the past ≤5 years and had not received a pneumococcal vaccine (eg, Prevnar 7, 13, 20 or PPSV23) in the past ≤10 years.	30 mg/kg loading dose at Week 0 then 15 mg/kg at Week 2 and Week 4 nipocalimab 0.5 mL single dose Tdap (GSK Boostrix®) 0.5 mL single dose PPSV23 (MSD Pneumovax®23)	32
80202135EDI1006	Healthy adults	15 or 45 mg/kg	160
MOM-M281-008	Healthy adults	225 mg fremanezumab 30 mg/kg nipocalimab	24
80202135EDI1003	Healthy adults	50 mg etanercept 400 mg (2x200 mg) HCQ 15 mg/kg nipocalimab	48

Phase 2 studies			
MOM-M281-004	Adults with gMG and insufficient response to SOC therapy	5, 30, or 60 mg/kg	68
MOM-M281-005	Adults with gMG	30 or 60 mg/kg	37
Phase 2/3 study			
80202135MYG2001 ^a (Cohort 1)	Pediatric participants aged 12 to <18 years (Cohort 1) with gMG and insufficient response to SOC gMG therapy	15 or 30 mg/kg	7
Phase 3 study			
MOM-M281-011 ^a	Adults who were gMG-seropositive	15 or 30 mg/kg	199 randomized; 196 treated
Other supportive clinical study			
MOM-M281-003 ^a	Participants with an obstetric history of severe fetal anemia, hydrops, or stillbirth related to HDFN at GA Week ≤ 24 , with titers for anti-D ≥ 32 or antikell ≥ 4 , who were pregnant with an antigen-positive fetus	30 mg/kg	13

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical methods

Determination of nipocalimab concentrations

Two validated immunoassay methods, an ELISA method and an electrochemiluminescence immunoassay (ECLIA) method were used to determine nipocalimab concentrations in human serum samples.

Determination of ADA to nipocalimab

Two validated immunoassay methods, ECLIA methods were used to assess the antibodies to nipocalimab in human serum samples. The assay sensitivity of assay applied for Phase-3 studies was below 10 ng/mL (PC: MOMN005-6H4). As validated, the drug tolerance at 100 ng/mL of antibodies to nipocalimab in human serum could be detected in the presence of up to 1280 µg/mL of nipocalimab in human serum samples.

Determination of NAb to nipocalimab

Two validated immunoassay methods, a cell-based flow cytometry method and a non-cell-based competitive ligand binding ECLIA method validated were used to assess NAb to nipocalimab in human serum samples.

Model based population PK analysis

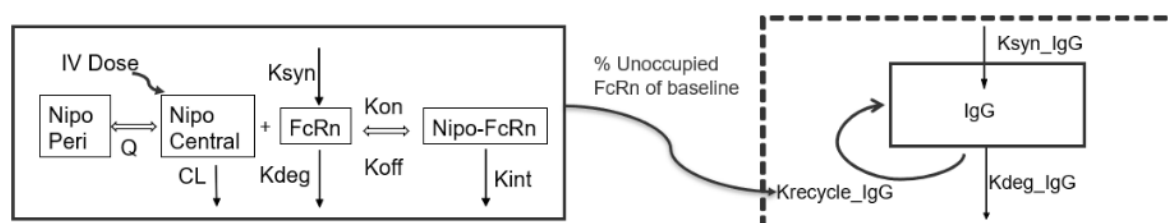
Data from five Phase 1 healthy volunteer studies (M281-001, M281-007, M281-010, EDI1001, and EDI1002), one Phase 2 study in participants with gMG (M281-004), and the pivotal Phase 3 study in participants with gMG (M281-011) were used to conduct the population PK analyses. For information on the population analyses of the pharmacodynamics of nipocalimab, please refer to PD section)

For the overall nipocalimab-treated population (ie, all included nipocalimab-treated healthy volunteers (HVs) and participants with gMG), demographic characteristics were as follows: participants' ages at baseline ranged from 18 to 81 years, with a median of 44 years, and bodyweights at baseline ranged from 41 to 188 kg, with a median of 73.3 kg. Approximately half were women (57.0%), 52.7% were white (not Hispanic or Latino), and 28.5% were Asian. The mean (SD) baseline IgG was 10.1 (2.50) g/L. Participants with gMG represented 54.5% of all nipocalimab-treated participants (277) from the 7 clinical studies that were included in the analyses.

RO; FcRn was only measured in the healthy volunteers (M281-001, EDI1001, and EDI1002). In the Phase 2 and Phase 3 studies in gMG patients, only sparse PK (one pre-dose sample and one sample 45 minutes after end-of infusion, pre-dose samples were mostly Below Limit of Quantification (BLQ)) and total serum IgG samples were collected. The reported RO model was informed by the PK and IgG data in patients with gMG under the assumption of similar RO dynamics between gMG patients and healthy participants.

The time course of serum nipocalimab concentrations, RO, and the associated variability were quantitatively characterized in HVs and participants with gMG receiving IV dosing of nipocalimab using an open 2-compartment disposition model with nonspecific linear distribution to a peripheral compartment and parallel linear and nonlinear FcRn-mediated clearance, which was modelled using the Quasi-Steady-State (QSS) approximation of the general TMDD model (Figure 1). The clearances (clearance (CL) and intercompartmental flow (Q)) and volumes of distributions (central (Vc) and peripheral (Vp)) were scaled allometrically with fixed theoretical exponents of 0.75 and 1.00, respectively. Parameter estimates of the final nipocalimab population PK model are provided in Table 3. The goodness of fit (GOF) and visual predictive check (VPC) (Figure 2) plots indicate that the final PK model adequately described the serum nipocalimab concentrations and its variability in participants with gMG from Phase 3 Study M281-011, the Phase 2 Study M281-004 and healthy volunteers.

Figure 1. Schematic of Nipocalimab IV population PK-IgG model structure



CL=central compartment clearance; FcRn=neonatal Fc receptors; IgG=total serum immunoglobulin G; IV=intravenous; Kdeg=degradation rate of FcRn receptor; Kdeg_IgG=degradation rate of IgG without FcRn mediated recycling; Kint=nipocalimab-FcRn internalization rate constant; Koff=dissociation rate constant; Kon=second-order association rate constant; Krecycle_IgG=FcRn mediated recycling rate when free FcRn is fully available at time 0; Ksyn=synthesis rate of FcRn receptor; Ksyn_IgG=synthesis rate of IgG; Nipo=nipocalimab; Peri=peripheral; PK=pharmacokinetics; Q=intercompartmental flow; RO=receptor occupancy.

Table 3. Parameter estimates of the base and final population PK models for IV Nipocalimab

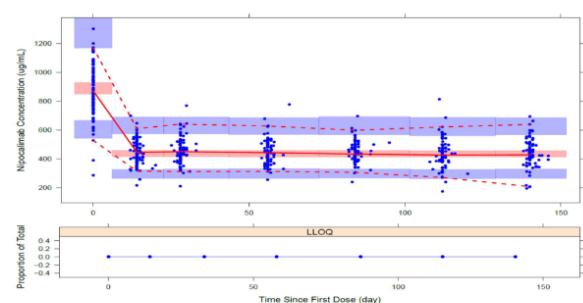
Parameter (Unit)	Description	Base Model		Final Model	
		Population Estimate	RSE (%)	Population Estimate	RSE (%)
CL (L/d) ^a	Linear serum clearance	0.658	2.66	0.692	2.10
CL difference in Chinese (%)	Linear serum clearance difference in Chinese	-	-	-28.0	-
V _c (L) ^a	Volume of the central compartment in Phase 3 study	2.43	1.67	2.41	1.59
V _c in Phase 1 and 2 (L) ^a	Volume of the central compartment in Phase 1 and 2 studies	3.23	1.41	3.17	1.28
V _c difference in Japanese (%)	Volume of the central compartment difference in Japanese	-	-	+14.0	-
Q (L/d) ^a	Intercompartmental clearance	0.260	8.96	0.303	0.521
V _p (L) ^a	Volume of the peripheral compartment	0.619	9.10	0.759	8.63
FcRn0 (nmol/L)	Total (free) FcRn receptor at baseline	145	3.46	134	2.07
FcRn0 in Chinese (nmol/L)	Total (free) FcRn at baseline in Chinese	-	-	214	-
FR _{max} (-) ^b	Maximal fraction of FcRn bound to nipocalimab	0.947	0.191	0.947	0.341
K _{ss} (μg/mL)	Quasi-steady state constant for FcRn-nipocalimab complex	6.15*	12.7	5.81*	0.932
k _{int} (d ⁻¹)	Internalization rate constant for FcRn-nipocalimab complex	63.8	9.12	67.4	20.6
k _{deg} (d ⁻¹)	Degradation rate constant of the free FcRn	1.3 FIX	-	1.3 FIX	-
IIV (CV %)					
ω CL	IIV for linear serum clearance	23.7	6.34	19.0	3.64
ω V _c	IIV for Volume of the central compartment	15.5	4.85	14.7	0.169
ω FcRn0	IIV for total (free) FcRn receptor at baseline	24.6	6.48	15.4	0.0445

Residual variability

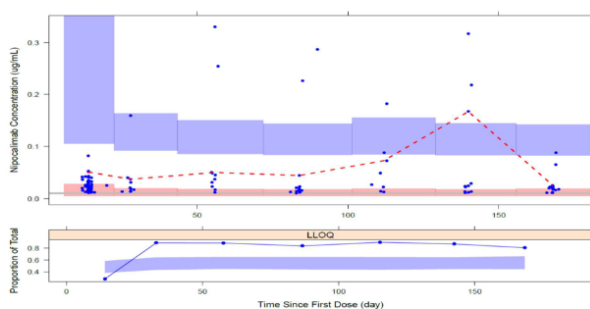
ADD1 RUV PK (nmol/L)	SD of additive residual error for ELISA PK assay	0.446	7.67	0.454	6.10
ADD2 RUV PK (nmol/L)	SD of additive residual error for ECLIA PK assay	0.0354	8.64	0.0350	8.83
PROP1 RUV PK (fraction)	SD of proportional residual error for PK for Phase 1 studies	0.0833	2.35	0.0824	2.51
PROP2 RUV PK (fraction)	SD of proportional residual error for Phase 2 study	0.366	6.89	0.388	11.7
ADD3 RUV PK (nmol/L)	SD of additive residual error for Phase 3 study	0.629	5.79	0.406	5.76
PROP3 RUV PK (fraction)	SD of proportional residual error for Phase 3 study	0.121	3.09	0.116	3.13

Figure 2. VPC of Nipocalimab serum concentrations vs time since first dose for the final PK model (figures on the left A post-dose and B pre-dose samples: Study M281-011, and figure on the right A. Study M28-004 (phase II gMG patients) and B. Phase I studies (healthy volunteers)), stratified by population (participants with gMG and HVs)

A: Postdose Samples

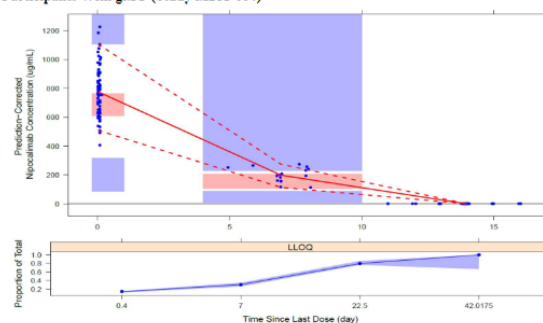


B: Predose Samples

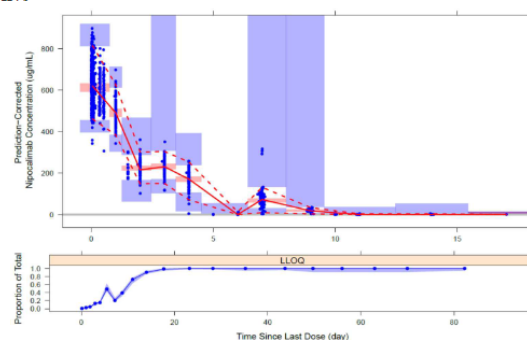


Reference: run019, Dataset B (with 5 CWRES>6 excluded).
 CI=confidence interval; CWRES=conditional weighted residuals; LLOQ=lower limit of quantification;
 PK=pharmacokinetic(s); VPC=visual predictive check.
 Blue points represent serum nipocalimab concentrations; red solid and dashed lines represent the median (50th), 2.5th and 97.5th percentiles of binned observations; red band indicate 95% CI of the median of the model prediction and blue bands indicate 95% CI of 2.5th and 97.5th percentiles of model predictions (1,000 replicates).

A: Participants With gMG (Study M281-004)



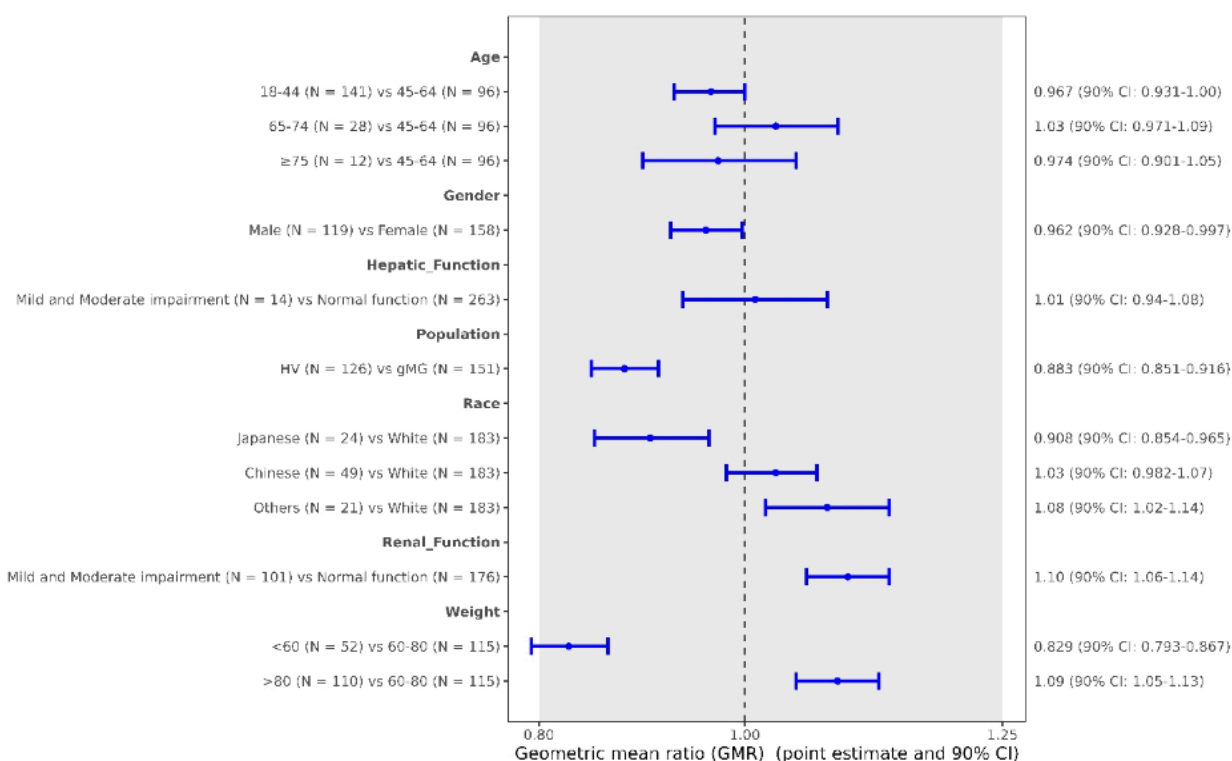
B: HV's



Reference: run019, Dataset B (with 5 CWRES>6 excluded).
 CI=confidence interval; CWRES=conditional weighted residuals; gMG=generalized myasthenia gravis; HV=healthy volunteer; LLOQ=lower limit of quantification; pcVPC=prediction-corrected visual predictive check;
 PK=pharmacokinetic(s); RO=neonatal Fc receptor occupancy.
 For visualization purposes, 13 aberrant data were excluded (which represent 0.38% of the total PK data included in

Other than body weight, only the impact of race/ethnicity on CL, Vc and FcRn baseline were statistically significant in the gMG participants in study M281-011 (Figure 3). As their median predicted effect on area under the curve over the dose interval at steady state (AUC_{tau, ss}) was <12.5% and the effect on predose total serum IgG reduction from baseline at steady state was <3.75 percentage-points, they were not considered clinically relevant.

Figure 3. Forest plot of the covariate evaluation for $AUC_{tau,ss}$ of nipocalimab using the final PK model, demographic covariates



Absorption

Nipocalimab drug product is intended to be administered as an IV infusion. Therefore, most clinical studies in the clinical pharmacology program have utilized IV administration route, and no absorption data for nipocalimab are available. Bioavailability of 100% is assumed.

Distribution

Volume of distribution of nipocalimab was estimated from the population PK as well as from non-compartmental PK analysis where applicable.

From the population PK analysis, the V_c and V_p compartment in adult gMG patients (Phase 3 study) was estimated to 2.41 L and 0.759 L, respectively. The mean volume distribution at steady state was determined to 2.84 L (0.0359 L/kg) by non-compartmental analysis (NCA) analysis of 15 mg/kg IV in EDI1006 study.

Overall, relatively small volume of distribution parameter values were obtained, which implies that nipocalimab is primarily retained in the systemic blood circulation with limited extravascular tissue distribution. This is in line with general IgG distribution characteristics.

Elimination

The exact pathway, through which nipocalimab is metabolized has not been characterized. As a fully human IgG1 mAb, nipocalimab is expected to be metabolized in the same manner as any other endogenous IgG (i.e., degraded into small peptides and amino acids via catabolic pathways) and is subject to elimination through similar routes. Renal excretion and hepatic enzyme-mediated metabolism are therefore unlikely to represent major elimination routes.

Based on the non-compartmental PK analysis from Phase I studies, observed mean total systemic CL ranged from 0.0549 to 0.0627 L/h and mean terminal half-life ($t_{1/2}$) ranged from 14.3 to 29.3 hours following a single IV infusion of 15 mg/kg nipocalimab in healthy participants.

Dose proportionality and time dependencies

Dose proportionality

There are several clinical Phase I studies conducted with nipocalimab which have contributed to data about the dose-proportionality of nipocalimab.

MOM-M281-001 was a Phase I first-in-human clinical study which investigated single-ascending-doses (SAD) and multiple-ascending-doses (MAD) of nipocalimab in HVs and thereby provided PK data regarding the dose-proportionality aspects of nipocalimab. In the SAD Part, 6 groups received a single IV infusion of placebo (N=10) or escalating doses of nipocalimab at 0.3 mg/kg (N=3), 3 mg/kg (N=3), 10 mg/kg (N=6), 30 mg/kg (N=6), or 60 mg/kg (N=6).

SAD cohorts involved frequent PK sampling at pre-specified time points which allowed for determination of PK profiles and corresponding AUCs of nipocalimab. On the other hand, MAD cohorts involved only sparse PK sampling. In general, C_{max} of nipocalimab increased in a dose-proportional manner while AUC increased in a greater than dose proportional manner across all SAD cohorts.

Table 4. Summary of PK parameters after a single IV dose administration (Study MOM-M281-001; SAD part)

Treatment (N) Nipocalimab IV (sd)	C_{max} ($\mu\text{g/mL}$) ^a	T_{max} (h) ^b	AUC_{last} ($\mu\text{g}\cdot\text{h/mL}$) ^a	AUC_{inf} ($\mu\text{g}\cdot\text{h/mL}$) ^a	$t_{1/2}$ (h) ^a	C_{max} ($\mu\text{g/mL}$)/[mg/kg] ^a	AUC_{last} ($[\mu\text{g}\cdot\text{h/mL}]/[\text{mg/kg}]$) ^a	AUC_{inf} ($[\mu\text{g}\cdot\text{h/mL}]/[\text{mg/kg}]$) ^a
0.3 mg/kg (N=3)	0.446 (0.428-0.461)	2.00 (2.00-2.02)	0.569 (0.500-0.672)	NC	NC	1.45 (1.39-1.54)	1.85 (1.66-2.25)	NC
3 mg/kg (N=3)	53.8 (53.1-54.5)	2.03 (2.02-2.08)	844 (793-876)	940 (869-1085)	7.36 (5.61-11.9)	18.1 (18.0-18.3)	284 (268-298)	317 (289-367)
10 mg/kg (N=6)	205 (189-248)	2.07 (2.00-12.03)	9181 (7880-10854)	9684 (8150-11666)	23.8 (16.9-32.7)	20.4 (18.9-24.5)	914 (786-1050)	970 (812-1170)
30 mg/kg (N=6)	598 (539-658)	2.00 (2.00-12.03)	37961 (29733-48161)	38640 (30971-48174)	30.5 (23.7-33.9)	19.9 (17.8-22.1)	1262 (1021-1589)	1285 (1060-1590)
60 mg/kg (N=6)	1313 (1155-1535)	2.06 (2.00-2.13)	112245 (93492-140536)	113458 (93692-142133)	32.2 (17.9-43.4)	21.8 (17.9-25.3)	1863 (1447-2317)	1883 (1450-2344)

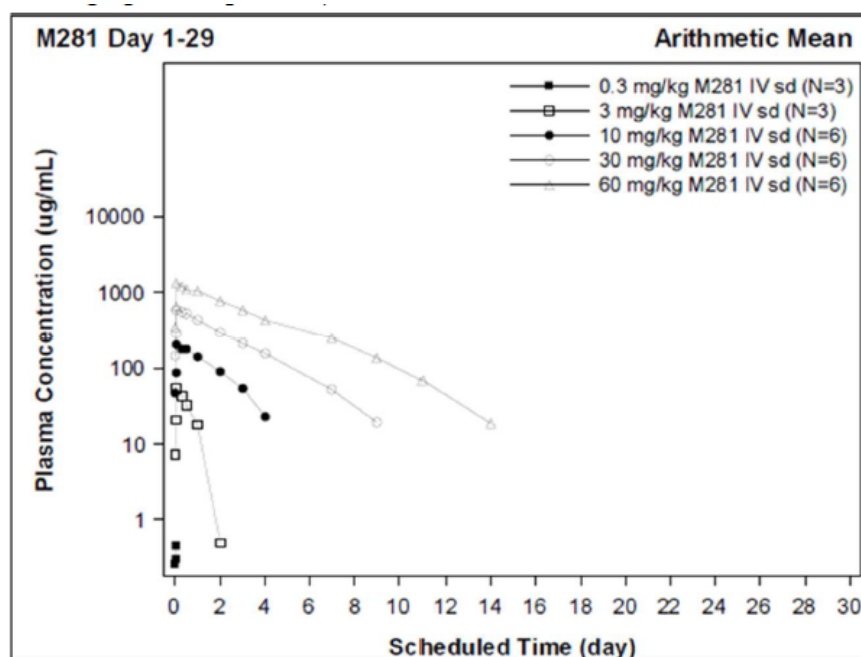
AUC_{inf} =area under the serum concentration vs time curve from time 0 to infinity with extrapolation of the terminal phase; AUC_{last} =area under the serum concentration vs time curve from time zero to the time corresponding to the last quantifiable concentration; C_{max} =maximum observed serum concentration; IV=intravenous; N=number of participants exposed to treatment per population; NC=not calculated; PK=pharmacokinetic(s); SAD=single ascending dose; sd=single dose; $t_{1/2}$ =half-life; T_{max} =time correspondent to the maximum observed serum concentration (single dose), or the first time to reach the C_{max} (multiple doses).

^a Geometric mean and range.

^b Median and range.

NC for insufficient concentration data available for reliable PK parameter calculation.

Figure 4. Arithmetic mean serum nipocalimab concentration-time profiles (Study MOM-M281-001; SAD part, 0.3 to 60 mg/kg)



IV=intravenous; M281=nipocalimab; N=number of participants; PK=pharmacokinetic(s); SAD=single ascending dose; sd=single dose.

Another Phase I study denoted as MOM-M281-007 also provided SAD nipocalimab data in HVs but only at the two dose levels of 30 and 60 mg/kg. C_{max} appeared to increase dose-proportional (i.e., about 2-fold increase) when increasing the nipocalimab dose from 30 to 60 mg/kg. AUC seemed to increase a bit more than dose-proportional when doubling the nipocalimab dose from 30 to 60 mg/kg. These results seem to be consistent with MOM-M281-001 study in terms of dose-proportionality.

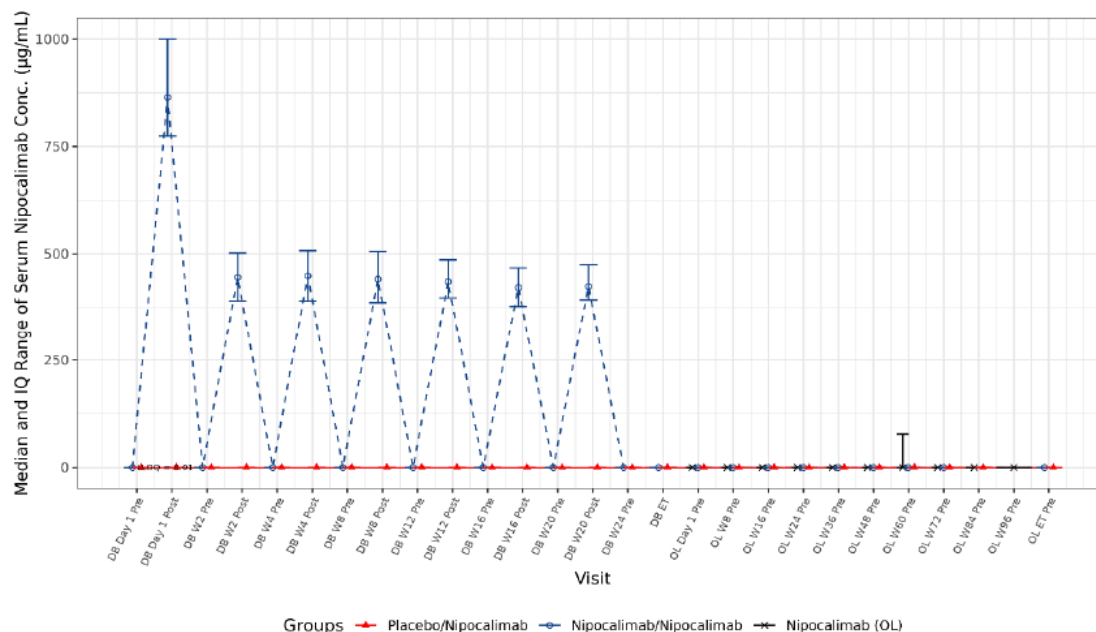
Moreover, there are some additional Phase I studies which also provided PK data related to dose-proportionality. Study 80202135EDI1001 investigated two IV cohorts of HVs at fixed IV doses of nipocalimab at 300 mg and 1200 mg. Results implied about dose-proportional increase in C_{max} with more than dose-proportional increase in AUC with increasing nipocalimab doses. Moreover, Phase I studies conducted in healthy Japanese (Study MOM-M281-010) and Chinese (Study 80202135EDI1002) subjects also tested single ascending IV doses of nipocalimab and implied similar non-linearity trends.

Time dependency

The proposed therapeutic regimen of nipocalimab (i.e., maintenance dose of 15 mg/kg given every 2 weeks) together with a relatively short half-life of nipocalimab (i.e., $t_{1/2}$ of about 29 h) imply no potential for the accumulation of nipocalimab after its repeated dosing. Indeed, Phase II and Phase III studies implementing the proposed therapeutic regimen of nipocalimab have demonstrated that nipocalimab systemic levels were below the lower limit of quantification (LLOQ) prior to the administration of each maintenance dose (i.e., pre-dose PK samples were below LLOQ).

Figure below presents sparse PK data collected in Phase III study (MOM-M281-011). No accumulation in serum nipocalimab concentrations over time was observed based on the median C_{trough} (pre-infusion trough serum concentrations) and C_{eoi} (end of infusion serum concentrations) values.

Figure 5. Median ($\pm$ IQR) serum nipocalimab concentrations ($\mu\text{g/mL}$) by visit; PK analysis set (Study MOM-M281-011)



DB=double-blind; IQ=interquartile; IQR=IQ range; LLOQ=lower limit of quantification; OL=open-label;

PK=pharmacokinetic(s); W=week.

At each time point, the error bars represent the first and third quartile.

Concentration values below LLOQ are considered as 0.

Immunogenicity

In study EDI1006 (Process 2.0 vs Process 3.0), the incidences of treatment-emergent ADA through Day 57 were 82.5%, 60.0%, 75.0%, and 50.0%, respectively, in Intervention A, B, C, and D. The overall incidences of NAb to nipocalimab through Day 57 were 32.5%, 25.0%, 30.0%, and 7.5%, respectively, in Intervention A, B, C, and D.

In Phase 2, Phase 2/3, and Phase 3 studies in patients with gMG, the overall incidence of treatment-emergent ADA to nipocalimab ranged from 13.8% to 71.4%.

In Study M281-011, among the 97 participants who received nipocalimab during the double-blind (DB) phase and had appropriate samples, 48 participants (49.5%) were considered positive for treatment-emergent ADA through 24 weeks. ADA titers were generally low. All 48 participants were evaluable for NAb, of which 17 were positive (overall NAb incidence of 17.5%).

Through the open-label extension (OLE) phase of the study (CCO date of 23 August 2024), a total of 194 participants treated with nipocalimab had post-treatment serum samples that were evaluated for antibodies to nipocalimab. Among them, 83 participants (42.8%) were considered positive for treatment-emergent ADA (up to 120 weeks after the first dose with nipocalimab). ADA titers were generally low. All 83 ADA-positive participants were evaluable for NAb, of which 44 were NAb-positive. The overall incidence of NAb to nipocalimab was 22.7% of the 194 participants treated with nipocalimab.

The presence of detectable ADA or NAb to nipocalimab did not alter the PK profile of nipocalimab.

Special populations

No dedicated clinical studies have been performed to investigate the impact of hepatic impairment or renal impairment on the PK of nipocalimab.

The impact of renal impairment, hepatic impairment, gender, ethnic factors, body weight and age were evaluated either graphically or tested as covariates in the population model-based analysis. Only body weight was determined to have a clinically relevant impact on nipocalimab exposure. The geometric mean ratio point estimate (90% CI) of $AUC_{tau,ss}$ for subjects weighing <60 kg (N=55) and >120 kg (N=7) was 0.854 (0.814-0.897) and 1.26 (1.13-1.41), respectively, compared to subjects weighing 60-80 kg.

None of the nipocalimab Phase I PK studies included participants with age ≥ 65 years. Elderly participants in the Phase 2 (MOM-M281-004) and Phase 3 (MOM-M281-011) gMG studies are summarized in the table below. Of note, studies MOM-M281-011 and MOM-M281-004 have only provided sparse PK data.

Table 5. Age distribution for elderly subjects in phase 2 (MOM-M281-004) and phase 3 (MOM-M281-011)

	Age 65 - 74 (Older subjects number/total number)	Age 75 - 84 (Older subjects number/total number)	Age 85+ (Older subjects number/total number)
PK trials	None	None	None
MOM-M281-011	30/203 (14.8%)	22/203 (10.8%)	0/203 (0%)
MOM-M281-004	14/54 (25.9%)	5/54 (9.3%)	0/54 (0%)

Paediatric population

Study 80202135MYG2001 is an ongoing study in eligible adolescents (12 to <18 years of age; Cohort 1) and children (2 to <12 years of age; Cohort 2) with gMG. Clinical pharmacology data from Cohort 1 with the data cut-off date 15 December 2023 (n=7 in the PK analysis set) has been analysed using a population PK model. Due to limited data in a limited number of adolescent subjects (two subjects only had one PK sample collected each, and in total 42% of all collected samples were below quantification limit), the approval in adolescents has to rely on exposure-matching between adolescents (from 12 years and 30 kg) and adults with gMG (i.e. extrapolation of efficacy and safety from adults to adolescents based on exposure matching).

Participants in Cohort 1 received a single IV 30 mg/kg loading dose followed by 15 mg/kg Q2W. The active treatment phase was 24 weeks long. Sparse PK samples were collected at the end of infusion and prior to each administration. Comparison of observed serum Nipocalimab concentrations after initial dose and at steady-state and individual total serum IgG concentration versus time between adolescents and adults are displayed in Figure 6, Figure 7 and Figure 8.

Figure 6. Boxplot of observed serum Nipocalimab concentrations after an initial dose between adolescents in Study MYG2001 and adults in Study MOM-M281-011 - C_{max} (left) and C_{trough} (right)

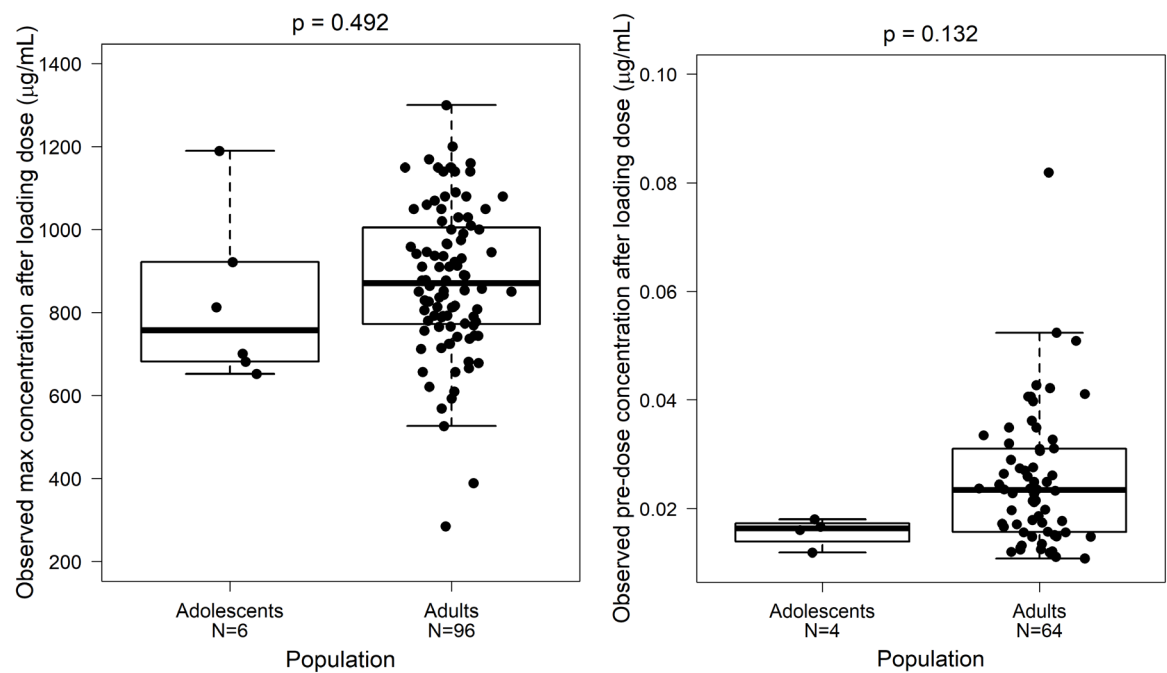


Figure 7. Boxplot of observed serum Nipocalimab concentrations at steady-state between adolescents in Study MYG2001 and adults in Study MOM-M281-011 - C_{max} (left) and C_{trough} (right)

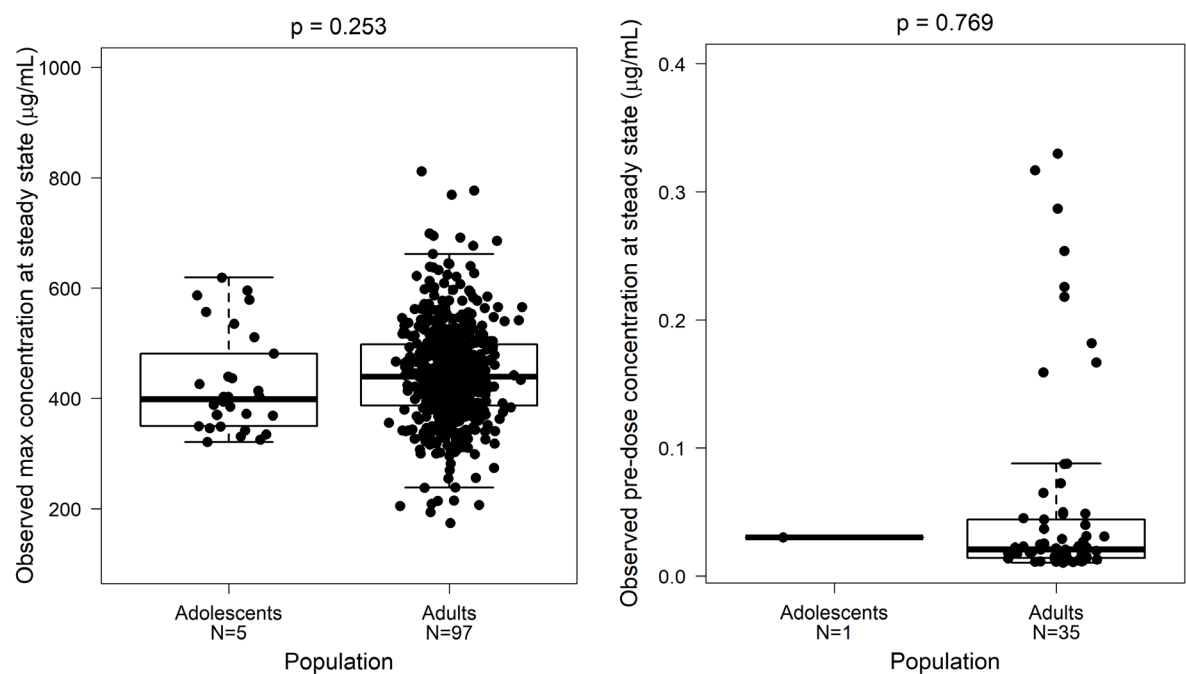
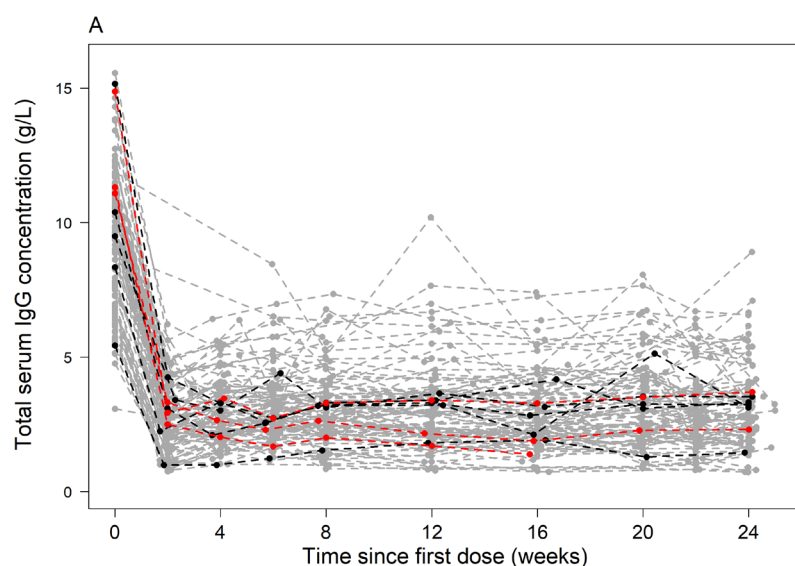


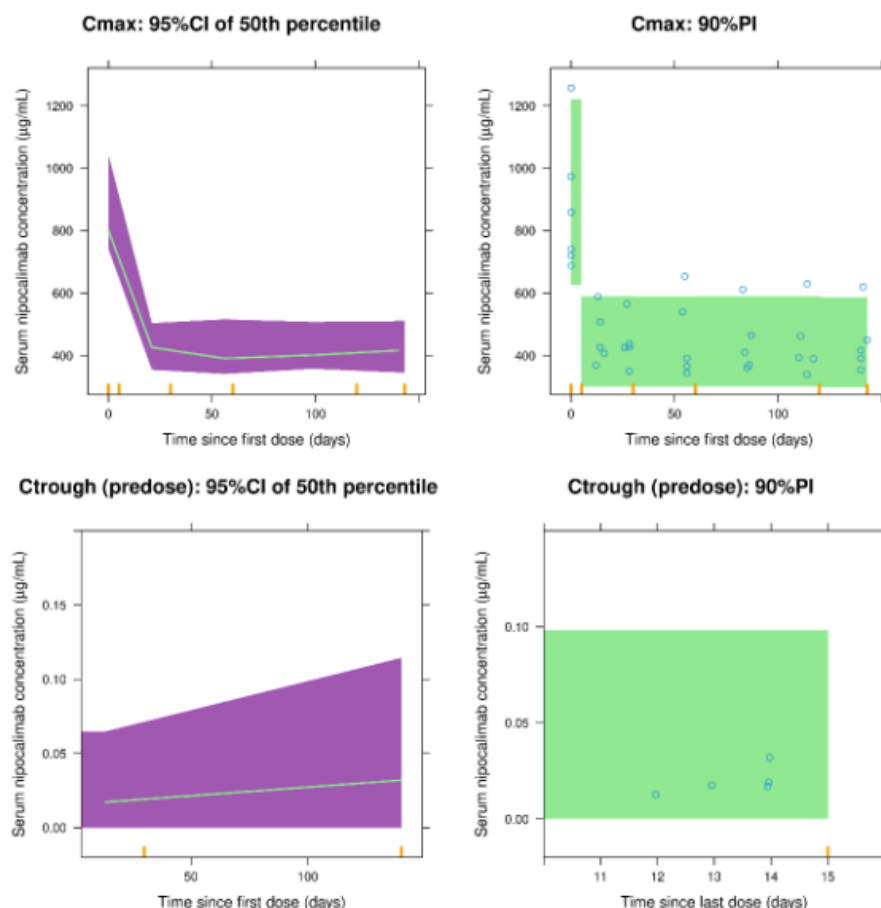
Figure 8. Comparison of observed individual total serum IgG concentration versus time profiles between adolescents in cohort 1 (n=8) of study 80202135MYG2001 (based on the data up to 23 August 2024) and adults in Study MOM-M281-011 (n=96)



The final adult model was adapted for the adolescent PK-IgG modelling analysis. The PK components of the adult PK/RO/IgG (described in PD section.) were adapted to consider the expected age- and weight-related changes in the baseline FcRn in the paediatric gMG population. While binding affinity of nipoalimab to the FcRn receptor and internalization of the complex were assumed to be the same between paediatrics and adults, the total amount of FcRn receptors normalized by body weight is assumed to be higher in paediatric populations at lower ages relative to adult populations. Baseline FcRn was therefore considered a function of age and body weight for adolescents aged 12 to <18 years, instead of a single value as for adults. The VPC Plots of Serum Nipoalimab Concentrations Using the Adapted Population PK-IgG Model for Adolescents in Study MYG2001 is presented in Figure 9.

For the nipoalimab effect on IgG turnover in paediatrics, please refer to PD section.

Figure 9. VPC Plots of serum Nipocalimab concentrations using the adapted population PK-IgG model for adolescents in Study MYG2001



CI=confidence interval; C_{max} =maximum serum nipocalimab concentrations; C_{trough} =predose serum nipocalimab concentrations; IgG=total serum immunoglobulin G; PI=prediction interval; PK=pharmacokinetics; VPC=visual predictive check.

Upper panels: VPC for C_{max} ; lower panels: VPC for C_{trough} .

Solid green lines are the 50th percentiles of the observed maximum (postinfusion) and predose (trough) serum nipocalimab concentrations and blue open circles are the observed serum nipocalimab concentrations. Purple shaded areas are the 95% CI of the predicted 50th percentile and green shaded areas are the 90% PI (5th to 95th percentiles). Orange bars represent the bins based on the x-axis.

Pharmacokinetic interaction studies

As an IgG1 antibody that selectively binds to the FcRn with high specificity and high affinity, nipocalimab is not anticipated to alter the activity of drug-metabolizing enzymes (e.g., Cytochrome P450 enzymes) nor drug transporters. Thus, no “conventional” drug-drug interactions mediated via drug metabolizing enzymes and/or drug transporters are expected.

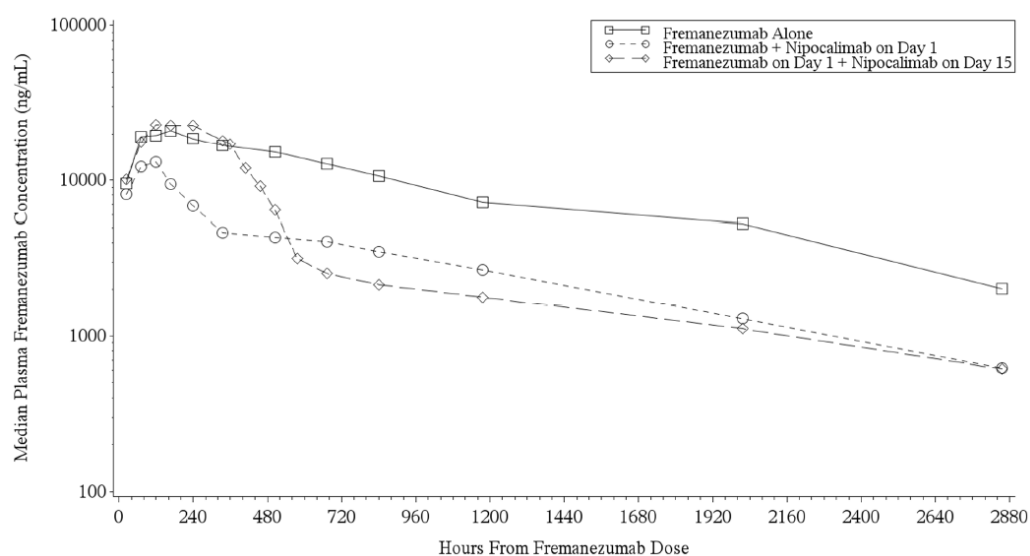
However, it is important to emphasize that nipocalimab still has a drug-drug interaction (DDI) potential due to its mechanism of action (i.e., its binding to FcRn and a general reduction of circulating IgGs). Hence, nipocalimab has a potential to act as a “perpetrator” of DDIs with other concomitantly administered IgG-based medicines. Therefore, the applicant has performed two dedicated DDI Phase I studies MOM-M281-008 and 80202135EDI1003 to investigate these perpetrator aspects of nipocalimab. A brief overview of PK aspects and PK results of these two DDI studies is presented below.

MOM-M281-008 was a Phase I dedicated DDI study to investigate nipocalimab as a potential “perpetrator” which could affect the systemic exposure of a “victim” drug - fremanezumab as a representative IgG-based therapeutic. The applicant included one treatment arm A with fremanezumab

alone, and another treatment arm B with simultaneous administration of fremanezumab and nipocalimab on the same day (Day 1). In addition, the applicant has also included third treatment arm C, to investigate the “offset” DDI effect of nipocalimab in which fremanezumab was administered on Day 1 and nipocalimab two-weeks after that (i.e., on Day 15). Nipocalimab was administered in the study as a single IV infusion of 30 mg/kg.

Overall, the study results have implied a significant reduction of fremanezumab systemic exposure when co-administered with nipocalimab (in both B versus A, and C versus A treatment arm comparisons). AUC of fremanezumab decreased to a greater extent when nipocalimab was administered on the same day (i.e., fremanezumab AUC decreased by about 66%) compared to the “offset” administration of nipocalimab at Day 15 (i.e., where fremanezumab AUC decreased by about 53%). It is also worth noting that C_{max} of fremanezumab decreased by about 42% when co-administered with nipocalimab on the same day, while C_{max} did not seem to be impacted by nipocalimab when nipocalimab was given two-weeks after the fremanezumab dose.

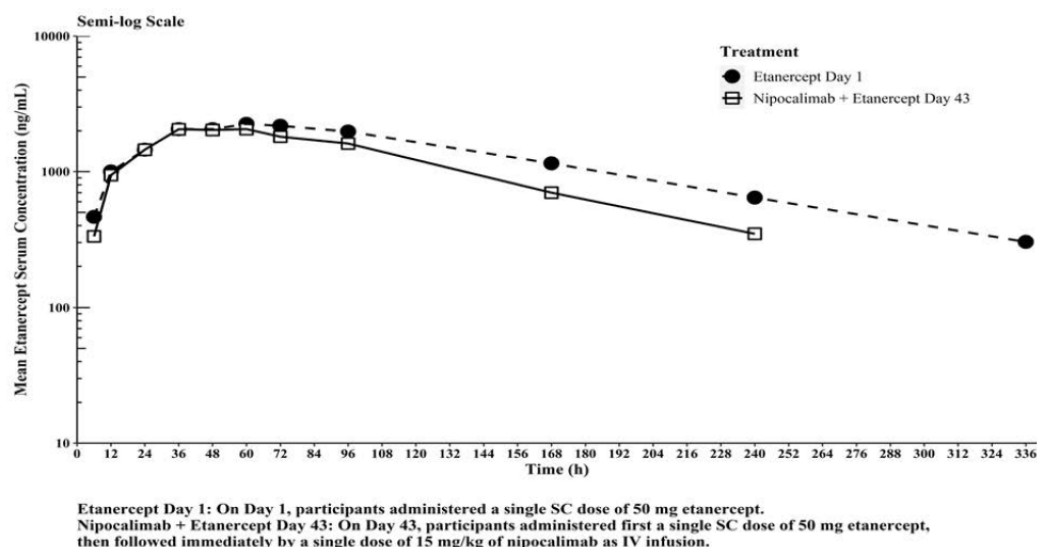
Figure 10. Median plasma fremanezumab concentration-time profiles following administration of treatments A, B and C (Semi-Log Scale). Study MOM-M281-008



Study 80202135EDI1003 was another dedicated DDI study. This study was conducted with etanercept (as a potential “victim” drug) because etanercept contains a Fc portion of human IgG1 and therefore its systemic exposure can potentially be impacted by nipocalimab. Nipocalimab was administered at doses of 15 mg/kg as IV infusion (corresponding to its proposed therapeutic maintenance dosing regimen). Three nipocalimab doses were administered during the study period in order to ensure the achievement and maintenance of steady-state nipocalimab levels and thereby provide its potentially maximum DDI impact as a perpetrator.

The study results have implied decrease in etanercept systemic exposure as a consequence of nipocalimab co-administration. C_{max} and AUC of etanercept with co-administration of nipocalimab were approximately 0.91 and 0.72-fold, respectively, compared to without the co-administration of nipocalimab (on Day 1).

Figure 11. Semi-logarithmic mean serum concentration-time profiles of etanercept at day 43 (with nipocalimab) and at day 1 (without nipocalimab); (Part 1; Study 80202135EDI1003)



Pharmacokinetics using human biomaterials

No dedicated *in vitro* PK studies/experiments were conducted with nipocalimab regarding its metabolism, DDI aspects nor other PK-related aspects.

2.6.2.2. Pharmacodynamics

Mechanism of action

Nipocalimab is a fully human IgG1 monoclonal antibody that selectively binds to FcRn with high specificity and high affinity at both neutral (extracellular) and acidic pH (intracellular) resulting in the reduction of circulating IgG, including IgG autoantibodies without affecting other immunoglobulins (IgA, IgE or IgM). In MG specifically, IgG autoantibodies impair neuromuscular transmission by binding to AChR, MuSK or LRP4, leading to a decreased transmission of the brain impulse to the muscle.

Primary and Secondary pharmacology

Following 30 mg/kg IV on Day 1 and 15 mg/kg IV Q2W from Week 2 in the Phase 3 study in participants with gMG, rapid and sustained reductions in total IgG were observed. The observed median (IQR) predose percent reduction in total IgG from baseline was 74.6% (79.4%; 68.7%) at Week 2 and 68.8% (75.3%; 62.2%) at Week 24.

Similar to reductions in total IgG, rapid and sustained reductions in all IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were also observed in participants with gMG. The observed median predose percent reductions in IgG1, IgG2, IgG3, and IgG4 from baseline were 67.5%, 69.1%, 57.1%, and 54.5%, respectively, at Week 24.

Similar to reductions in total IgG, rapid and sustained reductions in anti-AChR binding autoantibodies were also observed in participants who were seropositive for anti-AChR autoantibodies at baseline. Reductions in anti-MuSK levels were observed in participants who were seropositive for anti-MuSK autoantibodies at baseline. Rapid and sustained reductions in total IgG and in IgG1 and IgG3 subclasses associated with anti-LRP4 autoantibodies were observed during the DB phase through Week 24 for the 2 anti-LRP4+ participants in the nipocalimab group.

No changes in IgA, IgE, or IgM levels were observed following treatment with nipocalimab.

In healthy humans, the half-life of serum albumin is approximately 21 days. This unusually long half-life is regulated by FcRn [2]. This regulation occurs via pH-dependent engagement by the receptor, directing recycling or transcytosis across polarized cell layers and resulting in rescue of albumin from intracellular degradation.

Antibody-based drugs targeting the IgG binding site on FcRn block the interaction of FcRn with endogenous IgG but some have also been shown to have an effect on serum albumin concentration as well. Reductions of albumin has been demonstrated in phase 1, phase 2, and phase 3 studies of nipocalimab.

A Proof-of-concept (POC) and randomized, DB placebo-controlled trial of another FcRn targeted drug was evaluated for the treatment of thyroid eye disease [6]. This effect on lipid levels have not been described for FcRn targeted drugs currently approved for treatment of gMG.

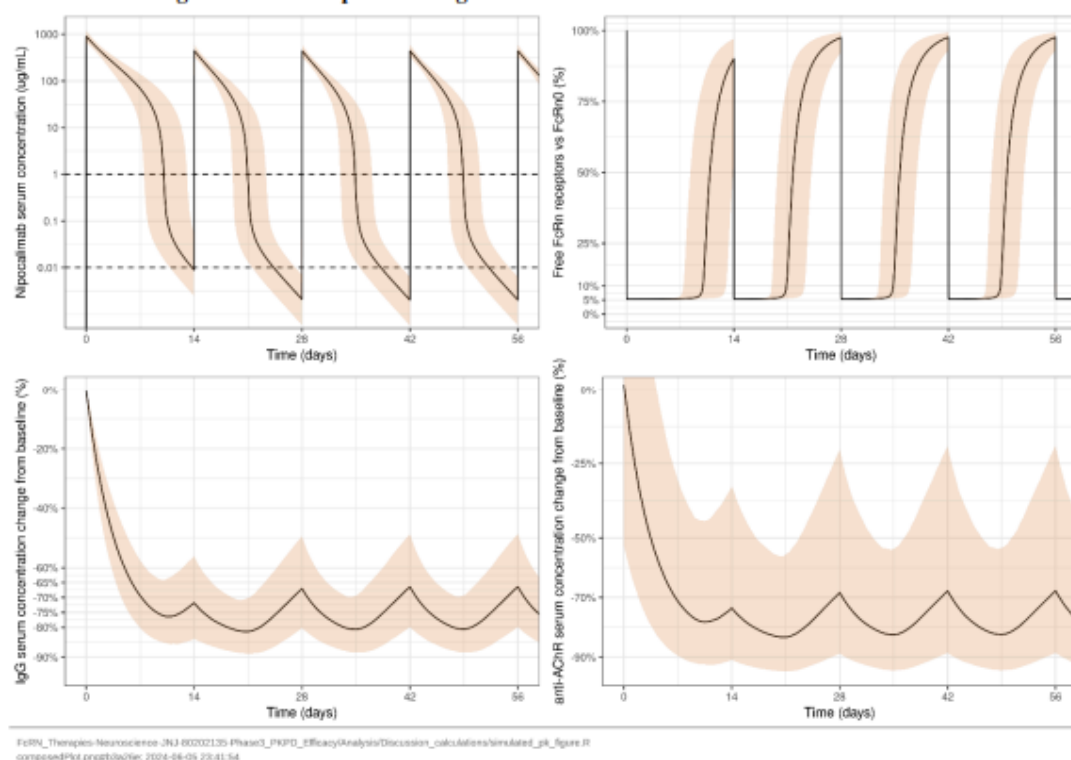
Relationship between plasma concentration and effect and safety

Binding of nipocalimab to FcRn receptor inhibits IgG recycling. The applicant has described the relationship between the plasma concentrations, binding to FcRn and subsequent reduction in IgG and Anti-AChR Autoantibodies using model-based analysis.

For the PK-IgG model, an indirect response model, that empirically accounts for the FcRn-induced IgG recycling, was used to describe the time course of total serum IgG concentrations and its variability after nipocalimab IV administration in HVs and participants with gMG. A sequential modelling approach was used, where the individual PK, RO, and IgG parameters (empirical Bayesian estimates) were fixed to those obtained with the PK-IgG model. The PK-IgG model was extended to describe the time course of anti-AChR autoantibody concentrations in the Phase 3 study through a linear relationship between anti-AChR autoantibodies reduction from baseline and total serum IgG reduction from baseline. The model included the correlation between the longitudinal changes from baseline in total serum IgG and anti-AChR autoantibodies. In addition, the time course of absolute Myasthenia Gravis-Activities of Daily Living (MG-ADL) change from baseline and its variability in participants with gMG receiving nipocalimab IV administration were quantitatively characterized by a linear relationship between nipocalimab-induced MG-ADL change from baseline and percentage total serum IgG change from baseline (in a virtual effect compartment). In addition, the limited data from adolescent were used as external evaluation to show that the model could capture the median IgG change. The model slightly overpredicts the IgG change from baseline for the Phase 3 IgG adult population, but adequately captures the observations from Phase 2 and HV data. The models describe the change in Anti-AChR antibody and MG-ADL change sufficiently well. The model parameter relative standard error (RSE)% and inter-individual variability (IIVs) are low to moderate.

The applicant used the developed models to illustrate the relationship between nipocalimab exposure, FcRn occupancy, reduction from baseline in IgG and Anti-AChR Autoantibody.

Figure 12. Time profiles for serum Nipocalimab concentration, FcRn RO; total serum IgG reduction from baseline and anti-AChR autoantibody reduction from baseline for phase 3 dosing regimen in participants with gMG



AChR=acetylcholine receptor; FcRn=neonatal Fc receptors; gMG=generalized myasthenia gravis;

IgG=immunoglobulin G; RO=neonatal Fc receptor occupancy

Black line represents model-predicted median and shaded areas represent 95% prediction intervals for serum nipocalimab concentration (top left), FcRn RO (top right), total serum IgG reduction from baseline (bottom left) and anti-AChR autoantibody reduction from baseline (bottom right) for the Phase 3 dosing regimen in participants with gMG.

The selected safety endpoints for the E-R safety analysis were the incidence of hypoalbuminemia, hyperlipidemia, serious or severe infections, serious adverse events (SAEs), headache, muscle spasms and peripheral oedema over the DB 24-week period. For dichotomous endpoints, the univariate logistic regression analysis was conducted to assess association between the exposure metric(s) and AE(s). The event was treated as a binary variable (presence or absence). The corresponding odds ratio (OR), 95% CI, and p-values were calculated. For continuous endpoints, a regression analysis was conducted, where linear models were investigated. The corresponding parameters, 95% confidence interval (CI), and p-values were calculated. As only Phase 3 data were used in the safety exposure-response (E-R) analysis, only exposures achieved within the 15 mg/kg-treatment arm are presented. No clear relationship between exposure and safety endpoints within the 15 mg/kg-treatment arm were found.

The applicant also conducted a univariate linear regression analysis for serum Albumin, total cholesterol change from baseline (CFB), and low density lipoprotein (LDL) CFB vs mean predose IgG CFB at Steady-State, for the Pooled Phase 2 and Phase 3 data (Table 6).

Table 6. Parameters of the univariate linear regression analysis for serum albumin, total cholesterol CFB, and LDL CFB vs mean predose IgG CFB at steady-state, for the pooled phase 2 + phase 3 data

Variable	Parameter	Phase 3, incl placebo	Phase 3, no placebo	Phase 3+ Phase 2, no placebo	Phase 3+ Phase 2, incl placebo	Lower 95% CI	Upper 95% CI	p-Value
Median albumin concentration (g/L)	Intercept (g/L)	44.7	41.7	44.2	44.7	44.1	45.2	4.81e-239***
	Slope (g/L per 10% IgG CFB)	0.339	-0.0996	0.422	0.483	0.368	0.597	7.45e-15***
Median total cholesterol CFB (%)	Intercept (%)	-2.09	-3.17	-5.47	-2.42	-4.32	-0.525	1.25e-02*
	Slope (% per 10% IgG CFB)	-1.78	-1.99	-2.44	-1.93	-2.32	-1.54	3.96e-19***
Median LDL CFB (%)	Intercept (%)	0.575	3.48	-5.87	-0.576	-3.71	2.56	7.18e-01
	Slope (% per 10% IgG CFB)	-1.68	-1.34	-2.76	-1.89	-2.53	-1.24	2.54e-08***

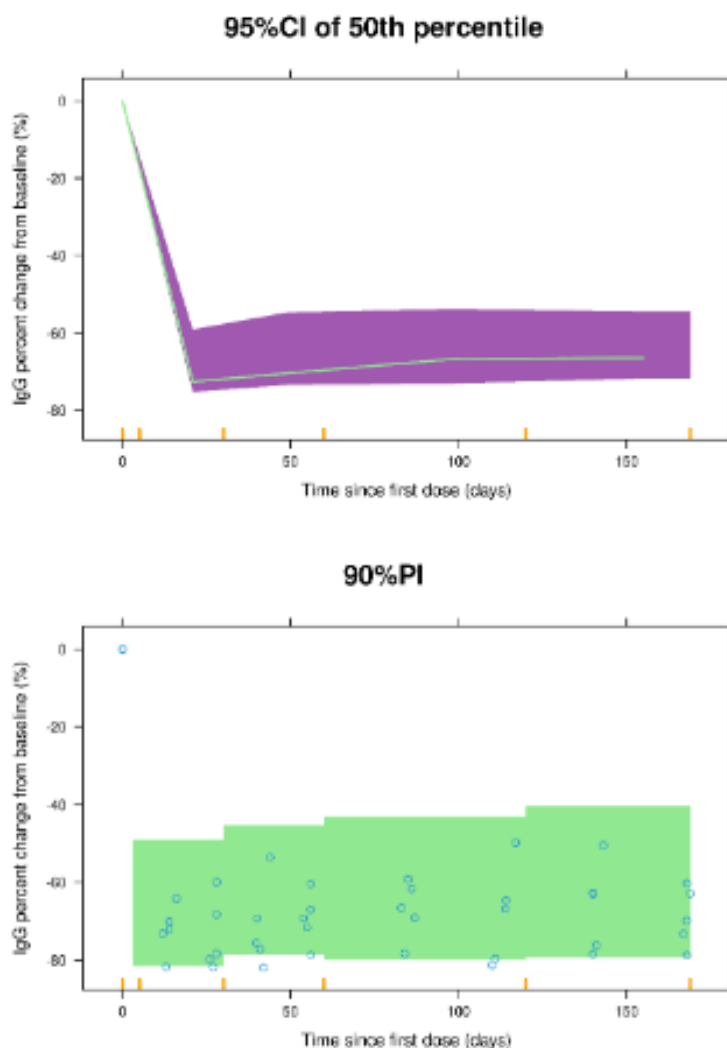
CFB=change from baseline; CI=confidence interval; IgG=immunoglobulin G; LDL=low-density lipoprotein.

*=p<0.05; **=p<0.01; ***=p<0.001

Paediatric population

The adapted final adult model (including the expected age- and weight-related changes in the baseline FcRn in the paediatric gMG population) was used to describe the effect of nipocalimab on IgG turnover. The effect of nipocalimab on IgG turnover was assumed to be identical between adults and paediatrics. Although the baseline total amount of IgG is known to be different for the paediatric population (ie, 2 to <12 years), the IgG baseline has similar values in adolescents (12 to <18 years of age) and adults. Also, the relationship between IgG and anti-AChR was assumed to be identical between adolescents and adults. The VPC Plots of Serum Nipocalimab Concentrations Using the Adapted Population PK-IgG Model for Adolescents in Study MYG2001 is presented in Figure 13.

Figure 13. VPC plots of total IgG percent change from baseline using the adapted population PK-IgG model for adolescents in study MYG2001



CI=confidence interval; IgG=total serum immunoglobulin G; PI=prediction interval; PK=pharmacokinetics; VPC=visual predictive check.

Solid green line is the 50th percentile of the observed total IgG percent change from baseline and blue open circles are the observed total IgG percent change from baseline. The purple shaded area is the 95% CI of the predicted 50th percentile and the green shaded area is the 90% PI (5th to 95th percentiles). Orange bars represent the bins based on the x-axis.

2.6.3. Discussion on clinical pharmacology

Nipocalimab is a fully human, aglycosylated IgG1/ λ mAb that binds to the IgG binding site on human FcRn at both neutral and acidic pH to inhibit IgG recycling.

The initially proposed indication for nipocalimab was as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are antibody positive (anti-acetylcholine receptor [AChR], anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor 4 [LRP4]). During the evaluation, the applicant has agreed on the restriction of the indication to those with antibody positive either against AChR or MuSK. The proposed dosing regimen for nipocalimab in adults and adolescents is an initial single dose of 30 mg/kg administered IV, followed by a maintenance dose of 15 mg/kg every 2 weeks thereafter.

Analytical methods

The immunoassay methods used to determine nipocalimab in human serum samples, and to assess ADA and NAb to nipocalimab in human serum samples can overall be considered adequately validated for the intended purpose.

ADME properties

NCA was applied by the applicant in those Phase I clinical studies which implemented rich PK sampling. On the other hand, Phase II and Phase III studies have only implemented "sparse" PK sampling and therefore were not used for the NCA PK analysis. Population PK analysis was used where applicable.

Nipocalimab is intended to be administered as an IV infusion.

In vitro distribution studies (such as plasma protein binding and distribution to red blood cell of nipocalimab) were not performed, which is regarded acceptable for an IgG antibody. Volume of distribution of nipocalimab was estimated from the population PK as well as from non-compartmental PK analysis where applicable. Overall, the small volume V_{ss} of 2.84 L indicates that nipocalimab is primarily retained in the systemic blood circulation with limited extravascular tissue distribution. This is in line with general IgG distribution characteristics.

The proteolytic degradation is expected for nipocalimab (i.e., as an IgG antibody), and therefore the lack of dedicated studies characterizing the elimination processes of nipocalimab is acceptable. Following a single IV administration of 15 mg/kg of nipocalimab, the mean clearance is 0.0627 L/h and half-life is 29.3 hours. The selected parameter values are taken from the non-compartmental analysis conducted in the Phase I study 80202135EDI1006, and are considered adequate to be included in the SmPC.

Several Phase I studies have implied non-linearity aspects of nipocalimab. Generally, C_{max} appeared to increase dose-proportional with increasing nipocalimab doses, while AUC seemed to increase more than dose-proportional. Overall, it can be concluded that nipocalimab PK parameters obtained across different SAD cohorts in Phase I studies demonstrated dose-dependency and implied TMDD.

The applicant has not presented data on time-dependency. It is important to emphasize that according to the proposed therapeutic regimen of nipocalimab (i.e., maintenance dose of 15 mg/kg given every 2 weeks) no accumulation is expected after its repeated dosing. Clinical data from Phase II and Phase III studies implementing the proposed therapeutic regimen of nipocalimab have demonstrated that nipocalimab systemic levels drop below the lower limit of quantification prior to the administration of each maintenance dose.

Population PK analysis in adults (HV and gMG patients)

A population PK analysis was used to characterise the PK of nipocalimab in healthy volunteers and patients. The primary goals of the population PK and PK/PD modeling analyses were to: (1) characterize the PK profiles of nipocalimab; (2) explore the relationships between serum nipocalimab concentrations, FcRn receptor occupancy, total serum IgG, and anti-AChR autoantibodies; and (3) quantitatively evaluate how intrinsic and extrinsic factors influence the PK and PD (reduction in total serum IgG and anti-AChR autoantibodies) of nipocalimab after IV administration in adults with gMG. The applicant had a stepwise modelling approach (the model was updated as more data became available) with reasonable decision making during the model development, using adequate numerical and visual evaluation tools. The model development is deemed appropriate. The final population PK model incorporated data from five Phase 1 studies involving healthy volunteers (M281-001, M281-007, M281-010, EDI1001, and EDI1002), one Phase 2 study in gMG participants (M281-004), and the pivotal Phase 3 gMG study (M281-011). The final model, that includes the phase 3 patient data is presented, as the focus is on description of the PK in patients with gMG, and as this is the model used for description of pharmacokinetics and exposure in adolescents. The time course of serum nipocalimab concentrations and the associated

variability were quantitatively characterized in HVs and participants with gMG receiving IV dosing of nivalimab using an open 2-compartment disposition model with nonspecific linear distribution to a peripheral compartment and parallel linear and nonlinear FcRn-mediated clearance, which was modelled using the QSS approximation of the general TMDD model. The clearances (CL and intercompartmental flow) and volumes of distributions (Vc and Vp) were scaled allometrically with fixed theoretical exponents of 0.75 and 1.00, respectively.

For the final model, the RSE% were very low, while the shrinkage in CL and baseline FcRn were quite high; 35% and 44%, respectively, which is not unexpected with inclusion of sparse sampled data. The shrinkage of Vc was lower, 11%. The %RSE were derived from the variance-covariance matrix. The 95%-CIs were provided for the final model parameter estimates. None contained the null value. As shrinkage on CL is high, the covariate analysis should be cautiously interpreted. In addition, the high shrinkage may also have high impact on the interpretation of the results from the PK/PD models. Five outliers (three from M281-011 and two from M281-001 with CWRES >|6|) were excluded, and a sensitivity analysis was performed. While the exclusion did not affect parameter estimates, it increased parameter uncertainty. The removal of these outliers is considered justified. The proportion of BLQ data was substantial (~38%). BLQ data were handled using the M3 method in the population PK model. Separate additive residual errors were estimated for bioanalytical assays with different LLOQs. BLQ observations were excluded from standard GOF plots, and in VPC, BLQ observations were included and displayed in a separate panel showing the proportion of BLQ. The handling of BLQ data is considered appropriate. The Phase 3 pre-dose BQL data appear to not be well captured (predicts approximately 50% BQL instead of as observed approximately 90%). The 40% of the observed predose BQL (<0.010 µg/mL) serum nivalimab concentrations in the Phase 3 study that were predicted to be above the lower limit of quantification (≥0.010 µg/mL), were predicted to be below 1 µg/mL. The standard GOF plots of nivalimab serum concentrations for the final PK model (all studies and Study M281-011) show no major model misspecifications. Due to computational limitations, the full covariate modeling approach, although used in previous modeling steps, was abandoned, and a stepwise covariate modeling approach was implemented with forward inclusion criteria of $p < 0.01$ and backward elimination criteria of $p < 0.001$. Only the effects of race/ethnicity on CL, Vc, and FcRn baseline were found to be statistically significant. IIV was included on linear serum clearance, Vc, and total (free) FcRn receptor at baseline and estimated at 19.0%CV, 14.7%CV and 15.4%CV, respectively. IIV was included for linear CL, the Vc, and total (free) FcRn receptor at baseline (FcRn0), with estimates of 19.0% CV, 14.7% CV, and 15.4% CV, respectively. Shrinkage was high for CL at 34.4% and FcRn0 at 43.8%, but low for Vc at 10.8%. ETA distributions appear to confirm the assumption of normality. The overall model performance was confirmed based on the prediction-corrected VPCs, suggesting no significant trends across the different percentiles, with the exception of overprediction predose samples. The final population PK model is not considered able to reliably predict predose samples (C_{trough}). Separate residual unexplained variabilities are estimated for Phase 1, Phase 2 and Phase 3 data. This makes interpretation of the model difficult. The applicant has not described potential differences between HVs (that mainly informed the model PK-parameters) and the patients in phase 3 with respect to distribution/elimination. As patients with gMG underwent sparse sampling (both in phase 2 and phase 3 studies), a difference in CL between HVs and patients may be hard to separate. As implemented in the model, the main difference appears to be on Vc, however, the difference has not been divided on HVs and patients as one Vc was simultaneously estimated for Phase 1 (HVs) and phase 2 data (gMG patients), and one Vc for phase 3 data (gMG patients). There appears to be some difference in the exposure in the gMG patients in the Phase 3 study, however, the reason for this difference could not be identified. The model appears to adequately predict the C_{max} exposures, however overpredicts the C_{trough} concentrations, indicating that the elimination rate may possibly be different in gMG patients, compared to healthy volunteers. Body weight was tested as a covariate on baseline FcRn (FcRn0). It remains unclear if there may be a difference in total FcRn0 with bodyweight. Bodyweight was investigated as a covariate on IgG and not found to have a significant impact. The FcRn

at baseline was only measured in Phase 1 studies MOM-M281-001, 80202135EDI1001, and 80202135EDI1002 in healthy participants and not in Phase 2 and 3 studies in patients with gMG. The reported RO model was informed by the PK and IgG data in patients with gMG under the assumption of similar RO dynamics between gMG patients and healthy participants. The model estimated baseline FcRn and RO should be interpreted with caution.

The applicant has not specified a therapeutic window of nipocalimab. With respect to efficacy, the maintenance dose of 15 mg/kg resulted in a mean (range) IgG change from baseline (%) of -69.7 (-87.0; -38.1) versus 60 mg/kg (Phase 2 study data) which resulted in a -82.5 (-87.2; -63.0), respectively. The applicant did not consider the further decrease in IgG to be clinically relevant. Long-term effects of the higher dose are unknown. With respect to safety, there is an association between higher dose and change in LDL and cholesterol. However, the Phase 2 study was a short-term study that does not provide information on the long-term consequences of this change.

Special populations

No dedicated clinical studies in subjects with hepatic impairment or renal impairment were conducted which is regarded acceptable considering that nipocalimab is an IgG antibody. The population PK model included data from clinical trial participants from 18 to 81 years. The participants were grouped into 3 age ranges: 18-44 years (n = 144), 45-64 years (n = 96), 65-74 years (n = 28) and > 75 years (n = 12). Age was not identified as a relevant covariate in the population PK analysis. Body weight was determined to have a clinically relevant impact on nipocalimab exposure.

Paediatrics

Study 80202135MYG2001 is an ongoing clinical study in the patient population below 18 years of age. The study provides only sparse PK data which are collected at the end of infusion (i.e., C_{eoi}) and prior to the maintenance dose administrations (i.e., C_{trough}). The current data cut-off date was 23 August 2024. The population PK analysis describes the PK of nipocalimab in adolescents with gMG enrolled in Cohort 1 of Study MYG2001. The aims were to characterize the population PK in adolescents with gMG (Cohort 1; aged 12 to <18 years) and compare with those in adults with gMG and to confirm that the adult dose regimen (ie, 30 mg/kg IV followed by 15 mg/kg IV Q2W) is appropriate for adolescents with gMG (aged 12 to <18 years). As there is limited efficacy and safety data from adolescent subjects, the approval in adolescents has to rely partly on exposure-matching between adolescents (from 12 years and 30 kg) and adults with gMG (i.e. extrapolation of efficacy and safety from adults to adolescents based on exposure matching).

While the proposed posology appears to be adequate for adolescents, this conclusion is based on an adult model and limited data from gMG patients from age 12 and 30 kg. The applicant made several assumptions: a) The applicant claims that baseline FcRn varies with age and bodyweight for subjects 12 to <18-year-old, based on one publication. It is unclear if there is a true difference in FcRn with age and body weight, however, the implemented equation appears to not result in major differences in predicted exposure in adolescents. A sensitivity analysis indicated that the adaptation only results in a minor impact on the PK-profile; b) Baseline IgG levels and IgG dynamics are assumed to be the same in adolescents as in adults; c) PK IIV is assumed to be the same in adolescents as in adults. This is acceptable and often implemented in cases where limited paediatric data is available as further information on this is not possible to attain; d) Nipocalimab and target (FcRn) interaction is same in adolescents as in adults. While it is likely that the structure and function of FcRn is similar, there is no literature data on this. The assumption is accepted with some uncertainty. The model could describe the limited adolescent concentrations without further model refinement. The applicant has provided simulations for adolescents using both the adult [unadapted] model and [adolescent] adapted model, showing limited impact of the assumption of changing FcRn with body weight and age on C_{max} . The simulations show that the expected C_{max} in adolescents from 35-95 kg falls within the 5th and 95th

exposure observed in adults. In addition, the applicant has boxplots which compares C_{eoi} , C_{trough} , after the loading dose and at steady state, of adolescents in the MYG2001 study with the corresponding data from the pivotal adult study MOM-M281-011. Furthermore, similar boxplots were provided comparing the total levels of IgG change in the two populations after loading dose and at steady state. The boxplots show that the C_{eoi} (C_{max}) after first dose and steady state, and C_{trough} after the loading dose is comparable in the two populations. Furthermore, also the total level of IgG change in adolescents was in range with that of the adult population. Overall, it has been demonstrated that PK and PD in adolescents is comparable with adults. The data thus supports the PK and PD driven paediatric extrapolation of nipocalimab. The exposure in adolescents is expected to be comparable to the exposure in adults of similar body weights.

Interactions

As an IgG1 antibody that selectively binds to the human FcRn, nipocalimab is not expected to be involved in “conventional” DDIs mediated via drug metabolizing enzymes (e.g. CYP enzymes) nor drug transporters. However, due to its mechanism of action (i.e., its binding to FcRn and a general reduction of circulating IgGs) nipocalimab has a potential to act as a “perpetrator” of DDIs with other concomitantly administered IgG-based medicines.

Two dedicated DDI studies with nipocalimab as a “perpetrator” (study MOM-M281-008 and 80202135EDI1003) provided PK data about “victim” drugs fremanezumab (representative IgG-based mAb) and etanercept (drug containing a Fc portion of human IgG1). According to the obtained clinical DDI data, nipocalimab can lower the systemic exposure of IgG-based medicines and a corresponding information is provided in 4.5 section in its SmPC.

Nipocalimab has implied a potential to lower the systemic levels of albumin in the clinical studies. Therefore, due to its impact on albumin levels there is also a DDI potential to impact the PK of other (concomitantly administered) highly albumin-bound drugs. The applicant was therefore asked to further justify the absence of DDI risks between nipocalimab and highly albumin-bound drugs. Considering the overall data and a relatively mild magnitude of albumin reductions (i.e., the mean percent reduction of albumin from the baseline values was -7.2% in the Phase III study), it can be assumed that this would not be reflected in a significant increase of unbound drug fractions (f_u) and therefore no relevant consequences from a PK perspective. In addition, some supportive clinical data are also available with highly albumin-bound drugs that were concomitantly administered with nipocalimab in the Phase III study. No adverse effects that could be related to highly-albumin bound drugs were seen in the study.

Immunogenicity

The applicant has presented the ADA status per timepoint for studies EDI1006, M281-011 and MYG2001, allowing for an assessment of the kinetics of ADA development and persistence. Additionally, spaghetti plots of nipocalimab concentrations over time stratified by ADA status and/or titer have also been presented.

Study EDI1006 (PK similarity study; Process 2.0 vs Process 3.0): The incidences of ADA were slightly higher in the Process 3.0 intervention arms compared with the Process 2.0 intervention arms at every timepoint. There were no differences in serum nipocalimab concentrations over time observed between ADA-positive and ADA-negative participants.

Study MOM-M281-011 (adult participants with gMG): The incidence of ADA appeared to be diminished over time. There were no differences in serum nipocalimab concentrations over time observed between ADA-positive and ADA-negative participants.

Study 80202135MYG2001 (adolescent participants with gMG): Only 1 participant was ADA-positive through the end of study visit. The ADA-positive sample with very low titer (1:10) was observed prior to

nipocalimab administration at Week 2. After Week 2, no additional samples were tested positive for ADA. Serum nipocalimab concentrations over time in the ADA-positive participant were within the range of serum nipocalimab concentrations in ADA-negative participants.

Relationship between exposure and response - model-based assessment

PK-IgG model: An indirect response model, that empirically accounts for the FcRn-induced IgG recycling, was used to describe the time course of total serum IgG concentrations and its variability after nipocalimab IV administration in HVs and participants with gMG. The population PK and RO parameters were fixed to those obtained after modelling only the PK and RO data, while the population IgG parameters were estimated in presence of the PK and RO data. The parameters were estimated with a low RSE%. The final GOF plots and VPCs indicate that the model can capture most of the observed IgG data; however, there appears to still be a slight overprediction of the median total IgG change-from-baseline (CFB) for the Phase 3 study M281-011. A sequential modelling approach was used, where the individual PK, RO, and IgG parameters (empirical Bayesian estimates) were fixed to those obtained with the PK-IgG model. Despite the small overprediction of the median CFB IgG for Phase 3 patients, the model is considered good enough for use of characterisation of Anti-AChR and MG-ADL, as further model-based analyses are not pivotal for the assessment of benefit-risk of this treatment.

The PK-IgG model was extended to describe the time course of anti-AChR autoantibody concentrations in the Phase 3 study through a linear relationship between anti-AChR autoantibodies reduction from baseline and total serum IgG reduction from baseline. The model included the correlation between the longitudinal changes from baseline in total serum IgG and anti-AChR autoantibodies, and its link with the absolute CFB in MG-ADL in the Phase 3 Study M281-011. Model-predicted median anti-AChR autoantibody average CFB was –78.4% over the entire dosing interval period, with a pre-dose value of –69.9%, consistent with the observed values and similar to the IgG lowering effects at the same dose level, but more variable.

The time course of absolute MG-ADL change from baseline and its variability in participants with gMG receiving nipocalimab IV administration were quantitatively characterized by a linear relationship between nipocalimab-induced MG-ADL change from baseline and percentage total serum IgG change from baseline (in a virtual effect compartment). The parameters were estimated with a moderate to low RSE%. The model could reasonably well predict the median of the MG-ADL change-from-baseline, however the percentiles were not as well predicted, especially for the placebo treated arm in study M281-011. A 70% decrease in pre-dose total serum IgG CFB was predicted to result in a 1.19-point (95% CI: 0.74 to 1.78), 1.69-point (95% CI: 1.14 to 2.25) and 2.48-point (95% CI: 1.59 to 3.60) decrease in placebo-corrected MG-ADL absolute CFB for participants with baseline MG-ADL scores of 6 (5th percentile of baseline score), 9 (50th percentile of baseline score) and 14 (95th percentile of baseline score) points, respectively.

Safety Exposure-response analysis: The selected safety endpoints for the E-R safety analysis were the incidence of hypoalbuminemia, hyperlipidemia, serious or severe infections, SAEs, headache, muscle spasms and peripheral oedema over the DB 24-week period.

An exposure-safety analysis with data from gMG patients from the Phase 2 Study M281-004 pooled with the Phase 3 study data was performed. The analysis was focused on median albumin concentrations and change in cholesterol and LDL versus mean predose IgG change from baseline. Nipocalimab at the recommended maintenance dose of 15 mg/kg Q2W presents changes in albumin, total cholesterol, and LDL. There is an association between dose of nipocalimab and change in cholesterol, LDL and albumin. Statins as comedication were not found to have a significant effect on the slope and intercept of the E-R relationship for total cholesterol and LDL.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of nipocalimab is adequately characterised in healthy volunteers and patients with gMG.

2.6.5. Clinical efficacy

Study ID Status First Patient First Visit; Completion date	Study Phase	Number of Treated Participants
MOM-M281-011 Start Date:15 Jul 2021 End Date: DB phase completed. OLE phase ongoing. (OLE phase data through cutoff of 23 August 2024)	Phase 3	DB Phase Total: 196 - Nipocalimab: 98 - Placebo: 98 OLE Phase - Nipocalimab Ph3: 176 - Nipocalimab Ph2 rollovers: 19
80202135MYG2001 Cohort 1 Start Date:20 Jul 2022 End Date: Study ongoing (Primary CSR: Cohort 1 data through cutoff of 23 August 2024)	Phase 2/3	Total: 7 ATP Nipocalimab:5
MOM-M281-004 Start Date:18 Dec 2018 End Date: Completed: 25 Jun 2020 Participants who completed the study had the option to enrol in the OLE study MOM-M281-005.	Phase 2 POC	Total: 68 Nipocalimab: 54 • 5 mg/kg Q4W: 14 • 30 mg/kg Q4W:13 • 60 mg/kg single dose: 13 • 60 mg/kg Q2W: 14 Placebo: 14

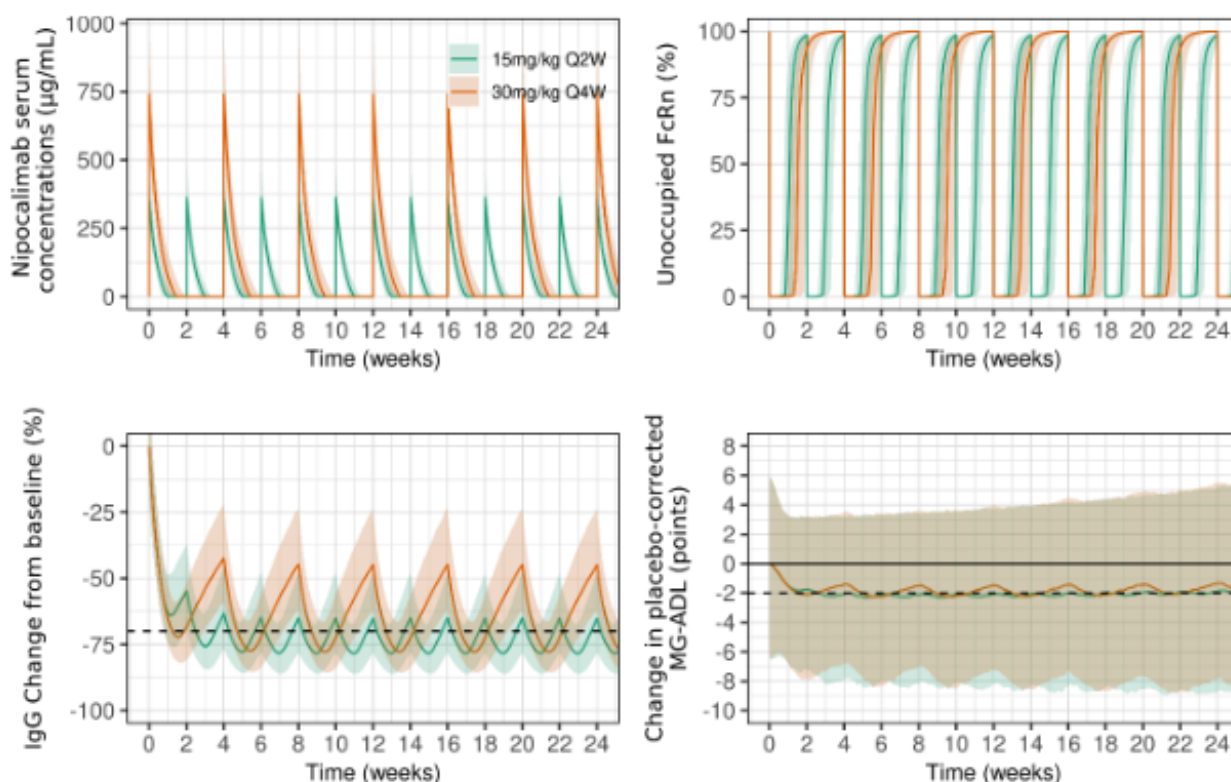
2.6.5.1. Dose response study

The chosen dose level and dosing regimen for the Phase 3 study in participants with gMG of 30 mg/kg IV loading dose on Day 1 followed by 15 mg/kg IV Q2W maintenance doses from Week 2 was based on observed data from the Phase 2 study and extensive modelling and simulation of the dose response relationships for IgG and MG-ADL.

The dose regimens evaluated in the Phase 2 study (5 mg/kg Q4W, 30 mg/kg Q4W, 60 mg/kg single dose, and 60 mg/kg Q2W), i.e. not the final posology chosen for the Phase 3 study (M281-011). Together with data from the five Phase 1 studies in healthy participants (M281-001, M281-007, M281-010, EDI1001, and EDI1002) a population PK, PK-IgG and MG-ADL simulations were conducted with the aim to support the nipocalimab IV dose regimen selected for the Phase 3 pivotal study in adult participants with gMG (for details on model-based analysis please refer to PK and PD sections).

It was predicted that the IV dose of 15 mg/kg Q2W, starting 2 weeks after a 30 mg/kg IV loading dose was the lowest Q2W dose that provided rapid, deep (>90%), and sustained FcRn inhibition during the first 6 days of the 2 weeks dose interval period in 68% of participants. This would lead to an average total serum IgG change from baseline of around -70% and provide a clinically meaningful reduction of 1.95 points in the placebo-corrected absolute MG-ADL score change from baseline in participants with gMG, assuming a mean (range) of 9.8 (6 - 24) points in baseline MG-ADL distribution. The results presented in Figure 14 supported that at identical total dose, it is better to administer lower doses more frequently, as 15 mg/kg Q2W provided markedly better IgG and MG-ADL reductions than 30 mg/kg Q4W.

Figure 14. Simulated PK, RO, IgG, and MG-ADL over time profiles after Nipocalimab IV 15 mg/kg Q2W vs 30 mg/kg Q4W in participants with gMG



FcRn=neonatal Fc receptors; gMG=generalized myasthenia gravis; IgG=immunoglobulin G; MD-AGL=myasthenia gravis activities of daily living; PK=pharmacokinetic; Q4W=every 4 weeks; RO=receptor occupancy.

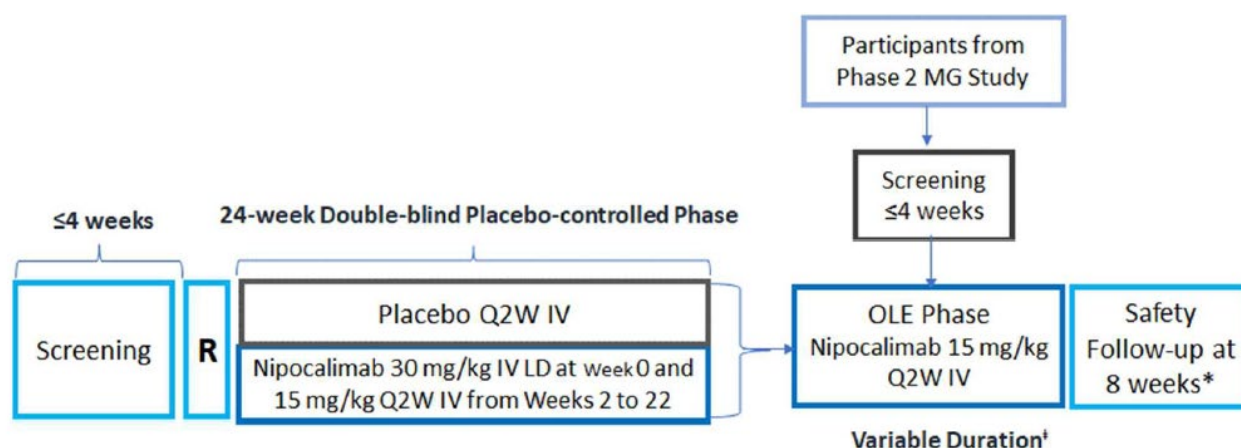
2.6.5.2. Main study

MOM-M281-011: A multicenter, randomized, double blind, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥18 years) with gMG inadequately controlled with standard-of-care therapy

Methods

Study MOM-M281-011 was a Phase 3, multicenter, randomized DB, placebo-controlled study to evaluate the efficacy and safety of nipocalimab compared to placebo in participants with gMG who are inadequately controlled with SoC therapy. The study consisted of a screening phase of up to 4 weeks, a 24-week DB, placebo-controlled phase, and an OLE phase of variable duration for participants outside the EU. Within the EU, participants will continue treatment until 192 weeks after the DB phase of the study has completed. The OLE phase is currently ongoing and data from this phase, up to the clinical cut-off date of 23 August 2024 , are included in the results summarized below (supportive studies).

Figure 15. Study design



R: randomization into double-blind phase (1:1); LD: loading dose; OLE: open-label extension

* Participants who withdraw or discontinue after receiving any amount of study intervention are required to complete a safety follow-up visit 8 weeks after their last dose.

† In the EU, the OLE phase will be up to 192 weeks.

A schematic overview of Study MOM-M281-011 is provided in the figure above. Comprehensive descriptions of the design, methodology, study endpoints, and statistical methods were included in the clinical study report (CSR).

The Full Analysis Set included both seropositive and seronegative participants.

This study was conducted at 81 centers that enrolled participants in Australia (1), Belgium (5), Canada (3), China (10), Czech Rep (3), Denmark (1), France (3), Germany (2), Italy (5), Mexico (2), Japan (14), Poland (5), S. Korea (3), Spain (7), Sweden (2), Taiwan (2), and US (13).

• Study Participants

Main Inclusion Criteria (Amendment 1: 21 July 2022, Amendment 2: 11 January 2023):

Age

1. Criterion modified per Amendment 1 (clarification of age).

1.1 ≥ 18 years of age at the time of consent, and as applicable, must also meet the legal age of consent in the jurisdiction in which the study is taking place.

Type of Participant and Disease Characteristic

2. Criterion modified per Amendment 2; 11 January 2023 (Added footnote to clarify that the study is no longer recruiting seronegative participants)
 - 2.1 Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for gMG as defined by the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II a/b, III a/b, or IV a/b at screening.¹
3. MG-ADL score of ≥ 6 at screening and baseline.
4. Criterion modified per Amendment 1; 21 July 2022 (clarification of type and timing of immunosuppressants).

¹ Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG-related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

4.1 Has suboptimal response to current stable therapy for gMG according to the investigator. Stable therapy is defined as the following, as applicable to their specific therapy(ies):

- a. If taking an acetylcholinesterase inhibitor, the participant must have been on a stable dose and regimen for at least 2 weeks prior to screening. Changes to the dose of acetylcholinesterase inhibitors may be permitted if medically necessary during any phase of the trial.
- b. If taking a glucocorticosteroid, the participant must have been on a stable dose and regimen for at least 4 weeks prior to baseline.
- c. If currently receiving immunosuppressants, the participant must have been on the given immunosuppressant for ≥ 6 months and on a stable dose for ≥ 3 months prior to baseline. Allowed concomitant immunosuppressants are azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.

OR

Has discontinued corticosteroids and/or immunosuppressants/immunomodulators including eculizumab or other novel approved immune agents at least 4 weeks prior to screening due to intolerance or lack of efficacy.

Note: All above background medications must be optimized and unchanged for the duration specified in Criteria #4 prior to screening and/or baseline visits. Investigators are encouraged to consider all treatment escalation options, including thymectomy, prior to enrolling. Participants started on new treatments must meet the above stable dose duration rules, and cannot meet exclusion criterion #6.

5. A participant using herbal, naturopathic, traditional Chinese remedies, ayurvedic or nutritional supplements, or medical marijuana (with a doctor's prescription) is eligible if the use of these medications is acceptable to the investigator. These remedies must remain at a stable dose and regimen from baseline through the DB placebo-controlled phase of the study.

6. Criterion modified per Amendment 1.

6.1 Participants who have undergone splenectomy (if local regulatory authority has not requested exclusion of participants with splenectomy) must be at least 3 months post resection prior to screening and must be vaccinated as per the United States Center for Disease Control and Prevention annual Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States. (<https://www.cdc.gov>) OR must be vaccinated as per country- or territory-specific guidelines or local regulations.

Note: This criterion is not applicable if splenectomy is excluded by the local authority.

7. Criterion modified per Amendment 1.

7.1 Is recommended to be up to date on all age-appropriate vaccinations prior to screening as per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) coronavirus 19 (COVID-19) vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labeling, guidelines, and standards-of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment.

Main Exclusion Criteria

A full list has been provided. Here, the main criteria are presented. Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Coexisting Medical Conditions or Past Medical History

1. Criterion modified per Amendment 1; 21 July 2022

1.1 Has a history of severe and/or uncontrolled hepatic (e.g, viral/alcoholic/autoimmune hepatitis/cirrhosis and/or metabolic liver disease), gastrointestinal, renal, pulmonary, cardiovascular, psychiatric, neurological musculoskeletal disorder, hypertension, any other medical disorder(s) (e.g, diabetes mellitus), or clinically significant abnormalities in screening laboratory, that might interfere with the patient's full participation in the study, and/or might jeopardize the safety of the participant or the validity of the study results.

Note: Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participants (e.g, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.

2. Has any confirmed or suspected clinical immunodeficiency syndrome not related to treatment of his/her gMG, or has a family history of congenital or hereditary immunodeficiency unless confirmed absent in the participant.
3. Criterion modified per Amendment 1 (Clarified that to be eligible for the study, participants should not meet the definition of Clinical Deterioration).
 - 3.1 Has MGFA Class I disease or presence of MG crisis (MGFA Class V) at screening, history of MG crisis within 1 month of screening, or fixed weakness (and/or 'burnt out' MG). (Note: Participants should not be actively deteriorating at the screening or baseline visit such that they meet the criteria for Clinical Deterioration).
4. Is dependent on gastric tube for nutritional needs or is ventilator-dependent.
5. Is actively undergoing radiation or chemotherapy for an unresected thymoma/malignant thymoma. Participants with stable, benign thymoma (stage I or IIa, for example) for which no treatment has been undertaken in the past 3 years may be allowed following discussion with the sponsor's medical monitor.
6. Has had a thymectomy within 12 months prior to screening, or thymectomy is planned during the study.
7. Has current or a history of any neurologic disorder other than MG that might interfere with the accuracy of study assessments, including but not limited to any chronic neurodegenerative disease, altered level of consciousness, dementia, abnormal mental status, major congenital neurologic defect, Lambert-Eaton myasthenic syndrome, drug induced MG, or hereditary forms of myasthenic syndrome.
8. Currently has a malignancy or has a history of malignancy within 3 years before screening (with the exception of localized basal cell carcinoma and/or squamous cell carcinoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months [defined as a minimum of 12 weeks] before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention administration).

9. Has known allergies, hypersensitivity, or intolerance to nipocalimab or its excipients (refer to the IB).
10. Has shown a previous severe immediate hypersensitivity reaction, such as anaphylaxis to therapeutic proteins (e.g, mAb).
11. Has experienced myocardial infarction, unstable ischemic heart disease, or stroke within 12 weeks of screening.
12. Is planning to father a child while enrolled in this study or donate sperm within 90 days after the last administration of study intervention.
13. Is currently breastfeeding, pregnant, intends to become pregnant during the study, or is planning egg donation during the study or within 30 days after the last dose of study intervention.
14. History of moderate or severe substance or alcohol use disorder according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) criteria, except nicotine or caffeine, within 1 year before screening.

Concomitant or Previous Medical Therapies Received

15. Criterion modified per Amendment 1 (Added eculizumab or other novel therapeutic agents to prohibited therapies).
 - 15.1 Is currently taking eculizumab or other novel immune agents, IgG Fc-related protein therapeutics, or Fc-conjugated therapeutic agents, including factor or enzyme replacement.
16. Has received, rituximab within 6 months prior to first administration of study intervention.
17. Criterion modified per Amendment 1 (added referral to 33).
 - 17.1 Has received, or is expected to receive, a live vaccine within 4 weeks prior to screening or has a known need to receive a live vaccine during the study, or within 8 weeks after the last administration of study intervention. For the Bacille Calmette Guerin (BCG) vaccine, see exclusion criterion 33. Participants are allowed to receive a vaccine conditionally approved by their regional health advisory for emergency use for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), unless it is a live vaccine. Concomitant enrollment in an investigational trial for any SARS-CoV-2 (COVID-19) vaccine while participating in this study is not permitted.
18. Has received plasmapheresis, immunoadsorption therapy, or IVIg within 6 weeks prior to baseline.
19. Has another medical condition that requires oral or parenteral corticosteroids unless the dose has been stable for at least 4 weeks prior to baseline and is expected to remain stable during the study. Inhaled, intra-articular, topical or ocular corticosteroids are not exclusionary.
20. Has another medical condition that requires an immunosuppressive agent unless the medication has been used for at least 6 months, the dose has been stable for at least 3 months prior to baseline and the medication and the dose are expected to remain stable during the study.
21. Has previously received nipocalimab.

Prior/Concurrent Clinical Study Experience

22. Has received an investigational intervention (including investigational vaccines) within 3 months or 5 half-lives (whichever is longer) or used an invasive investigational medical device within 3 months before the planned first dose administration of study intervention [or is currently enrolled in an investigational study]. Participants are allowed to receive a vaccine conditionally approved by their regional health advisory for emergency use for SARS-CoV-2.

Infections or Predisposition to Infections

23. Has a severe infection including opportunistic infections (e.g, pneumonia, biliary tract infection, diverticulitis, *Clostridium difficile* infection, cytomegalovirus, pneumocystosis, aspergillosis, etc.) requiring parenteral anti-infectives and/or hospitalization, and/or is assessed as serious/clinically significant by the investigator, within 8 weeks prior to screening. The participant may be rescreened after the 8-week exclusionary period has passed.
24. Has a chronic infection (e.g, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or requires chronic treatment with anti-infectives (e.g, antibiotics, antivirals).
25. Tests positive for hepatitis B virus infection.
26. Is seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy 1 of the following conditions:
- Has a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment, and has a negative HCV RNA test result at screening,
- OR
- While seropositive, has a negative HCV RNA test result at least 24 weeks prior to screening and a negative HCV RNA test at screening.
27. History of being human immunodeficiency virus (HIV)1 or HIV2 antibody-positive, or tests positive for HIV at screening.
28. COVID-19 infection

Infections or Predisposition to Infections

29. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening (Granulomatous infection added per Amendment 1; 21 July 2022).

• **Treatments**

Eligible participants were randomized in a 1:1 ratio to receive either placebo or nipocalimab by IV infusion at 30 mg/kg for the Day 1 loading dose followed by 15 mg/kg Q2W thereafter during the 24-week DB phase.

Rescue therapy

Clinical Deterioration was defined as any of the following:

- An MG crisis, defined as MG-related weakness sufficiently severe to necessitate intubation, or requires noninvasive ventilation to avoid intubation, or would be severe enough to delay extubation following surgery (Sanders 2016), with the respiratory failure being due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness may accompany respiratory muscle weakness, or may be the predominant feature in some patients.
- An MG flare, exacerbation or deterioration reflected by worsening in MG strength or clinical assessment scores, warranting hospitalization or MG rescue therapy. Of note, an MG worsening

in strength or clinical assessment scores that does not warrant hospitalization or rescue therapy would not be considered clinical deterioration.

- Any participant whom the investigator believed will jeopardize his/her health if MG rescue therapy is not given (e.g, emergent situations).

In participants experiencing a clinical deterioration, the use of rescue therapy (IV Ig, plasmapheresis) was permitted, as per the clinical judgment of the investigator. The use of other medications as rescue therapy, such as increasing doses of background SoC medications, or prescribing oral or IV corticosteroids, was not permitted.

- Objectives and endpoints**

Primary and key secondary objectives of the Phase 3 study M281-011 and the corresponding endpoints are summarized in Table 7.

Table 7. Primary and key secondary objectives and the corresponding endpoints

Objective of Study M281-011	Endpoints (Outcome Measures) of Study M281-011
Primary Objective	
To evaluate the efficacy of nipocalimab compared to placebo based on the MG-ADL scale, in seropositive gMG participants	Average change from baseline in MG-ADL score over Weeks 22, 23, and 24 of DB phase.
Key Secondary Objectives	
To evaluate the efficacy of nipocalimab compared to placebo based on the quantitative myasthenia gravis (QMG) scale, in seropositive gMG participants	Average change in QMG score over Weeks 22 and 24 of DB phase.
To evaluate the effect of nipocalimab compared to placebo in <u>achieving the minimum clinically important difference (MCID) or better</u> based on the MG-ADL scale, in seropositive gMG participants	Percentage of participants whose average improvement in MG-ADL total score over Weeks 22, 23, and 24 of DB phase is at least a 2-point improvement compared to baseline.
To evaluate the <u>efficacy of nipocalimab loading dose</u> compared to placebo based on the MG-ADL scale, in seropositive gMG participants	Percentage of participants with improvement in MG-ADL total score ≥ 2 points at Week 1 and/or Week 2 of DB phase.
To evaluate <u>sustainability of therapeutic response</u> of nipocalimab compared to placebo based on the MG-ADL scale, in seropositive gMG participants	Percentage of participants with improvement in MG-ADL total score ≥ 2 points at Week 4 through Week 24 of DB phase with no more than 2 non-consecutive excursions allowed between Week 6 through Week 23 (excursion defined as loss of improvement in MG-ADL score ≥ 2 points from baseline).
To evaluate the effect of nipocalimab compared to placebo on the <u>percentage of participants achieving $\geq 50\%$ symptom improvement</u> based on the MG-ADL scale, in seropositive gMG participants	Percentage of participants whose average improvement in MG-ADL total score over Weeks 22, 23, and 24 of the DB phase is at least a 50% improvement from baseline.
The relationship between IgG lowering and MG-ADL and QMG was also assessed in the study.	

Myasthenia Gravis –Activities of Daily Living The MG-ADL is administered by a trained qualified healthcare professional (e.g, physician, physician assistant, nurse practitioner, nurse) and provides a rapid assessment of the patient’s MG symptom severity. The MG-ADL should be administered by the same healthcare professional for a given participant throughout the study. In certain circumstances a change in rater may be permitted when it is unavoidable (e.g, rater left the institution, rater unavailable for several weeks, etc). It is recommended that the reasons for an upcoming rater change be discussed in advance with the sponsor, if possible. The assessment should be performed at approximately the same time of day from screening Visit, throughout the study. The participant’s acetylcholinesterase inhibitor

dose must be withheld for approximately 12 hours or longer prior to performing MG-ADL at all visits, and attempts made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior. Eight functions (talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair, double vision, eyelid droop) are rated on a 4-point scale. The total score can range from 0 to 24. A higher score indicates greater symptom severity.

Quantitative Myasthenia Gravis

The QMG test is a standardized quantitative strength assessment comprising 13 components (and is administered by a trained qualified healthcare professional e.g, physician, physician assistant, nurse practitioner, nurse). The QMG should be administered by the same healthcare professional for a given participant throughout the study. In certain circumstances a change in rater may be permitted when it is unavoidable (e.g, rater left the institution, rater unavailable for several weeks, etc). It is recommended that the reasons for an upcoming rater change be discussed in advance with the sponsor, if possible. The assessment should be performed at approximately the same time of day from Screening Visit throughout the study. The participant's acetylcholinesterase inhibitor dose must be withheld for approximately 12 hours or longer prior to performing QMG at all visits, and attempts made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior. The quantitative results of each strength component are mapped to the following 4-point scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. The total score can range from 0 to 39. A higher score indicates greater weakness.

Table 8. Other secondary objectives

To evaluate sustainability of therapeutic response of nipocalimab compared to placebo based on the QMG scale, in seropositive gMG participants, when treatment is taken as directed.	☐ Percentage of participants with improvement in QMG of ≥ 3 points from baseline at Week 2 through Week 24 of the DB placebo-controlled phase with no more than 2 non-consecutive excursions allowed at Weeks 4 through 22 (excursions defined as loss of improvement in QMG score of ≥ 3 points from baseline).
To evaluate the effect of nipocalimab compared to placebo on fatigue based on the Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue scale, in seropositive gMG participants when treatment is taken as directed.	☐ Average change from baseline in the Neuro-QoL Fatigue total score over Weeks 22 and 24 of the DB placebo-controlled phase.
To evaluate the effect of nipocalimab compared to placebo on health-related quality of life based on the Revised Myasthenia Gravis Quality of Life –15 (MG-QoL15r) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) scale, in seropositive gMG participants when treatment is taken as directed.	☐ Average change from baseline in the MG-QoL15r score over Weeks 22 and 24 of the DB placebo-controlled phase. ☐ Change from baseline in the visual analog scale and health status index of the EQ-5D-5L over 24 weeks of the DB placebo-controlled phase.
To evaluate the effect of nipocalimab compared to placebo on gMG minimum symptom expression based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed.	☐ Percentage of participants with MG-ADL score of 0 or 1 over time in the DB, placebo-controlled phase. ☐ Percentage of participants with MG-ADL score of 0 or 1 at any time during the DB, placebo-controlled phase. ☐ Percentage of participants with MG-ADL score of 0 or 1 at 50% of timepoints during the DB, placebo controlled phase

Revised Myasthenia Gravis Quality of Life –15

The MG-QoL15r is a patient-reported outcome instrument that measures MG-specific health-related quality of life. The MG-QoL15r contains 15 items that evaluate patients' experience related to Myasthenia Gravis over the "past few weeks" on a 3-point Likert-type scale (0=Not at all; 1=Somewhat; 2=Very much). The total score can range from 0 to 30. A higher score indicates more limitation.

Neuro-QoL-Fatigue

The Neuro-QoL Fatigue version 1.0 is a 19-item questionnaire developed and validated for use in common neurological conditions which assesses patient-reported fatigue and associated impact on physical, mental, and social activities during the past 7 days (Health Measures n.d.). Each item included in the Neuro-QoL Fatigue questionnaire is graded on a 5-point Likert-type scale (1=Never; 2=Rarely; 3=Sometimes; 4=Often; 5=Always) with higher scores reflecting more fatigue. The total raw scores are calculated by summing 19 items and raw score is converted to a T-score.

EuroQol 5-Dimension 5-Level

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems). The participant selects an answer for each of the 5 dimensions considering the response that best matches his or her health “today.” The descriptive system can be represented as a health state. The EQ-VAS self-rating records the respondent’s own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

- **Sample size**

A sample size of 75 seropositive participants per group was needed to provide at least 90% power to detect standardized effect sizes of at least 0.57 at a two-sided significance level of 0.05, assuming a drop-out rate of 20% at Week 24. A standardized effect size of 0.57 was based on estimates of between-group differences (≥ 1.7) and standard deviations (approximately 3) from clinical trial simulations of the MG-ADL total score. The sample size calculation was based on a mixed effects model for repeated measures (MMRM) assuming 12 post-baseline assessments over 24 weeks and a constant within-participant correlation of 0.5 (Lu 2008; Donohue 2020) in a two-armed, DB placebo-controlled study.

The sample size of 75 participants per group also provided at least 90% power to detect a standardized effect size of at least 0.57 for the QMG key secondary endpoint (corresponding to a between-group difference of approximately 2.9).

- **Randomisation and blinding (masking)**

All eligible participants were centrally assigned/randomized in a 1:1 ratio to study intervention using an interactive web response system in this study. Participants were randomly assigned to 1 of 2 intervention groups (nipocalimab or placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization was balanced by using randomly permuted blocks and was stratified by autoantibody status (anti-AChR positive and/or anti-MuSK positive, anti-AChR negative and anti-MuSK negative), Day 1 MG-ADL total score (≤ 9 >9), and region (East Asia, US, ROW).

The participant, investigator, and sponsor were blinded to study treatment for the duration of the blinded period. An unblinded site pharmacist was responsible for storage, preparing, and documentation of the study intervention for infusion while all other site personnel remained blinded. Selected data was handled with special care to minimize any potential impact on blinding/bias. This included masking/segregating the data in question from view by the investigators, clinical team, or others as appropriate until the primary analysis CSR was completed.

- The following measurements obtained after screening (during the DB period) were masked to the investigator, study team members and participants during study conduct: nipocalimab

concentrations, total serum IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4), IgA, IgM, IgE, anti-AChR/anti-MuSK/anti-LRP4 autoantibodies, ADA, total serum protein, and serum albumin.

- The following measurements remained masked to the investigator, study team members, and participants during the DB placebo-controlled phase: serum lipid profiles, c-reactive protein, complement proteins (C3, C4, CH50, C5a), circulating immune complexes, and striational antibodies.

Given that albumin laboratory results were masked, the investigator and sponsor was notified if their patient meet the laboratory criteria for hypoalbuminemia. These hypoalbuminemia adverse event of special interest (AESI) cases was handled similarly to an SAE for reporting purposes and reviewed by the data monitoring committee as they occurred. Similarly, the investigator and sponsor were alerted if LDL and/or triglycerides were significantly elevated.

A given participant's treatment assignment could be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board, and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions. If a participant was unblinded by the site, the information was to be entered in the appropriate section of the eCRF and in the participant's source documents.

The blind were maintained until the last participant completed the DB placebo-controlled phase Week 24 evaluations (or the last participant completed their last visit in DB placebo-controlled phase), and the data was locked. Investigative sites and participants were remained blinded to initial intervention assignment until after the primary analysis CSR was completed. Participants who have had their intervention assignment unblinded continued to return for scheduled evaluations.

• Statistical methods

Estimands

Different primary estimands for the primary endpoint were defined for submissions to European Union (EU), Japan, and US/Rest of World (US/ROW). For a given estimand, the attributes, including strategies for ICEs, will apply to all participants from every region. The primary estimand of a given region will be supplementary estimands for the other regions.

Table 9: Estimands for primary objective (EU)

Population	Seropositive participants with gMG who are on a stable MG therapy or who discontinued MG therapy due to intolerance or lack of efficacy.
Treatment condition<s>	Assignment to Nipocalimab 30 mg/kg loading dose followed by 15 mg/kg every 2 weeks in addition to stable gMG therapy, compared to assignment to matching Placebo in addition to stable gMG therapy, regardless of discontinuation or changes in assigned treatment or stable gMG therapy, in the hypothetical scenario of no rescue medication.
Endpoint (variable)	Average change from baseline in MG-ADL total score over Weeks 22, 23, and 24 of the DB phase.
Population-level summary	The difference in mean average change from baseline over Weeks 22, 23, and 24 of the DB phase between the nipocalimab and placebo intervention groups
Intercurrent events (ICE) and strategy to handle them	
Discontinuation of study intervention or stable gMG therapy	Treatment policy strategy
Changes in stable gMG therapy	Treatment policy strategy
Initiation of rescue therapy	Hypothetical strategy

The estimand for the QMG Total score over weeks 22 and 24 endpoint followed the same approaches as defined for the primary endpoint.

The estimands for binary key secondary endpoints based on MG-ADL score followed a composite strategy for all ICEs with the endpoint defined as “non-response” at timepoints after the ICE.

Analysis sets

Table 10. Analysis sets

Analysis Sets	Description
Enrolled	All participants who sign the ICF.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set	The full analysis set includes all randomized participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Full Analysis Set (OL)	The full analysis set (OL) includes all participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase
Primary Efficacy Analysis Set	The primary efficacy analysis set includes all randomized seropositive participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Anti-AChR Positive Efficacy Analysis Set	The anti-AChR positive efficacy analysis set includes all randomized anti-AChR positive participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Seropositive Efficacy Analysis Set (OL)	The seropositive efficacy analysis set (OL) includes all seropositive participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase
Safety (DB)	The safety analysis set includes all randomized participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Safety (OL)	The safety analysis set (OL) includes all participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase
Safety	The safety analysis set includes all participants who received at least 1 dose (partial or complete) of any study intervention in either the double-blind or OLE phase
All Nipocalimab	The all nipocalimab analysis set includes all participants who received at least 1 dose (partial or complete) of nipocalimab in either the double-blind or OLE phase
Pharmacokinetics (PK) Analysis Set	The PK analysis set is defined as all participants who received at least 1 complete dose of nipocalimab in either the double-blind or OLE phase and have at least 1 valid post-dose blood sample drawn for PK analysis
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all participants who received at least 1 dose (partial or complete) of nipocalimab in either the double-blind or OLE phase and have at least 1 post-dose serum sample evaluable for antibodies to nipocalimab
Pharmacodynamic (PD) Analysis Set	The PD analysis set is defined as all participants who received at least 1 dose (partial or complete) of nipocalimab in either the double-blind or OLE phase and have at least 1 valid post-dose blood sample drawn for PD analysis

The main analysis set for efficacy analyses was the *Primary efficacy analysis set* which included all randomized seropositive participants who received at least 1 dose (partial or complete) of any study intervention in the DB phase.

Analysis of primary endpoint

The primary efficacy endpoint (the average change from baseline in MG-ADL total score over Weeks 22, 23, and 24 of the DB phase) was analyzed using a MMRM with weekly change from baseline as the dependent variable, factors for study intervention group, autoantibody status ("anti-AChR positive or anti-MuSK positive" or "anti-AChR negative and anti-MuSK negative", as randomized), region, week, and study intervention group-by-week interaction; baseline MG-ADL total score as a covariate; and participant as a random effect. Baseline was defined as the arithmetic mean of the screening and Day 1 assessments. An unstructured variance-covariance matrix was used first. In case of convergence problems, alternative variance-covariance structures was used in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1). The Kenward-Roger method was used for approximating the denominator degrees of freedom. The between-group difference of the average change over Weeks 22, 23, and 24 was tested with an F-test of the linear contrast that averages the change from baseline over those time points.

Analysis of key secondary endpoints

Estimands and analysis methods, including sensitivity analyses, for the average change from baseline in QMG total score over Weeks 22 and 24 followed the same approaches defined for the primary endpoint above. Baseline QMG total score replaced baseline MG-ADL total score in the MMRM.

For each of the MG-ADL binary responder endpoint (as listed above), the percentage of participants who were responders according to the endpoint criteria was analyzed by Cochran-Mantel-Haenszel tests controlling for the baseline MG-ADL total score randomization strata (≤ 9 , > 9), autoantibody status, and region. Between-intervention differences in proportions and 95% Wald CI (based on the normal approximation) were provided.

Analysis of other secondary endpoints

Between-intervention differences in proportions of participants with **Sustained therapeutic QMG response** was calculated and 95% Wald CI of the difference (based on the normal approximation) were provided.

Analysis of the **Neuro-QoL Fatigue total score**, **Neuro-QoL Fatigue short-form total score**, and the **MG-QoL-15r total score** followed the approach, of the Primary Estimand for US/ROW (hypothetical strategy for all ICEs and missing at random (MAR) assumption) and analysis methods as for the primary endpoint. The between-group difference of the average change over Weeks 22 and 24 and its 95% CIs was estimated by a linear contrast that averages the change from baseline over those time points. Least squares (LS) mean estimates, with 95% CIs, of change from baseline at each time point were provided and displayed graphically over time by intervention group.

For **EQ-5D-5L**, the frequency distribution of scores for each item (Mobility, Self-Care, etc.) were summarized at each time point in the DB phase by study intervention group. Values and changes from baseline at each time point in the DB phase for the health status index and the visual analogue scale were summarized with descriptive statistics by study intervention group.

Handling of missing data

If there were participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns were created first by imputing the intermediate missing values using methods

such as the MCMC (Markov Chain Monte Carlo) method. MAR was assumed for intermediate missing data.

For monotone missing data Missing not at random (MNAR) was assumed in the nipocalimab group after the last observed value for participants who experienced an ICE. MAR was assumed for the placebo group. The "Copy Reference" multiple imputation (MI) estimator were used to impute missing data in the nipocalimab group after the last observed value for participants who experienced an ICE. By this method, the model-expected mean for imputations was derived as if the participant had always been a member of the placebo group.

Sensitivity and supplementary analyses

As a sensitivity analysis, the "Jump to Reference" MI estimator were used to impute missing data in the nipocalimab group after the last observed value for participants who experienced an ICE. By this method, the model-expected mean for imputations was derived under the nipocalimab group, but then shifted to be relative to the placebo group of the imputed visit, instead of relative to the nipocalimab group at the visit. Under this approach, nipocalimab participants were considered as not being treated any longer (and therefore being similar to placebo participants).

The analyses for the estimands for USA/ROW and Japan are to be considered as supplementary analyses.

Planned subgroup analyses

Subgroup analyses of MG-ADL total score were performed under the US/ROW- Estimand (equivalent to the Primary Estimand, except addressing all ICEs with a hypothetical MAR-strategy, as if these ICEs would not have occurred).

For each subgroup analysis, the subgroup variable was added as a main effect to the MMRM model defined for the primary Estimand, and study intervention-by-subgroup variable and study intervention-by-time point-by-subgroup variable interaction terms were also added. The between-intervention difference of the average change from baseline over Weeks 22, 23, and 24 at each level of the subgroup variable, and its 95% CI, was estimated from the MMRM with a linear contrast. Estimates and 95% CIs were displayed with forest plots, including only those levels of the subgroup variables with ≥ 5 participants in each study intervention group.

Subgroups analysed were: region (US, East Asia, and ROW), country/territory (Australia, France, Spain, Belgium, Germany, South Korea, Canada, Italy, Sweden, China, Japan, Taiwan, Czech Republic, Mexico, US, Denmark and Polen), age group (18 to <45 years, ≥ 45 to <65 years and ≥ 65 years), sex (female or male), race (white or non-white), body mass (normal, over weight and obese), autoantibody (seronegative or seropositive), autoantibody status (seronegative, Anti-AChR+, Anti-MuSK+ or Anti-LRP4+) baseline MG-ADL total score (≤ 9 or > 9), type of stable gMG therapy (with immunosuppressant or without), duration of gMG (≤ 5 or > 5 years), and age at onset of gMG (≤ 50 or > 50 years).

When country/territory was the subgroup variable, region was removed from the MMRM. When specific autoantibody status was the subgroup variable, autoantibody status as randomized was removed from the MMRM. When specific autoantibody status (negative, anti-AChR+, anti-MuSK+, or anti-LRP4+) or autoantibody positive/negative was the subgroup variable, the *Full analysis set* was used (ie not only seropositive participants as in the *Primary efficacy analysis set*).

Error probabilities, adjustment for multiplicity and interim analyses

The primary and key secondary null hypotheses were tested in a pre-specified hierarchical order to address the key secondary objectives based on the endpoints specified for those objectives. Family-wise Type 1 error was controlled at 0.05 within estimand and testing hierarchy for each region separately (USA, EU and Japan).

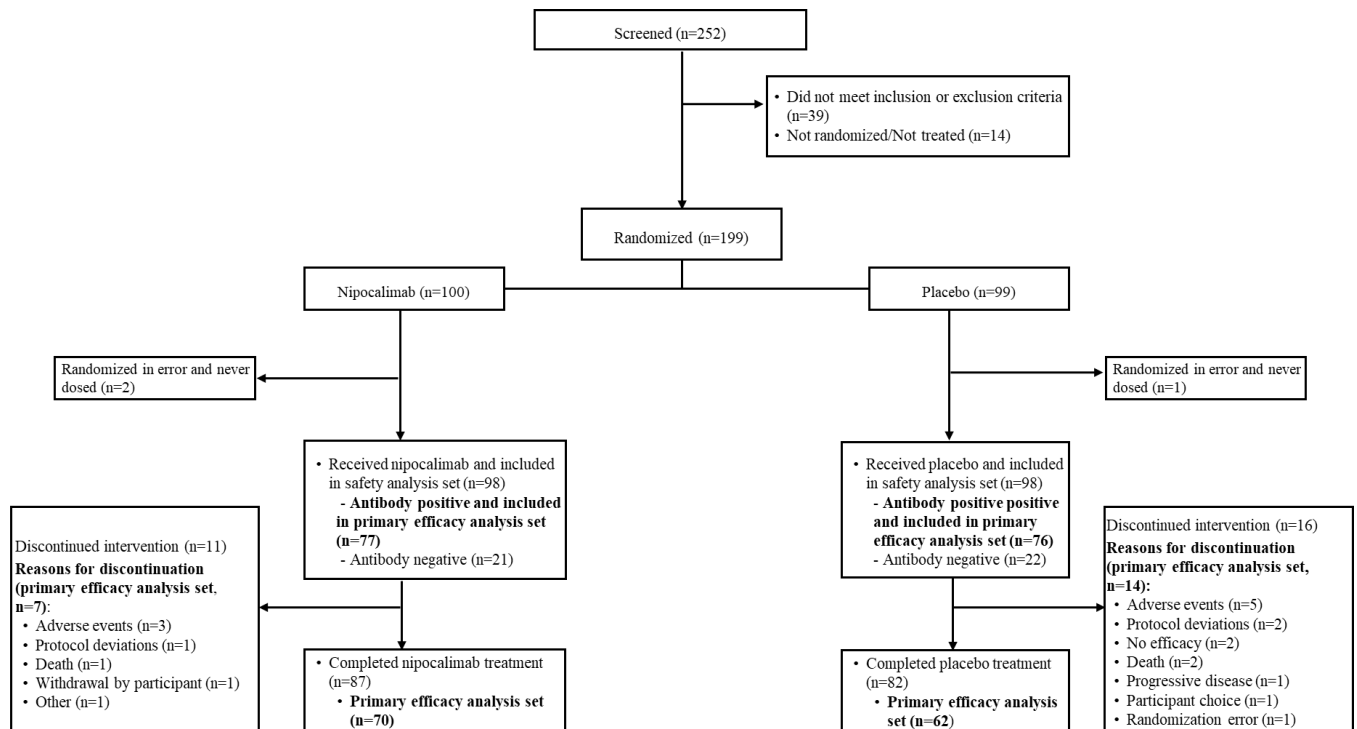
The 5 key secondary endpoints were analyzed sequentially and considered statistically significant at the 2-sided 0.05 level only if the endpoint was individually significant at the 2-sided 0.05 level and previous endpoints in the hierarchy were significant at the 2-sided 0.05 level, including the primary efficacy endpoint.

Results

• Participant flow

Participant disposition of study MOM-M281-011 is shown in Figure 16. Primary efficacy analysis set is shown in bold text.

Figure 16. Participant flow diagram (MOM-M281-011 Study)



Note: Primary efficacy analysis set is shown in **bold** text.

• Recruitment

Date first patient enrolled: July 15, 2021

Date last patient completed: OL phase is still ongoing.

Database lock eCRF data: November 17, 2023. During the procedure, additional data was provided with cut-off of 23 August 2024

• Conduct of the study

Table 11. Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document	Country/Territory Affected	Date
Amendment 3	All	15 AUGUST 2024
Amendment 2	All	11 JANUARY 2023
Amendment 1	All	21 JULY 2022

Original Protocol	All	19 MARCH 2021
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Changes in the conduct of the study that were implemented by protocol amendments are described in the protocol. Substantial changes in the conduct of the study are described below (Table 12). There were 2 global amendments.

Table 12. Protocol amendments

Amendment No. and Date	Substantive Changes to Study Conduct
Global Amendments	
Amendment 1, 21 July 2022	Addition of an exploratory endpoint for the use of an actigraphy watch to assess physical activity, mobility, and sleep at selected sites. Addition of 2 exclusion criteria (#33 and #34) to align with standard language across the nipocalimab program Clarifications from the latest sponsor protocol template to standardize language across the nipocalimab program
Amendment 2, 11 January 2023	Revision of the key secondary endpoints Removal of the 30mg/kg Q4W dosing option from the OLE Updating the protocol based on EU Clinical Trial Regulation

A summary of MPDs for the primary efficacy analysis set in the DB phase of the MOM-M281-011 study is shown below (Table 13).

Table 13. Summary of subjects with major protocol deviations in the DB screening or DB treatment phases; primary efficacy analysis set (Study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Primary Efficacy Analysis	76	77
Subjects with major protocol deviations in the DB screening or DB treatment phases	26 (34.2%)	17 (22.1%)
Entered but did not satisfy criteria	6 (7.9%)	5 (6.5%)
Received a disallowed concomitant treatment	6 (7.9%)	2 (2.6%)
Other	14 (18.4%)	11 (14.3%)

Note: Subjects may appear in more than one category.

A summary of the type of ICE by treatment group is provided in Table 14.

Table 14. Number and percentage of subjects intercurrent events; primary efficacy analysis set (Study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Primary Efficacy	76	77
Subjects with ICE events	14 (18.4%)	13 (16.9%)
ICE 1: Discontinuation of study intervention not due to initiation rescue medication	8 (10.5%)	5 (6.5%)
ICE 2: Discontinuation of study intervention due to initiation rescue medication	3 (3.9%)	2 (2.6%)
ICE 3: Discontinuation of stable gMG therapy not due to initiation of rescue medication	0	1 (1.3%)
ICE 5: Change in stable gMG therapy	3 (3.9%)	5 (6.5%)

- **Baseline data**

Across both treatment groups, most participants entered the study due to “lack of efficacy” on current MG medications (75 out of 76 participants in the placebo group and 74 out of 77 participants in the nipocalimab group). A few participants reported either “intolerance” or both “intolerance” and “lack of efficacy” on current medications upon study entry.

Overall, 55.6% of the participants were from the EU/ROW (Australia, Canada, and Mexico), 28.6% were from East Asia (China, Japan, South Korea, and Taiwan), and 15.8% were from the US (Full Analysis Set).

Table 15. Summary of demographics and baseline characteristics; primary efficacy

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W	Total
Analysis set: Primary Efficacy	76	77	153
Age, years			
N	76	77	153
Mean (SD)	52.3 (16.37)	52.5 (15.66)	52.4 (15.97)
Median	51.5	53.0	52.0
Range	(20; 81)	(20; 81)	(20; 81)
>=18-44	30 (39.5%)	21 (27.3%)	51 (33.3%)
>=45-64	27 (35.5%)	38 (49.4%)	65 (42.5%)
>=65-74	9 (11.8%)	12 (15.6%)	21 (13.7%)
>=75	10 (13.2%)	6 (7.8%)	16 (10.5%)
Sex			
N	76	77	153
Female	42 (55.3%)	50 (64.9%)	92 (60.1%)
Male	34 (44.7%)	27 (35.1%)	61 (39.9%)
Race			
N	76	77	153
American Indian or Alaska Native	0	1 (1.3%)	1 (0.7%)
Asian	25 (32.9%)	24 (31.2%)	49 (32.0%)
Black or African American	1 (1.3%)	1 (1.3%)	2 (1.3%)
White	47 (61.8%)	49 (63.6%)	96 (62.7%)
Not reported	3 (3.9%)	2 (2.6%)	5 (3.3%)
Ethnicity			
N	76	77	153
Hispanic or Latino	4 (5.3%)	8 (10.4%)	12 (7.8%)
Not Hispanic or Latino	69 (90.8%)	68 (88.3%)	137 (89.5%)
Not reported	3 (3.9%)	1 (1.3%)	4 (2.6%)
Weight, kg			
N	76	77	153
Mean (SD)	81.3 (20.20)	76.0 (16.73)	78.7 (18.66)
Median	78.0	75.7	75.8
Range	(43; 135)	(41; 124)	(41; 135)
Height, cm			
N	76	77	153
Mean (SD)	168.2 (9.39)	165.7 (10.07)	166.9 (9.79)
Median	170.0	163.0	167.0
Range	(140; 189)	(145; 186)	(140; 189)
Body mass index, kg/m ²			
N	76	77	153
Mean (SD)	28.5 (5.78)	27.6 (5.39)	28.1 (5.59)

Median	27.5	27.6	27.5
Range	(16; 44)	(16; 40)	(16; 44)
Underweight <18.5	1 (1.3%)	1 (1.3%)	2 (1.3%)
Normal 18.5-<25	24 (31.6%)	25 (32.5%)	49 (32.0%)
Overweight 25-<30	20 (26.3%)	25 (32.5%)	45 (29.4%)
Obese ≥30	31 (40.8%)	26 (33.8%)	57 (37.3%)

Note: N's for each parameter reflect non-missing values.

Table 16. Summary of myasthenia gravis disease characteristics at baseline; primary efficacy analysis set (Study MOM-M281-011)

		Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W	Total
Analysis set: Primary Efficacy	76		77	153
MG-ADL total score				
N	76		77	153
Mean (SD)	9.0 (1.97)		9.4 (2.73)	9.2 (2.38)
Median	9.0		8.5	8.5
Range	(6; 13)		(6; 18)	(6; 18)
<=9	45 (59.2%)		48 (62.3%)	93 (60.8%)
>9	31 (40.8%)		29 (37.7%)	60 (39.2%)
QMG total score				
N	76		73	149
Mean (SD)	15.7 (4.92)		15.1 (4.78)	15.4 (4.85)
Median	15.0		14.5	15.0
Range	(5; 28)		(7; 28)	(5; 28)
Duration of MG (years)				
N	69		68	137
Mean (SD)	8.9 (8.13)		6.9 (7.44)	7.9 (7.83)
Median	7.0		5.0	6.0
Range	(0; 37)		(0; 38)	(0; 38)
Age at onset of MG (years)				
N	69		68	137
Mean (SD)	42.6 (18.70)		45.1 (17.27)	43.8 (17.98)
Median	41.0		45.5	43.0
Range	(7; 80)		(4; 78)	(4; 80)
Autoantibody status at screening				
N	76		77	153
Seropositive	76 (100.0%)		77 (100.0%)	153 (100.0%)
Anti-AChR+	71 (93.4%)		63 (81.8%)	134 (87.6%)
Anti-MuSK+	4 (5.3%)		12 (15.6%)	16 (10.5%)
Anti-LRP4+	1 (1.3%)		2 (2.6%)	3 (2.0%)
MGFA classes				
N	76		77	153
I	0		1 (1.3%)	1 (0.7%)
IIa	10 (13.2%)		7 (9.1%)	17 (11.1%)
IIb	10 (13.2%)		11 (14.3%)	21 (13.7%)
IIIa	29 (38.2%)		34 (44.2%)	63 (41.2%)
IIIb	15 (19.7%)		17 (22.1%)	32 (20.9%)
IVa	10 (13.2%)		3 (3.9%)	13 (8.5%)
IVb	2 (2.6%)		4 (5.2%)	6 (3.9%)

Note: N's for each parameter reflect non-missing values.

Table 17. Medical history by subcategory; full analysis set (Study MOM-M281-011)

	Placebo Total	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W	
Analysis set: Full	98	98	196
Subcategory	98	98	196
Neurologic	87 (88.8%)	91 (92.9%)	178 (90.8%)
Endocrine and metabolic	56 (57.1%)	60 (61.2%)	116 (59.2%)
Cardiovascular	58 (59.2%)	55 (56.1%)	113 (57.7%)
Musculoskeletal	53 (54.1%)	35 (35.7%)	88 (44.9%)
Respiratory	40 (40.8%)	34 (34.7%)	74 (37.8%)
Gastrointestinal	36 (36.7%)	34 (34.7%)	70 (35.7%)
Allergic/immunologic	38 (38.8%)	28 (28.6%)	66 (33.7%)
Other	29 (29.6%)	35 (35.7%)	64 (32.7%)
Genito-urinary	30 (30.6%)	28 (28.6%)	58 (29.6%)
Psychiatric	23 (23.5%)	25 (25.5%)	48 (24.5%)
Eyes	25 (25.5%)	16 (16.3%)	41 (20.9%)
Hematopoietic/lymphatic	19 (19.4%)	16 (16.3%)	35 (17.9%)
Reproductive/breast	20 (20.4%)	15 (15.3%)	35 (17.9%)
Ears, nose and throat	18 (18.4%)	11 (11.2%)	29 (14.8%)
Dermatologic	14 (14.3%)	11 (11.2%)	25 (12.8%)

Note: Subjects may appear in more than one category.

Stable concomitant therapy received for the treatment of gMG was generally balanced across treatment groups for the Primary Efficacy Analysis Set; similar percentage of participants were on acetylcholinesterase inhibitors (nipocalimab: 83.1%, placebo: 86.8%) or immunosuppressants (nipocalimab: 53.2%, placebo: 53.9%); A greater percentage of participants in the placebo group compared to the nipocalimab group received corticosteroids (nipocalimab: 61.0%, placebo: 71.1%).

Table 18. Stable generalized myasthenia gravis (gMG) therapy; primary efficacy analysis set MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Primary Efficacy	76	77
Subjects with 1 or more concomitant medications	76 (100.0%)	75 (97.4%)
ATC Level 2		
Standardized medication name		
Other nervous system drugs	66 (86.8%)	64 (83.1%)
Pyridostigmine bromide	53 (69.7%)	53 (68.8%)
Pyridostigmine	6 (7.9%)	12 (15.6%)
Ambenonium chloride	7 (9.2%)	4 (5.2%)
Ambenonium	1 (1.3%)	0
Distigmine	1 (1.3%)	0
Corticosteroids for systemic use	54 (71.1%)	47 (61.0%)
Prednisone	26 (34.2%)	27 (35.1%)
Prednisolone	14 (18.4%)	7 (9.1%)
Methylprednisolone	7 (9.2%)	6 (7.8%)
Prednisone acetate	6 (7.9%)	6 (7.8%)
Deflazacort	0	1 (1.3%)
Hydrocortisone butyrate	1 (1.3%)	0
Immunosuppressants	41 (53.9%)	41 (53.2%)
Tacrolimus	4 (5.3%)	14 (18.2%)

Azathioprine	14 (18.4%)	13 (16.9%)
Mycophenolate mofetil	14 (18.4%)	7 (9.1%)
Ciclosporin	8 (10.5%)	6 (7.8%)
Methotrexate	0	1 (1.3%)
Mycophenolate sodium	1 (1.3%)	1 (1.3%)
Tacrolimus monohydrate	1 (1.3%)	0
Analgesics	0	1 (1.3%)
Cannabis sativa	0	1 (1.3%)
Note: Includes gMG medications started before the first dose of study intervention and continued after the first dose of study intervention.		

- **Numbers analysed**

Table 19. Number of subjects in each analysis set; all randomized analysis set (Study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
All randomized	99	100
Full analysis set	98 (99.0%)	98 (98.0%)
Primary efficacy analysis set	76 (76.8%)	77 (77.0%)
Anti-AChR positive efficacy analysis set	71 (71.7%)	63 (63.0%)
Safety analysis set	98 (99.0%)	98 (98.0%)

Primary efficacy analysis set includes all seropositive participants, i.e. those of essence for the claimed indication.

- **Outcomes and estimation**

Primary efficacy analysis

Under the primary estimand for the EU, ICes of discontinuation of study intervention or stable gMG therapy that are not due to initiation of rescue therapy, or changes in stable gMG therapy (for any reason) were addressed with the treatment policy strategy and missing observations were handled with the CR multiple imputation method. Nipocalimab demonstrated statistically significant improvement in MG-ADL total score change from baseline over Weeks 22, 23, and 24 compared to placebo in the Primary Efficacy Analysis Set. The LS means (SE) change from baseline in MG-ADL total score over Weeks 22, 23, and 24 was -4.68 (0.324) for the nipocalimab group and -3.29 (0.333) for the placebo group. The difference between treatment groups was statistically significant in favor of nipocalimab (2-sided; $p=0.003$; LS means difference: -1.39 (95% CI: -2.31, -0.47).

Figure 17. MG-ADL total score: LS mean estimates (+/- SE) for change from baseline over time in DB phase; copy reference imputation; primary efficacy analysis set (Study MOM-M281-011)

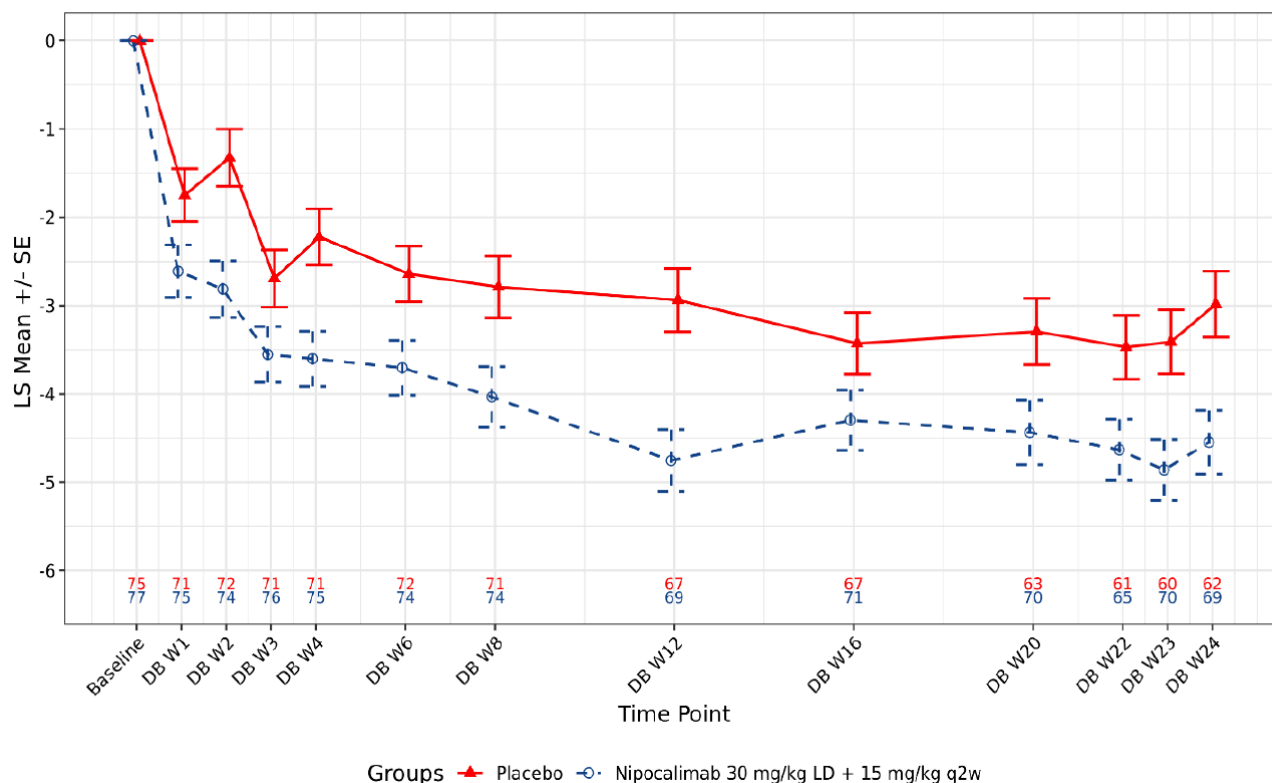


Table 20. Myasthenia gravis - activities of daily living (MG-ADL) total score: average change from baseline over DB weeks 22, 23, and 24 - MMRM copy reference imputation; primary efficacy analysis set (Study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Primary Efficacy	76	77
Baseline		
N	76	77
Mean (SD)	8.98 (1.971)	9.40 (2.727)
Median	9.00	8.50
Range	(6.0; 13.0)	(5.5; 17.5)
DB Week 22		
N	61	65
Mean (SD)	5.67 (2.982)	4.28 (3.462)
Median	5.00	3.00
Range	(0.0; 14.0)	(0.0; 12.0)
Change from baseline		
N	61	65
Mean (SD)	-3.33 (2.622)	-5.25 (3.344)
Median	-3.50	-5.00
Range	(-9.0; 2.5)	(-13.5; 1.0)
DB Week 23		
N	60	70
Mean (SD)	5.52 (2.908)	4.21 (3.443)
Median	5.00	4.00
Range	(0.0; 15.0)	(0.0; 12.0)
Change from baseline		

N	60	70
Mean (SD)	-3.45 (2.774)	-5.16 (3.325)
Median	-3.50	-5.00
Range	(-9.5; 2.5)	(-15.5; 1.0)
DB Week 24		
N	62	69
Mean (SD)	6.10 (2.924)	4.52 (3.775)
Median	6.00	4.00
Range	(0.0; 12.0)	(0.0; 15.0)
Change from baseline		
N	62	69
Mean (SD)	-2.94 (2.802)	-4.82 (3.572)
Median	-2.50	-5.00
Range	(-10.0; 2.0)	(-14.5; 2.0)
Analysis of average change from baseline over Week 22, 23 and 24 ^a		
LS Means (SE)	-3.29 (0.333)	-4.68 (0.324)
95% CI	(-3.95; -2.63)	(-5.32; -4.04)
Diff. of LS Means (SE)		-1.39 (0.464)
95% CI		(-2.31; -0.47)
2-sided p-value (minus Placebo)		0.003

^a Based on MMRM model with treatment group (Placebo, Nipocalimab), autoantibody status ("anti-AChR positive or anti- MuSK positive" or "anti-AChR negative and anti-MuSK negative," as randomized), week, region and treatment group-by- week interaction and baseline MG-ADL Total Score as a covariate. The between-group difference of the average change over Weeks 22, 23, and 24 was estimated from a linear contrast of model coefficients.

Note: ICes of discontinuation of study intervention of stable gMG therapy that are due to initiation of rescue therapy are handled with the hypothetical strategy; observations after the ICE are deemed missing. Other ICes are addressed with the treatment policy strategy; observations after the ICE are included in the analysis. Missing observations are imputed using the Copy Reference MI method (N=500 imputations).

Note: Negative change in score indicates improvement.

Note: One patient who met eligibility at screening with an MG-ADL of 8, had a baseline MG-ADL of 3 (noted as an MPD of eligibility)

Sensitivity analysis

An analysis using the J2R MI method was performed to assess the robustness of the results using the CR method. For the J2R method, the LS mean difference (95% CI) between nipocalimab and placebo was -1.35 ([-2.30, -0.41]; 2-sided; p=0.005), which is similar to results obtained for the CR MI method.

Key Secondary Endpoints and Other Efficacy Considerations

A summary of the results of the key secondary efficacy endpoints for the Primary Efficacy Analysis Set (seropositive participants) is shown in Table 21 according to the sequential testing procedure. Nipocalimab demonstrated statistically significant improvements over placebo for the first 2 key secondary endpoints (ie, average change from baseline in QMG score over Weeks 22 and 24 and the proportion of MG- ADL Responders). Since the between-group difference was not statistically significant for response at Week 1 and/or Week 2 (p=0.234), 2 subsequent key secondary endpoints could not be formally tested according to the predefined testing sequence.

Table 21. Key secondary endpoints and application of fixed sequence testing approach

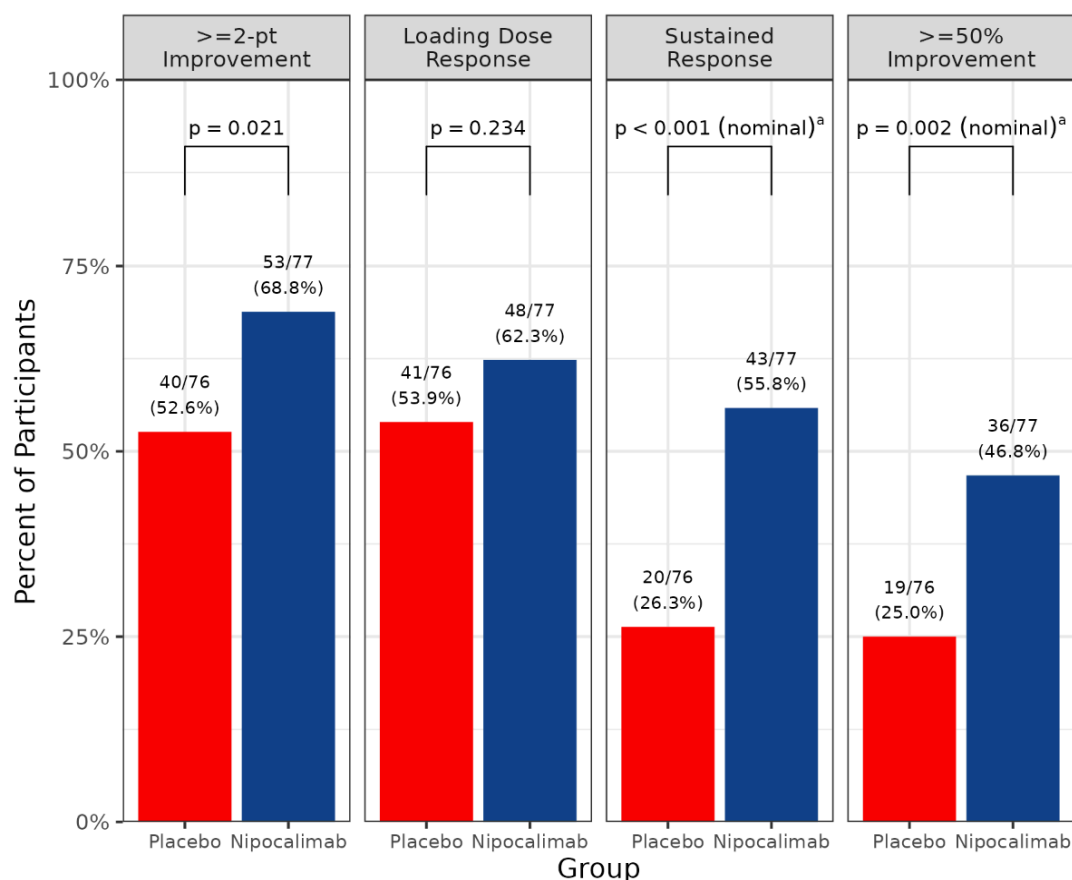
Key Secondary Endpoints	Placebo	Nipocalimab	Between-group difference (95% CI)	p-value
QMG Total Score: Change from Baseline (LS mean [SE])				
Average change from baseline in QMG total score over Weeks 22 and 24	-1.90 (0.491)	-4.77 (0.488)	-2.87 (-4.23, -1.50)	<0.001
MG-ADL Responder Endpoints (% of participants)				
≥ 2-point Improvement in MG-ADL				
Average change in MG-ADL over Weeks 22, 23, and 24 is at least a 2-point improvement	52.6%	68.8%	16.2 (0.9, 31.5)	0.021

Loading Dose Response At least 2-point improvement in MG-ADL total score at Week 1 and/or Week 2	53.9%	62.3%	8.4 (-7.2, 24.0)	0.234
Sustained Response At least 2-point improvement in MG-ADL total score at Week 4 through Week 24, with no more than 2 non-consecutive excursions from Week 6 to 23	26.3%	55.8%	29.5 (14.7, 44.4)	<0.001 ^a
≥ 50% Improvement Average change in MG-ADL over Weeks 22, 23, and 24 is at least 50% improvement	25.0%	46.8%	21.8 (7.0, 36.6)	0.002 ^a
NOTE: Results for change from baseline in QMG total score are shown for the EU estimand. Estimands for the MG-ADL key secondary endpoints are applicable for all regions. ^a Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Since a preceding comparison was not statistically significant at 2-sided alpha=0.05 nominal p-value is shown				

An analysis using the J2R MI method was performed to assess the robustness of the key secondary endpoint (CBL QMG) using the CR method. For the J2R method, the LS mean difference (95% CI) between nipocalimab and placebo was -2.46 ([-3.89, -1.03]; 2-sided; p=0.001).

Results for the four MG-ADL key secondary endpoints measuring response are shown in Figure 18.

Figure 18. MG-ADL secondary endpoints; primary efficacy analysis set (Study MOM-M281-011)



Values for ≥2-pt and ≥50% improvement: Based on average improvement in MG-ADL over Weeks 22, 23, and 24. Loading dose response: At least 2-point improvement at Week 1 or Week 2. Sustained response: At least 2-point improvement from Week 4 to Week 24 with no more than 2 non-consecutive excursions from Week 6 to Week 23. P-values from CMH test controlling for baseline MG-ADL total score (<9, ≥9), autoantibody status, and region.

^aBased on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested because a preceding comparison was not statistically significant at 2-sided alpha=0.05; nominal p-value is shown.

Other Secondary Endpoints

- Minimal symptom expression, defined as an MG-ADL score of 0 or 1, is a clinically meaningful endpoint that is considered a desired treatment goal, an endpoint of symptom remission in this study.
 - at Week 24, minimal symptom expression was observed in a greater proportion of nipocalimab participants compared to placebo (20.8% vs. 3.9%, respectively).
 - the results were consistent over the course of the study: minimal symptom expression was observed in a greater proportion of the nipocalimab group compared to placebo group at any time point; at ≥50% of all time points; and at ≥75% of all time points.
- Proportion of QMG Responders (based on reductions in QMG response from baseline across a range of response criteria from ≥3 points to ≥9 points) was observed in a higher percentage of nipocalimab participants compared to placebo participants at each timepoint. Percent difference was 24.4% (95% CI 10.0, 38.8)
- MG-QoL15r Total Score Change from Baseline: decreases in the mean change in MG-QoL15r total score over time from baseline through Week 24 numerically favoured nipocalimab compared with placebo. The LS mean difference (95% CI) was -1.45 (-3.30, 0.40).
- Neuro-QoL Fatigue Total Scores reflected less fatigue experienced over time by participants treated with nipocalimab than with placebo. The LS mean difference (95% CI) between nipocalimab and placebo was -3.15 (-8.32, 2.02).
- EQ-5D-5L Visual Analog Scale and Health Status Index: All 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) improved over the 24 weeks of the DB phase to a larger extent in the nipocalimab group than in the placebo group. Mean (SD)improvement from baseline to Week 24 in the EQ-5D-5L health status index and visual analog scale was 0.13 (0.214) and 14.55 (20.950), respectively, for participants receiving nipocalimab and 0.07 (0.184) and 7.27 (18.799), respectively, for participants receiving placebo.

Additional endpoints for response

Table 22. Myasthenia gravis - activities of daily living (MG-ADL) total score: number of subjects with response based on average change from baseline over weeks 22, 23, and 24 in DB phase; primary efficacy analysis set (Study MOM-M281-011)

	Placebo 76	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W 77
Analysis set: Primary Efficacy		
Subjects with ≥2-point improvement ^a	40 (52.6%)	53 (68.8%)
% Difference (95% CI) ^b		16.2 (0.9, 31.5)
Subjects with ≥3-point improvement ^a	32 (42.1%)	46 (59.7%)
% Difference (95% CI) ^b		17.6 (2.0, 33.2)
Subjects with ≥4-point improvement ^a	20 (26.3%)	37 (48.1%)
% Difference (95% CI) ^b		21.7 (6.8, 36.7)
Subjects with ≥5-point improvement ^a	15 (19.7%)	32 (41.6%)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
% Difference (95% CI) ^b		21.8 (7.6, 36.0)
Subjects with ≥6-point improvement ^a	13 (17.1%)	25 (32.5%)
% Difference (95% CI) ^b		15.4 (1.9, 28.8)
Subjects with ≥7-point improvement ^a	7 (9.2%)	19 (24.7%)
% Difference (95% CI) ^b		15.5 (3.8, 27.1)
Subjects with ≥8-point improvement ^a	3 (3.9%)	12 (15.6%)
% Difference (95% CI) ^b		11.6 (2.4, 20.8)

^a Improvement is based on the change from baseline of the average MG-ADL total score over Weeks 22, 23, and 24. The average score for a subject is the average of the non-missing values at weeks 22, 23, and 24. A subject must have a non-missing value at week 24 and at least 1 non-missing value at week 22 or 23 to have a non-missing average score. Observations after an ICE are treated as missing. Subjects with a missing average score will be considered non-responders.

^b Between-intervention differences in proportions and 95% Wald confidence intervals are calculated based on the normal approximation.

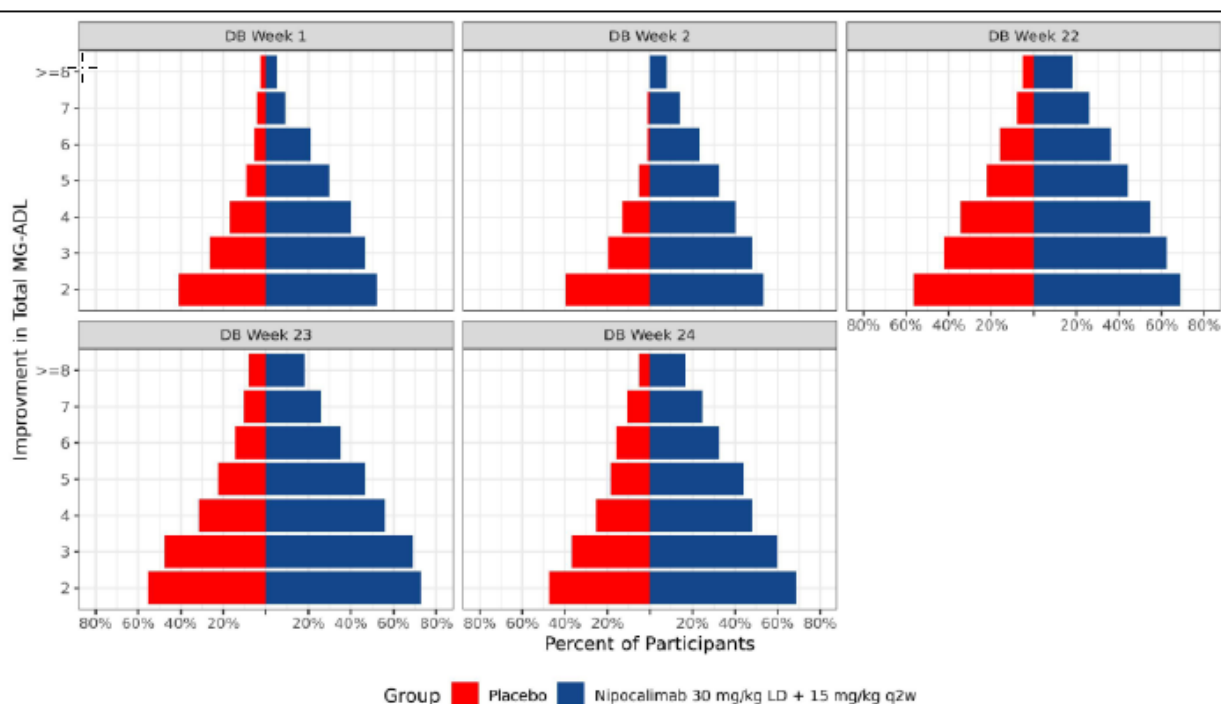
Table 23. MG-ADL item scores: number and percentage of subjects with ≥1-point improvement from DB day 1 to DB week 24; primary efficacy analysis set (Study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W	% Difference between groups(95%CI)
Analysis set: Primary Efficacy	76	77	
Talking			
DB Week 24			
N	61	62	
≥1-point improvement	24 (39.3%)	29 (46.8%)	7.4 (-10.0, 24.9)
≥2-point improvement	1 (1.6%)	10 (16.1%)	14.5 (4.8, 24.2)
3-point improvement	0	0	- (-,-)
Chewing			
DB Week 24			
N	61	62	
≥1-point improvement	32 (52.5%)	39 (62.9%)	10.4 (-6.9, 27.8)
≥2-point improvement	5 (8.2%)	10 (16.1%)	7.9 (-3.5, 19.4)
3-point improvement	0	0	- (-,-)
Swallowing			
DB Week 24			
N	61	62	
≥1-point improvement	22 (36.1%)	28 (45.2%)	9.1 (-8.2, 26.4)
≥2-point improvement	4 (6.6%)	9 (14.5%)	8.0 (-2.8, 18.7)
3-point improvement	0	0	- (-,-)
Breathing			
DB Week 24			
N	61	62	
≥1-point improvement	16 (26.2%)	26 (41.9%)	15.7 (-0.8, 32.2)
≥2-point improvement	2 (3.3%)	6 (9.7%)	6.4 (-2.2, 15.0)
3-point improvement	0	0	- (-,-)
Impairment Brush Teeth Comb Hair			
DB Week 24			
N	61	62	
≥1-point improvement	25 (41.0%)	36 (58.1%)	17.1 (-0.3, 34.5)
≥2-point improvement	9 (14.8%)	17 (27.4%)	12.7 (-1.6, 26.9)
3-point improvement	0	2 (3.2%)	3.2 (-1.2, 7.6)
Impairment Arise From Chair			
DB Week 24			
N	61	62	

		Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W	% Difference between groups(95%CI)
≥1-point improvement	Placebo 19 (31.1%)	34 (54.8%)	23.7 (6.7, 40.7)
≥2-point improvement	7 (11.5%)	7 (11.3%)	-0.2 (-11.4, 11.0)
3-point improvement	0	2 (3.2%)	3.2 (-1.2, 7.6)
Double Vision			
DB Week 24			
N	61	62	
≥1-point improvement	18 (29.5%)	29 (46.8%)	17.3 (0.4, 34.2)
≥2-point improvement	6 (9.8%)	10 (16.1%)	6.3 (-5.5, 18.1)
3-point improvement	1 (1.6%)	1 (1.6%)	0.0 (-4.5, 4.4)
Eyelid Droop			
DB Week 24			
N	61	62	
≥1-point improvement	23 (37.7%)	33 (53.2%)	15.5 (-1.9, 32.9)
≥2-point improvement	7 (11.5%)	13 (21.0%)	9.5 (-3.4, 22.4)
3-point improvement	2 (3.3%)	3 (4.8%)	1.6 (-5.4, 8.5)

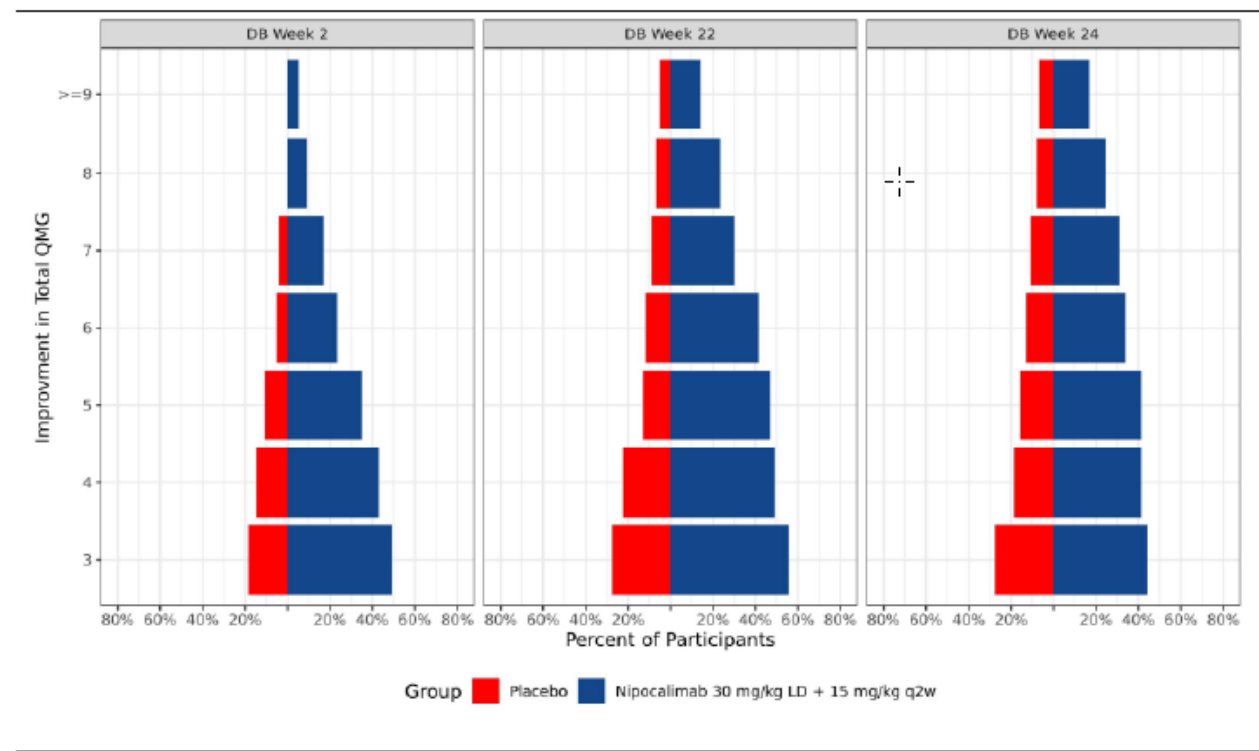
Note: N is the number of subjects with at least 1 postbaseline value.

Figure 19. MG-ADL total score: cumulative distribution of improvement at selected timepoints ("Christmas tree" plot) - DB phase; primary efficacy analysis set (Study MOM-M281-011)



Note: Observations after an ICE are treated as having <2-point improvement.

Figure 20. Quantitative Myasthenia Gravis (QMG) total score: cumulative distribution of improvement at selected timepoints ("Christmas tree" plot) - DB phase; primary efficacy analysis set (Study MOM-M281-011)

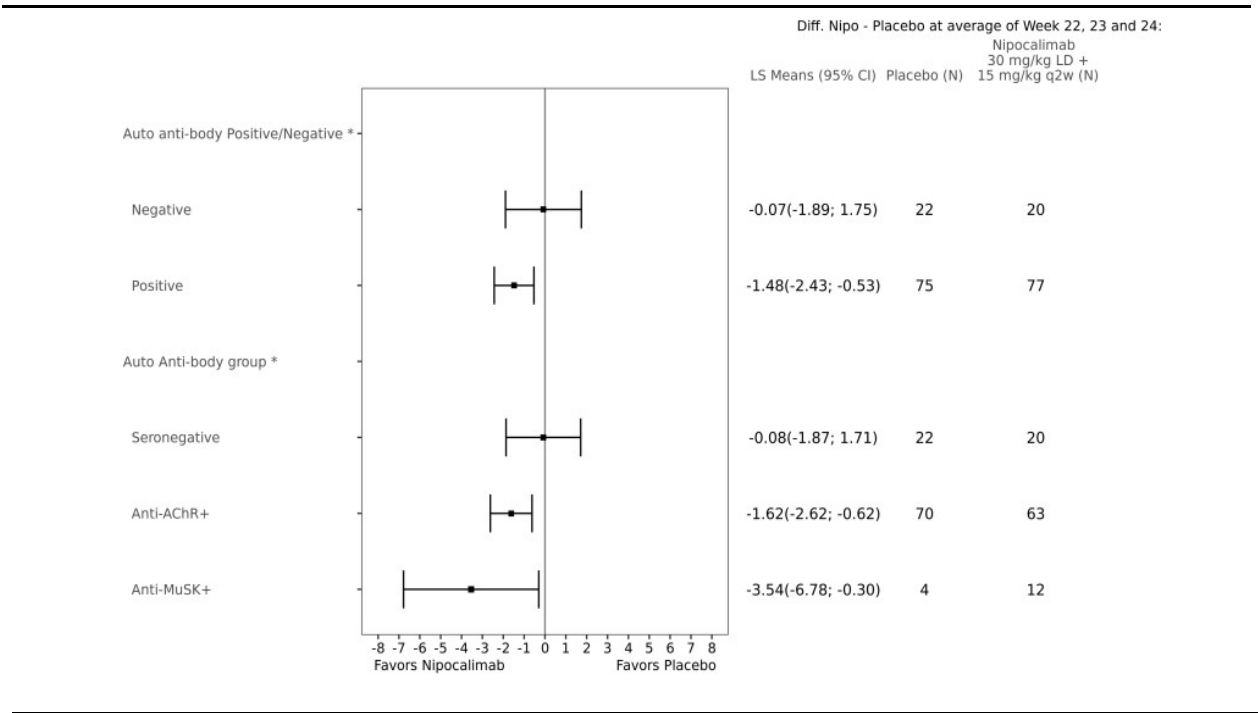


Note: Observations after an ICE are treated as having <3-point improvement.

• **Ancillary analyses**

Estimates of change from baseline in MG-ADL total score over Weeks 22, 23, and 24 in each treatment group, the between-group differences (nipocalimab - placebo), and 95% CIs in the seropositive and seronegative subgroups are summarized in Figure 21. The forest plot shows results for the full analysis set i.e. also including seronegative participants.

Figure 21. Myasthenia Gravis - activities of daily living (MG-ADL) total score: average change from baseline over DB weeks 22, 23, and 24 by Serostatus - MMRM observed case; full analysis set (Study MOM-M281-011)



LRP4+

There were only 3 participants with anti-LRP4 positive gMG in the Phase 3 study. Among these anti-LRP4+ participants, rapid and sustained reductions were observed in total IgG, as well as in IgG1 and IgG2 subclasses, during the DB phase through Week 24 in the two nipocalimab-treated participants, while these reductions were not observed in the single placebo-treated participant. The trajectories of anti-LRP4 antibody titers, MG-ADL and QMG are shown below (Figure 22, Figure 23 and Figure 24).

Figure 22. Anti-LRP4 antibody titers over time through the open-label phase; Anti-LRP4+ subjects; pharmacodynamic analysis set (Study MOM-M281-011)

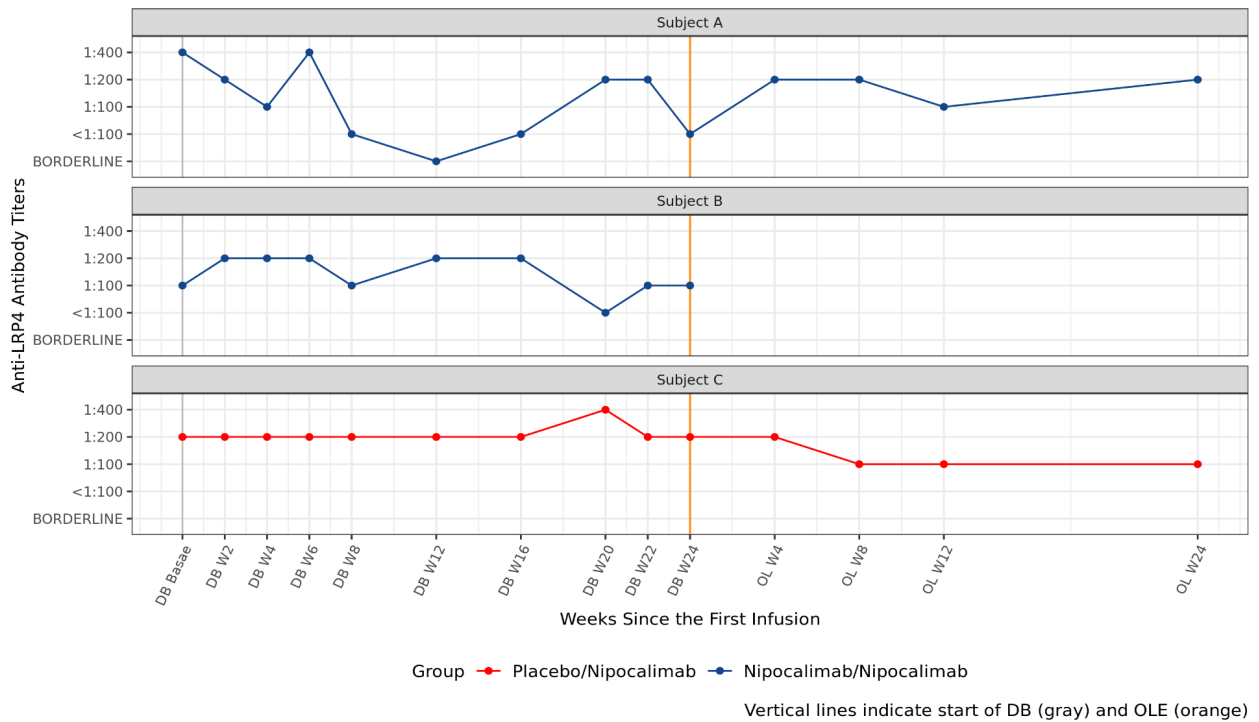


Figure 23. MG-ADL total score: values over time through the open-label phase for anti-LRP4+ subjects; primary efficacy analysis set (Study MOM-M281-011)

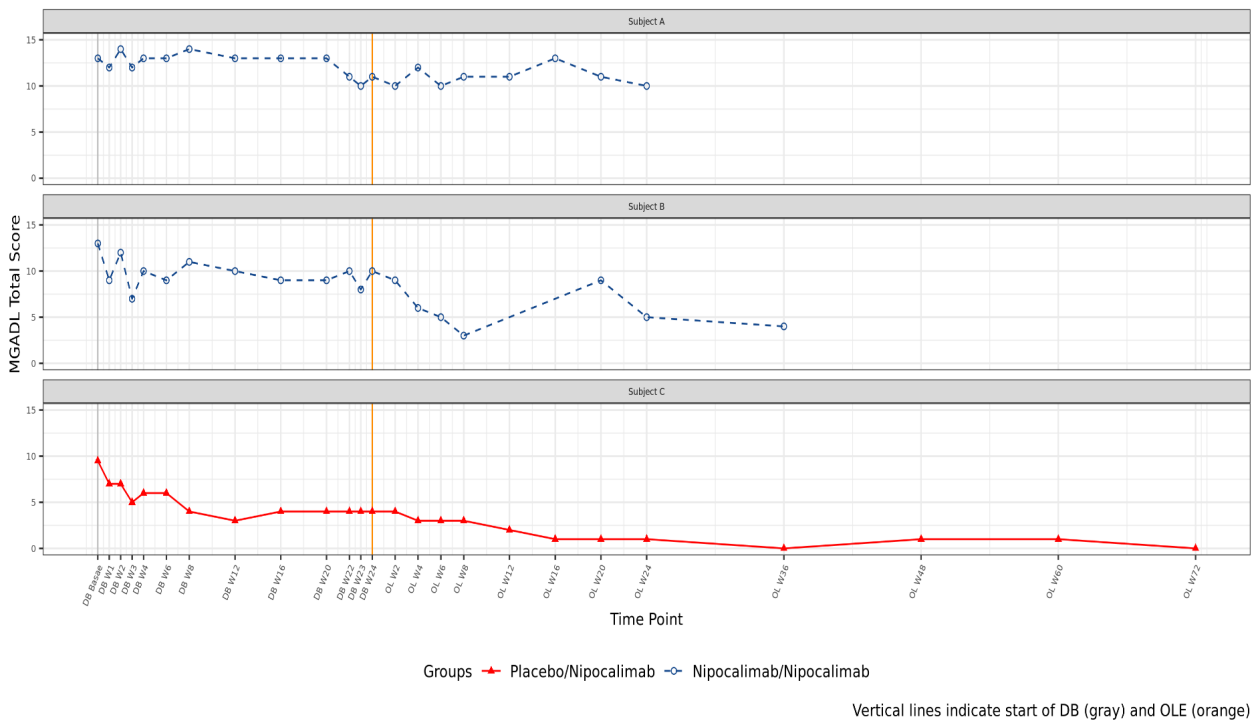
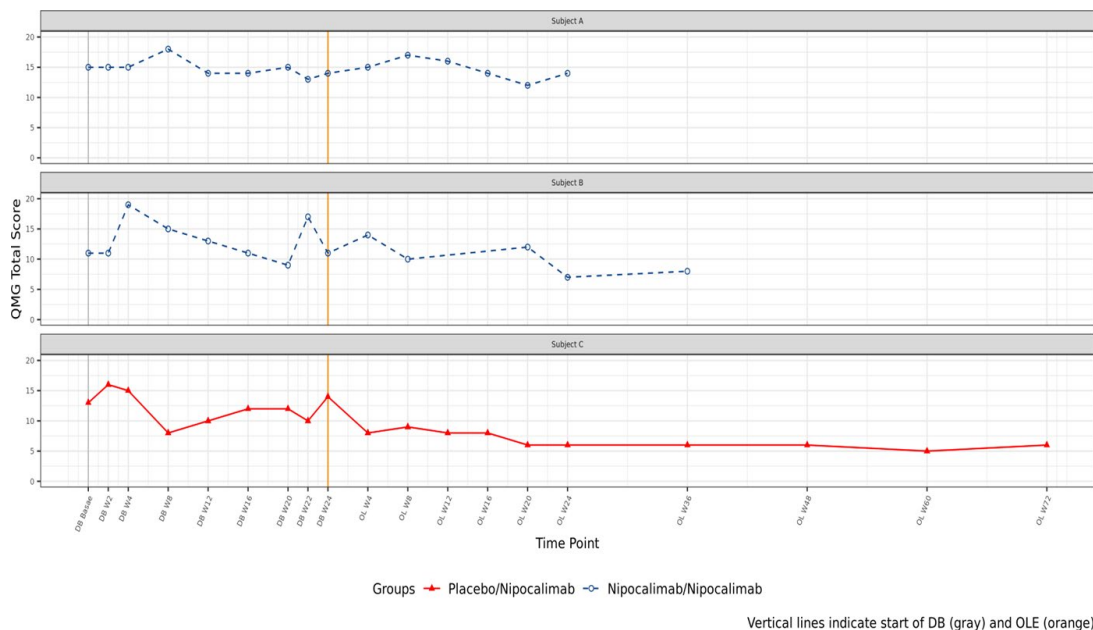
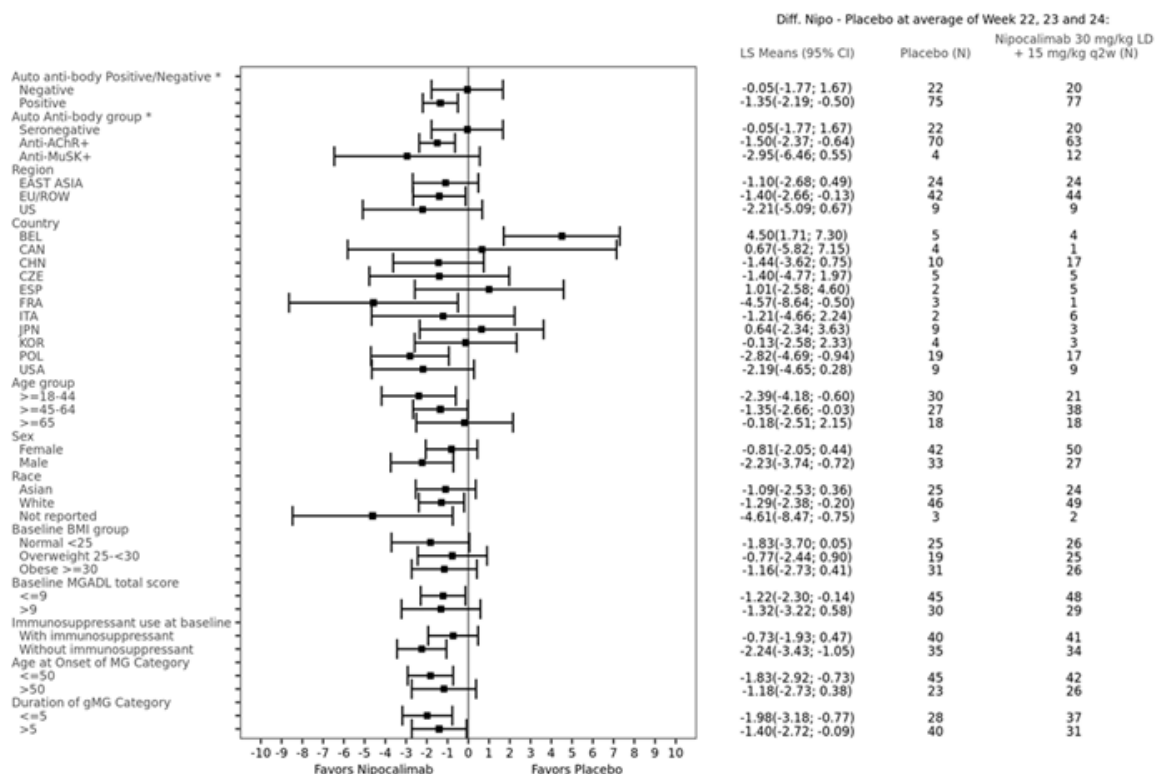


Figure 24. QMG total score: values over time through the open-label phase for anti-LRP4+ subjects; primary efficacy analysis set (Study MOM-M281-011)



Consistent efficacy results were observed in most of the subgroup analyses based on demographic and baseline characteristics, with the exception of age (Figure 25 and Figure 26).

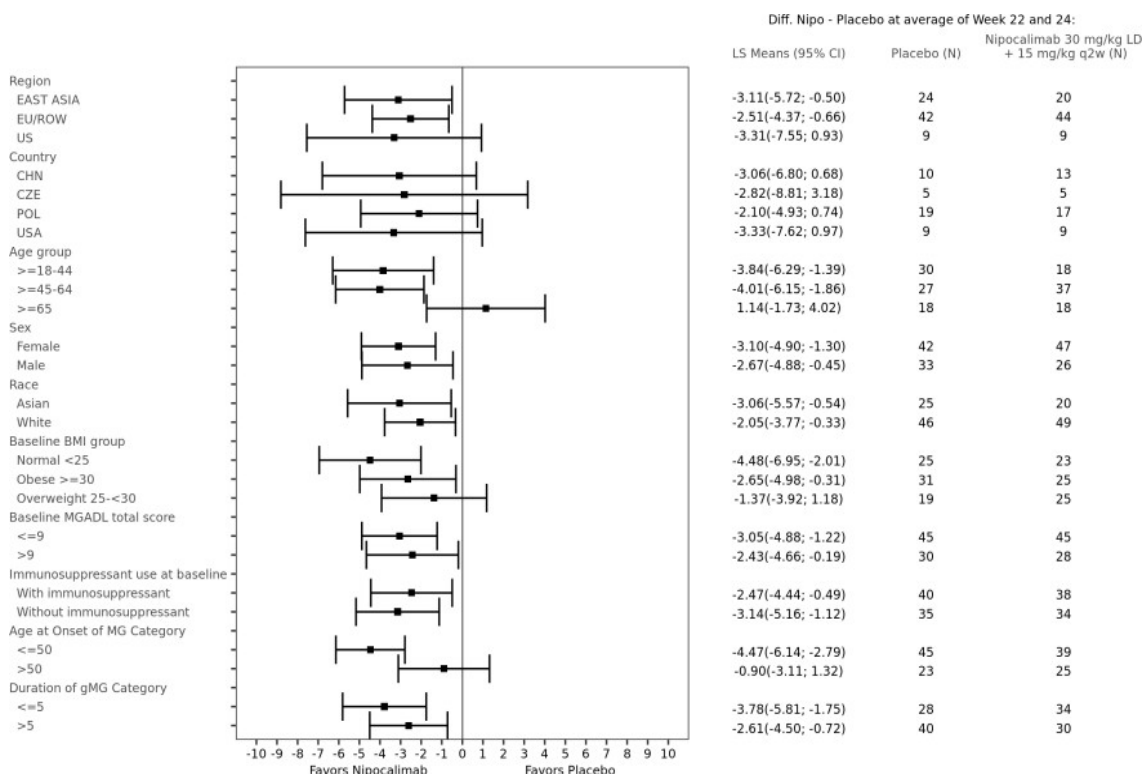
Figure 25. Myasthenia Gravis - activities of daily living (MG-ADL) total score: average change from baseline over DB weeks 22, 23, and 24 by demographic and baseline disease characteristics - MMRM observed case; primary efficacy analysis set (Study MOM-M281-011)



Note: Including only those levels of the subgroup variables with ≥ 5 participants in each study intervention group.

Note: The number of subjects under treatments is those who have at least one non-missing change scores at post-baseline.

Figure 26. Quantitative Myasthenia Gravis (QMG) total score: average change from baseline over DB weeks 22 and 24 by demographic and baseline disease characteristics - MMRM observed case; primary efficacy analysis set (Study MOM-M281-011)

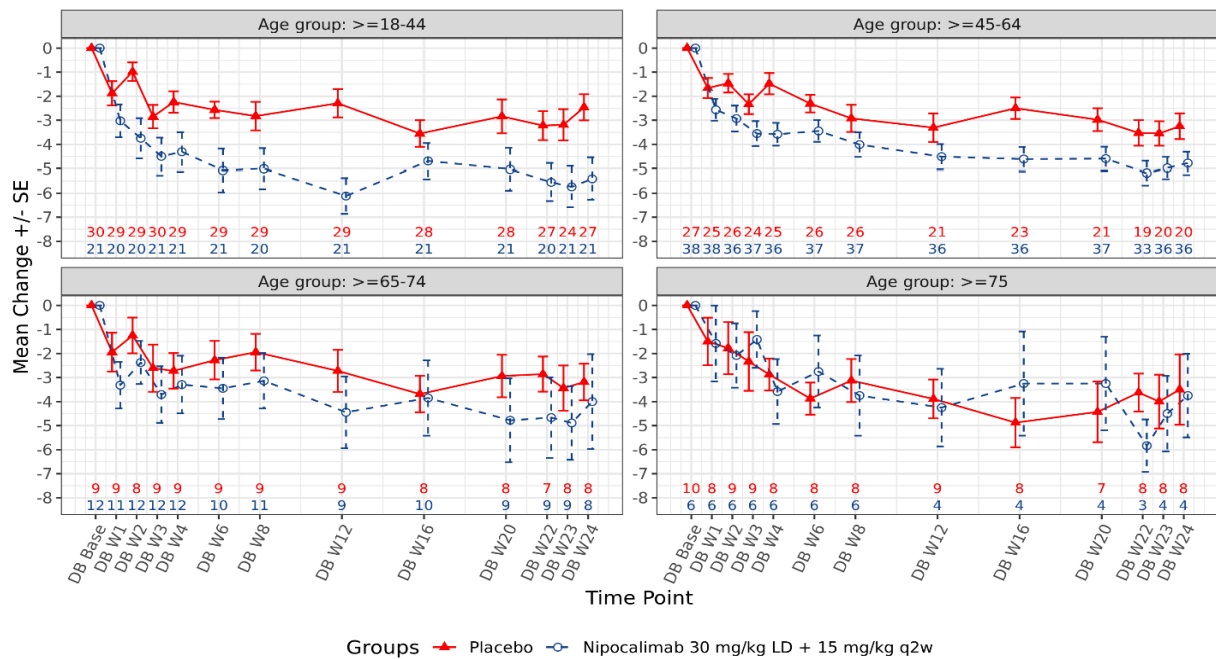


Subgroup Analyses Based on Age

Estimates of the treatment differences directionally favoured treatment with nipocalimab compared to placebo for the different age subgroups within the Primary Efficacy Analysis Set, with exception of participants in the age group ≥65 years.

To explore age subgroups, additional plots of mean change ($\pm$ SE) from baseline over time for MG-ADL are provided to further categorize age into 4 subgroups: 18 to <44, 44 to <65, 65 to <74, and ≥75 years (Figure 27). These plots show that in the subgroups of participants <75 years, the treatment differences favor nipocalimab over time. The elderly participants ≥75 years had more variable responses and less of a treatment difference; however, due to the small sample size in this age group (6 in the nipocalimab group, 10 in the placebo group) it cannot be determined if they respond differently from younger adult patients.

Figure 27. Myasthenia Gravis - activities of daily living (MG-ADL) total score: mean change from baseline (+/- SE) over time in DB phase by age group; primary efficacy analysis set (Study MOM-M281-011)



Post hoc subgroup analyses of the QMG total score were consistent with the MG-ADL total score subgroup analyses, including for age group. Estimates of the treatment differences directionally favoured treatment with nipocalimab, with exception of the age group of ≥ 65 years.

Relationship of IgG Lowering and MG-ADL Change from Baseline

Figure 28. Scatterplots of MG-ADL change from baseline versus total IgG percent change from baseline at weeks 22 and 24; pharmacodynamic (PD) analysis set (Study MOM-M281-011)

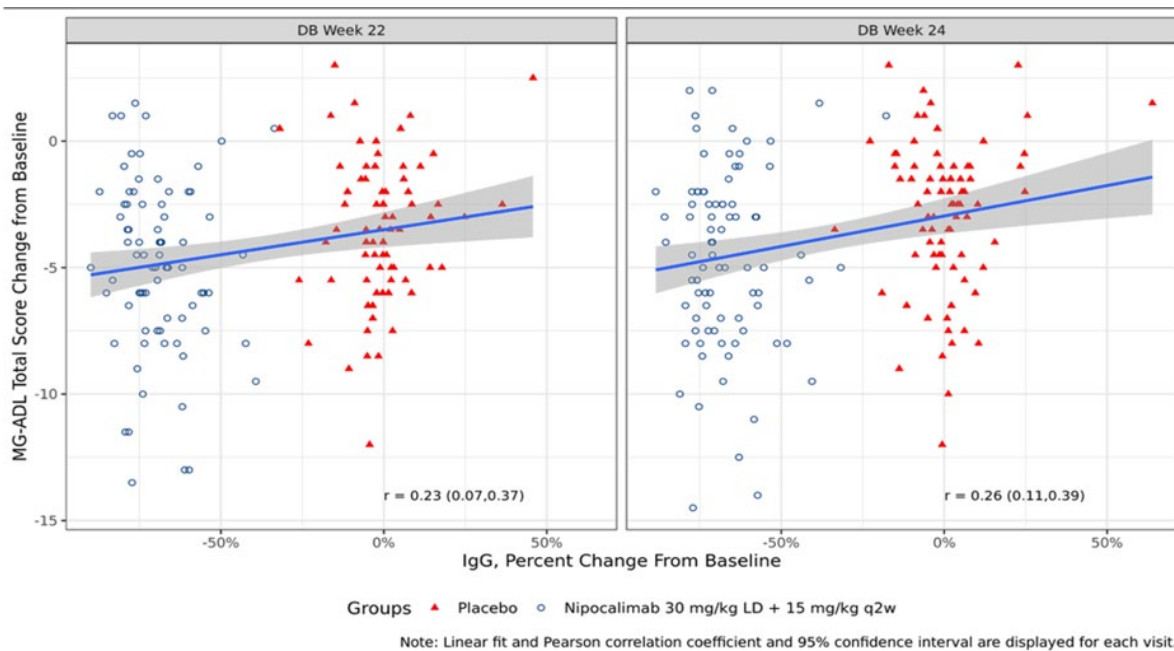
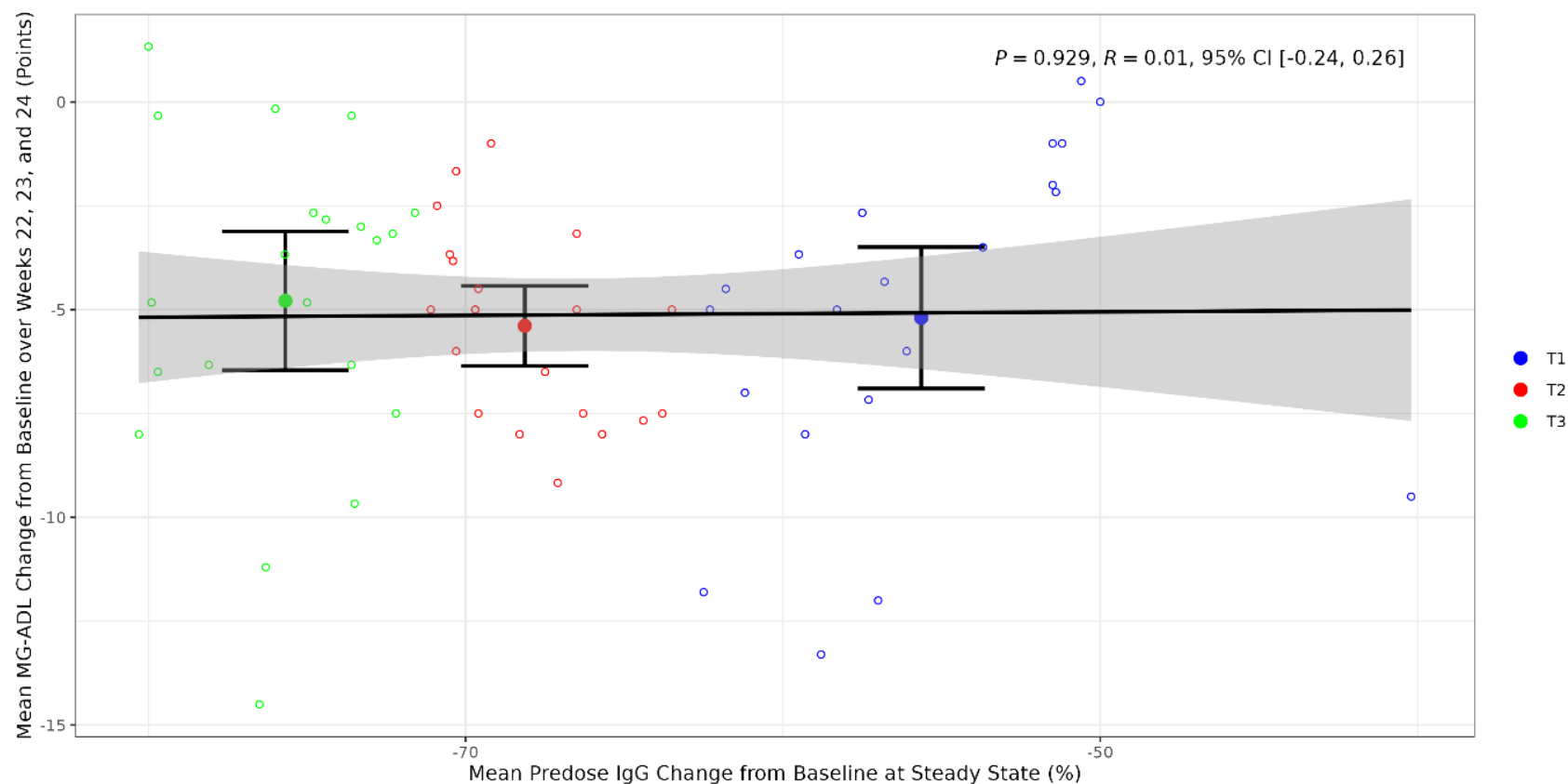


Figure 29. Exposure-response relationship between average week 22, 23 and 24 MG-ADL CFB and median steady-state predose IgG CFB in MOM-M281-011, Nipocalimab group only



Linear regression line (black) and 95% CI (grey area). Pearson correlation and 95% confidence interval shown in top right corner. Mean MG-ADL CFB per IgG %CFB tertile shown as colored points, 95% CI as error bars.

Immunogenicity

A total of 97 participants randomized to the nipocalimab group (seropositive and seronegative gMG) had post-treatment serum samples that were evaluated for antibodies to nipocalimab (ie, ADA) with a specific (to antibodies to nipocalimab), highly sensitive and drug-tolerant ECLIA method. The incidence of treatment-emergent ADA through the DB Week 24 was 49.5% (n=48). Titers of ADA were generally low (39 of 48 participants had peak titer levels $\leq 1:20$; 46 of 48 participants had peak titer levels $\leq 1:80$). The incidence of treatment-emergent ADA was 64.7%, 45.8%, and 50.0%, respectively, for participants with baseline weight <60, ≥ 60 to ≤ 100 , and >100 kg. The incidence of ADA was 35.7%, 43.8%, and 58.5% respectively in participants in East Asia (Japan and China), US and EU/ROW. For participants who used immunosuppressants at baseline compared with participants who did not use immunosuppressants at baseline the ADA incidence was 44.0% and 55.6%, respectively.

All 48 participants who were ADA-positive had post-treatment serum samples available for NAb assessment. Seventeen of the 48 treatment-emergent ADA-positive participants were positive for NAb to nipocalimab through the DB phase Week 24. The overall incidence of NAb to nipocalimab was 17 (17.5%) of the 97 participants treated with nipocalimab.

Antibodies to Nipocalimab and Efficacy

The presence of detectable ADA or NAb to nipocalimab did not appear to be associated with reduced efficacy of nipocalimab. In the nipocalimab treatment group, participants who were ADA-positive achieved a median 5.00-point reduction in MG-ADL total score from baseline prior to nipocalimab administration at DB Week 24, compared with a median 3.25-point reduction in ADA-negative participants. Similarly, no impact of development of NAb to nipocalimab on efficacy of nipocalimab was observed.

2.6.5.3. 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 24. Summary of efficacy

Title: A Multicenter, randomized, DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥ 18 years) with gMG inadequately controlled with standard-of-care therapy.	
Study identifier	Study code MOM-M281-011 EU CT number 2023-504152-97
Design	Randomized, multicenter, DB, parallel-group, placebo-controlled, fixed dose, stratified by autoantibody status, Day 1 MG-ADL total score and region, efficacy, safety, PK and PD study

Title: A Multicenter, randomized, DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥18 years) with gMG inadequately controlled with standard-of-care therapy.			
Study identifier	Study code MOM-M281-011 EU CT number 2023-504152-97		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks Up to 4-week Screening Period <time> <not applicable>	
Hypothesis	Superiority		
Treatments groups	Nipocalimab	Nipocalimab IV infusion at 30 mg/kg for the Day 1 loading dose followed by 15 mg/kg Q2W for 24 weeks Study participants randomized: not provided for the Primary Efficacy Analysis Set	
	Placebo	Placebo IV infusion Q2W for 24 weeks Study participants randomized: not provided for the Primary Efficacy Analysis Set	
Endpoints and definitions	Primary endpoint	CFB in MG-ADL over weeks 22-24.	Average change from baseline in MG-ADL score over Weeks 22, 23, and 24 of DB phase.
	Secondary endpoint	CFB in QMG over weeks 22-24	Average change in QMG score over Weeks 22 and 24 of DB phase.
	Secondary endpoint	RR for MG-ADL reduction ≥ 2 points over weeks 22-24	Percentage of participants (responder rate, RR) whose average improvement in MG-ADL total score over Weeks 22, 23, and 24 of DB phase is at least a 2-point improvement compared to baseline.
	Secondary endpoint	RR for MG-ADL reduction ≥ 2 points at Week 1 and/or Week 2	Percentage of participants (responder rate, RR) with improvement in MG-ADL total score ≥ 2 points at Week 1 and/or Week 2 of DB phase.
	Secondary endpoint	RR for MG-ADL reduction ≥ 2 points at Week 4 through Week 24	Percentage of participants (responder rate, RR) with improvement in MG-ADL total score ≥ 2 points at Week 4 through Week 24 of DB phase with no more than 2 non-consecutive excursions allowed between Week 6 through Week 23 (excursion defined as loss of improvement in MG-ADL score ≥ 2 points from baseline).

Title: A Multicenter, randomized, DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥18 years) with gMG inadequately controlled with standard-of-care therapy.			
Study identifier	Study code MOM-M281-011 EU CT number 2023-504152-97		
	Secondary endpoint	RR for MG-ADL reduction ≥ 50% from baseline, over Weeks 22-24	Percentage of participants (responder rate, RR) whose average improvement in MG-ADL total score over Weeks 22, 23, and 24 of the DB phase is at least a 50% improvement from baseline.
	Secondary endpoint	RR for QMG reduction ≥ 3 points at Week 2 through Week 24	Percentage of participants with improvement in QMG of ≥3 points from baseline at Week 2 through Week 24 of the DB phase with no more than 2 non-consecutive excursions allowed at Weeks 4 through 22 (excursions defined as loss of improvement in QMG score of ≥3 points from baseline).
	Other secondary endpoint	CFB in Neuro-QoL over Weeks 22 and 24	Average change from baseline (CFB) in the Neuro-QoL Fatigue total score over Weeks 22 and 24 of the DB phase.
	Other secondary endpoint	CFB in MG-QoL15r over Weeks 22 and 24	Average change from baseline (CFB) in the MG-QoL15r score over Weeks 22 and 24 of the DB placebo-controlled phase.
	Other secondary endpoint	Minimal symptom expression at week 24	Percentage of participants with MG-ADL score of 0 or 1 (minimal symptom expression) at week 24 of the DB phase
Database lock	November 17, 2023		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Seropositive participants with gMG who are on a stable MG therapy or who discontinued MG therapy due to intolerance or lack of efficacy. Treatment policy strategy except for rescue (hypothetical strategy). Hierarchical testing. Main timepoint of interest are Weeks 22, 23, and 24 where average (LS means) is calculated.		
	Treatment group	Placebo	Nipocalimab
	Number of subjects	n=76	n=77
Descriptive statistics, estimate variability and effect estimate per comparison	CFB in MG-ADL over weeks 22-24 LS Means (SE)	-3.29 (0.333)	-4.68 (0.324)
	95% CI	-3.95; -2.63	-5.32; -4.04
	Primary endpoint	Comparison groups	Placebo and nipocalimab
		Difference of LS-means (SE) vs Placebo	-1.39 (0.464)
		95% CI	(-2.31; -0.47)
		2-sided p-value (MMRM model)	0.003
	CFB in QMG over weeks 22-24 LS Means (SE)	-1.90 (0.491)	-4.77 (0.488)

Title: A Multicenter, randomized, DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥ 18 years) with gMG inadequately controlled with standard-of-care therapy.

Study identifier	Study code MOM-M281-011 EU CT number 2023-504152-97		
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference of LS-means vs Placebo	-2.87
		95% CI	(-4.23, -1.50)
		2-sided p-value (MMRM model)	<0.001
	RR for MG-ADL reduction ≥ 2 points over weeks 22-24	52.6%	68.8%
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	16.2%
		95% CI	0.9, 31.5
		p-value	0.021
	RR for MG-ADL reduction ≥ 2 points at Week 1 and/or Week 2	53.9%	62.3%
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	8.4%
		95% CI	-7.2, 24.0
		p-value	0.234
	RR for MG-ADL reduction ≥ 2 points at Week 4 through Week 24	26.3%	55.8%
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	29.5
		95% CI	14.7, 44.4
		Nominal p-value	<0.001
		Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Nominal p-value is given.	
	RR for MG-ADL reduction $\geq 50\%$ from baseline, over Weeks 22-24	25.0%	46.8%
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	21.8%
		95% CI	7.0, 36.6
		Nominal p-value	0.002
		Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Nominal p-value is given.	

Title: A Multicenter, randomized, DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥18 years) with gMG inadequately controlled with standard-of-care therapy.			
Study identifier	Study code MOM-M281-011 EU CT number 2023-504152-97		
	RR for QMG reduction ≥ 3 points at Week 2 through Week 24	7.9%	33.8%
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	25.9%
		95% CI	7.0, 36.6
		Nominal p-value	0.002
		Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Nominal p-value is given.	
	CFB in Neuro-QoL over Weeks 22 and 24	-10.02 (1.856)	-13.17 (1.833)
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	-3.15
		95% CI	-8.32, 2.02
		Nominal p-value	Not provided
		Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Nominal p-value is given.	
	CFB in MG-QoL15r over Weeks 22 and 24	-4.42 (0.664)	-5.87 (0.658)
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	-1.45
		95% CI	-3.30, 0.40
		Nominal p-value	Not provided
		Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Nominal p-value is given.	
	Minimal symptom expression at week 24	3.9%	20.8%
	Secondary endpoint	Comparison groups	Placebo and nipocalimab
		Difference vs Placebo	Not provided
		95% CI	Not provided
		Nominal p-value	Not provided
		Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested. Nominal p-value is given.	
Analysis description	Subgroup analysis by MG-specific autoantibodies, MuSK+ and AChR+ The subgroup analysis was pre-specified and is important for the claimed indication. Lrp+ group too small. Analysis done with under the US estimand.		

Title: A Multicenter, randomized, DB, placebo-controlled study to evaluate the efficacy, safety, PK, and PD of nipocalimab compared to placebo in adults (aged ≥18 years) with gMG inadequately controlled with standard-of-care therapy.			
Study identifier	Study code MOM-M281-011 EU CT number 2023-504152-97		
Analysis population and time point description	Treatment group	Placebo	Nipocalimab
	Number of subjects AChR+ subgroup	n=71	n=63
Descriptive statistics, estimate variability and effect estimate per comparison	RR for MG-ADL reduction ≥ 2 points over weeks 22-24 for AChR+ subgroup	54.9%	69.8%
	Subgroup analysis	Difference vs Placebo	14,9%
		95% CI	-1.3, 31.1
Analysis population and time point description	Treatment group	Placebo	Nipocalimab
Descriptive statistics, estimate variability and effect estimate per comparison	Number of subjects Musk+ subgroup	n=4	n=12
	RR for MG-ADL reduction ≥ 2 points over weeks 22-24 for Musk+ subgroup	0%	66,7%
	Subgroup analysis	Difference vs Placebo	66,7%
		95% CI	40.0, 93.3

2.6.5.4. Clinical studies in special populations

Paediatric Phase 2/3 Study MYG2001

Study MYG2001 is an open-label, uncontrolled, multicenter interventional study to evaluate pharmacokinetics, PD, safety, and activity of intravenous nipocalimab in paediatric gMG participants. The Active Treatment phase of the study is comprised of 2 cohorts: Cohort 1 includes adolescent gMG participants aged 12 to <18 years, and Cohort 2 includes children with gMG aged 2 to <12 years. The study enrolled participants who have a diagnosis of gMG, who have an insufficient clinical response to ongoing, stable SoC therapy, and meet the clinical criteria for gMG as defined by the MGFA Clinical Classification Class II a/b, III a/b, or IV a/b at screening. Additionally, participants must have a positive serologic test for a gMG-related pathogenic autoantibody (anti-AChR and/or anti-MuSK). The study did not specify a minimum MG-ADL or QMG total score at study entry. Eligible adolescents in Cohort 1 in the Active Treatment phase received nipocalimab (30 mg/kg IV initial single dose, followed by 15 mg/kg IV every two weeks thereafter). The proposed dose level and dosing regimen for nipocalimab in adolescents is the same as that selected for study M281-011 conducted in the adult gMG patient population and was based on extensive modeling and simulation of the dose-exposure-response relationships for IgG and MG-ADL using PK, PD, and efficacy data from the adult Phase 1 and Phase 2 studies (M281-001 and M281-004).

Results

An interval CSR based on the data cutoff of 23 August 2024 is provided. This interval analysis was conducted when the first 7 (out of the 8 enrolled) participants from Cohort 1 completed Week 24 of the Active Treatment phase. At the time of the data cutoff, of the 7 participants who completed the Active Treatment phase, 6 entered the long term extension (LTE) phase. Of the 6 participants in the LTE, 5

remained active in the LTE and 1 discontinued the study. In addition to these 7 participants, there is 1 enrolled participant that remains ongoing in the Active Treatment phase. Enrollment for Cohort 1 remains open and enrollment for Cohort 2 opened in 2024 but at the time of the clinical cutoff, no participants were enrolled. Thus, the interval CSR is limited to the analysis of the data collected from the adolescent Cohort 1 (≥ 12 to < 18 years of age) only.

Primary Endpoint

Rapid and sustained total serum IgG reduction was observed following 30 mg/kg initial dose and 15 mg/kg Q2W IV doses. At Week 24, the median (IQ range) predose (minimal) percent change in total IgG from baseline was -73.3% (-78.7%; -62.8%). The effect of nipocalimab on total serum IgG, assessed every 12 weeks, was generally sustained in the LTE. Similar to reductions in total serum IgG, rapid and sustained reductions in all serum IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were also observed. At Week 24, the median predose (minimal) percent changes in IgG1, IgG2, IgG3, and IgG4 from baseline were -68.7%, -74.4%, -53.9%, and -53.3%, respectively. At steady state, median serum nipocalimab concentrations after the end of infusion (C_{eoi}) ranged from 356.50 to 394.00 $\mu\text{g/mL}$ and median pre-infusion trough serum nipocalimab concentrations (C_{trough}) were all below the lower limit of quantification ($< 0.01 \mu\text{g/mL}$). No accumulations in serum nipocalimab concentrations over time were observed.

Secondary Endpoints

In the Active Treatment phase, of the 7 participants who had 24 weeks of treatment, the mean (SD) change from baseline in MG-ADL total score was -2.57 (0.535) at Week 24. In the Active Treatment phase, of the 7 participants who had 24 weeks of treatment, the mean (SD) change from baseline in QMG score was -4.93 (3.81) at Week 24. The applicant concludes that in the paediatric study, nipocalimab showed rapid and sustained IgG reduction. The pattern of improvement in MG-ADL and QMG observed in the adolescent participants was consistent with efficacy results from the adult study. These results support the similarity in PK, PD, and efficacy between adolescents and adults with gMG, allowing to extrapolate efficacy from the adult to the adolescent population.

Immunogenicity

The incidence of treatment-emergent antibodies to nipocalimab through the end of study visit was 1 (12.5%) participant. Titer of antibodies to nipocalimab was low (1:10). The participant who was positive for treatment-emergent antibodies to nipocalimab had post-treatment serum samples available for NAb assessment, and this ADA-positive participant was negative for NAb to nipocalimab through end of study visit. Therefore, none of the 8 participants were positive for NAb to nipocalimab.

2.6.5.5. *In vitro* biomarker test for patient selection for efficacy

Not applicable.

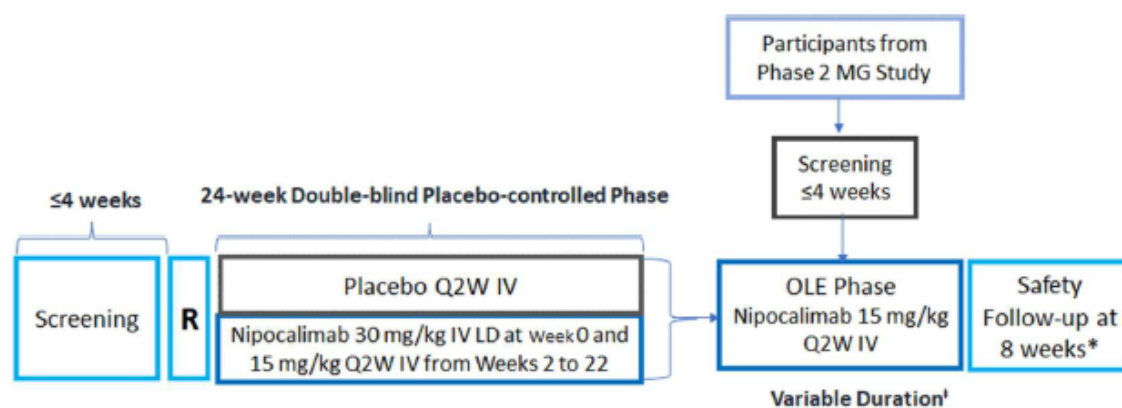
2.6.5.6. *Analysis performed across trials (pooled analyses and meta-analysis)*

Not applicable

2.6.5.7. *Supportive study(ies)*

Open-label Extension Phase of Study MOM-M281-011

Figure 30. Study design



R: randomization into double-blind phase (1:1); LD: loading dose; OLE: open-label extension

* Participants who withdraw or discontinue after receiving any amount of study intervention are required to complete a safety follow-up visit 8 weeks after their last dose.

† In the EU, the OLE phase will be up to 192 weeks.

Participants who completed the DB placebo-controlled phase could continue in an OLE phase where treatment with nipocalimab would continue until 2 years after marketing authorization in a participant's local country/territory or until nipocalimab would become available commercially or via other continued access program, whichever would come first. Assessments done at the Week 24 visit of the DB placebo-controlled phase served as baseline (first visit) of the OLE phase, and participants received their first infusion of open-label nipocalimab during the same visit after completion of the Week 24 visit assessments.

The OLE phase was open to 2 groups of participants: participants who had completed the 24-week DB placebo-controlled phase of MOM-M281-011, and former participants in the nipocalimab MOM-M281-004 study or MOM-M281-005 study. Participants from Study 004 and 005 underwent a screening assessment to confirm eligibility for entry into the OLE phase of the study. Participants who during the DB phase of Study 011 had study intervention discontinued for a reason other than a Clinical Deterioration requiring hospitalization or rescue therapy (IVIg, plasmapheresis), and who completed the scheduled of assessments for the full 24-week DB placebo-controlled phase, could enter the OLE based on the investigator's discretion. Participants who had study intervention discontinued because of rescue therapy during the DB phase were eligible to enter the OLE phase based on investigator's discretion after completion of an end of phase (EOP) visit. In these instances, the EOP visit assessments would not be combined with those of the OLE Day 1 assessments. Additionally, while there was no fixed duration limit between EOP and OLE Day 1, in instances where the interval was greater than 4 weeks, the investigator assessed if it was appropriate to continue treatment in the OLE phase in consultation with the sponsor's medical monitor. Participants who received IVIg as rescue treatment during the DB placebo-controlled phase would need to wait at least 4 weeks before receiving nipocalimab in the OLE.

Exclusion criteria were the same as for the double blind phase of MOM-M281-011.

All participants enrolling in the OLE phase received nipocalimab 15 mg/kg Q2W by IV infusion starting on OLE Day 1. No other nipocalimab dosing regimen should be used. Tapering one of the participant's concomitant MG medications every 4 weeks was allowed in the OLE phase if the disease had been stable in the past 4 weeks as reflected by MG-ADL scores and based on the investigator's discretion.

Of 153 seropositive participants in the DB phase, 137 transitioned to the OLE phase, including 66 participants from the placebo group and 71 participants from the nipocalimab group. Two participants

randomized to nipocalimab in the DB period who experienced an AE of myasthenia gravis worsening had a per protocol interruption of nipocalimab treatment prior to restarting nipocalimab in the OLE. Additionally, 19 participants entered the OLE phase of Study MOM-M281-011 from the Phase 2 gMG studies (MOM M281 004 or MOM-M281-005). Note, as MOM-M281-004 was completed in June 2020, MOM-M281-005 was paused in April 2020 and terminated in December 2020, and enrollment in the Phase 3 gMG study started in July 2021, all participants entering from the Phase 2 gMG studies had not received nipocalimab for over 1 year. The use (incidence rate) of rescue medication in the OLE phase was not higher than the one observed in the DB phase. The percentage of participants that discontinued the study because of lack of efficacy was low. MG-ADL and QMG total score (mean) change from baseline during the double blind and OLE phase from a clinical cutoff on 23 August 2024 are shown below.

Outcomes and estimation

Figure 31. Myasthenia Gravis-Activities of daily living (MG-ADL) total score: arithmetic mean (+/-SE) value over time through OL week 48; seropositive efficacy (DB+OL) analysis set (Study MOM-M281-011)

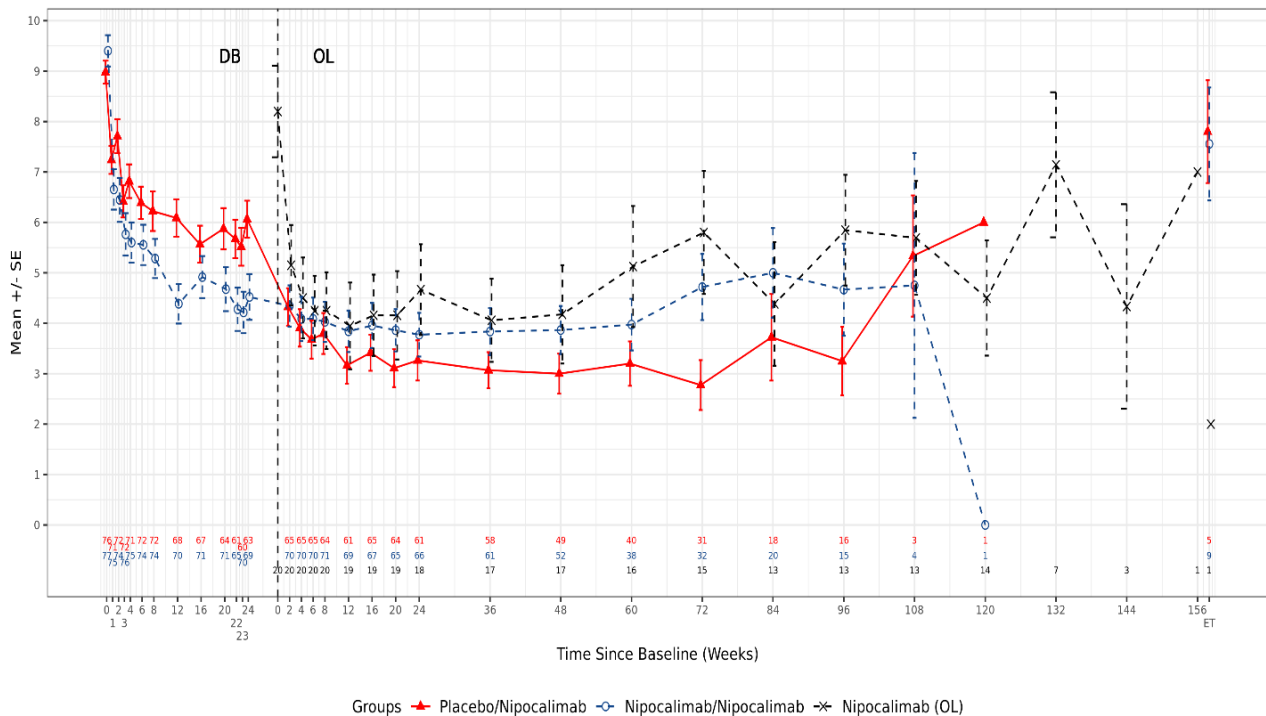
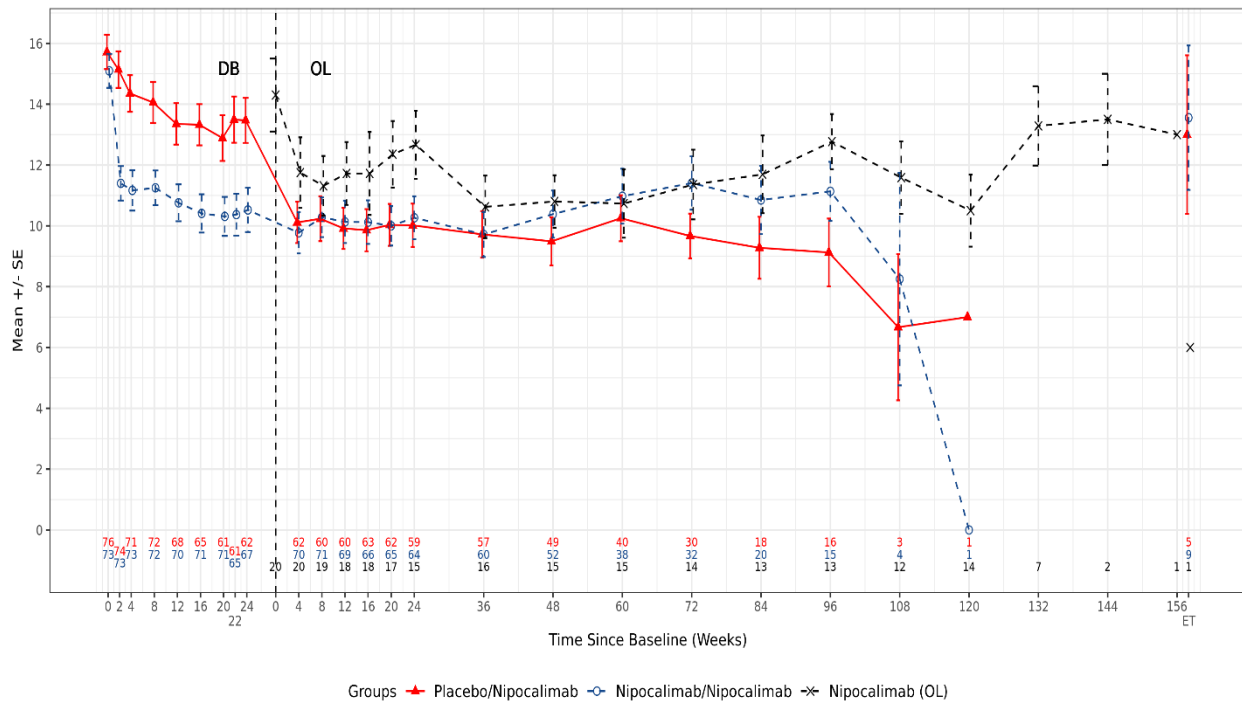


Figure 32. Quantitative Myasthenia Gravis (QMG) total score: arithmetic mean (+/-SE) value over time through OL week 48; seropositive efficacy (DB+OL) analysis set (Study MOM-M281-011)



Study MOM-M281-004

MOM-M281-004 (Study 004) was a POC, multicentre, randomized, DB, placebo-controlled study to evaluate the safety, tolerability, efficacy, PK, PD, and immunogenicity of nipocalimab compared with placebo when administered by IV infusion. Following a screening period of up to 4 weeks, eligible subjects were randomized 1:1:1:1:1 to one of 5 treatment groups (approximately 12 per group). The randomization was stratified first by autoantibody type (anti-MuSK vs anti-AChR), and for subjects positive for anti-AChR, the randomization was further stratified by baseline MG-ADL score (≤ 10 , > 10).

The treatment groups were as follows:

Treatment Arm	Infusion Timepoints				
	Day 1 Visit	Day 15 Visit	Day 29 Visit	Day 43 Visit	Day 57 Visit
Placebo Q2W	Placebo	Placebo	Placebo	Placebo	Placebo
Nipocalimab 5 mg/kg Q4W	Nipocalimab	Placebo	Nipocalimab	Placebo	Nipocalimab
Nipocalimab 30 mg/kg Q4W	Nipocalimab	Placebo	Nipocalimab	Placebo	Nipocalimab
Nipocalimab 60 mg/kg single dose	Nipocalimab	Placebo	Placebo	Placebo	Placebo
Nipocalimab 60 mg/kg Q2W	Nipocalimab	Nipocalimab	Nipocalimab	Nipocalimab	Nipocalimab

Efficacy was evaluated at Day 57. Upon completion of the study at Day 113, subjects had the option to enrol in a separate open-label extension study (MOM-M281-005) where all would receive treatment with nipocalimab.

No estimands were defined for this study. Efficacy analyses were conducted using the intention to treat population. The primary efficacy endpoint was the change from baseline to Day 57 in the total MG-ADL score for each treatment group compared with placebo, and was evaluated via dose-response analyses,

as well as MMRM analyses, using data at Days 15, 29, 43, and 57. Dose-response analyses included one-sided tests of linear trend and rank-based association. Models of MG-ADL Day 57 change score versus dose were explored. MMRM analyses included variables for baseline MG-ADL score, treatment-by-study week interaction, and autoantibody type, with variance-covariance structure assumed as compound symmetry. Covariates such as corticosteroids dose, use of immunosuppressants, and duration since MG diagnosis may be added to the model, and different variance-covariance structures may be explored. For MMRM analyses, two-sided tests with type I error rate of 5% were used.

All data was analysed as they were collected in the clinical database. Hence, missing values was generally not to be imputed except for in the specific situations: Missing MG-ADL, QMG, and MG-QOL15 individual item scores, Missing MG-ADL and QMG total scores. Because of mixed missing data patterns, the efficacy analysis will be performed using Multiple Imputation MCMC method.

Figure 33. Participant flow study 004

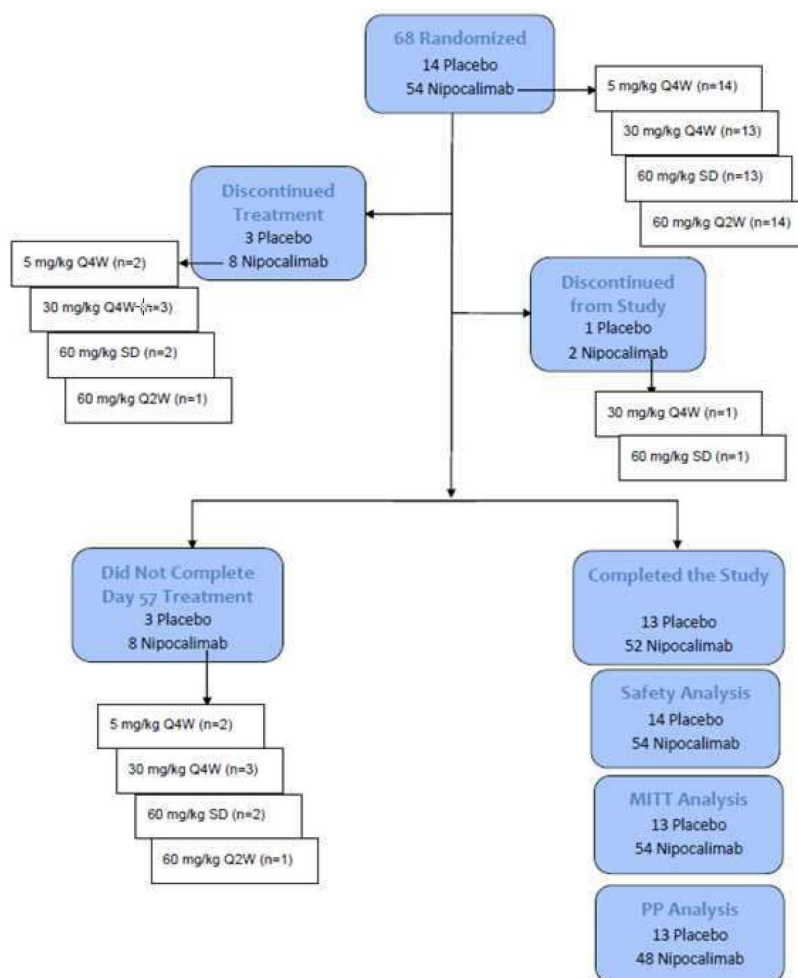


Table 25. Summary of baseline characteristics (ITT Population) study 004

All participants						
		Nipocalimab				
	Placebo Q2W	5 mg/kg Q4W	30 mg/kg Q4W	60 mg/kg Single Dose	60 mg/kg Q2W	Combined Nipocalimab
	(N=14)	(N=14)	(N=13)	(N=13)	(N=14)	(N=54)
Baseline MG-ADL Total Score						
n	14	14	13	13	14	54
Mean	7.3	8.0	8.0	7.9	8.1	8.0
Standard Deviation	2.79	2.75	2.61	2.78	3.25	2.78
Minimum	3	2	4	4	4	2
Median	6.5	8.0	8.0	8.0	7.0	7.5
Maximum	13	13	14	14	14	14
Baseline Quantitative Myasthenia Gravis Total Score						
n	14	14	13	13	14	54
Mean	17.6	15.9	17.1	16.1	16.9	16.5
Standard Deviation	4.20	2.93	4.23	4.07	2.79	3.48
Minimum	12	12	12	12	13	12
Median	17.0	16.0	16.0	15.0	17.0	16.0
Maximum	25	21	28	23	22	28
Time Since Symptom Onset (years)						
n	14	14	13	13	13	53
Mean	13.2	8.0	8.4	7.0	6.0	7.3
Standard Deviation	9.81	8.61	7.15	7.90	5.84	7.31
Minimum	1.8	0.7	0.8	0.7	0.6	0.6
Median	10.0	4.8	8.6	3.4	3.5	4.0
Maximum	29	26.3	25.8	27	22.9	27
Myasthenia Gravis Foundation of America Classification, n (%)						
I	0	0	0	0	0	0
IIa	2 (14.3)	2 (14.3)	2 (15.4)	3 (23.1)	2 (14.3)	9 (16.7)
IIb	3 (21.4)	4 (28.6)	1 (7.7)	2 (15.4)	4 (28.6)	11 (20.4)
IIIa	5 (35.7)	5 (35.7)	6 (46.2)	5 (38.5)	5 (35.7)	21 (38.9)
IIIb	3 (21.4)	3 (21.4)	2 (15.4)	3 (23.1)	3 (21.4)	11 (20.4)
IVa	1 (7.1)	0	2 (15.4)	0	0	2 (3.7)
IVb	0	0	0	0	0	0
V	0	0	0	0	0	0

All participants						
		Nipocalimab				
	Placebo Q2W	5 mg/kg Q4W	30 mg/kg Q4W	60 mg/kg Single Dose	60 mg/kg Q2W	Combined Nipocalimab
	(N=14)	(N=14)	(N=13)	(N=13)	(N=14)	(N=54)
Baseline BMI (kg/m ²)						
n	14	14	13	13	14	54
Mean	28.2	29.3	28.5	34.9	32.6	31.3
Standard Deviation	5.94	9.27	6.54	7.00	8.70	8.19
Minimum	17.5	17.6	19.7	21	17.9	17.6
Median	28.6	26.6	26.6	35.9	33.1	31.6
Maximum	42.7	50.3	41.2	44.1	51.6	51.6
Number of Myasthenia Gravis Crises						
n	13	13	13	10	13	49
Mean	0.8	0.4	0.8	0.8	0.8	0.7
Standard Deviation	1.14	0.65	1.36	1.62	1.24	1.21
Minimum	0	0	0	0	0	0
Median	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	3	2	4	5	4	5
Number of Clinical Deterioration Episodes						
n	13	13	12	12	14	51
Mean	2.9	1.1	2.7	2.8	1.4	2.0
Standard Deviation	1.80	1.32	2.81	2.12	2.06	2.20
Minimum	0	0	0	0	0	0
Median	3.0	1.0	2.0	2.0	0.5	2.0
Maximum	6	4	10	7	6	10
Antibody Status, n (%)						
Anti-AChR	13 (92.9)	13 (92.9)	12 (92.3)	13 (100)	13 (92.9)	51 (94.4)
Anti-MuSK	1 (7.1)	1 (7.1)	1 (7.7)	0	1 (7.1)	3 (5.6)
Thymectomy, n (%)						
All categories	11 (78.6%)	6 (42.9%)	8 (61.5%)	8 (61.5%)	6 (42.9%)	28 (53.8%)

All subjects received concomitant medications for the treatment of gMG during this study. The most commonly prescribed concomitant medications were anticholinesterases (90.7% subjects in the combined nipocalimab group and 85.7% subjects in the placebo group) followed by glucocorticoids (68.5% subjects in the combined nipocalimab group and 78.6% subjects in the placebo group) and by

non-steroidal immunosuppressants (42.6% subjects in the combined nipocalimab group and 57.1% subjects in the placebo group).

Outcomes and estimation Study 004

Primary analysis

The primary efficacy endpoint was the change from baseline to Day 57 in the MG-ADL total score for each nipocalimab dose group compared with placebo. At the primary efficacy time point, the greatest and most consistent reductions of MG-ADL were observed in subjects in the nipocalimab 30 mg/kg Q4W and 60 mg/kg Q2W treatment groups, though the differences between these groups and placebo at Day 57 did not reach statistical significance (LS mean difference vs placebo: -1.3 for both 30 mg/kg Q4W and 60 mg/kg Q2W groups).

A statistically significant linear trend over the placebo, 5 mg/kg Q4W, 30 mg/kg Q4W, and 60 mg/kg Q2W groups, with a positive dose-response trend, was observed for the change from baseline at Day 57 ($p=0.0310$). A similar analysis based on the rank of the change from baseline at Day 57 was also statistically significant ($p=0.0042$).

Figure 34. Mean change from baseline in MG-ADL by treatment group and study week (ITT population) study 004b

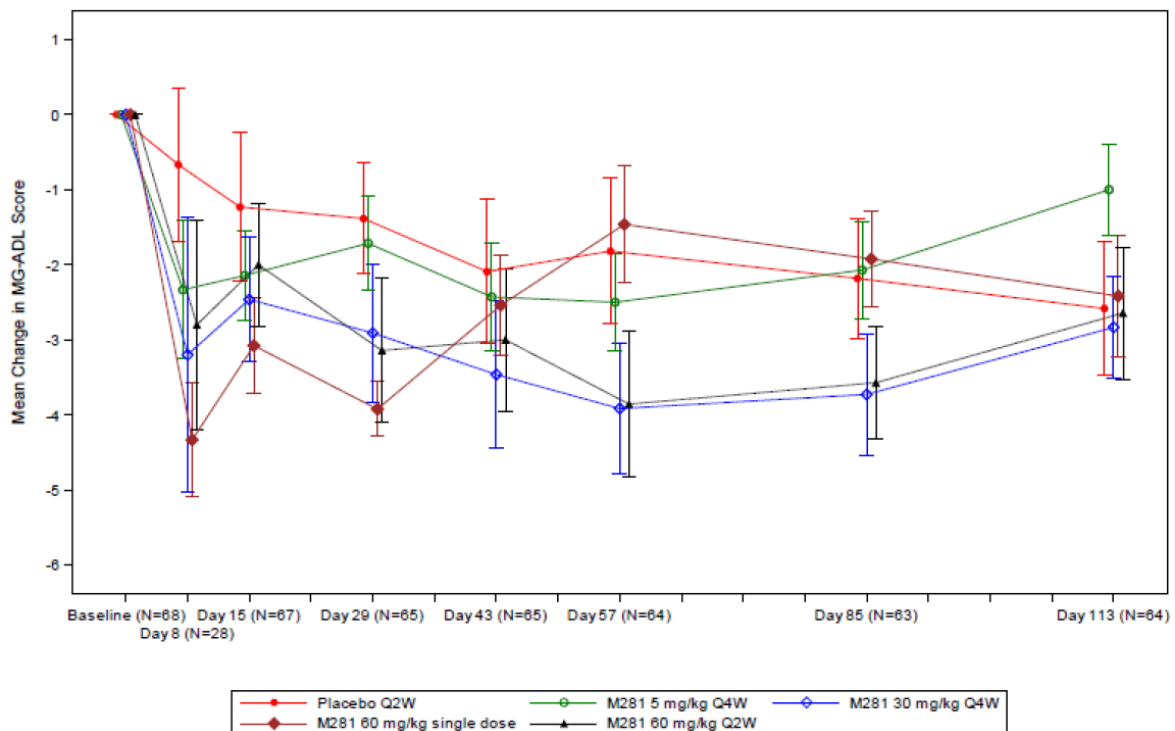


Table 26. MG-ADL by visit (ITT population) study 004

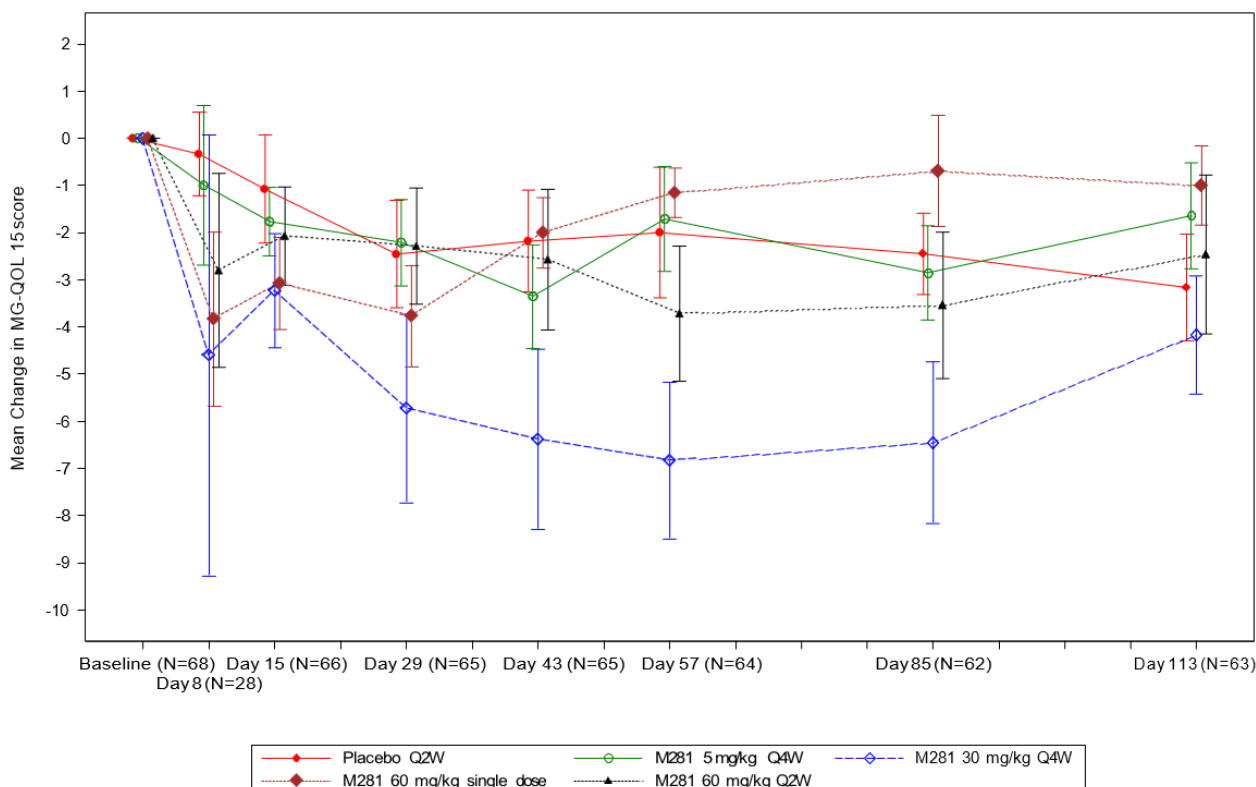
		Nipocalimab			
	Placebo q2w (N=14)	5 mg/kg q4w (N=14)	30 mg/kg q4w (N=13)	60 mg/kg Single Dose (N=13)	60 mg/kg q2w (N=14)
n	14	14	13	13	14
Mean	7.3	8.0	8.0	7.9	8.1
Standard Deviation	2.79	2.75	2.61	2.78	3.25
Minimum	3	2	4	4	4
Median	6.5	8.0	8.0	8.0	7.0
Maximum	13	13	14	14	14
Day 57					
n	11	14	12	13	14
Mean	5.2	5.5	4.0	6.5	4.3
Standard Deviation	3.09	3.32	2.63	3.84	2.95
Minimum	2	0	0	0	1
Median	4.0	6.0	4.0	5.0	3.5
Maximum	12	10	10	13	9
Day 57 Change from Baseline					
n	11	14	12	13	14
Mean	-1.8	-2.5	-3.9	-1.5	-3.9
Standard Deviation	3.22	2.41	3.00	2.82	3.66
Minimum	-9	-7	-10	-6	-11
Median	-2.0	-3.0	-3.0	-2.0	-3.5
Maximum	3	1	0	3	3
LS Means (SE) ^a	-2.4 (0.9)	-2.4 (0.9)	-3.7 (0.9)	-1.4 (1.0)	-3.7 (0.9)
Difference in LS Means (Active vs. Placebo) ^a		-0.0 (1.1)	-1.3 (1.1)	1.0 (1.1)	-1.3 (1.1)
95% CIs ^a		(-2.1, 2.1)	(-3.5, 0.9)	(-1.2, 3.1)	(-3.4, 0.8)
p-value ^a		0.9907	0.2439	0.3633	0.2231
p-value of Linear Trend Test of Change from Baseline ^b	0.0310				
p-value of Linear Trend Test Based on the Rank of 0.0042 Change from Baseline ^c					

A reduction in total QMG scores over time was observed following the administration of study agent in all treatment groups, including placebo. On Day 57, the greatest reductions from baseline in the mean total QMG scores were observed in subjects in the nipocalimab 30 mg/kg Q4W and 60 mg/kg Q2W treatment groups, though the differences between these groups and placebo at Day 57 (LS mean difference: -0.5 and -1.8 for 30 mg/kg Q4W and 60 mg/kg Q2W, respectively) did not reach statistical significance. Single-dose administration of nipocalimab 60 mg/kg also produced large reductions in mean

total QMG scores through Day 29 (Week 4; mean change from baseline: -2.2), with the maximum reduction at Day 15 (mean change from baseline: -4.1), but scores increased thereafter.

A reduction in total MG-QoL-15r over time was observed following administration of study agent in all treatment groups, including placebo. On Day 57, the greatest reductions from baseline in the mean total MG-QoL-15r scores were observed in subjects in the nipocalimab 30 mg/kg Q4W and 60 mg/kg Q2W treatment groups. The difference between the 30 mg/kg Q4W and placebo treatment groups at Day 57 reached statistical significance (LS mean difference: -5.1; $p=0.0054$).

Figure 35. Mean change from baseline in MG-QOL 15 over time (ITT population)



Study MOM-M281-005

Study MOM-M281-005 was a long-term, OLE study of participants who completed the POC study (MOM-M281-004) without discontinuing study drug during the POC study for reasons other than the need for rescue therapy as specified in the POC protocol, and who completed the protocol-specified 8 weeks of follow-up after the last dose of study drug in the POC study.

The Screening Period for the OLE study began at Day 85 POC Visit and ended upon enrollment in the OLE study. Eligibility for the OLE study was assessed and enrollment into the OLE study occurred at the participant's last follow-up visit in the POC study (Day 113 POC Visit). Eligibility was determined based on results of safety laboratory testing from the participant's Day 85 POC Visit, the assessments from the participant's Day 113 POC Visit, and additional procedures to be performed predose on OLE Day 1. Participants who enrolled in the OLE study initially received nipocalimab 30 mg/kg Q4W by IV infusion. This starting dose and dosing frequency was to be revised if available results from the POC study revealed a different optimal dose for development (without exceeding 60 mg/kg every 2 weeks). Participants were maintained on a stable nipocalimab dose and dosing frequency for at least the first 8 weeks of the OLE study, after which, the dose and/or dosing frequency of nipocalimab could be individually adjusted at

the discretion of the Investigator and previous consultation with the Medical Monitor, based on the participant's tolerability to nipocalimab and the participant's MG status.

The duration of each participant's participation in the MOM-M281-005 study was planned to be approximately 1 year or until the study was terminated by the Sponsor. The study was paused due to the COVID-19 pandemic in April 2020. Out of an abundance of caution, the Sponsor suspended all dosing and site visits with nipocalimab to mitigate the potential exposure of participants to the SARS CoV-2. Subsequently, in December 2020, the Sponsor made the decision not to re-initiate the study due to continued global feasibility challenges posed by COVID-19.

Thirty-seven participants were enrolled in this study. In the All Nipocalimab group, the mean (SD) age was 53.2 (17.3) years with a median of 58 years (range: 24 to 83 years). Twenty-two participants were female (59.5%) and 15 were male (40.5%).

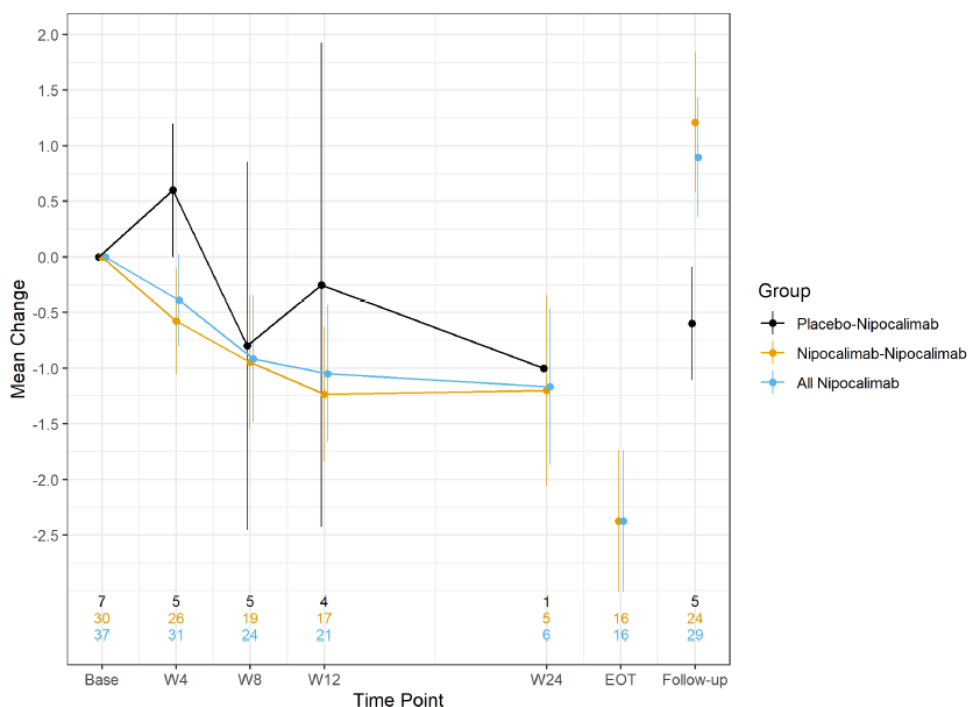
Efficacy results

Efficacy analyses were performed on the full analysis set. Six participants did not have a post-baseline visit and, therefore, did not contribute to summaries of change from baseline. The mean MG-ADL score at baseline in the All Nipocalimab group was 5.6. Mean change from baseline in the All Nipocalimab group for timepoints with at least 10 participants, was -0.4, -0.9, -1.0, -2.4, and 0.9 for Weeks 4, 8, 12, end of treatment, and follow up, respectively (Figure 36). According to the applicant, these results indicate a gradual improvement (ie, negative change) of MD-ADL scores over time.

For QMG scores, the mean change from baseline in score values was - 0.8, 0.1, -1.0, -2.7, -2.4, and - 1.8 for Weeks 4, 8, 12, 24, end of treatment, and follow up, respectively. Overall results indicate an improvement (ie, negative change) of QMG scores over time.

Results for MG-QoL-15r scores also show a gradual improvement over time. The mean change from baseline in score values for timepoints with at least 10 participants was -1.6, -1.6, -2.9, -3.7, and -0.2 for Weeks 4, 8, 12, end of treatment, and follow up, respectively.

Figure 36. MG-ADL total score: mean change from baseline ($\pm$ SE) over time study 005



2.6.6. Discussion on clinical efficacy

The proposed indication for nipocalimab was: *"as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are antibody positive (anti-acetylcholine receptor [AChR], anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor 4 [LRP4])."* The indication has been amended to *"as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive"*. Posology is based on results from MOM-M281-004, a phase 2, dose finding study that provided PK and efficacy data to simulate a posology to be studied in the phase three single pivotal trial. Four dosing regimens plus placebo were studied. The recommended dose regimen in SmPC is *"an initial single dose of 30 mg/kg administered intravenously, followed by a maintenance dose of 15 mg/kg every 2 weeks thereafter"*, the same posology that was used in the pivotal phase 3 trial.

The evidence of the efficacy of nipocalimab in the intended indication is based on data from one 24-week multicenter, randomized, DB, placebo-controlled study of nipocalimab compared to placebo in adults (aged ≥ 18 years) with gMG inadequately controlled with standard-of-care therapy (Study MOM-M281-011). The maintenance of the effect is based on data from the OLE of the MOM-M281-011 (ongoing, cut-off date of 23 August 2024). The data of a Phase 2/3 paediatric study MYG2001 were provided as supportive for the indication in adolescents.

No CHMP Guideline on the treatment of gMG is currently available. Prior to initiation of the Phase 3 study M281-011, the applicant received CHMP scientific advice (EMA/SA/0000049032; 25 February 2021) on the adequacy of the clinical development program, and specifically on the Phase 3 study design, to support the filing of a MAA for the indication of gMG. The CHMP broadly agreed with the study design. Given the rarity of gMG, the CHMP noted that a single pivotal trial may, potentially, suffice to support the indication, if compelling results across variables are shown in line with the EMA Points to Consider on *"Application with 1. Metaanalyses; 2. One pivotal study"*. The CHMP recommended to update the DB treatment phase from 3 to 6 months to show the maintenance of IgG reduction over a longer period of time, considering nipocalimab may conceivably be given chronically. Therefore, the treatment duration was increased to 6 months. The primary endpoint (ie, change from baseline to the average MG-ADL score at the end of the DB period) and secondary endpoints were considered acceptable. However, an average of MG-ADL score over the last 3 weeks of the DB treatment period was used, instead of 4 weeks proposed in the SA. As part of this scientific advice procedure, the CHMP agreed that no renal, hepatic, or special population studies were required.

Design and conduct of clinical studies

The design of the pivotal trial was a phase 3, multicenter, randomized, DB, placebo-controlled parallel group study. The trial included adult participants (≥ 18 years of age) who met MGFA Clinical Classification Class II a/b, III a/b, or IV a/b for gMG, and were not well controlled with their current SoC gMG therapy (MG-ADL scores ≥ 6 at screening and baseline) or, who had discontinued gMG therapy ≥ 4 weeks prior to screening due to intolerance or lack of efficacy. All participants received a planned total of 12 IV infusions over a 24-week period. Rescue therapy was permitted and resulted in discontinuation of the patient from the randomized treatment. The placebo-control design is acceptable since acetylcholinesterase inhibitors, glucocorticosteroids and other immunosuppressants were allowed in both arms. MG-ADL scores ≥ 6 at screening and baseline are also acceptable. Concomitant gMG medications accepted in both treatment arms through the trial were acetylcholinesterase inhibitors, steroids and other immunosuppressants specified in the inclusion and exclusion criteria. All other immunosuppressants were prohibited which is acceptable. The dose of acetylcholinesterase inhibitors could change during the trial while it was encouraged that the dose of steroids and immunosuppressants remain stable. Acetylcholinesterase

inhibitor dose was withheld for 12 hours before rating, which minimizes the effect of dose change on the endpoints (please see below). Permitted rescue therapy was intravenous immunoglobulin (IVIg) and plasmapheresis but not increasing doses of SoC medications such as steroids. If rescue therapy was needed, the participant was discontinued from the trial. Definition and statistical methodology for rescue treatment is acceptable.

The overall study design including the choice of comparator and patient selection is generally considered acceptable although the length of follow-up is in the shorter/middle spectrum.

The study included only patients with generalized MG as reflected by the *MGFA classification II-IV*. Patients with ocular myasthenia (I) and myasthenic crisis (V) within 1 month prior to screening were excluded which is supported. An appropriate statement in section 4.4 regarding the lack of data for MGFA class V with a reference to section 4.5 regarding interactions of nipocalimab with established therapies for myasthenic crisis is included in the SmPC. Patients with gMG crisis need rapid-onset, acute care, and nipocalimab has not been studied in this context. Of additional concern, nipocalimab could impair efficacy of IVIg which is used to treat myasthenic crisis. IVIg acts via saturation of the FcRn receptor, and IVIGs are dependent on FcRn "recycling" in order to sustain this saturation. Due to its mechanism of action, nipocalimab affects the elimination of therapeutic IgGs and this is currently addressed in Section 4.5 of the SmPC. Nipocalimab may also interact with therapeutic plasma exchange (PLEX), which is also used in MG crisis (PLEX, or plasmapheresis, would remove nipocalimab from the circulation). This is now also addressed in Section 4.5 of the SmPC.

Acetylcholinesterase inhibitor dose must be stable for 2 weeks at screening, but the dose can be changed during the trial. In clinical practice, frequent titrations of acetylcholinesterase inhibitors is not necessarily a reflection of significant changes in the underlying disease severity. gMG fluctuates and use of acetylcholinesterase inhibitors is often tailored to this. Acetylcholinesterase inhibitors have a short half-life and rapid onset-of-action. Dose change of acetylcholinesterase inhibitors was allowed in the DB phase which could potentially influence efficacy results (primary endpoint MG-ADL based on a 7-day recall period). The applicant explained that dose changes were permitted if "medically necessary" but had to be recorded. A stable dose for at least 2 weeks before trial entry was required. This is acceptable.

The evaluation of efficacy (primary and most secondary endpoints) was based primarily on the subjective assessment of MG symptoms by the patient (MG-ADL). MG-ADL is a validated clinical tool which reflects functional disability of MG patients in real life, has acceptable reliability and has good responsiveness to clinical change. A 2-point improvement in the MG-ADL indicates clinical improvement with 77% sensitivity and 82% specificity. (Muppidi et.al., 2011, PMID: 22006686) A ≥ 2 -point improvement in MG-ADL total score from Baseline at Week 24 can be considered as clinically meaningful threshold for the primary endpoint. The primary endpoint consists of an average of MG-ADL scores from weeks 22, 23 and 24. As gMG may fluctuate over time, the effort to administer the score at the same time of day and the use of average of three assessments instead of one single assessment, is acknowledged. A two-physician concept was not used in the MOM-281-011. Other efforts were made to ensure blinding, and the applicant argues that most sites enrolled a very low number of patients. A lower risk of functional unblinding with inclusion of a low number of patients per trial site is agreed (and furthermore use of a two-physician concept would likely be more complicated at minor trial sites). Functional unblinding would most likely occur after observing a pattern in several consecutive patients (i.e. common adverse events, consistent changes in efficacy parameters). This is especially true in a population of patients with clear fluctuations in both groups and on other SoC treatments with overlapping safety profiles (i.e. increased risk of infection). The key secondary endpoint defined as average change in QMG score over Weeks 22 and 24, was the only quantitative evaluation of relevant muscle groups by a physician. QMG is a quantitative, validated direct physician assessment scoring system of relevant muscle groups. A 3-point difference has been shown to correlate with clinically meaningful change. (Katzberg et.al., 2011, PMID: 24810970) QMG was scored after the patient had been off acetylcholinesterase inhibitors for 12 hours

which is routine in QMG assessment. The second in hierarchy key secondary endpoint was the percentage of participants whose average improvement in MG-ADL total score over weeks 22, 23, and 24 was at least a 2-point improvement compared to baseline. Other key secondary endpoints were: -Percentage of participants with improvement in MG-ADL total score ≥ 2 points at Week 1 and/or Week 2 of DB phase; - Percentage of participants with improvement in MG-ADL total score ≥ 2 points at Week 4 through Week 24; and -Percentage of participants whose average improvement in MG-ADL total score over Weeks 22, 23, and 24 of the DB phase is at least a 50% improvement from baseline. Overall, the primary endpoint and key secondary endpoints are acceptable and considered relevant to assess the benefit of nipocalimab. During evaluation of clinical significance and relevance, it should be kept in mind that the magnitude of change required to indicate an improvement or worsening of the condition is variable and depends on the severity of MG. (<https://myasthenia.org/Professionals/Resources-for-Professionals>)

Statistical issues

The applicant has defined three different primary estimands for three different geographical regions (EU, US/ROW and Japan). The estimand defined for EU regulatory interactions is considered as the primary estimand, the other estimands are considered as supplementary. The main analysis set for efficacy analyses for EU was the Primary efficacy analysis set which included all randomized seropositive participants who received at least 1 dose (partial or complete) of any study intervention in the DB phase. The primary estimand for EU is a treatment policy estimand with regards to termination or changes in randomised treatment or stable background gMG therapy, but hypothetical with regards to rescue treatment. A supplementary estimand handling all intercurrent events with a hypothetical strategy (primary for US/ROW) was used as well as a supplementary estimand handling all intercurrent events with a hypothetical strategy and using the full population i.e. not only seropositive subjects (one of the primary estimands for Japan). The population of the estimand should refer to the target population and not the trial population. Hence, population should have been defined as adult and adolescent patients aged 12 years of age and older who are anti-AChR, anti-MuSK or anti-LRP4 antibody positive. Other than that the defined estimands for the primary endpoint are acceptable.

For continuous secondary endpoints, estimands were defined as for the primary endpoint. For binary secondary endpoints all ICEs were handled with a composite strategy, i.e. "non-response" was imputed for all timepoints after the ICE. Although the reason for handling ICEs differently for binary endpoints is not completely understood, it is considered acceptable as the primary approach.

The main analysis set for efficacy analyses was the *Primary efficacy analysis set* which included all randomized seropositive participants who received at least one dose (partial or complete) of any study intervention in the DB phase. Supplementary analyses using the *Full analysis set* (seronegative and seropositive participants) were also performed.

The primary efficacy endpoint (the average change from baseline in MG-ADL total score over Weeks 22, 23, and 24 of the DB phase) was analysed using a MMRM. The between-group difference of the average change over Weeks 22, 23, and 24 was tested with an F-test of the linear contrast that averages the change from baseline over those time points. Secondary endpoint QMG total score over Weeks 22 and 24 was analysed similarly as the primary endpoint. The MG-ADL binary responder endpoints was analysed by Cochran-Mantel-Haenszel tests with a composite strategy for all ICEs (i.e. non-responder imputation). The primary and key secondary null hypotheses were tested in a pre-specified hierarchical order, controlling the family-wise Type 1 error rate at 0.05.

Non-monotone missing data were imputed using MCMC methods assuming MAR. In total 14 (18%) placebo subjects and 13 (17%) nipocalimab subjects had an ICE. The number of visits with missing data after an ICE ranges from 1 participant with missing observations at 11 of 12 visits to 5 participants with no missing data. In total, there are 69 participant-visits with missing data among the 14 placebo-treated

participants with an ICE and 48 participant-visits with missing data among the 13 nipocalimab-treated participants with an ICE. The number and reasons for ICE and missing data are sufficiently similar between the two treatment groups not to cause concern. Furthermore, the applicant states that among the 8 participants with a change in stable gMG therapy, 5 participants (2 placebo, 3 nipocalimab) had an increase in their steroid dose, 3 participants (1 placebo, 2 nipocalimab) had a decrease in their steroid dose, and 1 participant (nipocalimab) discontinued their immunosuppressant. This does not cause concern and it is agreed that no additional analyses are needed.

The sample size calculation assumed a difference between treatment groups of 1.7 in MG-ADL total score. In the central scientific advice, a difference between treatment groups of at least 2 units was suggested to be clinically relevant.

There were minor amendments to the statistical analysis plan (SAP), and the SAP were finalised before database lock. The total sample size was increased in an amendment to allow for inclusion of seronegative subjects (due to the primary estimand for Japan). In the end, 153 eligible seropositive participants were enrolled, which is in line with the initial sample size calculation.

Overall, the statistical analyses are considered appropriate and adequate for testing the study hypotheses.

Study population at baseline

196 patients were treated in the DB phase (98 in each group). The primary efficacy analysis set included 76 patients in the placebo and 77 patients in the nipocalimab arm. Across both treatment groups, most participants entered the study due to suboptimal response to current MG medications (75 out of 76 participants in the placebo group and 74 out of 77 participants in the nipocalimab group). Major protocol deviations (MPDs) related to not satisfying study criteria were balanced between the placebo and nipocalimab group. Aside from 7 MPDs, all others were addressed by pre-specified statistical methods for the estimand described in the SAP or were missed safety assessments that did not impact the overall safety of the participants. The applicant has performed an analysis excluding these 7 participants with MPDs which resulted in similar efficacy results for the primary outcome. Three participants were randomised in error but never treated with investigational product and, therefore, were not part of the primary analysis population. This is acceptable since this is not expected to have introduced any bias in the analyses. One randomised, seropositive placebo-treated participant did not have any post-baseline assessments and was not included in MMRM analyses of change from baseline. For analyses of response, this participant was treated as not meeting response criteria at any post-baseline timepoint (per the SAP-defined composite strategy). This subject should preferably have been included also in the MMRM analyses using suitable imputation. However, only one subject is not expected to alter any conclusions, and this is hence accepted.

It is noted that participants, in both groups, have moderate-severe baseline disease with a median MG-ADL of 8.5 (range: 6-18). The number of patients experiencing worsening of gMG, MG crisis and using rescue medication was similar across both treatment arms. The number is not higher than expected, given the moderate-severe disease status at baseline. Likewise, pre-trial history of MG crisis was similar across treatment groups (31.2-38.2%). In total 13 participants with thymoma were included in the primary efficacy analysis set. The distribution was similar between the placebo- and nipocalimab group (8 in placebo arm and 5 in nipocalimab arm, corresponding to 10.5% and 6.5%, respectively). It is further noted that thymomas were even rarer in the age group ≥ 65 years (0 in placebo, n=1 in nipocalimab arm). Only 2 patients had a thymoma which was classified as a neoplasm/malignant (1 in each arm) - it is unclear if this is compliant with "stage I or IIa" but given the low number, and similar distribution across study groups, no significant impact on efficacy is expected. The number of patients with prior thymectomy is considered low given disease severity, young age at onset for most patients, and highly frequent AChR-seropositivity (typical requirements for recommending thymectomy). This is

not considered to impact generalizability. Thymectomy frequency was similar in both treatment arms (n=16 in placebo and n=11 or n=12 in active arm, corresponding to ~16% and 11-12%, respectively). In terms of the timing thymectomy was done between 4-25 years prior to inclusion in placebo arm and between 1-33 years prior to inclusion in active arm. Only few had been thymectomized <5 years prior to inclusion (2 in placebo arm, 4 in active arm). The impact of any improvements mediated by thymectomy, and not by the study drug itself, is considered negligible.

The doses of immunosuppressants, including prednisone equivalent doses of corticosteroid, were within the expected range. Apart from the difference in proportion of tacrolimus and mycophenolate mofetil, there appears to be no substantial difference between the treatment regimes in terms of dose (variation is to be expected as several of these medications are titrated on basis of weight, clinical response and potentially subject to therapeutic drug monitoring). The studied population is sufficiently reflective of the intended target population, and no significant impact on the validity of the results is expected.

Discontinuations

Numerically, more patients discontinued in the placebo-group (n= 16, 16.3%) than the nipocalimab group (n=11, 11.2%). Two patients discontinued due to "lack of efficacy" in the placebo group, none in the nipocalimab group. AEs resulted in discontinuation in 7.1% (n=7) in the placebo arm and 4.1% (n=4) in the active arm. 6 patients had AEs related to MG, which could be potentially considered associated with lack of efficacy – but the number was higher in the placebo group. Discontinuation due to disease relapse and progressive disease were rare and occurred early in the trial (week 3-6) before significant benefit could have been expected. One discontinuation after a death was potentially related to lack of efficacy (MG crisis in nipocalimab arm in week 13). This outcome was not considered unexpected given the disease severity in the patient population. Thus, 7 patients potentially or certainly left the trial due to lack of efficacy in the placebo arm. In the nipocalimab arm this number was 5. It appears that these discontinuations favor nipocalimab slightly, even when other reasons potentially related to lack of efficacy are considered. Discontinuation after protocol deviations was similar in both arms, including the reason. Overall, the effects of discontinuations in the trial results is considered negligible.

Efficacy data and additional analyses

The pivotal phase 3 trial MOM-M281-011 met its primary endpoint with regard to statistical significance. Nipocalimab demonstrated statistically significant improvement in MG-ADL total score change from baseline over weeks 22-24 compared to placebo in the primary efficacy analysis set (p=0.003). In a development program with only one pivotal study statistically compelling results, usually referred to as a p-value <0.001, are required to reduce the risk of a type one error when robust support from other trials is lacking. However, p=0.003 can be regarded as sufficiently compelling being in the proximity of what is usually required and when considering the size of the study.

For primary analysis for EU, where ICE such as discontinuations of study intervention or stable gMG therapy and changes in stable MG treatment (not due to rescue) were addressed with a treatment policy strategy while rescue was handled with the hypothetical that the ICE had not occurred, the LS mean difference was 1.39 (95% CI: -2.31, -0.47). For primary analysis for US/ROW, where all ICEs were handled with the hypothetical that the ICE had not occurred, the LS mean difference was similar: 1.45 (95% CI: -2.38, -0.52, p=0.002). In the sensitivity analyses, missing observations were handled with the CR MI method. An analysis using the J2R MI method was performed to assess the robustness of the results using the CR method and the results were similar (LS mean -1.35 [95% CI: -2.30, -0.41]).

Average change in QMG score over Weeks 22 and 24 of DB phase was the first key secondary endpoint in testing hierarchy, and also displayed statistical significance with nipocalimab demonstrating improvement in change from baseline in QMG total score over Weeks 22 and 24 of treatment compared

to placebo ($p < 0.001$); LS means difference: -2.87 (95% CI: -4.23, -1.50). Sensitivity analyses with CR MI method and J2R displayed similar results (-2.46 [95% CI: -3.89, -1.03]). The percentage of MG-ADL responders was the second secondary endpoint and nipocalimab showed a statistically significant greater percentage of MG-ADL responders with average improvement from baseline in MG-ADL of at least 2 points compared to placebo (68.8% vs 52.6%, respectively; $p = 0.021$). The difference in responder proportion between nipocalimab and placebo is approximately 16% and thus number needed to treat to achieve one responder with ≥ 2 point change in MG-ADL is approximately 6. The third secondary endpoint regarding proportion of early responders during week 1 and/or 2 did not reach statistical significance and, thus, the formal testing stops after this endpoint. Other endpoints related to MG-ADL and QMG may, given their high clinical relevance be included in the discussion and may support nipocalimab efficacy meaningfulness as displaying higher proportion of MG-ADL responders with sustained response from Week 4 through Week 24 in nipocalimab-treated participants (55.8%) than placebo-treated participants (26.3%) (LS mean difference 29.5%; 95% CI: 14.7, 44.4). An average improvement in MG-ADL scores from baseline of at least 50% was also observed at a greater proportion in the nipocalimab group (46.8%) than in placebo group (25%) over Weeks 22, 23, and 24 (LS mean difference 21.8%; 95% CI: 7.0, 36.3). Other scales of interest e.g. MG-QoL15r, Neuro-QoL and EQ-5D-5L, showed a non-significant tendency supportive of nipocalimab.

The applicant concludes that "Nipocalimab demonstrated statistically significant and clinically meaningful improvement in MG-ADL scores compared to placebo, after 24 weeks of treatment". The second part of this conclusion was not fully agreed. The LS mean difference in MG-ADL between nipocalimab and placebo was -1.39 (95% CI: -2.31, -0.47), relatively far from what can be considered clinically meaningful. The MCID to classify an individual patient as a responder is 2 points (Muppidi et.al., 2011, PMID: 22006686) and as discussed in EMA/SA/0000049032 as well as in line with the guidance "*Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal Study*" (CPMP/EWP/2330/99)". The applicant refers to increased expectancy of efficacy as there were other new gMG products authorised before or during the phase 3 study, and claims this would result in a larger placebo effect. This may in principle be agreed, nevertheless, this placebo effect can be assumed to be of similar size in the two randomised groups and would therefore not affect the efficacy measured as the difference between nipocalimab and placebo. A more plausible explanation is a large regression to the mean effect depending on the inclusion criterion of MG-ADL ≥ 6 in gMG which is known to be a disease with relatively large fluctuations. In summary, no explanation for the large placebo effect can be established; albeit its effect in the interpretation of external validity can be considered minimal to negligible.

The LS mean difference in QMG between nipocalimab and placebo was -2.87 (95% CI: -4.23, -1.50), being marginally lower than the MCID which is considered to be 3 points (Katzberg et.al., 2011, PMID: 24810970). Minimal symptom expression was observed in a greater proportion of nipocalimab participants compared to placebo at week 24 (20.8% vs. 3.9%, respectively) and the results were consistent during the course of the study. Achieving minimal manifestation status is goal of treatment for MG patients in general and these results are thus in favour of clinical meaningfulness for nipocalimab.

Altogether, in the single pivotal study MOM-M281-011, with respect to the outcome of the primary endpoint (change in MG-ADL) it is noted that the effect size (-1.39 (95% CI: -2.31; -0.47)) can be considered as rather small. In addition, the large placebo response as well as other factors related to using an MCID to define responders, questioned the applicability of a ≥ 2 point improvement for MG-ADL for the definition of "responders" and queried the clinical relevance of the percentage difference in "responders" between nipocalimab and placebo. The applicant provided new requested data and analyses for a better characterisation of the clinical meaningfulness of the observed effect. The difference in percentages of "responders" between nipocalimab and placebo is observed to be driven by the participants that displayed ≥ 5 -point improvement for MG-ADL and ≥ 5 -point improvement for QMG while no apparent differences in percentages of patients that deteriorated was seen between nipocalimab and

placebo. The new analyses also suggest that the effect of nipocalimab in study MOM-M281-011 is more obvious in the group with baseline MG-ADL ≤ 9 , but that clinically meaningful effects can also be observed in patients with higher baseline MG-ADL. It is also observed that improvement for every individual component of MG-ADL is favoured by nipocalimab as compared to placebo. Differences in percentages between nipocalimab and placebo for ≥ 1 point improvement in individual components ranged from 7.4% to 23.7%.

Another clinically relevant endpoint was the one concerning the onset of response. Even if this was a secondary efficacy endpoint appearing below the breaking point of the sequential testing hierarchy, it may inform the physicians in clinical practice. There was no significant difference in the onset of response endpoint for the first 2 weeks while sustainability of response was reflected in 55.8% for nipocalimab and 26.3% of placebo participants (29.5% difference, 95% CI 14.7, 44.4). This information is important for the clinicians when evaluating the use of nipocalimab as bridging therapy or at the time of myasthenic exacerbations. Achieving minimal manifestation status is a goal of treatment for MG patients in general and thus the nominal improvement in the nipocalimab group versus the placebo group may support efficacy and also be a valuable piece of information to the prescribers.

During the DB phase changes to the dose of acetylcholinesterase inhibitors were allowed, and it was unclear if such changes could impact interpretation of efficacy. A graph of the longitudinal change in dose of acetylcholinesterase inhibitors, stratified by intervention group, was therefore requested. According to the data, the vast majority of the patients in the primary analysis were on stable doses of acetylcholinesterase inhibitors in both groups. The proportion was balanced between the two arms with only minor differences. Changes in a minor number of patients is not expected to impact overall interpretation of the B/R of nipocalimab. The concern was considered solved.

Efficacy in subgroup analyses

Variability of response was explored by subgroup analyses of MG-ADL and QMG total score performed under the Primary Estimand for US/ROW. Subgroup analyses results regarding AChR+ and MuSK+ patients, region Europe, sex, baseline MG-ADL and duration of MG were consistent with the overall group analyses. Even if few MuSK+ patients were included (5 placebo, 12 nipocalimab), the effect was similar to the whole group. The prerequisites for extrapolation of efficacy from anti-AChR+ gMG to anti-MuSK+ gMG have already been discussed and accepted for a product with similar mechanism of action as nipocalimab, and therefore, inclusion of anti-MuSK+ patients in the indication is accepted.

Subgroup analyses results in Region Europe, sex, body mass index (BMI), baseline MG-ADL and duration of MG were consistent with the overall group analyses. Regarding immunosuppressants (IST), for average MG-ADL change, the trend favoured nipocalimab in both groups, albeit with no nominal statistical significance in the "with IST" group. For the average QMG change from baseline over Weeks 22, and 24, the LS mean difference (95% CI) in the "with IST" group was -2.47 (-4.44; -0.49), and for the "without IST" group was -3.14 (-5.16; -1.12); both favoured nipocalimab and displayed nominal statistical significance.

More importantly age ≥ 65 years did not favour nipocalimab. An explorative analysis of age subgroups was performed, to further categorize age into 4 subgroups: 18 to <44, 44 to <65, 65 to <74, and ≥ 75 years. The applicant claims that plots show that in the subgroups of participants <75 years, the treatment differences favour nipocalimab over time, which is not agreed. This *post hoc* categorization does not seem to provide an explanation for a lack of effect in patients aged ≥ 65 years. Further analyses regarding baseline disease characteristics (thymoma, frequency/type of ISTs, co-morbidities) as well as changes in anti-AChR and anti-MuSK antibody levels did not provide any explanation for this result either. Although the numbers are small, it is observed that ICEs due to AEs were more frequent in the nipocalimab arm for patients aged ≥ 65 years (placebo 0, nipocalimab 2), as compared to those <65 years (placebo 5, nipocalimab 0). In summary, there is no apparent clinical or pathophysiological reason

that would explain a lack of effect of nipocalimab in patients aged ≥ 65 years. Furthermore, other FcRn targeting medications have shown an effect in this age subgroup. Overall, although a probable reason is that the limited sample size resulted in statistical uncertainties for the subgroup analyses, it is noted that an effect in patients aged ≥ 65 years, while presumed, has not been clinically demonstrated in this study.

Pharmacodynamic response, immunogenicity and efficacy

The effect of nipocalimab on total IgG, IgG-types and autoantibodies and correlation of total IgG with MG-ADL were also evaluated. Rapid and sustained reductions in all IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were observed during the DB phase through Week 24 in the nipocalimab group, which was consistent with reductions in total IgG and this is accepted and in accordance with other medications of the same type. Similar to reductions in total IgG, rapid and sustained reductions in pathogenic anti-AChR and anti-MuSK autoantibodies were observed. The results on anti-LRP4 autoantibodies are based on three patients and are more difficult to interpret. Adoptive transfer experiment from mice immunized with LRP4 and transfer of immunoglobulin from an anti-LRP4+ patient to mice suggest that anti-LRP4+ antibodies are pathogenic. Further, these antibodies are IgG1/IgG2 and nipocalimab reduces all IgG subclasses, including IgG1 and IgG2. Thus, a mechanistic rationale is suggested with studies supporting the pathogenicity of anti-LRP4+ antibodies and the fact that nipocalimab decreases levels of IgG1 and IgG2 subtypes, which are the IgG subtypes of anti-LRP4+ antibodies as reported earlier. An important question is whether it can then be expected that nipocalimab reduces specific anti-LRP4 antibodies since it generally lowers the levels of IgG1 and IgG2. Similarities or differences in the binding of specific antibodies as compared to their respective IgG subtype to FcRn does not appear to have been studied earlier. However, it is known that glycosylation can affect the binding of antibodies to FcRn (*Pizyk et.al., 2023, PMID: 36726033*). In rheumatoid arthritis, it has been previously reported that specific anti-citrullinated protein antibodies can have differences in degrees of fucosylation when compared to their IgG1 subtype (*Rombouts et. al., 2015; PMID: 24106048*). In a recent publication (*Cuquisana et. al., 2024, PMID: 38507656*), it was reported that anti-LRP4 and anti-AChR antibodies differ in how they activate complement, likely due to differences in glycosylation in the Fc region. Other studies have shown that specific variations in glycosylation might not affect binding to FcRn; albeit this has not been specifically studied for anti-LRP4 antibodies. In addition, even if an effect of nipocalimab on anti-LRP4+ antibodies would theoretically be anticipated, there is no such pattern observed from the 3 patients included in the study. Thus, extrapolating the effect of nipocalimab in reducing IgG1 and IgG2 subtypes to reducing specific anti-LRP4 antibodies may not be straightforward and more data that actually show that anti-LRP4 decreases with nipocalimab in a larger cohort are needed (PD marker). Moreover, the clinical trajectories "favour" the placebo arm in this small number of patients. Overall, due to the very low number of anti-LRP4+ patients in the study, no B/R assessment is possible for this subpopulation. The indication has been amended to: "*as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.*"

The correlation between baseline changes in MG-ADL and total IgG or anti-AChR antibodies has a low r of around 0.20-0.25 and might be driven by treatment as a confounder. The overall incidence of NAb to nipocalimab was 17 (17.5%) out of 97 participants treated with nipocalimab. The presence of detectable ADA or NAb to nipocalimab did not reduce the change and percent change in total IgG or anti-AChR from baseline. At week 24, patients with ADA ($n=35$) had a mean/median change from baseline in MG-ADL of -5.46/-5.50 and patients without ADA ($n=34$) had mean/median change from baseline in MG-ADL of -4.16/-3.25. Nab, thus, do not seem to reduce efficacy.

Long-term efficacy

Long-term efficacy was evaluated in the OLE study that included patients from studies 011, 004 and 005. The discrepancies in the inclusion criteria resulted in minor differences in baseline variables in Study

004 and 011 respectively: a) MG-ADL 8.0 vs 9.2 (≥ 4 in 004, ≥ 6 required in 011), b) QMG 16.5 vs 15.4 in Study 011 (≥ 12 required in 004), c) MGFA ≥ 3 63% vs 75%, d) MGFA ≥ 4 3.7% vs 12.4% (IVb not included in 004). The results from the OL study, with well-known caveats of open label design and withdrawal bias, supports the notion that treatment effect seems to be maintained over time in the open label period for the nipocalimab group and that the placebo and (OL) 004/005 group improved in MG-ADL and QMG scores. The percentage of participants that discontinued the study because of lack of efficacy was low ($< 3\%$ per 24 weeks) and the use (incidence rate) of rescue medication in the OLE phase was not higher than the one observed in the DB phase. A sustained response in the nipocalimab group is thus observed while a possible treatment effect in the placebo group is suggested. Although a treatment effect is also suggested for the (OL) 004/005 group by the data, this cannot be firmly established when considering the strong placebo response observed in the DB phase. Also, the strong placebo effect observed in the DB phase complicates the interpretation with regard to the effect size in both (OL) 004/005 and placebo groups.

Participants who received IVIg as rescue treatment during the DB phase would wait at least 4 weeks before receiving nipocalimab in the OLE. The applicant has explained the choice of 4 weeks between IVIg and nipocalimab based on the half-life of IVIg. However, some IgG-based monoclonal therapeutic antibodies may have longer (or shorter) half-life than IVIg. It is therefore not possible to introduce a specific time-interval recommendation that covers all medicinal products that bind to the immunoglobulin (IgG) binding site of the human FcRn. Such a recommendation is therefore not included in the SmPC.

Supportive proof of concept, dose-finding phase 2 study

Study 004 was a dose finding study and was not powered to reach statistical significance for efficacy. Four dosing regimens plus placebo were studied. Inclusion- and exclusion criteria reflect a broad adult gMG population with insufficient treatment response of SoC. Study drug or placebo was given as add on therapy to SoC. The primary efficacy endpoint (change from baseline in MG-ADL) was evaluated at day 57 which is early and change from baseline at one time point does not give any information about durability/stability of efficacy. The primary efficacy endpoint, change from baseline in MG-ADL at day 57 did not provide any statistically significant results but there were some numerical differences between placebo and 30 mg/kg Q4W, 60 mg/kg single dose, and 60 mg/kg Q2W, -1.3, -1.0 and -1.3 points, respectively, in favour of nipocalimab. These results might weakly support the results of the study 011. The applicant used PK and efficacy data from Study 004 in simulations to find an optimal posology, please see the pharmaceutical part and the dose finding section. Study 005 was an OLE of study 004. It started in mid-2019 and was paused due to the COVID19 pandemic in April 2020, and in December 2020, the Sponsor made the decision not to re-initiate the study due to COVID-19. Of the 68 patients who were randomised in the POC study 004, 37 entered the OLE 005 and of these 6 patients did not have a post-baseline visit and, therefore, did not contribute to summaries of change from baseline. During the study, there was a further loss of participants. This hampers the interpretation of the results substantially and the unfavourable study conditions have disabled reliable conclusions of this study.

Assessment of paediatric data on clinical efficacy

A paediatric study (MYG2001) is also included in the application as a supportive study with regard to the claimed indication for adolescents aged 12 to < 18 years. This study is an open-label, uncontrolled, multicenter interventional study to evaluate pharmacokinetics, PD, safety, and activity of intravenous nipocalimab in paediatric gMG participants. The Active Treatment phase of the study is comprised of 2 cohorts and the results from cohort 1, which includes adolescent gMG participants aged 12 to < 18 years, are presented.

At submission 7 patients were included and 5 completed 24 weeks. The mean (SD) change in MG-ADL after 24 weeks was -2.40 (0.418) with 100% ($n=5$) being MG-ADL responders (minimum of 2-point improvement at week 24). In 80% ($n=4$) MG-ADL reduction was $\geq 50\%$ improvement from baseline. QMG

mean (SD) change from baseline at week 24 was -3.80 (2.68). The applicant has also provided updated clinical efficacy data from study 80202135MYG2001 from an interval analysis (based on the data cutoff of 23 August 2024) that was conducted when the first 7 (out of the total 8 enrolled) adolescent participants from Cohort 1 completed Week 24 of the Active Treatment phase. An improvement in MG-ADL and QMG over time was noted for all 7 participants: a) Mean (SD) change from baseline in MG-ADL total score was -2.57 (0.535) at Week 24, b) mean (SD) change from baseline in QMG score was -4.93 (3.81) at Week 24. The applicant also conducted a sensitivity analysis which indicates that the adaptation only results in a minor impact, that is not considered clinically relevant, on the PK-profile. In addition, the observed concentrations and measured decrease in IgG in adolescents is within the range observed in adults. The data in adolescent support the dosing regimen, and the additional analyses add support to the proposed dose in adolescents. A thorough justification of similarity between adults with gMG and adolescents with gMG in terms of disease characteristics, treatment guidelines and response to treatment, drug pharmacology as well as differences in other factors that would affect response to treatment has been provided. The applicant has also provided thorough justifications for the indication of gMG for adolescents who are ≥ 12 years regardless of the pre/post pubertal onset of the disease. Both are acceptable.

2.6.7. Conclusions on the clinical efficacy

The clinical efficacy of nipocalimab in gMG has been evaluated in a single, pivotal Phase 3 multi-center, DB, randomized, placebo-controlled 24-week study (MOM-281-011) and an open-label study in 7 adolescents with seropositive gMG (MYG2001). The applicant initially proposed the following indication:

"... add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are antibody positive (anti-acetylcholine receptor [AChR], anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor 4 [LRP4])"

Evidence of the efficacy of nipocalimab on anti-AChR and -MuSK positive gMG with regard to MG-ADL and QMG reductions and responder variables was demonstrated in the single pivotal phase 3 study. Careful examination of the primary and key secondary endpoints in terms of effect characteristics and size suggests a clinically meaningful effect. Other secondary endpoints such as sustainability of response, $\geq 50\%$ change and the clinical treatment goal of achieving minimal manifestation status, even if appearing below the testing hierarchy breaking point, lend some support to relevant efficacy. The applicant has also provided thorough justifications for the indication of gMG for adolescents who are ≥ 12 years regardless of the pre/post pubertal onset of the disease and PK data and additional analyses support the dosing regimen extrapolation of the indication to adolescents who are ≥ 12 years. The OLE study suggests a sustained efficacy of nipocalimab. Otherwise, it is to be noted that although a probable reason is that the limited sample size resulted in statistical uncertainties for the subgroup analyses, an effect in patients aged ≥ 65 years, while presumed, has not been clinically demonstrated in this study.

Due to the very low number of anti-LRP4+ patients in the study, extrapolation from nipocalimab induced reductions of IgG1/2 to reductions of anti-LRP4 antibodies and a B/R assessment are not possible. Hence, the indication wording should not include anti-LRP4+ patients. The indication has therefore been amended to: *"as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive."*

In conclusion, at the present time, clinically relevant efficacy of nipocalimab as add-on to standard therapy in patients aged 12 years of age and older with seropositive gMG (anti-AChR+ or anti-MuSK+ but not anti-LRP4+) has been demonstrated.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In total, 297 adults and 8 adolescents with gMG have been exposed to nipocalimab in Phase 2, Phase 2/3, and Phase 3 studies (data cutoff 23 August 2024). Of these, 187 adults and 7 adolescents were exposed for at least 6 months, and 157 adults and 3 adolescents were exposed for at least 12 months. A summary of exposure to nipocalimab in each gMG study is presented in Table 27. The safety evaluation mainly rests on data from the phase 3 placebo-controlled gMG study (MOM-M281-011), including its OLE.

Table 27. Exposure in gMG studies ^a

	Phase 3 gMG Study* (Adults)	DB Phase 2 gMG Study (Adults)	OLE Phase 2 Study gMG (Adults)	Paediatric gMG Study* (Adolescents)
Number exposed to nipocalimab	206	54	37	8
Number exposed to nipocalimab for ≥6 months	187	0	5	7
Number exposed to nipocalimab for ≥12 months	157	0	0	3
Number exposed to nipocalimab for ≥24 months	59	0	0	0
Cumulative exposure to nipocalimab (patient-years)	314.3	7.95	10.0	5.0

* Through a cutoff date of 23 August 2024

^a As participants from the double-blind Phase 2 gMG study may have entered the Phase 2 OLE gMG study and/or the Phase 3 OLE, the total number of participants exposed to nipocalimab is not the sum of those exposed in the individual studies.

The median duration of nipocalimab treatment for all participants in the OLE was 128.1 weeks (range: 12 to 156 weeks). Only 59 patients were exposed for >24 months.

In the adolescent study, the total treatment exposure to nipocalimab is 5.0 patient-years when including exposure during the LET phase.

It is notable that the doses used in the phase 2 studies 004 and 005 were different from the posology in the phase 3 trial. Of the six participants in the adolescent study who entered the LTE phase, four of them switched from 15 mg/kg Q2W to 30 mg/kg Q4W at variable timepoints.

Overall, while the rarity of MG should be acknowledged, the currently available safety data only allow characterisation of very common, and to some extent common, AEs.

2.6.8.2. Adverse events

In the DB phase of the Phase 3 gMG study approximately 90% of subjects experienced AEs both in the nipocalimab group (average 34 administrations) and in the placebo group (average 35 administrations). Serious AEs were seen in 9% in the nipocalimab group and in 14% in the placebo group.

Observations for specific AEs:

- The overall frequency of infections was approximately 43% both in the nipocalimab and the placebo group. There were, however, more cases of *urinary tract infections*, *lower respiratory tract infections*, and *herpes infections* in the nipocalimab group (please see further discussion below).
- *Muscle spasms*, *peripheral edema*, *urinary tract infection*, *dizziness*, *nausea*, and *insomnia* were more common in the nipocalimab group.
- The occurrence of adverse events related to gMG were overall comparable between the nipocalimab group and the placebo group.

No additional concern is raised from the OLE phase of the Phase 3 gMG study. Related AEs were reported in 40.8% of patients in the OLE phase.

Treatment of gMG is expected to be long-term. The currently available characterisation of the AE profile for nipocalimab should therefore be viewed with caution, because of the limited number of patients in the safety database, the relatively short duration of follow-up available, and the safety concerns raised based on the pharmacodynamic mechanism, and the laboratory findings discussed below that suggest an increased long-term cardiovascular risk.

Infections

The general decrease in serum IgG concentrations resulting from nipocalimab's mechanism of action can potentially increase the risk for infections and/or adversely affect the outcome of infections. During the DB phase of the phase 3 gMG study, the overall proportion of participants who experienced an infection in the nipocalimab group was similar to that in the placebo group (Table 28). Even with this small study population there are, however, more cases of *urinary tract infections*, *lower respiratory tract infections*, and *herpes infections* in the nipocalimab group.

"Cough" is among the most common Treatment-Emergent AEs (TEAEs) in the System Organ Class (SOCs) Respiratory, thoracic and mediastinal disorders in the DB phase of the Phase 3 gMG clinical study with an incidence in the nipocalimab group $\geq 5\%$ and twice the incidence in placebo. It is also noted that there are 6 events (in 5 unique patients) of *pneumonia/bronchitis* in the nipocalimab group, vs. 2 events (in 2 unique patients) in the placebo group. "Lower respiratory tract infections" was added to section 4.8 in the SmPC.

Table 28. Number of subjects with treatment-emergent adverse events by system organ class, preferred term; DB phase; safety (DB) analysis set (study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Safety (DB)	98	98
Avg duration of follow-up (weeks)	23.03	22.99
Avg exposure (number of administrations)	10.81	10.87
Subjects with 1 or more AEs	82 (83.7%)	82 (83.7%)
Infections and infestations	42 (42.9%)	42 (42.9%)
COVID-19	10 (10.2%)	12 (12.2%)
Nasopharyngitis	10 (10.2%)	9 (9.2%)
Upper respiratory tract infection	8 (8.2%)	6 (6.1%)
Urinary tract infection	2 (2.0%)	5 (5.1%)
Pneumonia	1 (1.0%)	3 (3.1%)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Bronchitis	1 (1.0%)	2 (2.0%)
Gastroenteritis	0	2 (2.0%)
Herpes simplex	0	2 (2.0%)
Herpes zoster	0	2 (2.0%)
Pharyngitis	0	2 (2.0%)
Sinusitis	1 (1.0%)	2 (2.0%)
Coronavirus infection	1 (1.0%)	1 (1.0%)
Ear infection	0	1 (1.0%)
Erysipelas	1 (1.0%)	1 (1.0%)
Herpes zoster oticus	0	1 (1.0%)
Infection	0	1 (1.0%)
Influenza	1 (1.0%)	1 (1.0%)
Klebsiella infection	0	1 (1.0%)
Oral candidiasis	0	1 (1.0%)
Oral herpes	2 (2.0%)	1 (1.0%)
Paronychia	0	1 (1.0%)
Pericoronitis	0	1 (1.0%)
Pneumonia bacterial	0	1 (1.0%)
Pulpitis dental	0	1 (1.0%)
Rhinitis	1 (1.0%)	1 (1.0%)
Skin infection	0	1 (1.0%)
Suspected COVID-19	0	1 (1.0%)
Tooth abscess	0	1 (1.0%)
Tooth infection	1 (1.0%)	1 (1.0%)
Urinary tract infection bacterial	0	1 (1.0%)
Vulvovaginal mycotic infection	0	1 (1.0%)
Acute sinusitis	1 (1.0%)	0
Appendicitis	1 (1.0%)	0
Borrelia infection	1 (1.0%)	0
Cellulitis	1 (1.0%)	0
Conjunctivitis	2 (2.0%)	0
Cystitis	1 (1.0%)	0
Gastroenteritis salmonella	1 (1.0%)	0
Gastroenteritis viral	2 (2.0%)	0
Oral fungal infection	1 (1.0%)	0
Respiratory tract infection viral	1 (1.0%)	0
Sepsis	1 (1.0%)	0
Viral tonsillitis	1 (1.0%)	0

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.

The number of observed cases in the study population may be fewer than expected as a result of the social restrictions in relation to the COVID-19 pandemic in place during the study period. Some support for such an effect is seen in the regional differences, with 32% of study participants in East Asia experiencing an infection, 61% in the US, and 42% in the EU/rest of the world.

Opportunistic infections and activation of latent virus

In the 24-week DB phase of the phase 3 gMG study, 6.1% (6/98 subjects) reported an AE potentially associated with activation of latent virus, compared with 2.0% (2/98 subjects) in the placebo group. There were 3 cases of Herpes zoster in the nipocalimab group (none in the placebo group), including one event of serious and severe Herpes zoster oticus. In the OLE phase there were 5 more subjects (2.6%) with Herpes zoster. Of these, one event was serious and severe. In the 16-week, DB phase 2 gMG study, 2 subjects in the combined nipocalimab group experienced an event of Herpes zoster. No event of Herpes zoster led to treatment discontinuation.

Increased plasma lipid levels

Increases of fasting total cholesterol (Figure 37), LDL (Figure 38) and high-density lipoprotein (HDL) (Figure 39) were observed in the nipocalimab group the entire 24-week DB period in the phase 3 trial. In the nipocalimab group, 29.9% had treatment-emergent markedly abnormal total cholesterol (≥ 6.2 mmol/L), compared to 4.1% in the placebo group. There were 23.5% with markedly abnormal LDL cholesterol (≥ 4.1 mmol/L) in the nipocalimab group, compared to 10.3% in the placebo group. At week 24, 17.3% in the nipocalimab group shifted to a higher risk category (LDL ≥ 4.1 mmol/L) compared to 6.7% in the placebo group. Reported rates of events of hyperlipidaemia from the phase 3 trial are uninformative since lipid results were masked for the clinicians during the study.

The distributions of lipid levels are reasonably symmetric. While most patients in the nipocalimab group have an increase in lipid levels, the trends of the upper and lower quartile suggest that some patients have only small changes, while others have substantially increased lipid levels. This pattern is particularly apparent for total cholesterol and LDL cholesterol, but not equally clear for HDL cholesterol.

Most participants experienced their first increase in lipid levels by Week 4 of the DB period. Patients that discontinued treatment during the DB treatment did not have higher cholesterol or LDL levels compared with those that completed the DB treatment phase. This is expected since prescribers and patients were blinded for these, unless they exceeded a critical level. The trends over time for lipid levels, including all patients, are therefore not biased to any important degree from treatment discontinuation.

Figure 37. Box plot of total cholesterol values over time; DB phase; safety analysis set (Study MOM-M281-011)

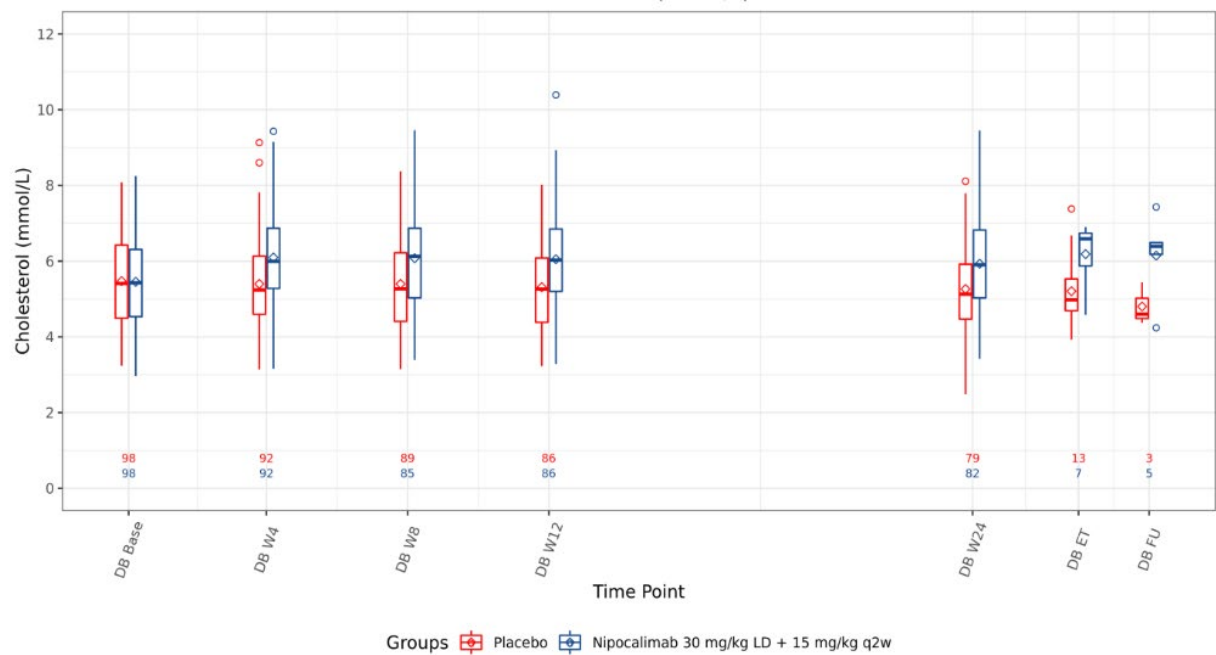


Figure 38. Box plot of LDL cholesterol values over time; DB phase; safety analysis set (Study MOM-M281-011)

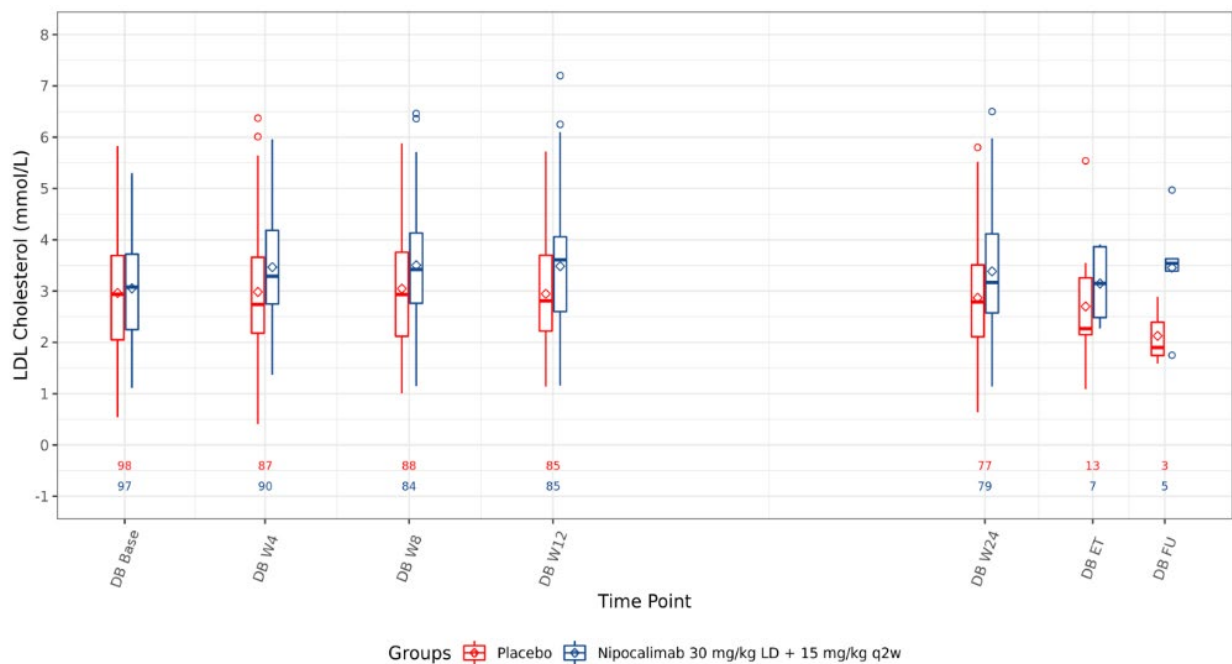
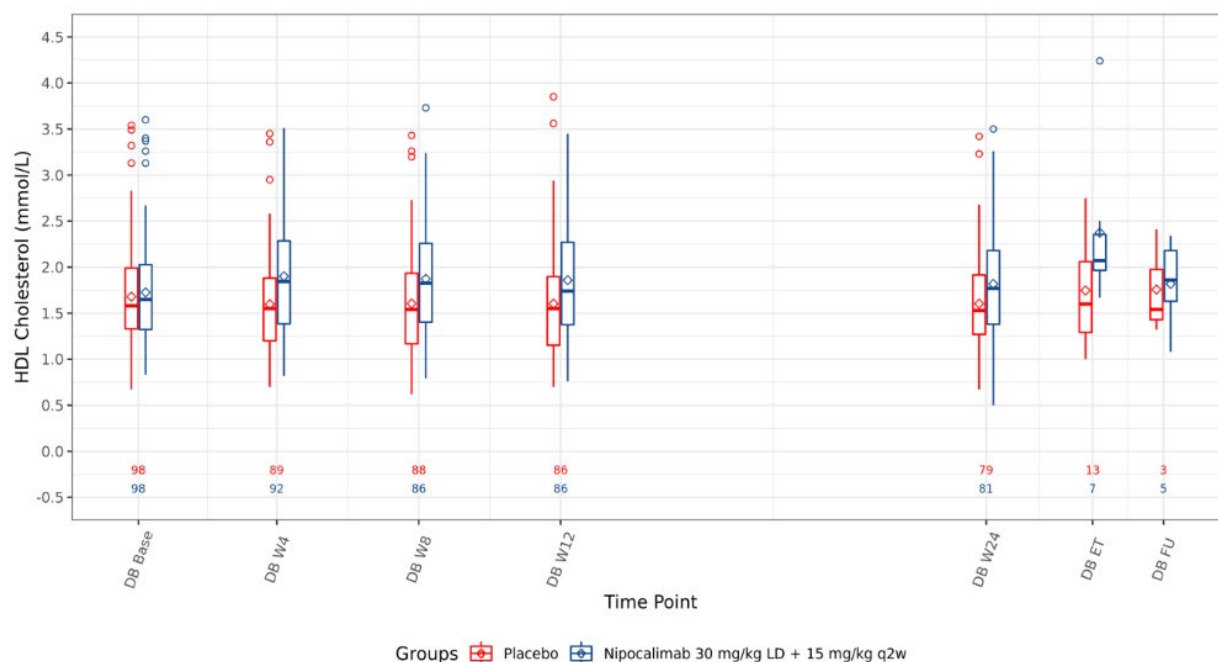


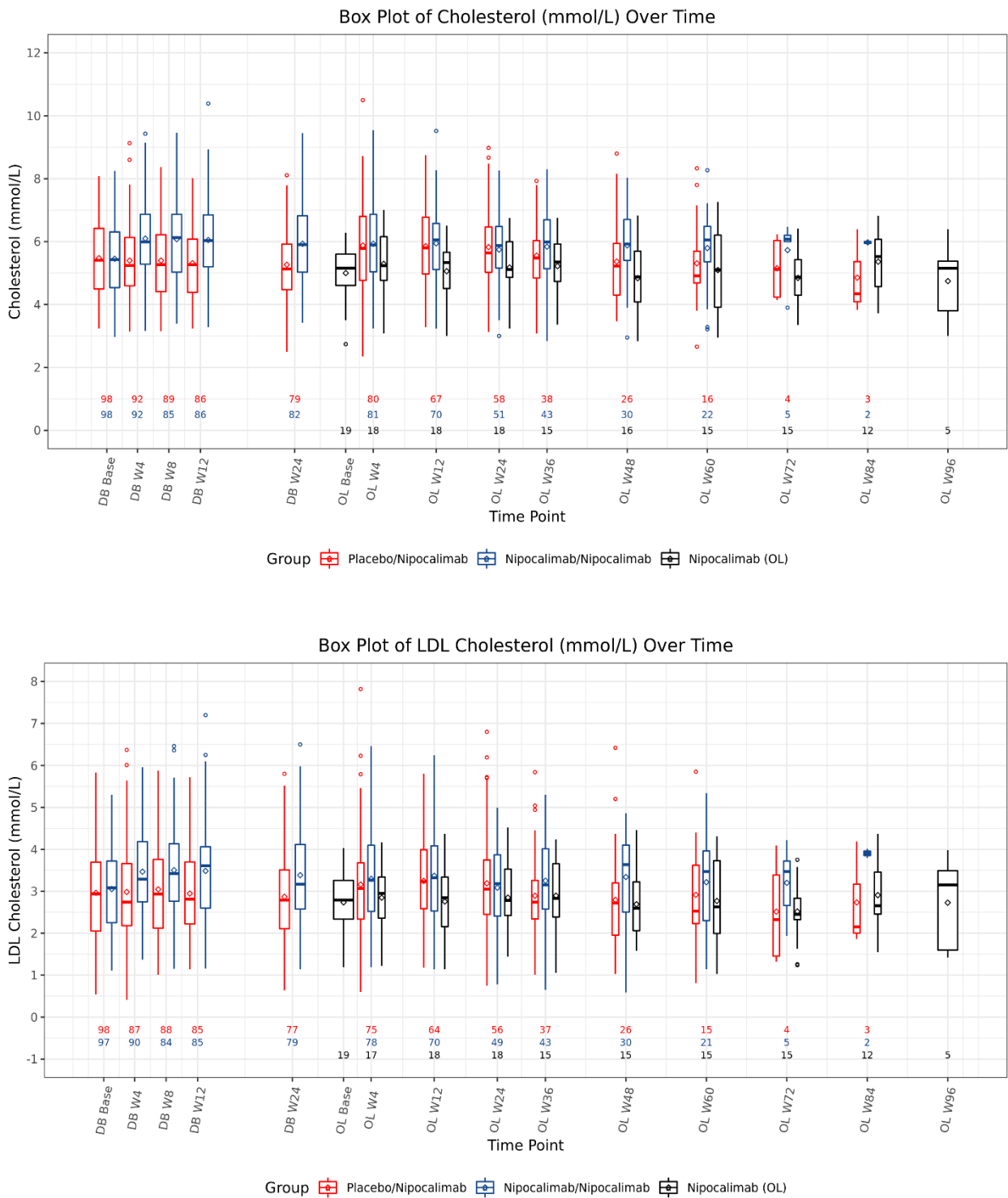
Figure 39. Box plot of HDL cholesterol values over time; DB phase; safety analysis set (Study MOM-M281-011)

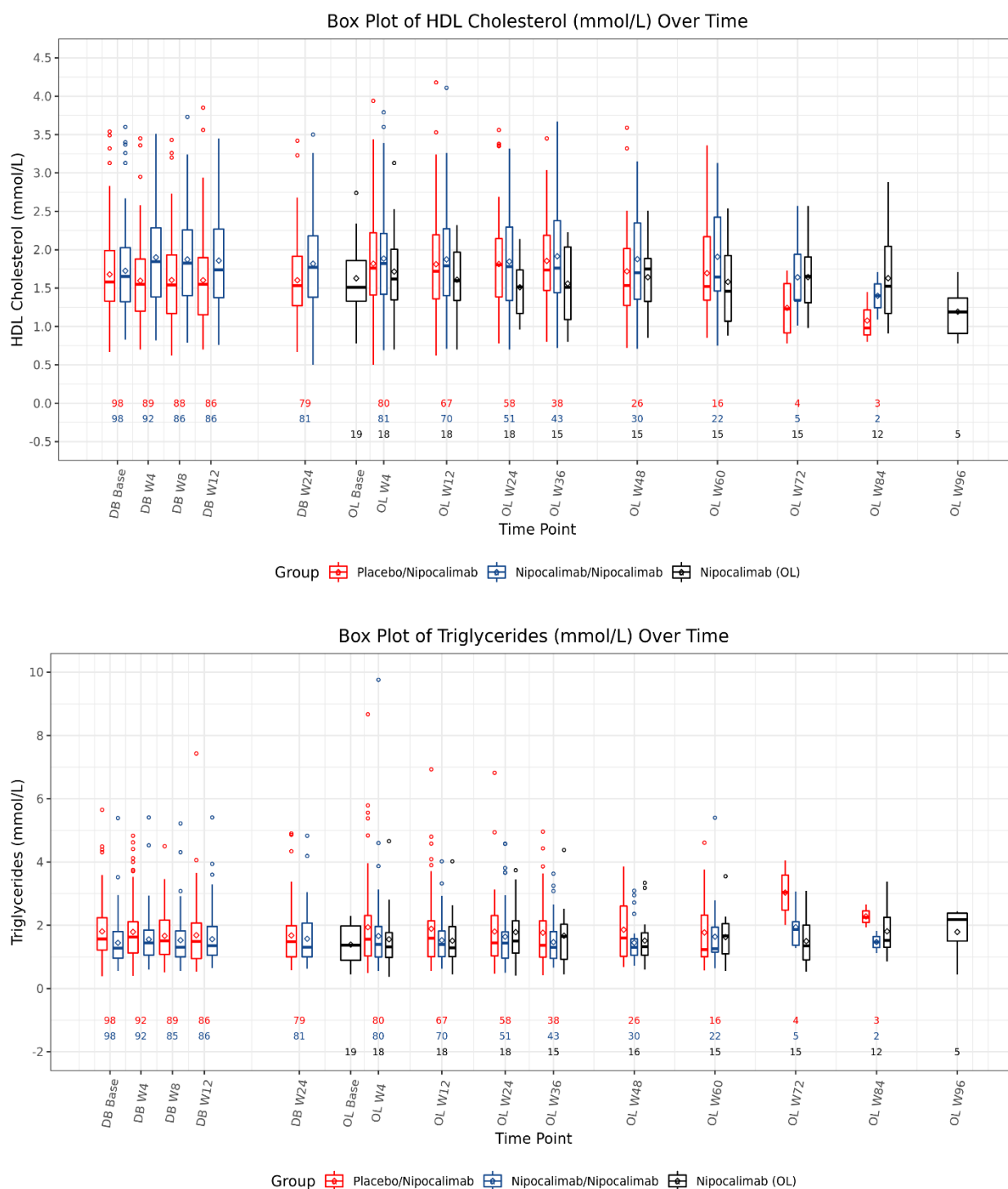


Lipid levels in the long-term extension phase

Overall, the average increased lipid levels remained increased throughout treatment (Figure 40). In the OLE phase of the phase 3 trial (when there was no blinding for lipid levels) 10.8% of patients in the study experienced an AE of hyperlipidemia. Patients with increased lipid levels in the DB phase maintained stable increased levels also in the OLE. Treatment-emergent markedly abnormal fasting LDL cholesterol values were observed in 21.5% of participants at any time during the OLE through the cutoff date.

Figure 40. Box plot of lipid laboratory values over time; all phases; safety analysis set (Study MOM-M281-011)





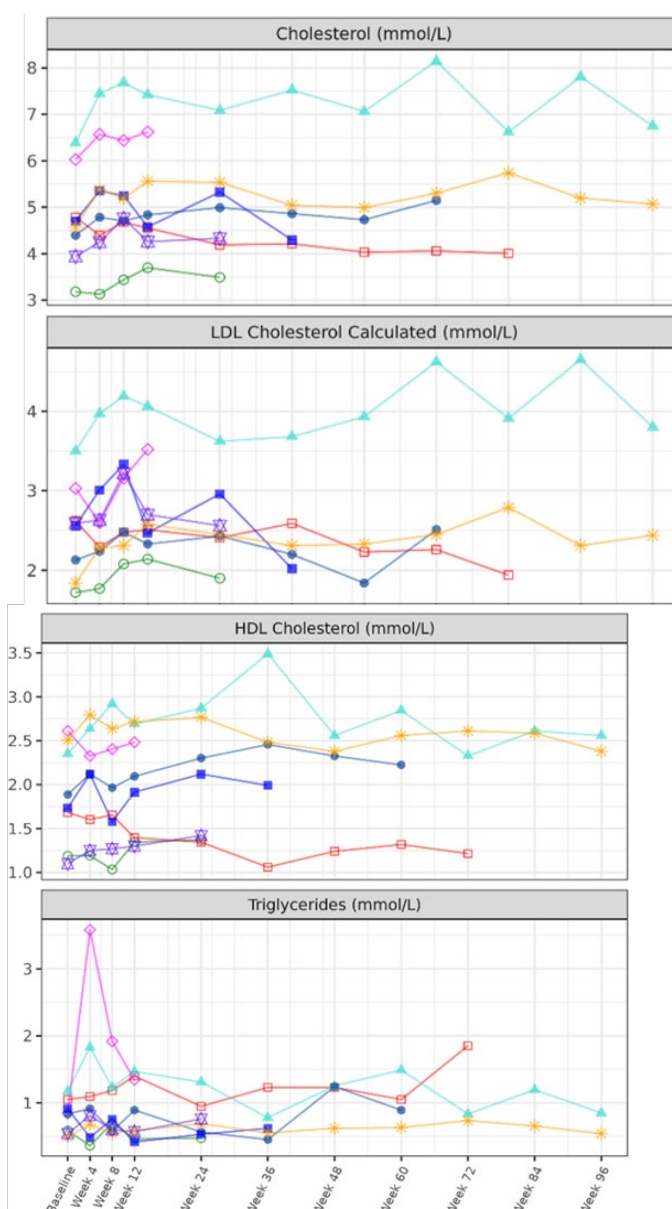
Treatment with lipid modifying agents

Twenty-six percent (26%) of subjects (26/98) in the nipocalimab arm and 24% (24/98) in the placebo arm received lipid modifying agents during the DB phase of the phase 3 trial. Of those, 7 participants were newly initiated on this treatment during the DB phase. Again, prescribers and patients were blinded for lipid levels during the DB phase, unless they exceeded a critical level.

Lipid levels in the paediatric study

Lipid changes in the adolescent participants followed a similar trend as that described for adults (Figure 41). Two patients experienced hyperlipidemia during the 24-week active treatment phase, and one patient experienced an event of *LDL increased* during the LTE phase. It is noted that the maximum increase in LDL from baseline varies between 24-40% in the subjects observed over the 24-week period. Similarly, the maximum increase of triglycerides ranges from 19-56%. These observations in the paediatric study are particularly concerning since it indicates that this safety concern is relevant for the entire age range of the target population, including paediatric patients.

Figure 41. Spaghetti plots for CHOL, LDL, HDL and triglycerides laboratory values over time; all phases; safety analysis set (Study 80202135MYG2001)



Decreased serum albumin

Reduced serum albumin levels are not unexpected based on the PD effects of nipocalimab. All nipocalimab-treated participants with a post-baseline albumin measurement had a decrease in albumin from baseline at some point during the DB phase, compared to 86.6% in the placebo group.

The mean changes from baseline during the DB phase were -8.4% at Week 2 and -7.2% at Week 24 with nipocalimab, and -0.5% at Week 2 and -2.1% at Week 24 with placebo (Figure 42). Of the patients with a post-baseline decrease in albumin, 92.8% (90 of 97) of patients treated with nipocalimab experienced their first decrease in albumin by Week 2 of the DB period. The distributions are reasonably symmetrical, but the variability is notable, indicating that a subgroup had more substantial reductions of their albumin levels. The mean percent change from baseline during the OLE was similar to that observed in the DB phase (Figure 43).

The lowering of serum albumin is seen already at the first observation two weeks after treatment initiation, the level of decrease is maintained during the DB and OLE phase, and the pattern is similar across age groups. No patient had serum albumin below the lower limit of normal range in the DB phase of the phase 3 study, but this was observed in 5.6% (2 of 36 subjects) in the phase 2 trial. No patient had any adverse effect recorded directly attributable to a lowered albumin level. This is, however, not fully reassuring considering the association between serum albumin levels and long-term cardiovascular risk (see discussion below).

Figure 42. Box plot of albumin laboratory values over time; DB phase; safety (DB) analysis set (study MOM-M281-011)

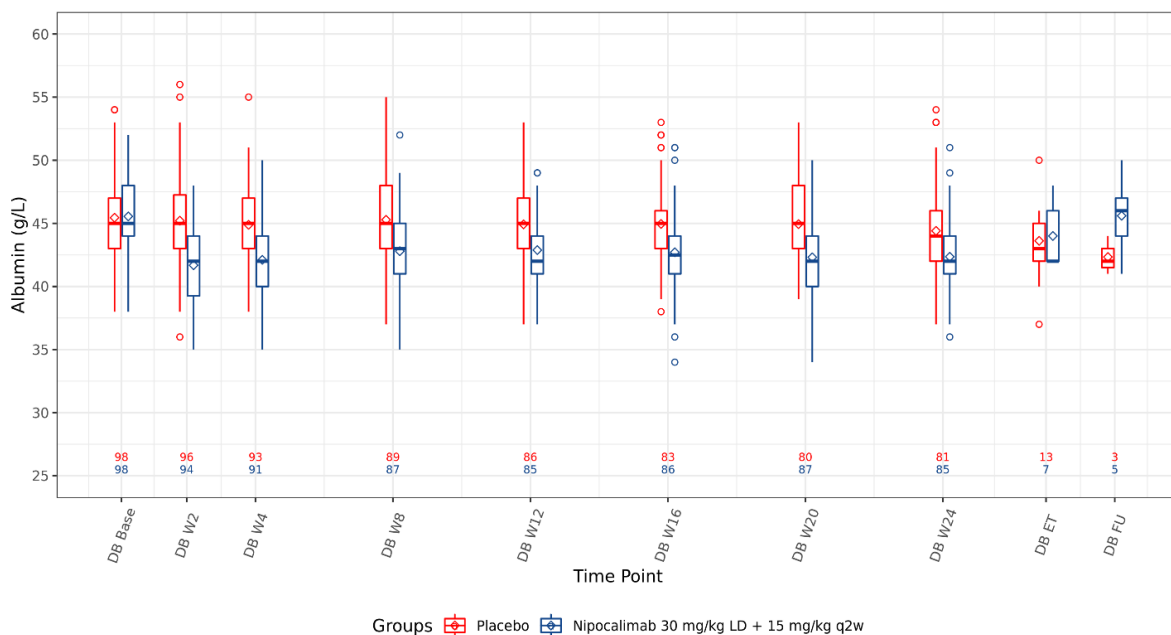
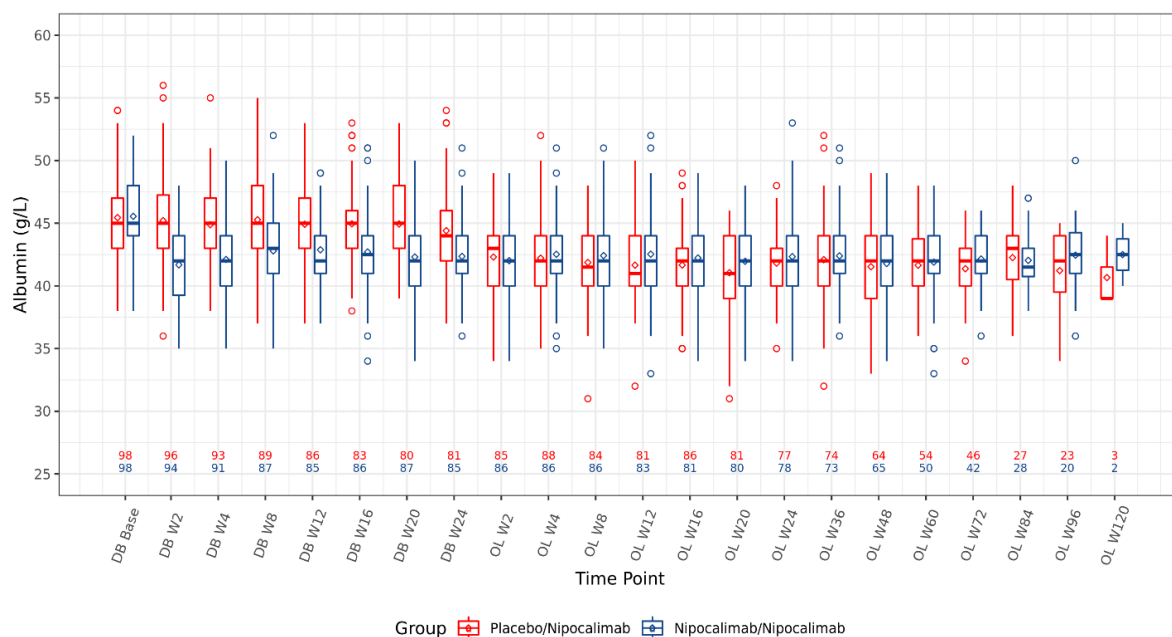


Figure 43. Box plot of albumin laboratory values over time; all phases; safety analysis set (study MOM-M281-011)



Infusion-related reactions (IRR) and infusion-site reactions (ISR)

During the DB phase of the Phase 3 gMG study, the frequencies of IRRs and ISRs in the nipocalimab group were similar to those in the placebo group. Headache was the only IRR reported by 2 or more participants in either treatment group (3 [3.1%] participants in the nipocalimab group and 7 [7.1%] participants in the placebo group) during the DB phase. Three participants (2 in the nipocalimab group and 1 in the placebo group) experienced ISRs. In the OLE phase, 13 (6.7%) participants experienced an adverse event of clinical interest (AECI) of IRR; Erythema and Fatigue were the only IRRs reported in 2 or more participants. Seven (3.6%) participants experienced an AECI of ISR. The occurrence of IRR and ISR is adequately addressed in the proposed section 4.4 of the SmPC.

Anaphylaxis, serum sickness, and other hypersensitivity reactions

In the Phase 3 gMG study, 1 participant in the placebo group experienced an anaphylactic reaction to the IV contrast during coronary angiography (anaphylactic shock) in the DB phase. Across studies in other indications, 1 SAE of anaphylactic reaction was reported in a Sjögren's disease study (SJS2001) 15 minutes after the participant's 10th dose of nipocalimab. The subject recovered shortly thereafter and then was discontinued from the study.

No participant experienced a serum sickness reaction. The frequency of hypersensitivity reactions in the nipocalimab group (8.2%, 8 participants) was similar to that in the placebo group (7.1%, 7 participants).

Hypersensitivity reactions experienced by 2 or more participants in either treatment group were Rash (nipocalimab: 1 [1.0%] participant; placebo: 3 [3.1%] participants) and Urticaria (nipocalimab: 2 [2.0%] participants; placebo: 0 participants). Urticaria and rash (5 [2.6%] participants each) were the most frequently reported hypersensitivity reactions in the OLE phase.

The event of anaphylactic shock was serious and severe; the other hypersensitivity reactions were nonserious or mild or moderate in severity; 1 event of urticaria in the nipocalimab group during the DB phase led to treatment discontinuation.

The case of anaphylaxis is mentioned in section 4.4 of the proposed SmPC but not in section 4.8. This is appropriate considering the small safety database.

Suicidal ideation or behaviour

No concern has been identified regarding suicidal ideation and behaviour.

Myasthenia Gravis

Phase 3 gMG Study: 24-week DB Phase

The proportion of patients experiencing events of MG (worsening or crisis) was similar in the nipocalimab (12.2%, 12 participants) and placebo (13.3%, 13 participants) groups in the phase 3 trial. Three (3) subjects in each group discontinued treatment due to such events. The participant in the nipocalimab group who experienced an event of MG crisis died.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

There were 8 deaths in the gMG studies, 7 of them in the phase 3 gMG study.

A subject died from EBV-associated hemophagocytic lymphohistiocytosis after 5 doses of nipocalimab. Concomitant treatment with tacrolimus and prednisolone may have predisposed for the event. The case should be considered in the context of an increased risk for infections.

A subject died from gliosarcoma. The cancer was diagnosed 146 days after initiating treatment with nipocalimab. The potential adverse impact of lowered IgG levels on cancer risk and progression of malignancy has been studied, but overall, study results from the literature estimating such associations are inconsistent [1, 2]. Lower total IgG levels have been associated with tumour progression and poor prognosis for gastric cancer patients [3]. An inverse association has also been observed between pre-diagnostic serum levels of IgG and the risk of pancreatic cancer [4]. Other studies have not identified such associations for other forms of cancer.

Six deaths (63-81 years old) were related to cardiovascular disease. While cardiovascular safety is a concern in this application, these deaths do not contribute any relevant information from that perspective.

One case of MG crisis resulting in death is not unanticipated considering the target population.

Major adverse cardiovascular events (MACE)

In the phase 3 gMG study, there were no events confirmed as major adverse cardiovascular events (MACE) in the nipocalimab group versus 3 events in the placebo group in the DB phase. There were 10 events confirmed as MACE in 3 participants in the OLE phase. There was no evidence of increased risk of MACE with longer-term exposure when considering exposure-adjusted incidence rates for the DB (0 and 6.98 participants per 100 patient-years in the nipocalimab and placebo group, respectively) and OLE phases (1.38 participants per 100 patient-years).

With the few patients studied and the short follow-up, events of MACE caused by increased lipid levels would, however, be unexpected in the study population. The events of MACE observed in the development program are expected to be mainly related to baseline risk factors. The results regarding MACE events are therefore not reassuring in relation to the major concern for cardiovascular safety.

Other serious adverse events (SAEs)

During the DB phases of the phase 2/3 gMG studies, the proportions of patients who experienced SAEs were largely comparable between nipocalimab and placebo groups (Table 29).

Table 29. Serious adverse events

Study Phase/Period	Treatment	N	Participants with at least 1 SAE
MOM-M281-011			
DB Phase	Nipocalimab 30 mg/kg loading dose, 15 mg/kg Q2W thereafter:	98	9 (9.2%)
	Placebo:	98	14 (14.3%)
Open-label Extension Phase	Nipocalimab 15 mg/kg Q2W:	195	41 (21.0%)
MOM-M281-004			
DB Period	Nipocalimab 5 mg/kg Q4W:	14	0
	Nipocalimab 30 mg/kg Q4W:	13	1 (7.7%)
	Nipocalimab 60 mg/kg Single Dose:	13	0
	Nipocalimab 60 mg/kg Q2W:	14	0
	Combined nipocalimab:	54	1 (1.9%)
	Placebo:	14	2 (14.3%)
MOM-M281-005			
Open-label Extension Phase	Nipocalimab 30 mg/kg Q4W for 8 weeks, 30 mg/kg Q2W or Q4W or 60 mg/kg Q2W or Q4W, thereafter:	37	5 (13.5%)
80202135MYG2001			
Active Treatment Phase	Nipocalimab 30 mg/kg loading dose, 15 mg/kg Q2W thereafter:	7	0
Long-term Extension Phase	Nipocalimab 15 mg/kg Q2W or 30 mg/kg Q4W:	4	0

While there is no apparent imbalance in SAEs between nipocalimab and placebo, this must be viewed in the context of the small safety database. The limited sample size available for the characterisation of safety means that only common or very common SAEs have a reasonable probability to be captured.

2.6.8.4. Laboratory findings

Albumin

Please see above section.

Lipids

Please see above section.

Liver enzymes

In the 24-week DB phase of the Phase 3 gMG study, mean liver enzyme values were within the reference range throughout the DB and OLE phases through the cutoff date. During the DB phase, there were no major differences between the treatment groups in markedly abnormal liver enzyme laboratory values (Table 30). The observed >1x upper limit of normal (ULN) increase of alkaline phosphatase (ALP) in the

DB phase of the Phase 3 gMG study has been further assessed based on additional data from the applicant. It is likely a non-specific finding without relevance for the safety profile of nipocalimab.

Table 30. Number and percentage of subjects with treatment-emergent markedly abnormal liver enzyme laboratory values; DB phase; safety (DB) analysis set (Study MOM-M281-011). Participants in an abnormality category are also counted in the preceding lower abnormality categories

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Safety (DB)	98	98
Avg duration of follow-up (weeks)	23.03	22.99
Alanine Aminotransferase (Enzyme U/L)		
N	97	97
>1xULN	10 (10.3%)	7 (7.2%)
≥3xULN	1 (1.0%)	2 (2.1%)
≥5xULN	1 (1.0%)	1 (1.0%)
≥10xULN	1 (1.0%)	1 (1.0%)
≥20xULN	0	0
Alkaline Phosphatase (Enzyme U/L)		
N	97	97
>1xULN	1 (1.0%)	11 (11.3%)
≥3xULN	0	0
≥5xULN	0	0
≥10xULN	0	0
≥20xULN	0	0
Aspartate Aminotransferase (Enzyme U/L)		
N	97	97
>1xULN	9 (9.3%)	3 (3.1%)
≥3xULN	1 (1.0%)	1 (1.0%)
≥5xULN	0	0
≥10xULN	0	0
≥20xULN	0	0
Bilirubin (umol/L)		
N	97	97
≥2xULN	1 (1.0%)	1 (1.0%)

One participant from the open-label Phase 2 gMG study (2.8%) had markedly abnormal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values reported. This participant had an ALT of ≥3xULN and AST of ≥5xULN during their week 4 study visit (reported as an AE of Hepatic enzyme increased) and AST values of ≥3xULN at Weeks 2 and 12. The case was a 25-year-old female with a medical history that included morbid obesity. Concomitant medications included prednisone, mestinon, and cyclosporine. Prednisone and cyclosporine can cause increased hepatic enzymes. The subject received IV infusion of nipocalimab every four weeks at a dose 30 mg/kg. Increase of hepatic enzymes

was reported after approximately 1 month of treatment. The nipocalimab dose was not changed and treatment continued. The event is reported as *Recovering/resolving*.

VitalsSigns – blood pressure

During the DB phase of the phase 3 trial there were 7 subjects (7.1%) in the placebo group and 12 subjects (12.2%) in the nipocalimab group reported with systolic blood pressure ≥ 160 mmHg and with ≥ 20 mmHg increase from baseline (Table 31).

AEs related to vital signs were reported in few nipocalimab-treated participants during the DB phase:

- Tachycardia and supraventricular tachycardia each reported in 1 participant,
- Hypertension reported in 2 participants,
- Blood pressure increased reported in 3 participants,

In addition, an AE of Hypertension was reported in 2 placebo-treated participants.

Table 31. Number and percentage of subjects with treatment-emergent markedly abnormal vital signs; DB phase; safety (DB) analysis set (Study MOM-M281-011)

	Placebo	Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W
Analysis set: Safety (DB)	98	98
Pulse Rate (beats/min)		
N	98	98
≤ 50 bpm and with ≥ 15 bpm decrease from baseline	3 (3.1%)	2 (2.0%)
≥ 120 bpm and with ≥ 15 bpm increase from baseline	1 (1.0%)	0
Systolic Blood Pressure (mmHg)		
N	98	98
≤ 90 mmHg and with ≥ 20 mmHg decrease from baseline	3 (3.1%)	7 (7.1%)
≥ 160 mmHg and with ≥ 20 mmHg increase from baseline	7 (7.1%)	12 (12.2%)
Diastolic Blood Pressure (mmHg)		
N	98	98
≤ 50 mmHg and with ≥ 15 mmHg decrease from baseline	3 (3.1%)	4 (4.1%)
≥ 100 mmHg and with ≥ 15 mmHg increase from baseline	4 (4.1%)	6 (6.1%)

Note: Markedly abnormal vital signs are defined in the Statistical Analysis Plan. N is the number of subjects with at least 1 postbaseline value for the specified vital sign parameter.

In the OLE phase *Hypertension* was reported in 7 (3.6%) participants, *Blood pressure increased* in 3 (1.5%) participants, and *Hypotension* reported in 2 (1.0%) participants.

Serious AEs were reported in 3 participants: *Hypertensive heart disease* (severe and fatal event in a participant with previous medical history of cardiovascular conditions: hypertension, paroxysmal atrial fibrillation coronary atherosclerosis), *Hypertension* (worsening of previous medical history of hypertension, considered moderate in intensity) and *Atrial fibrillation* (worsening of previous medical history of paroxysmal atrial fibrillation, considered moderate in intensity).

In the phase 3 trial (MOM-M281-011), systolic blood pressure was measured immediately prior to the start of each infusion, 30 minutes post-infusion, and 1-hour post-infusion (first 3 infusions). The measurements

could therefore be influenced by patient anxiety in relation to the healthcare intervention. In 10 of the 12 nipocalimab treated patients the SBP elevations were isolated incidents.

Nine of the 12 nipocalimab-treated patients that experienced systolic blood pressure elevations had a prior medical history of hypertension, and only 3 of these patients had their background anti-hypertensive medications increased during the study.

No incident event of hypertension was recorded in the nipocalimab group (57 subjects) with a total person-time of 25.6 years. This amount of person-time does not allow a meaningful estimation of incidence rate of hypertension. In a contextualisation of incidence of hypertension against external cohorts of gMG patients with comparable age distribution, and without pre-existing hypertension, the incidence rate of hypertension in these cohorts varied between 4.07 and 5.90 events per 100 person-years.

Overall, the data does not suggest that nipocalimab is associated with a clinically relevant adverse effect on blood pressure.

Electrocardiograms

Corrected QT interval values

At baseline in the DB phase of the phase 3 trial, corrected QT interval calculated using the Fridericia formula (QTcF) interval values between >450 and ≤480msec were observed in 2 (2.1%) participants in the placebo group, and 4 (4.2%) participants in the nipocalimab group. At Week 24, QTcF interval in this range was observed in 1 (1.3%) participant in the placebo group, and 7 (9.5%) participants in the nipocalimab group.

During the OLE phase through the cutoff date, shifts from baseline QTcF category ≤450 msec to >450 to ≤480 msec occurred for 5 participants. Of the 5 participants who shifted to the >450 to ≤480 msec category, 1 participant with a past medical history of left ventricle hypertrophy experienced an AE of supraventricular extrasystole (mild) at the time of the QTcF shift.

During the DB Phase 2 gMG study, post-baseline QTcB interval value >480 msec were noted in 3 nipocalimab participants (1 participant each in 5 mg/kg Q4W, 60 mg/kg single-dose, and 60 mg/kg Q2W dose groups). One participant in the 60 mg/kg single-dose group had a post-baseline increase in QTcB value >60 msec. None of these abnormalities in QTcB values were considered clinically relevant and were not reported as AEs. Shifts from normal baseline to post-baseline treatment-emergent abnormalities in ECG parameters were observed in 10 (18.5%) nipocalimab participants.

An association between nipocalimab and QT prolongation is unlikely. Of the five patients that had a new QT prolongation observed at week 24, four had a previous history of cardiovascular disease. The observations do not raise any concern, and this issue is not further pursued.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

The limited sample size available for the characterisation of safety means that only common or very common SAEs have a reasonable probability to be captured. This problem becomes even more pronounced in subgroup analyses. There is consequently a remaining uncertainty regarding the safety profile for nipocalimab also in relation to safety in special populations.

Age

The frequency of AEs is summarized by age group for the DB phase of Study MOM-M281-011. The common preferred terms (PTs) (with AE incidence $\geq 10\%$ in the age group) that had a higher or lower incidence (difference in incidence of $\geq 5\%$) in one of the 3 age groups are presented in Table 32.

Table 32. Number of subjects with common (incidence $\geq 10\%$ total) TEAE and difference in incidence between groups of $\geq 5\%$ by system organ class, preferred term, and age; DB phase; safety (DB) analysis set (Study MOM-M281-011)

Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W				
	Total	≥ 18 to <45 years	≥ 45 to <65 years	≥ 65 years
Analysis set: Safety (DB)	98	27	46	25
Avg duration of follow-up (weeks)	22.99	23.52	23.39	21.67
Avg exposure (number of administrations)	10.87	11.11	11.17	10.04
Subjects with 1 or more AEs	80 (81.6%)	23 (85.2%)	36 (78.3%)	21 (84.0%)
System organ class				
Preferred term				
Infections and infestations	42 (42.9%)	7 (25.9%)	24 (52.2%)	11 (44.0%)
COVID-19	11 (11.2%)	2 (7.4%)	9 (19.6%)	0
Nervous system disorders	37 (37.8%)	12 (44.4%)	13 (28.3%)	12 (48.0%)
Headache	14 (14.3%)	6 (22.2%)	6 (13.0%)	2 (8.0%)
Myasthenia gravis	12 (12.2%)	3 (11.1%)	3 (6.5%)	6 (24.0%)
Musculoskeletal and connective tissue disorders	27 (27.6%)	8 (29.6%)	13 (28.3%)	6 (24.0%)
Muscle spasms	12 (12.2%)	2 (7.4%)	8 (17.4%)	2 (8.0%)

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Sex

Among participants treated with nipocalimab in the DB phase in Study MOM-M281-011, there were 66 (67.3%) female participants, and 32 (32.7%) male participants. For female and male participants, the incidence of AEs was 83.3%, and 78.1%, respectively. The sex-stratified frequencies of AEs during the DB phase in Phase 3 gMG study do not raise any particular safety concern in relation to sex.

BMI

Among participants treated with nipocalimab in the DB phase in Study MOM-M281-011, there were 34 participants with normal BMI, 31 overweight participants, and 33 obese participants. The BMI-stratified frequencies of AEs during the DB phase in Phase 3 gMG study appear to increase, e.g. in the *Infections and infestations* category, in relation to increased body weight. The common PTs (with AE incidence $\geq 10\%$ in the group) that had a higher or lower incidence (difference in incidence of $\geq 5\%$) in one of the BMI categories are presented in Table 33.

Please see further discussion regarding body weight in the discussion regarding clinical pharmacology.

Table 33. Number of subjects with common (incidence $\geq 10\%$ total) treatment-emergent adverse events and difference in incidence between groups of $\geq 5\%$ by system organ class, preferred term, and body mass index (BMI); DB Phase; Safety (DB) Analysis Set

Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W				
	Total	Normal (<25 kg/m ²)	Overweight (≥ 25 kg/m ² to <30 kg/m ²)	Obese (≥ 30 kg/m ²)
Analysis set: Safety (DB)	98	34	31	33
Avg duration of follow-up (weeks)	22.99	23.34	23.36	22.28
Avg exposure (number of administrations)	10.87	11.00	11.26	10.36
Subjects with 1 or more AEs	80 (81.6%)	27 (79.4%)	24 (77.4%)	29 (87.9%)
System organ class				
Preferred term				
Infections and infestations	42 (42.9%)	11 (32.4%)	13 (41.9%)	18 (54.5%)
COVID-19	11 (11.2%)	4 (11.8%)	2 (6.5%)	5 (15.2%)
Nervous system disorders	37 (37.8%)	10 (29.4%)	12 (38.7%)	15 (45.5%)
Headache	14 (14.3%)	3 (8.8%)	4 (12.9%)	7 (21.2%)
Myasthenia gravis	12 (12.2%)	4 (11.8%)	3 (9.7%)	5 (15.2%)
Musculoskeletal and connective tissue disorders	27 (27.6%)	7 (20.6%)	8 (25.8%)	12 (36.4%)
Muscle spasms	12 (12.2%)	3 (8.8%)	2 (6.5%)	7 (21.2%)
General disorders and administration site conditions	24 (24.5%)	7 (20.6%)	6 (19.4%)	11 (33.3%)
Oedema peripheral	10 (10.2%)	4 (11.8%)	2 (6.5%)	4 (12.1%)

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Autoantibody status

Among participants treated with nipocalimab in the DB phase of Study MOM-M281-011, there were 77 seropositive participants, and 21 seronegative participants. For seropositive and seronegative participants, the incidence of AEs was similar (80.5%, and 85.7%, respectively). The common PTs (with AE incidence $\geq 10\%$ in the group) that had a higher or lower incidence (difference in incidence of $\geq 5\%$) in seropositive vs seronegative participants is presented in Table 34.

Table 34. Number of subjects with common (incidence $\geq 10\%$ total) treatment-emergent adverse events and difference in incidence between groups of $\geq 5\%$ by system organ class, preferred term, and autoantibody positive/negative; DB phase; safety (DB) analysis set (Study MOM-M281-011)

Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W			
	Total	Seronegative	Seropositive
Analysis set: Safety (DB)	98	21	77
Avg duration of follow-up (weeks)	22.99	22.48	23.13
Avg exposure (number of administrations)	10.87	10.33	11.01
Subjects with 1 or more AEs	80 (81.6%)	18 (85.7%)	62 (80.5%)

Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W			
System organ class			
Preferred term			
Nervous system disorders	37 (37.8%)	6 (28.6%)	31 (40.3%)
Headache	14 (14.3%)	0	14 (18.2%)
Musculoskeletal and connective tissue disorders	27 (27.6%)	3 (14.3%)	24 (31.2%)
Muscle spasms	12 (12.2%)	0	12 (15.6%)
General disorders and administration site conditions	24 (24.5%)	2 (9.5%)	22 (28.6%)
Oedema peripheral	10 (10.2%)	1 (4.8%)	9 (11.7%)

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Type of stable gMG therapy

Among participants treated with nipocalimab in the DB phase, there were 50 participants receiving stable gMG therapy with immunosuppressant, and 45 participants receiving stable gMG therapy without immunosuppressant. For participants receiving stable gMG therapy with and without immunosuppressant, the incidence of AEs was 84.0%, and 80.0%, respectively.

Region

Among participants treated with nipocalimab in the DB phase of Study MOM-M281-011, there were 54 participants from ROW, 28 from East Asia, and 16 from the US. For participants from ROW, East Asia, and the US, the incidence of AEs was 75.9%, 85.7%, and 93.8%, respectively. The common PTs (with AE incidence $\geq 10\%$ in the group) that had a higher or lower incidence (difference in incidence of $\geq 5\%$) in one of the regions is presented in (Table 35). No safety concern related to region has been identified.

Table 35: Number of subjects with common (incidence $\geq 10\%$ total) treatment-emergent adverse events and difference in incidence between groups of $\geq 5\%$ by system organ class, preferred term, and region; DB phase; safety (DB) analysis set (Study MOM-M281-011)

Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W				
	Total	US	East Asia	ROW
Analysis set: Safety (DB)	98	16	28	54
Avg duration of follow-up (weeks)	22.99	21.82	23.07	23.29
Avg exposure (number of administrations)	10.87	10.25	10.61	11.19
Subjects with 1 or more AEs	80 (81.6%)	15 (93.8%)	24 (85.7%)	41 (75.9%)
System organ class				
Preferred term				
Infections and infestations	42 (42.9%)	8 (50.0%)	10 (35.7%)	24 (44.4%)
COVID-19	11 (11.2%)	3 (18.8%)	4 (14.3%)	4 (7.4%)
Nervous system disorders	37 (37.8%)	9 (56.3%)	8 (28.6%)	20 (37.0%)
Headache	14 (14.3%)	2 (12.5%)	3 (10.7%)	9 (16.7%)
Myasthenia gravis	12 (12.2%)	5 (31.3%)	2 (7.1%)	5 (9.3%)
Musculoskeletal and connective tissue disorders	27 (27.6%)	9 (56.3%)	6 (21.4%)	12 (22.2%)
Muscle spasms	12 (12.2%)	5 (31.3%)	2 (7.1%)	5 (9.3%)

Nipocalimab 30 mg/kg LD + 15 mg/kg Q2W				
General disorders and administration site conditions	24 (24.5%)	5 (31.3%)	8 (28.6%)	11 (20.4%)
Oedema peripheral	10 (10.2%)	2 (12.5%)	5 (17.9%)	3 (5.6%)

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

2.6.8.7. Immunological events

Among participants treated with nipocalimab in the DB phase of Study MOM-M281-011, there were 77 seropositive participants, and 21 seronegative participants. For seropositive and seronegative participants, the incidence of AEs was similar (80.5%, and 85.7%, respectively).

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

Medications that bind to human FcRn (e.g., IgG products, IgG-based mAb, antibody derivatives containing the human Fc domain of the IgG subclass, or Fc fusion proteins) may interact with nipocalimab. The time interval that should be recommended between treatment with nipocalimab and subsequent treatment with FcRn-binding products, and the time interval that should be recommended between treatment with FcRn-binding products and subsequent nipocalimab treatment need further evaluation. Safety issues mostly relate to lack of efficacy.

Vaccine study

The Nipocalimab Vaccine Study (80202135EDI1009) was a phase 1 randomized, open-label, parallel, interventional study conducted at a single site in Europe. The study evaluated the effect of nipocalimab on the extent and kinetics of humoral response to Tdap and PPSV[®]23 vaccines. The study population consisted of healthy male and female participants, 18 to 65 years of age, who had not received a tetanus vaccine in the past 5 years and had not received a pneumococcal vaccine in the past 10 years. The study subjects had no concomitant medications, immunosuppressive treatments, or pre-existing comorbidities. Overall, 32 subjects were randomized into the study and assigned to the *Control Arm* (n=15) or the *Active Arm* (n=17; 16 received nipocalimab). The baseline characteristics were comparable across treatment groups.

Figure 44. Median ($\pm$ IQ) anti-tetanus IgG percent change from baseline over time; completers analysis set

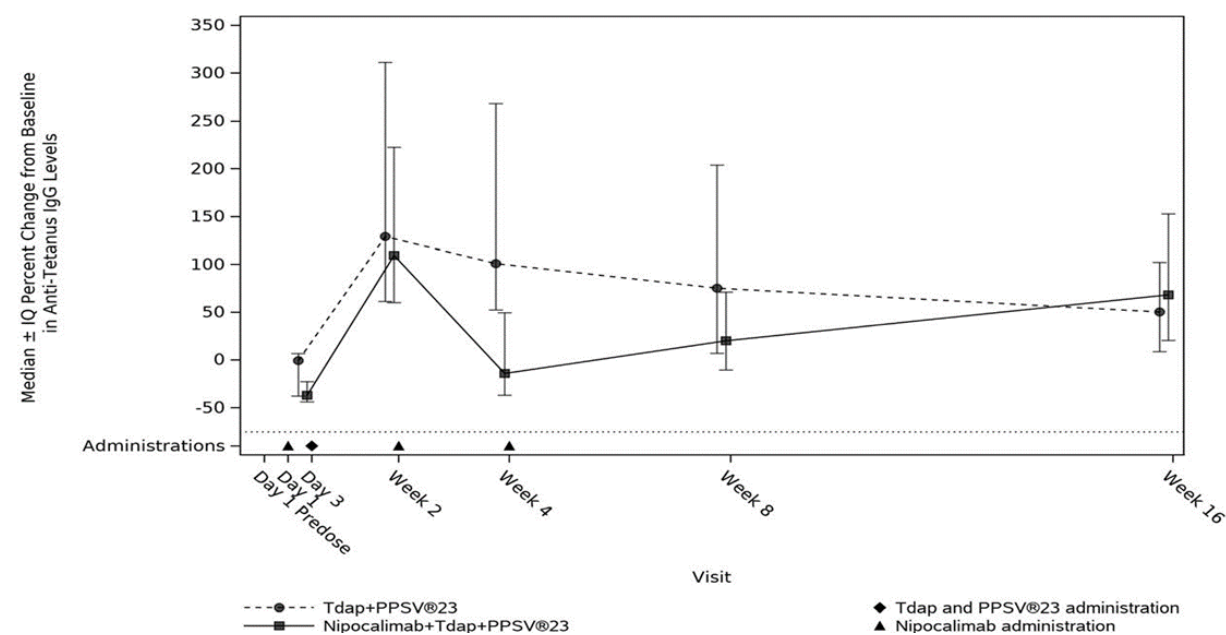
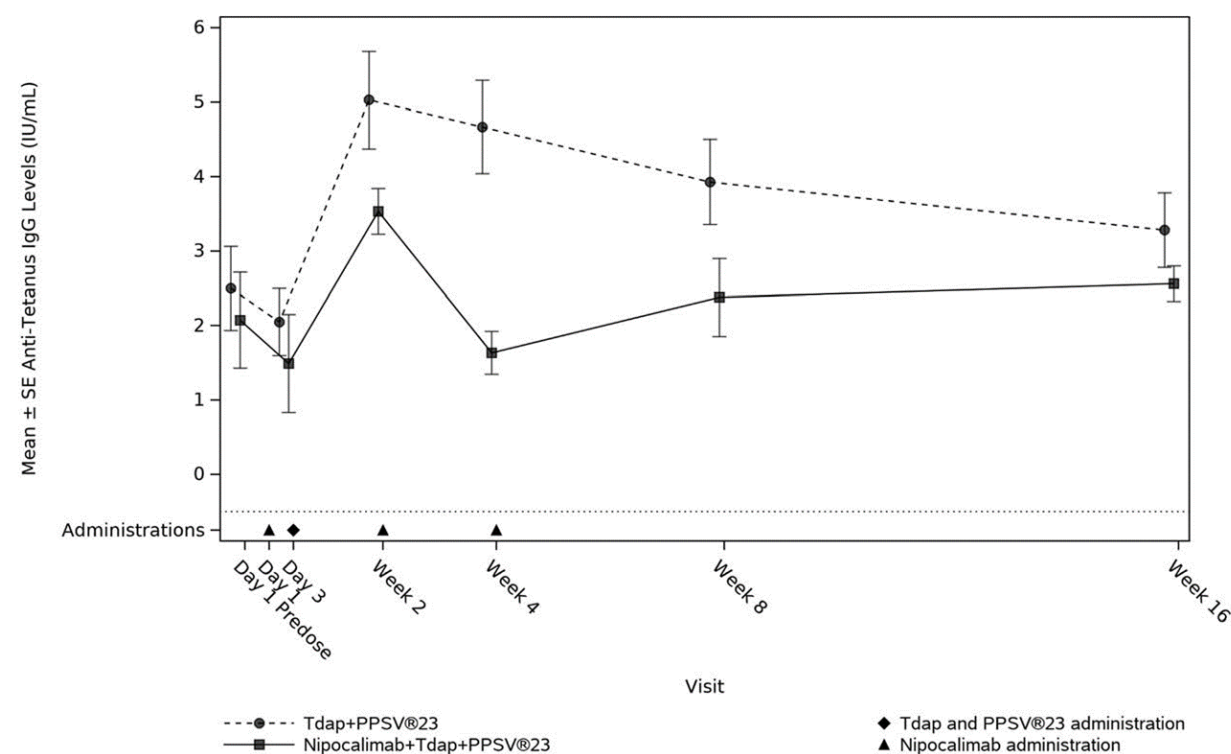


Figure 45. Mean ($\pm$ SE) anti-tetanus IgG levels over time; completers analysis set



2.6.8.9. Discontinuation due to adverse events

The proportion of patients discontinuing treatment due to adverse events was relatively low and balanced between treatment groups. During the DB phase of the Phase 3 gMG study, the percentage of participants who experienced AEs leading to permanent treatment discontinuation in the nipocalimab group was similar to that in the placebo group; 5.1% in the nipocalimab group and 7.1% in the placebo group. In the OLE of the Phase 3 gMG study 16 (8.2%) of patients experienced at least 1 AE leading to permanent treatment discontinuation. The only AE leading to treatment discontinuation in 2 or more participants was Myasthenia gravis (worsening) in the DB and OLE phases of the Phase 3 gMG study. None of the nipocalimab-treated participants in the adult Phase 2 gMG studies or the paediatric gMG study experienced an AE leading to treatment discontinuation.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Available safety data

MG is a rare disease and the available safety database for nipocalimab in this indication is consequently small. The intended target population covers children ≥ 12 years and adults. Since MG is a chronic disease, the treatment is expected to be chronic, and long-term safety therefore becomes a particular concern.

In the safety database there are 187 adults and 7 adolescents exposed for at least 6 months. Of these, 157 adults and 3 adolescents were exposed for at least 12 months but only 59 adults exposed for >2 years. The currently available safety data therefore only allows characterisation of very common ($\geq 1/10$) and to some extent common ($\geq 1/100$ to $< 1/10$) adverse events. Long-term effects have not been captured. Additional pharmacovigilance measures in terms of PASS are therefore required for adequate characterisation of the safety profile.

The main data source for adverse events is the DB phase of the phase 3 trial MOM-M281-011 with 98 patients exposed to nipocalimab and 98 to placebo. The phase 2 trial MOM-M281-004 was terminated early and mainly used doses other than the currently proposed posology. It therefore does not contribute substantially to characterisation of safety. Some supportive information comes from the OLE phases of phase 2/3 trials. Trials in other indications are also to some extent supportive.

Adverse events profile

In the DB phase of the Phase 3 gMG study approximately 90% of subjects experienced AEs both in the nipocalimab group and in the placebo group. Serious AEs were seen in 9% in the nipocalimab group and in 14% in the placebo group. Muscle spasms, peripheral oedema, urinary tract infection, lower respiratory tract infections, herpes zoster, dizziness, nausea, and insomnia were more common in the nipocalimab group.

The proportion of patients discontinuing treatment due to adverse events was relatively low and balanced between treatment groups. The only AE leading to treatment discontinuation in 2 or more participants was *Myasthenia gravis (worsening)*. Acknowledging the limitations of the safety database, no major safety concern of relevance for the benefit-risk balance is raised by these observations.

Main outstanding safety concerns

The problem with a small safety database and relatively short exposure durations is well illustrated by the two main safety concerns identified - serious infections and cardiovascular safety.

Serious infections

An increased incidence and/or severity of infections is a key concern based on the PD mechanism, and characterisation of this risk is hampered by the small safety database and the short follow-up available. To detect an increased risk for unfavourable outcome of severe infections, enough patients must be observed contracting such an infection under treatment with nipocalimab. This requires a substantially larger number of exposed patients for a longer duration than currently available.

The overall frequency of infections was approximately 43% and balanced between groups. The few events of serious infections in the phase 3 trial were equally balanced between nipocalimab and placebo. Urinary tract infection occurred in $\geq 5\%$ of participants in the nipocalimab treatment group with a frequency 2 times that in the placebo group in a combined pool of phase 2/3 studies.

Weakness of respiratory muscles represents the most severe MG manifestation, and 10–15% of all patients experience an MG crisis with the need of mechanical ventilatory support at least once in their life. MG patients with respiratory muscle weakness need long term active immunosuppressive drug treatment, and they need regular specialist follow-up. Comorbidities affecting respiratory function need attention and optimal treatment. Respiratory tract infections can lead to MG exacerbations and precipitate an MG crisis [5].

During the DB part of the Phase 3 gMG study, the most frequently reported SAE next to MG and MG crisis, was pneumonia. Lower respiratory tract infections were more common in the DB phase of the phase 3 trial, with 5 patients in the nipocalimab group and 2 in the placebo group. The term “*Lower respiratory tract infection*” has been included as a common adverse reaction in the tabulated overview and as text in the SmPC section 4.8.

Overall, there were no strong concerns raised for serious infections in the currently available data, but this is based on too few patients and too short follow-up to allow reliable characterisation of this important potential risk. To detect an increased risk for unfavourable outcome of severe infections, enough patients must be observed contracting such an infection under treatment with nipocalimab. The impact of nipocalimab on the risk for serious infections has been included in the summary of safety concerns in the RMP and the risk should be further characterised in a PASS.

Opportunistic infections and activation of latent virus

As for infections in general, the currently available data is based on too few patients and too short follow-up to allow good characterisation of this important potential risk. The cases of Herpes zoster observed were all in the nipocalimab groups in the DB phases of the phase 2/3 gMG studies. This observed imbalance in terms of *Herpes zoster* in the placebo-controlled phase, the plausible mechanistic rationale, the potential seriousness of this infection, and the availability of vaccine for potential prevention, is considered sufficient evidence to warrant labelling with frequency *common* in section 4.8 of the SmPC. The PASS should also aim to further characterise the risk for opportunistic infections and activation of latent virus.

Long-term cardiovascular safety – dyslipidaemia

Increased levels of fasting total cholesterol, LDL, HDL, and triglycerides were consistently observed in patients treated with nipocalimab. In the nipocalimab group, 30% had treatment-emergent markedly abnormal total cholesterol (≥ 6.2 mmol/L), compared to 4% in the placebo group. Markedly abnormal fasting LDL cholesterol values (≥ 4.1 mmol/L) were observed for 23% in the nipocalimab group and 10%

in the placebo group. Most patients experienced their first increase in lipid levels already by Week 4 of the DB period.

These adverse effects on blood lipids are not entirely unexpected since another FcRn blocker has demonstrated similar effects, when evaluated for the treatment of thyroid eye disease [6]. Any durable increase in blood lipids is expected to compromise cardiovascular safety, and since increased lipid levels appear to be frequent, durable, and also observed in the paediatric age group, together with the fact that treatment with nipocalimab is intended to be chronic, these findings are a major safety concern with an impact on the overall benefit-risk balance of the product.

Assessment of this safety concern must rest on actual measurements rather than reported events of hyperlipidaemia, since lipid levels were per protocol masked (unless very high) to the study site and sponsor during the DB phase of the phase 3 trial. Patients who discontinued treatment during the DB treatment phase did not have higher lipid levels compared with those that completed the DB treatment phase. The trends over time for lipid levels, including all patients, are therefore not biased to any important degree from treatment discontinuations.

The distributions of lipid levels are reasonably symmetric. While most patients in the nipocalimab group have some increase in lipid levels, the trends of the upper and lower quartiles suggest that some patients have only small changes, while others have substantially increased lipid levels. This pattern is particularly apparent for cholesterol and LDL, but not as clear for HDL. Overall, the increase remained at similar levels during continued treatment.

The increased lipid levels are consistent across age groups. In the adolescent cohort of the paediatric study (80202135MYG2001), similar patterns in lipid profiles as those described for the adult population were observed. That a clear pattern with increased lipid levels is evident also in this small number of adolescent patients is a particular concern.

In the intended target population for nipocalimab the expected prevalence of a history of cardiovascular events is in the range of 16-20%. These estimates of prevalent cardiovascular history at baseline should be compared with the phase 3 trial population, where the observed prevalences were 6.1% and 7.1% in the placebo and nipocalimab groups, respectively. When evaluating cardiovascular risk based on the phase 3 trial results, it should be recognized that the trial population had a lower burden of cardiovascular disease at baseline as compared to the intended target population.

It is also important to recognise the distribution of lipid levels, and not just focus on the mean or median values in the study population. The patterns of change indicate that there is a subpopulation with more marked increase in lipids, and that this subpopulation is sufficiently large to increase the average levels.

An additional and equally important basis for the discussion is that the relation between cardiovascular risk factors and cardiovascular risk is a continuum. Categorisation can serve to simplify description, but the underlying biology is a continuum. Reduction/removal of a risk factor reduces risk.

Long-term cardiovascular safety – applicant's arguments for not accepting this risk and the need for risk minimisation

The applicant argues for absence of an increased cardiovascular risk based on the systematic coronary risk estimation (SCORE) system. This is a method used to predict the 10-year risk of fatal cardiovascular disease (CVD) based on various risk factors, including lipids. The SCORE system integrates the following risk factors: Sex, age, smoking status, systolic blood pressure, and either total cholesterol or the cholesterol/HDL ratio. SCORE predicts the risk of fatal CVD events over a 10-year period. A threshold of 5% or greater in 10-year absolute risk is defined as high risk for fatal CVD events.

The applicant concludes that, given that no increased risk in the 10-year composite CV risk assessment using the SCORE chart was observed with nipocalimab treatment, there is consequently no need to

define a high-risk population to appropriately mitigate the risk of adverse effects of hypercholesterolemia on CV risk. None of the arguments underlying this conclusion are accepted.

The focus on the SCORE system fails to recognize the fundamental limitations of this prediction model, its intended use, and the need to recognize the individual risk profile of the patient. The model was developed based on fatality rather than morbidity. The model focuses on 10-year risk, rather than lifetime risk.

One particular problem relates to young patients for whom a low absolute risk may conceal a very high relative risk, and the 10-year risk window is in this context too short to be relevant. This is a major concern when discussing CV risk in the target population for nipocalimab. Treatment with nipocalimab causes increased lipid levels already in adolescence. Lifetime risk is a more appropriate approach to illustrate the impact of risk factors in younger people. The greater the burden of risk factors, the higher the lifetime risk. This approach will produce higher risk estimates for younger patients because of their longer exposure duration. This has not been acknowledged by the applicant.

The most important concern is that the applicant focuses on average risk rather than recognizing individual patient risk. The calculation of an average 10-year risk is of very limited relevance. The distribution of change in plasma lipids must be considered. It is e.g. evident that at 24 weeks the maximum increase in SCORE is 2.04 in the placebo group, compared to 5.13 in the nipocalimab group. Individual patients who experience increased lipid levels must be identified and evaluated early during treatment.

As recognised in the 2019 ESC/EAS Guidelines for the management of dyslipidaemias, a total CV risk estimate is part of a continuum [7]. The cut-off points that are used to define high-risk are, in part, both arbitrary and based on the risk levels at which treatment benefit is evident in clinical trials. It is essential to recognise that the uncertainty in the predictions has not been reflected and that the SCORE chart in this context is a surrogate outcome measure in a clinical and regulatory context for which it has not been validated.

The SCORE chart is for use in people without overt cardiovascular disease, diabetes (type 1 and 2), chronic kidney disease, familial hypercholesterolaemia, or very high levels of individual risk factors because such people are already at high-risk and need intensive risk factor management. As noted above, the prevalence of cardiovascular disease at treatment start is high in the gMG target population, considerably higher than the clinical trial population.

The beneficial impact of increased HDL-cholesterol levels from nipocalimab treatment is stressed by the applicant. The applicant argues that the simultaneous increase in HDL, and total cholesterol/HDL ratios <5 , are suggestive of low risk for cardiovascular events, and that there is a beneficial impact on the risk prediction from SCORE. These arguments are not agreed.

As stated in the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: "...at extremely high values [above ~ 2.3 mmol/L (90 mg/dL)] of HDL-C there appears to be an increased risk of CVD, so at such levels HDL-C cannot be used as a risk predictor..." [7]. As seen in Figure 39, the proportion with HDL-C >2.3 mmol/L increases with nipocalimab treatment.

The old findings in the Framingham study of an inverse relation between HDL and both cardiovascular disease and total mortality have consistently been challenged in more recent studies. There is an important distinction between if HDL is an indicator of risk and if an increase in HDL is truly causally related to cardiovascular risk. In a mendelian randomisation study, genetic mechanisms that raise plasma HDL cholesterol did not seem to lower the risk of myocardial infarction, challenging the concept that raising of plasma HDL cholesterol will translate into reductions in risk of myocardial infarction [8]. It rather appears that the relation is U-shaped and that high HDL levels may increase risk.

In a study pooling data from 6 community-based cohorts including 11 515 men and 12 925 women with a total of 307 245 person-years of follow-up there was an inverse association between HDL-C and coronary heart disease events [9]. However, at HDL-C values >90 mg/dL there was a plateau effect in men. In women, at HDL-C values >75 mg/dL there were no further reductions in the hazard ratio point estimates for coronary heart disease.

In a cohort study of 1 764 986 men spanning a median observation period of 9.1 years intermediate HDL cholesterol levels (>25 to <34, ≥34 to ≤42, and >42 to <50 mg/dl) were associated with lower risk of death compared to the referent group of patients with low HDL cholesterol (≤25 mg/dl) [10]. Analysis by HDL cholesterol deciles and spline analyses suggest that the relationship between HDL cholesterol and death follows a U-shaped curve. The 4-week HDL levels from study MOM-M281-011 would according to that data rather lead to an increased cardiovascular risk. While there may be substantial differences making a comparison between these study populations difficult, this is a reminder that an increased HDL level in this range should not be ignored as an added risk factor and not be seen as a mitigation of risk. Other more recent studies also indicate that very high HDL-C levels are paradoxically associated with higher mortality risk, as observed in individuals with coronary artery disease [11] and men with hypertension [12]. It is therefore concerning rather than reassuring that treatment with nipoalimab also causes an increase of HDL levels.

Long-term cardiovascular safety – literature data on the level of risk

To further contextualise the CV risk associated with the effects of nipoalimab on LDL levels, a recent 30-year follow-up of a US cohort is of relevance to evaluate the potential long-term effects of the change in LDL levels observed in the nipoalimab phase 3 trial. Women's Health Study (WHS) is a prospective cohort study of 27 939 initially healthy U.S. women who had high-sensitivity C-reactive protein, LDL cholesterol, and lipoprotein(a) measured at baseline and were followed for a period of 30 years to assess the occurrence of incident myocardial infarction, coronary revascularization procedures, stroke, or death from cardiovascular causes [13].

The baseline mean LDL levels in the phase 3 nipoalimab study of around 3 mmol/L corresponds to LDL quintile 2 (2.48 – 2.94 mmol/L) in the WHS study. In this group no increased MACE risk was seen compared to the lowest LDL quintile (covariable-adjusted HR 1-30 years, 1.00; 95% CI 0.89–1.12). The mean LDL levels following treatment with nipoalimab group in the phase 3 study of around 3.5 mmol/L corresponds to quintile 4 (3.35 – 3.90 mmol/L) in the WHS study. This quintile had an increased rate of MACE events (covariable-adjusted hazard ratio 1-30 years, 1.23; 95% CI 1.10–1.37). Restricting the analysis to the first 15 years, the rate was even higher (covariable-adjusted hazard ratio 1-15 years, 1.35; 95% CI 1.14–1.59). This suggests that the increase in LDL levels observed in the development program for Imaavy likely has a clinically relevant impact on the cardiovascular safety profile of long-term treatment with nipoalimab.

Increased triglyceride levels may confer an increased risk of cardiovascular disease. The REDUCE-IT RCT enrolled 8179 patients who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg/dL (1.52 to 5.63 mmol/L) and a low-density lipoprotein cholesterol level of 41 to 100 mg/dL (1.06 to 2.59 mmol/L) and followed them for a median of 4.9 years [14]. Treatment with icosapent ethyl reduced the risk for MACE (hazard ratio, 0.75; 95% CI, 0.68 to 0.83). In contrast, the STRENGTH RCT evaluating the effects of omega-3 CA on clinical outcomes in patients at high cardiovascular risk was prematurely terminated due to futility [15]. In summary, the increased triglyceride values associated with nipoalimab are an added concern to the increased LDL levels.

Long-term cardiovascular safety – risk minimisation

That there is a subgroup with substantially increased lipid levels shortly after treatment initiation clearly signals the need for risk minimisation focusing on the early identification of affected individual patients,

i.e., targeting the identification of these patients following treatment initiation. Regular monitoring of lipid levels should therefore be recommended in the SmPC, along with a recommendation to evaluate the findings in the context of the patient's other cardiovascular risk factors and weighing these against the effectiveness of nipocalimab on the patient's symptoms of gMG. When nipocalimab causes a rise in lipids to levels that may have a relevant impact on the individual patient's cardiovascular risk profile, then other gMG treatment options should be considered. The SmPC has been clearly worded to inform the prescriber accordingly.

The applicant argues that no additional monitoring beyond what is established by '*standard clinical practice*' is supported by the data. This is not agreed. Irrespective of any other additional rationale to monitor cardiovascular risk factors in patients with gMG, the knowledge that nipocalimab can have important adverse effects on lipid levels should be adequately communicated in the SmPC, along with a recommendation to monitor for these adverse effects as a part of overall risk minimization for cardiovascular events. This has been implemented in the SmPC

The applicant's conclusion regarding increased lipid levels in early life, and that there is no added relevance to these findings, is not agreed. Rather, it is considered essential that an adverse impact on lipid levels already in adolescence be timely identified and incorporated in a continuous benefit-risk assessment for the individual patient.

The discussion on reduced need for corticosteroids is acknowledged, but again, the individual patient must be considered, and for those patients remaining on corticosteroids the lipid-raising effects of nipocalimab can reversely be viewed as an additional cardiovascular risk factor that should be considered in the patient's individual benefit-risk balance.

Long-term cardiovascular safety – reduced serum albumin levels

In relation to cardiovascular safety, the effects on albumin levels must also be considered. Reduced serum albumin levels are not unexpected based on the PD effects of nipocalimab. This effect appears more pronounced compared to currently approved medicinal products with the same mechanism of action on the FcRn receptor.

Apart from albumin's obvious role to maintain plasma oncotic pressure and regulate distribution of body water between different compartments, a decreased serum albumin concentration is also associated with increased risk for hyperlipidaemia, cardiovascular disease, and mortality [16].

From the perspective of CV risk, it is not entirely reassuring that the reduced albumin levels are within the normal range. Low serum albumin levels, also within the normal range, have been linked to increased long-term CV risk at the population level in some studies.

It is established that nipocalimab can reduce serum albumin. Considering the anticipated long duration of treatment with nipocalimab, the wide age range of the target population, the impact of other effects of nipocalimab on CV risk, and the potential impact of other prevalent CV risk factors in the patient, it should at this stage be considered that reduced albumin levels can contribute to an increased long-term CV risk. Decreased albumin levels have been added as ADR with frequency very common (section 4.8) It is, however, difficult to translate this into direct advice regarding monitoring, as there is no clinical guideline to refer to regarding the association with serum albumin and cardiovascular risk.

Seropositive vs. seronegative patients

The demographics of the Phase 3 Study M281-011 population is representative of the gMG population. However, the proportion of seronegative participants is higher than expected. A similar proportion of seropositive and seronegative patients treated with nipocalimab experienced at least 1 TEAE (80.5%, and 85.7%, respectively) during the DB phase of study MOM-M281-011. In the seropositive patients,

the most common ($\geq 5\%$) TEAEs with nipocalimab that occurred at least twice as frequently compared to the placebo group were generally similar to those in the overall safety analysis.

Hemophagocytic Lymphohistiocytosis (HLH)

Fc receptors serve as sensors for the adaptive immune response. HLH is characterized by a wide range of etiologies, symptoms, and outcomes, but have a common etiopathogenic pathway leading to organ damage: an excessive inflammatory response. Biological therapies have been proposed as a therapeutic option for refractory HLH but have also been related to the development of HLH in severe immunosuppressed patients. It is a paradox, that the biological agent involved in the triggered disease is also often included in the current treatment indications for the same disease.

Epstein-Barr virus is the most common pathogen triggering HLH/ macrophage activation syndrome. A Japanese study estimated the annual incidence of HLH at 1 in 800,000 persons per year, with 90% of these cases being secondary (i.e no genetic predisposition) and one-third of these secondary cases being related to EBV. This leads to an estimated annual incidence of 0.4 cases of EBV-associated HLH per million persons.

Prior immunosuppressive treatment is part of many gMG patient's medical history. The death from HLH was considered related to investigational product by the investigator in spite of EBV infection and immunosuppressive treatment since 2015.

Vaccinations

In the pivotal study MOM-M281-011, vaccination of patients with live or live attenuated vaccines was prohibited during the study, as well as within 4 weeks prior to screening or within 8 weeks after the last administration of study intervention. In section 4.4 of the SmPC vaccination is prohibited at least 4 weeks before start of nipocalimab and at least 2 weeks after the last dose of nipocalimab. Given the PK half-life of nipocalimab, this is acceptable.

Regarding non-live vaccines, in study 80202135EDI1009 it was observed that patients on nipocalimab can mount humoral IgG responses, but due to the MoA of nipocalimab, titers decrease rapidly after the initial response. Upon treatment discontinuation, after short term treatment (4 weeks), antibody IgG levels increased again. The antibody response after long-term treatment was not tested but it is reasonable to assume that vaccine induced antibodies will increase again, even after long-term treatment, and after stopping the medication. Anti-TT IgG levels remained above the protective threshold (0.16 IU/mL) throughout the study for all participants. However, this could be due to the design of the study since nipocalimab was discontinued after the second dose, which would be a specific and most probably rare clinical scenario. On the other hand, if nipocalimab dosing was continued, it cannot be excluded that anti-TT IgG levels would decrease even further and subsequently to below 0.16 IU/ml. This information would therefore be misleading if included in the SmPC. Consequently, the inclusion of the statement "*Anti-TT IgG levels remained above the protective threshold (0.16 IU/mL) throughout the study for all participants*" in the SmPC was not agreed.

Assessment of paediatric data on clinical safety

Eight adolescents with gMG have been exposed to nipocalimab in Phase 2, Phase 2/3, and Phase 3 studies. Seven adolescents were exposed for at least 6 months, and 3 for at least 12 months. There is consequently very limited data from this age group.

Lipid changes in the adolescent participants followed a similar trend as that described for adults. Two patients experienced hyperlipidemia during the 24-week active treatment phase, and one patient experienced an event of *LDL increased* during the LTE phase. It is noted that the maximum increase in LDL from baseline varies between 24-40% in the subjects observed over the 24-week period. Similarly, the maximum increase of triglycerides ranges from 19-56%. These observations in the paediatric study

are particularly concerning since it indicates that this safety concern is relevant also for paediatric patients.

2.6.10. Conclusions on the clinical safety

The characterisation of safety is hampered by a small safety database, but this is expected since MG is a rare disease. The risk in relation to serious infections is expected based on the mechanism of action and no new concern is raised concerning this issue from the available data.

The impact on blood lipids is unexpectedly large and could be associated with adverse effects on cardiovascular risk. Further a reduction of albumin levels was noted, which also potentially could have an impact on cardiovascular risk. This raises a serious concern for long-term cardiovascular safety, considering that the treatment is expected to be chronic when tolerated. It is, however, notable that this impact on cardiovascular risk factors is amenable to monitoring, and therefore potentially also for an effective risk minimisation strategy to identify an appropriate target population with a beneficial benefit/risk balance.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 36. Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infections Long-term cardiovascular risk
Missing information	Use during pregnancy

2.7.2. Pharmacovigilance plan

Table 37. Summary of ongoing and planned additional pharmacovigilance activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3: Required additional pharmacovigilance activities				
OLE of Trial MOM-M281-011 Ongoing	To evaluate the maintenance of nipocalimab's effect and the long-term safety of nipocalimab in adults with gMG.	- Serious infections - Long-term cardiovascular risk	Final study report submission	31 May 2028
LTE of Trial 80202135MYG2001 Ongoing	To evaluate the maintenance of nipocalimab's effect and the long-term safety of nipocalimab in children aged 2 to less than 18 years with gMG.	- Serious infections - Long-term cardiovascular risk	Final study report submission	30 April 2029

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Retrospective cohort study in pregnancy Planned	To assess the use of nipocalimab among MG patients in pregnancy and to estimate the incidence proportions of pregnancy, maternal, and infant outcomes among women with MG exposed to nipocalimab or comparator treatments during pregnancy.	• Use during pregnancy	Protocol submission First interim report submission Second interim report submission Final study report submission	Q2 2026 Q4 2030 Q4 2033 Q4 2036
PASS 1 (United States) Planned	To assess the long-term safety of nipocalimab among cohorts of patients with gMG treated with nipocalimab and those treated with other gMG medications.	• Serious infections • Long-term cardiovascular risk	Protocol submission First interim report submission Second interim report submission Final study report submission	Q2 2026 Q3 2028 Q3 2031 Q3 2034
PASS 2 (France) Planned	To assess the long-term safety of nipocalimab among cohorts of patients with gMG treated with nipocalimab and those treated with other gMG medications.	• Serious infections • Long-term cardiovascular risk	Protocol submission First interim report submission Second interim report submission Final study report submission	Q2 2026 Q3 2030 Q3 2033 Q4 2036

2.7.3. Risk minimisation measures

Table 38. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infections	Routine risk communication - SmPC Section 4.4 - PL Section 2 Specific clinical measures - Advice to delay initiation of IMAAVY treatment in patients with active infection until the infection resolves and to monitor patients for clinical signs and symptoms of infection during treatment with IMAAVY: SmPC Section 4.4. - Advice on the management of clinically important active infection: SmPC Section 4.4. - Advice for patients report any signs and symptoms of infection before starting treatment with IMAAVY or during treatment to their doctor: PL Section 2. Other routine risk minimization activities - Restricted medical prescription Additional risk minimization activities - None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection - None Additional pharmacovigilance activities - OLE of Trial MOM-M281-011 Final study report due date: 31 May 2028 - LTE of Trial 80202135MYG2001 Final study report due date: 30 April 2029 - PASS 1 (United States) Final study report due date: Q3 2034 - PASS 2 (France) Final study report due date: Q4 2036
Long-term cardiovascular risk	Routine risk communication - SmPC Section 4.4 - SmPC Section 4.8 - PL Section 4 Specific clinical measures - Recommendation to measure plasma lipid levels: SmPC Section 4.4. - Advice on monitoring in adolescents and patients with high body weight or BMI: SmPC Section 4.4. - Advice on the continued monitoring of plasma lipid levels and alternative treatment options: SmPC Section 4.4. - Information on the measurement of blood fat (cholesterol) levels: PL Section 2. Other routine risk minimization activities - Restricted medical prescription Additional risk minimization activities - None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection - None Additional pharmacovigilance activities - OLE of Trial MOM-M281-011 Final study report due date: 31 May 2028 - LTE of Trial 80202135MYG2001 Final study report due date: 30 April 2029 - PASS 1 (United States) Final study report due date: Q3 2034 - PASS 2 (France) Final study report due date: Q4 2036
Use during pregnancy	Routine risk communication - SmPC Section 4.6 - PL Section 2 Specific clinical measures - None Other routine risk minimization activities - Restricted medical prescription Additional risk minimization activities - None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection - None Additional pharmacovigilance activities - Retrospective cohort study in pregnancy Final study report due date: Q4 2036

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.5 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 the 29th April 2025. 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, Imaavy (Nipocalimab) 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

Nipocalimab is a monoclonal antibody that binds to FcRn, resulting in the reduction of circulating IgG including pathogenic IgG autoantibodies. The recommended indication for nipocalimab is: "as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are *anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive*."

MG is a rare IgG autoantibody-mediated neuromuscular disease. Approximately 10% to 15% of new cases of MG are diagnosed in the adolescent population. In both adolescents and adults, MG is defined as a neuromuscular disease characterized by fluctuating muscle weakness and fatigability due to

pathogenic IgG-mediated disruption of cholinergic transmission at the neuromuscular junction. MG can present as a purely ocular form, affecting only oculomotor muscles, in 15% of cases, or as a more generalized form (gMG) in 85% of cases, which affects ocular, bulbar, proximal extremity, neck, and respiratory muscles. Approximately 95% of gMG patients are considered “seropositive” based on the presence of known autoantibodies: of these, approximately 85% are anti-AChR+, approximately 8% are anti-MuSK+, and approximately 1-2% are anti-LRP4+. The remaining 5-6% of patients with gMG have no known autoantibodies and are considered “seronegative”. The aims of new treatments are to treat symptoms, to manage myasthenic exacerbations, to reduce or prevent worsening of muscle weakness and achieve minimal manifestation status.

3.1.2. Available therapies and unmet medical need

There is no cure for gMG, and most patients require lifelong treatment. Symptomatic treatment with acetylcholinesterase inhibitors may provide some relief in mild cases of gMG. However, most gMG patients also require thymectomy and/or treatment with SoC therapies, including corticosteroids and/or immunosuppressive medications such as azathioprine, mycophenolate mofetil/mycophenolic acid, cyclosporine, and tacrolimus. These treatments for gMG are generally associated with slow onset of action and carry significant risks. Other therapeutic modalities aimed at removing autoantibodies, such as plasma exchange and immunoadsorption, or producing immunomodulatory effects, such as IVIg, are faster acting but are typically used for patients with myasthenic crisis.

Newer agents focused on either C5 complement (eculizumab, ravulizumab, zilucoplan) or inhibition of FcRn (e.g. efgartigimod, rozanolixizumab) have been recently approved for gMG. The use of advanced therapeutic options in gMG is associated with some challenges. Treatment with C5 inhibitors is restricted to only anti-AChR positive patients because of their mechanism of action; they also have a warning for serious meningococcal infections. The dosing approach approved for available FcRn blockers is a symptom-based, cyclic dosing regimen, which can be suboptimal in some patients with a chronic disease like gMG. Of the recently approved FcRn blockers, efgartigimod is only approved for anti-AChR positive adult gMG patients (Vyvgart SmPC) and rozanolixizumab is approved for anti-AChR positive and anti-MuSK positive adult gMG patients (Rystiggo SmPC).

gMG patients who are positive for anti-MuSK and anti-LRP4 antibodies present with more severe symptoms (such as life-threatening respiratory crisis in about one-third of the anti-MuSK population), resulting in a more significant disease burden and greater unmet medical need. The only approved advanced treatment for anti-MuSK+ patients is rozanolixizumab. There remains an unmet medical need for immunoselective treatments that are safer and faster acting than the SoC options and provide sustained efficacy in a broad population of adult and adolescent patients with gMG.

3.1.3. Main clinical studies

The main evidence of the efficacy of nipocalimab in the intended indication is based on data from a single 24-week multi-center, randomized, DB, placebo-controlled study of nipocalimab (n=77) compared to placebo (n=76) in adults (aged ≥18 years) with gMG inadequately controlled with standard-of-care therapy (Study MOM-M281-011).

3.2. Favourable effects

Primary efficacy endpoint

The pivotal phase 3 trial MOM-M281-011 met its primary endpoint with regard to statistical significance for the EU estimand. Nipocalimab demonstrated statistically significant improvement in MG-ADL total score change from baseline over weeks 22-24 compared to placebo ($p=0.003$); LS mean difference 1.39 (95% CI: -2.31, -0.47). Sensitivity analyses displayed similar results (LS mean -1.35 [95% CI: -2.30, -0.41]). The primary endpoint for the US/ROW estimand, where ICEs were handled with the hypothetical estimand that the ICE had not occurred, the LS mean difference was also significant and similar: 1.45 (95% CI: -2.38, -0.52, $p=0.002$).

Secondary efficacy endpoints

The first two secondary endpoints also displayed significant difference between nipocalimab and placebo:

- Average change in QMG score displayed statistical significance with nipocalimab demonstrating improvement in QMG change from baseline to Weeks 22 to 24 of treatment compared to placebo ($p<0.001$); LS means difference: -2.87 (95% CI: -4.23, -1.50).
- The percentage of MG-ADL responders showed a statistically significant greater percentage of MG-ADL responders with average improvement from baseline in MG-ADL of at least 2 points compared to placebo (68.8% vs 52.6%, respectively; $p=0.021$)

Other endpoints failed the testing hierarchy, but may support nipocalimab efficacy as they displayed a higher proportion of MG-ADL responders with sustained response from Week 4 through Week 24 in nipocalimab-treated participants (55.8%) than placebo-treated participants (26.3%) (LS mean difference 29.5%; 95% CI: 14.7, 44.4); an average improvement in MG-ADL scores from baseline of at least 50% was also observed at a greater proportion in the nipocalimab group (46.8%) than in placebo group (25%) over Weeks 22, 23, and 24 (LS mean difference 21.8%; 95% CI: 7.0, 36.3); and a higher proportion of nipocalimab participants with minimal symptom expression compared to placebo at week 24 (20.8% vs. 3.9%, respectively) and the results were consistent during the course of the study. Other scales of interest e.g. MG-QoL15r, Neuro-QoL and EQ-5D-5L, showed a non-significant tendency supportive of nipocalimab.

Subgroup analyses

MuSK+ patients (4 placebo, 12 nipocalimab) analysed under the US Estimand, had an average improvement in MG-ADL scores from baseline over Weeks 22, 23, and 24 of -3.54 (95% CI -6.78; -0.30).

Only three participants with anti-LRP4 positive gMG were included in the Phase 3 study (2 nipocalimab, 1 placebo) and a B/R risk assessment was not possible.

Efficacy in subgroups based on age

In the paediatric study, for 5 participants aged 12 to <18 years, the median percent change from baseline to the end of Week 24 of the pre-dose (minimal) total serum IgG was -69.87%.

Long term efficacy

The group of participants that had nipocalimab in the DB phase, 24 weeks in the open label extension study displayed a mean (SD) change from the baseline of the DB study of -5.30 (3.745) ($n=40$ participants).

3.3. Uncertainties and limitations about favourable effects

The number of anti-LRP4+ patients in the study was very limited. While mechanistically it would be expected that nipocalimab reduces specific anti-LRP4 antibodies since it generally lowers the levels of IgG1 and IgG2, no effect on anti-LRP4+ antibodies was observed in the small number of patients studied and the clinical trajectories appeared to favour the placebo arm. It is therefore not considered appropriate to extrapolate the effect of nipocalimab to this patient subgroup. Accordingly, inclusion of anti-LRP4+ patients in the indication was not agreed and the indication was restricted to patients *who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.* Regarding other subgroups, because of the small number of patients ≥65 years old included in the study, characterisation of efficacy in older patients is uncertain. Nevertheless, it is acknowledged that there is no apparent clinical or pathophysiological reason that would explain a lack of effect of nipocalimab in patients aged ≥65 years. Furthermore, other FcRN targeting medications have shown an effect in this age subgroup. Therefore, it is agreed not to exclude the indication to the population aged 65 years and older from the indication.

3.4. Unfavourable effects

In the DB phase of the Phase 3 gMG study approximately 90% of subjects experienced AEs both in the nipocalimab group (average 34 administrations) and in the placebo group (average 35 administrations). Serious AEs were seen in 9% in the nipocalimab group and in 14% in the placebo group. Muscle spasms, peripheral oedema, urinary tract infection, dizziness, nausea, and insomnia were more common in the nipocalimab group. The proportions of patients discontinuing treatment due to adverse events were balanced between treatment groups, 5% in the nipocalimab group and 7.1% in the placebo group. In the OLE of the Phase 3 gMG study 8.2% (16 patients) experienced at least 1 AE leading to permanent treatment discontinuation. Acknowledging the limitations of the safety database, with a relatively low number of patients and limited follow-up, no major safety concern of relevance for the benefit-risk balance is raised from these observations.

Serious infections

An increased incidence and/or severity of infections is a key concern based on the PD mechanism. The overall frequency of infections was approximately 43% and balanced between nipocalimab and placebo groups. The few events of serious infections in the phase 3 trial were equally balanced between nipocalimab and placebo. Urinary tract infection occurred in ≥5% of participants in the nipocalimab treatment group with a frequency two times higher than that in the placebo group in a combined pool of phase 2/3 studies. During the DB part of the Phase 3 gMG study, the most frequently reported SAE next to MG and MG crisis, was pneumonia. Lower respiratory tract infections were more common in the DB phase of the phase 3 trial, with 5 patients in the nipocalimab group and 2 in the placebo group. There were few cases of Herpes zoster observed, but all were in the nipocalimab groups in the DB phases of the phase 2/3 gMG studies.

Increased plasma lipids

Increased fasting levels of total cholesterol, HDL and LDL were observed in the nipocalimab group the entire 24-week DB period in the phase 3 trial. In the nipocalimab group, 29.9% had treatment-emergent markedly abnormal total cholesterol (≥6.2 mmol/L), compared to 4.1% in the placebo group. There were 23.5% with markedly abnormal LDL cholesterol (≥4.1 mmol/L) in the nipocalimab group, compared to 10.3% in the placebo group. At week 24, 17.3% in the nipocalimab group shifted to a higher risk category (LDL ≥4.1 mmol/L) compared to 6.7% in the placebo group. Notably increased lipid levels were also observed in the few adolescent patients studied. The assessment of increased plasma lipids cannot be

based on reported events of hyperlipidaemia, since lipid levels were per protocol masked (unless very high) to the study site and sponsor during the DB phase of the trial.

Decreased serum albumin levels

Reduced serum albumin levels are not unexpected, based on the PD effects of nipocalimab. This effect appears more pronounced compared with currently approved medicinal products with the same mechanism of action via the FcRn receptor.

All nipocalimab-treated participants with a post-baseline albumin measurement had a decrease in albumin from baseline at some point during the DB phase, compared to 86.6% in the placebo group. The mean changes from baseline during the DB phase were -8.4% at Week 2 and -7.2% at Week 24 with nipocalimab, compared to -0.5% at Week 2 and -2.1% at Week 24 in the placebo group.

The lowering of serum albumin is seen already at the first observation two weeks after treatment initiation, the level of decrease is maintained during the DB and open-label extension phase, and the pattern is similar across age groups. No patient had serum albumin below the lower limit of normal range in the DB phase of the phase 3 study. No patient had any adverse effect recorded directly attributable to a lowered albumin level. This is, however, not fully reassuring considering the association between serum albumin levels and long-term cardiovascular risk.

3.5. Uncertainties and limitations about unfavourable effects

MG is a rare disease and the available safety database for nipocalimab in this indication is consequently small. The intended target population covers the entire age range from adolescents aged 12 years to older adults. Since gMG is a chronic disease, the treatment is expected to be chronic, and long-term safety is currently not characterised. The assessment of currently available data has identified two main outstanding concerns regarding long-term safety - serious infections and cardiovascular safety.

Serious infections

An increased incidence and/or severity of infections is a key concern based on the PD mechanism. Characterisation of this risk is hampered by the small safety database and short follow-up currently available. Respiratory tract infections can lead to MG exacerbations and precipitate an MG crisis. To detect an increased risk for unfavourable outcome of serious infections, enough patients must be observed contracting such an infection under treatment with nipocalimab. This requires a substantially larger number of patients exposed for a longer duration than currently available in the safety database. Overall, there were no strong concerns raised for serious infections in the currently available data, but this is based on too few patients and too short follow-up to allow reliable characterisation of this important potential risk. Further characterisation in a PASS has therefore been agreed.

Cardiovascular safety

The adverse effects on plasma lipids are not entirely unexpected since another FcRn blocker has demonstrated similar effects, in a study evaluating the treatment of patients with thyroid eye disease [6]. This effect has not been observed with the other FcRn blockers currently approved for treatment of gMG.

In relation to cardiovascular safety, the effects on albumin levels must also be considered. Reduced serum albumin levels are not unexpected based on the PD effects of nipocalimab. However, this effect of nipocalimab appears more pronounced compared to currently approved medicinal products with the same mechanism of action on the FcRn receptor. The potential impact on long-term cardiovascular safety remains uncertain.

Blood lipid levels can be monitored during treatment. A risk minimisation strategy targeting the adverse effects on blood lipid levels is considered feasible, but the potential overall impact on long-term cardiovascular safety remains uncertain. A PASS has therefore been agreed to further characterise long term cardiovascular safety.

Dose in patients with high body weight

Nipocalimab doses are administered per kilogram and there is no cap with an upper body weight limit on dose in the proposed posology. This leads to higher exposure of nipocalimab in subjects with higher body weights. The weight range in the Phase 3 study (active treatment arm) was 41-124 kg. Higher exposure does not appear to provide any improved efficacy, but there is an association between higher dose and increase in LDL and cholesterol. The SmPC highlights that closer monitoring should be considered for patients with high body weight/BMI (e.g. ≥ 125 kg or BMI > 35 kg/m²).

Table 39. Effects table for Nipocalimab in qMG

Effect	Short Description	Unit	Nipocalimab N=77	Placebo n=76	Uncertainties/ Strength of evidence
MG-ADL reduction	Average change from baseline in MG-ADL score over Weeks 22, 23, and 24	LS means (SE)	-4.68 (0.324)	-3.29 (0.333)	Missing participant flow/baseline data/information; Not clinically meaningful change; Only 3 LRP+ participants; No effect on age>65 years; IST and BMI might affect efficacy; // Compelling p-value
		Difference vs placebo (95% CI)	-1.39 (-2.31; -0.47)		
		P value	0.003		
QMG reduction	Average change from baseline in QMG score over Weeks 22 and 24	LS means (SE)	-4.77 (0.488)	-1.90 (0.491)	Missing participant flow/baseline data/information; Does not reach clinically meaningful change; Only 3 LRP+ participants; No effect on age>65 years; IST and BMI might affect efficacy// Compelling p-value
		Difference vs placebo (95% CI)	-2.87 (-4.23, -1.50)		
		P value	<0.001		
RR ≥ 2 points from baseline	MG-ADL responders over Weeks 22, 23, and 24	% responders	68.8%	52.6%	Missing participant flow/baseline data/information; 16.2% modest difference (NNT 6); Not compelling p-value// Clinically meaningful change
		Difference vs placebo (95% CI)	16.2 (0.9, 31.5)		
		P value	0.021		
RR	MG-ADL responders at	% responders	55.8%	26.3%	

Effect	Short Description	Unit	Nipocalimab N=77	Placebo n=76	Uncertainties/ Strength of evidence
≥2 point from baseline, sustained response	Week 4 through Week 24	Difference vs placebo (95% CI)	29.5 (14.7, 44.4)		Missing participant flow/baseline data/information// This endpoint cannot be formally tested based on testing hierarchy. Nominal p-value is given. Sustainability of effect over 6 months
		Nominal P value	<0.001		
RR ≥50% from baseline	MG-ADL responders over Weeks 22, 23, and 24	% responders	46.8%	25.0%	Missing participant flow/ baseline data/information// This endpoint cannot be formally tested based on testing hierarchy. Nominal p-value is given.
		Difference vs placebo (95% CI)	21.8 (7.0, 36.6)		
		Nominal P value	0.002		
Minimal symptom expression	Percentage of patients with MG-ADL score of 0 or 1 at Week 24	%	20.8	3.9	Missing participant flow/ baseline data/information; Missing analysis// This endpoint cannot be formally tested based on testing hierarchy. Nominal p-value is given.
Lower respiratory tract infections	Number of observed cases of bronchitis or pneumonia	N	5	2	Insufficiently characterised level of risk
Urinary tract infections	Number of observed cases	N	6	2	Insufficiently characterised level of risk
Herpes zoster infections	Number of observed cases	N	3	0	Insufficiently characterised level of risk
Total cholesterol	Proportion with markedly abnormal total cholesterol (≥6.2 mmol/L)	%	29.9	4.1	Insufficiently characterised long-term CV risk
LDL cholesterol	Proportion with markedly abnormal LDL cholesterol (≥4.1 mmol/L)	%	23.5	10.3	Insufficiently characterised long-term CV risk
Serum albumin	Mean change from baseline at week 24	%	7.2	-2.1	Insufficiently characterised long-term CV risk

Abbreviations: NNT = Numbers needed to treat; RR = Responder rate.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

MG is a rare disease which for a long time was treated symptomatically with Ach-esterase inhibitors and general immune-suppressive therapy. In recent years several disease-specific medications have been approved. Nipocalimab targets the FcRn, being the third in its class. The application for marketing approval of nipocalimab also included adolescents, patient groups not approved for the other FcRn targeting product.

Statistically significant efficacy was shown in a single pivotal trial with weak support from earlier clinical phases in the development program. Careful examination of the primary and key secondary endpoints in terms of effect characteristics and size suggest a modest but clinically meaningful effect. Other secondary endpoints such as sustainability of response, $\geq 50\%$ change and the clinical treatment goal of achieving minimal manifestation status, even if appearing below the testing hierarchy breaking point, lend some support to relevant efficacy. The applicant has also provided thorough justifications for the indication of gMG for adolescents who are ≥ 12 years regardless of the pre/post pubertal onset of the disease and PK data and additional analyses support the dosing regimen extrapolation to adolescents who are ≥ 12 years. The OLE study suggests a sustained efficacy of nipocalimab.

There were only 3 anti-LRP4+ patients included in the study and no effect on anti-LRP4+ antibodies was observed. Additional PD data in a larger patient cohort, showing that treatment with nipocalimab is followed by a decrease in anti-LRP4, would have been needed to support a positive B/R balance also for this patient subpopulation. Accordingly, inclusion of anti-LRP4+ patients in the indication is not supported. The applicant agrees and the indication has therefore been amended to: *"as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive."*

Most identified adverse reactions do not overall raise any serious concern with a notable impact on the benefit-risk balance. The extent of a potential adverse impact on the outcome of severe infections is difficult to quantify based on available data, but no major concern was raised during the procedure. Lower respiratory tract infections and Herpes zoster have been included in section 4.8 of the SmPC. This issue also requires additional pharmacovigilance activities and the requirement from a PASS with the objective to study impact on severe infections has been agreed.

The main safety concern with an impact on the overall benefit/risk balance relates to long-term cardiovascular safety, mainly from the increased blood lipid levels. Any durable increase in blood lipids is expected to compromise cardiovascular safety, and since increased lipid levels appear to be frequent, durable, of a magnitude associated with increased cardiovascular risk, and also observed in the adolescent age group, together with the fact that treatment with nipocalimab is intended to be chronic, these findings were considered a major safety concern with an impact on the overall benefit-risk balance of the product. However, sufficient risk minimisation activities have been agreed at this stage.

A decreased serum albumin concentration is also associated with increased risk for hyperlipidemia, cardiovascular disease, and mortality [16]. Considering the anticipated long duration of treatment with nipocalimab and the wide age range of the target population, the reduced albumin levels can potentially contribute to an overall increased cardiovascular risk.

3.6.2. Balance of benefits and risks

The primary and key secondary endpoints in terms of effect characteristics and size suggest a clinically meaningful but modest effect for anti-AChR+ and anti-Musk+ gMG. Due to the very low number of anti-LRP4+ patients in the study, no B/R assessment is possible for this subpopulation and, hence, the indication does not include anti-LRP4+ patients. The applicant agrees and the indication has been amended to: *“as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.”*

The main impact on the benefit risk balance came from the adverse impact on long-term cardiovascular safety, mainly from the increased blood lipid levels. Generalised MG is a chronic disease and treatment can be anticipated to be long, sometimes lifelong. Concerns regarding long-term cardiovascular safety therefore have an important impact on the overall benefit-risk balance. However, sufficient risk minimisation activities have been agreed at this stage.

3.7. Conclusions

The overall benefit/risk balance of Imaavy 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 Imaavy is not similar to Soliris, Vyvgart and Rystiggo 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 Imaavy is favourable in the following indication(s):

Imaavy is indicated as an add-on to standard therapy for the treatment of generalised Myasthenia Gravis (gMG) in adult and adolescent patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

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 (see Annex I: Summary of Product Characteristics, section 4.2).

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product

within 6 months following authorisation.

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.

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 nipocalimab 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.

Refer to Appendix on new active substance (NAS).

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0117/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. References

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