swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Imaavy

International non-proprietary name:	nipocalimab
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	1200 mg/6.5 mL, 300 mg/1.62 mL
Route(s) of administration:	intravenous use
Marketing authorisation holder:	Janssen-Cilag AG
Marketing authorisation no.:	69588
Decision and decision date:	approved on 18 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

Abs	Antibodies
AChR	Acetylcholine receptor
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATP	Active treatment phase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CV risk	Cardiovascular risk
CYP	Cytochrome P450
DB	Double blind
DDI	Drug-drug interaction
ECLIA	Electrochemiluminescence immunoassay
EMA	European Medicines Agency
ERA	Environmental risk assessment
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
gMG	Generalised myasthenia gravis
HDL	High-density lipoprotein
HPLC	High-performance liquid chromatography
ICE	Intercurrent events
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
jMG	Juvenile myasthenia gravis
LDL	Low-density lipoprotein
LoQ	List of Questions
LRP4	Lipoprotein receptor-related protein 4
LTE	Long-term extension
MA	Marketing authorisation
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular event
MAH	Marketing authorisation holder
Max	Maximum
MCID	Minimal Clinically Important Difference

MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis - Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
Min	Minimum
MRHD	Maximum recommended human dose
MuSK	Muscle-specific kinase
N/A	Not applicable
NAb	Neutralizing antibody
NO(A)EL	No observed (adverse) effect level
OL	Open-label
PBO	Placebo
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PMDA	Pharmaceutical and Medical Devices Agency
PMS	Post-market surveillance
PK	Pharmacokinetics
PLEX	Plasma exchange
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
q2w	every 2 weeks
q4w	every 4 weeks
QMG	Quantitative Myasthenia Gravis
RMP	Risk management plan
ROW	Rest of world
SAE	Serious adverse event
SoC	Standard of Care
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UTI	Urinary tract infection

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for nipocalimab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 20 June 2024.

Work-sharing procedure
The applicant requested a work-sharing procedure with Canada.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Imaavy is indicated for the treatment of generalised myasthenia gravis (gMG) in adults and adolescent patients who are antibody positive.

2.2.2 Approved indication

Imaavy is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in patients aged 12 years of age and older who are anti-acetylcholine receptor (AChR) or anti-muscle specific tyrosine kinase (MuSK) antibody positive.

2.2.3 Requested dosage

For adults and adolescents 12 years and older with gMG, the recommended initial dose is 30 mg/kg administered over approximately 30 minutes, followed by a maintenance dose of 15 mg/kg administered over approximately 15 minutes every 2 weeks thereafter.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	19 December 2024
Formal control completed	17 January 2025
List of Questions (LoQ)	16 May 2025
Response to LoQ	9 July 2025
Preliminary decision	22 August 2025
Response to preliminary decision	15 September 2025
Labelling corrections	29 October 2025
Response to labelling corrections	7 November 2025
Labelling corrections	1 December 2025
Response to labelling corrections	5 December 2025
Labelling corrections	10 December 2025
Response to labelling corrections	15 December 2025
Final decision	18 December 2025
Decision	approval

3 Medical context

Generalised myasthenia gravis
Myasthenia gravis (MG) is considered an immunoglobulin G (IgG) autoantibody-mediated disease leading to muscular weakness due to disruption of the electromechanical coupling at the neuromuscular junction characterised by day-time variability. Generalised MG (gMG) may involve ocular, bulbar, respiratory, neck and extremity muscles. Myasthenic crisis represents the most severe variant of gMG. It is a potentially life-threatening condition usually requiring intensive care, tube feeding, and mechanical ventilation. Disease activity is characterised by considerable natural variability and long intervals of spontaneous remission are not uncommon. At onset, symptoms are often restricted to external ocular muscles. In later stages, muscular weakness spreads to extraocular muscle in more than half of patients, leading to gMG. Adult and paediatric MG are similar with regard to their clinical presentation, underlying pathophysiology, diagnosis and therapy. Paediatric MG, though, has to be discriminated from congenital forms of MG that are primarily mediated by genetic factors.
Generalised MG is an orphan disease with an annual incidence of 0.8 - 1 adult and 0.1 to 0.5 juvenile (<18 years) cases per 100,000 individuals. 80 to 85% of adult MG patients are positive for anti-AChR antibodies (abs), 6 to 8% are positive for anti-MuSK abs and up to ~1-2% for anti-LRP4+ abs. Between 50% and 92% of paediatric gMG patients are tested positive for one or more of these abs. 10% to 15% of patients are double seronegative for AChR/MuSK abs. Some of these double seronegative cases refer to AChR abs that are difficult to detect by routine antibody testing, low-affinity AChR abs, clustered AChR abs, LRP4 or additional, so far unknown, abs.

Medical need in gMG. Despite numerous approved therapeutic approaches, there is still an unmet medical need, especially in gMG patients who are seronegative for the most common abs (i.e. AChR and MuSK abs). Furthermore, the current immunosuppressive treatment options have only a delayed onset of efficacy (except for plasma exchange (PLEX) and intravenous immunoglobulin (IVIg)). Another limitation arises from the mode of administration as all antibody therapies, including IVIg, have to be administered intravenously (IV).

Nipocalimab
This medicinal product represents a fully human IgG1λ monoclonal antibody (mAb) that binds to the neonatal Fc receptor (FcRn). A primary function of FcRn is to serve as a recycling or transcytosis receptor, contributing to the maintenance and homeostasis of circulating serum IgG. Nipocalimab blocks the binding of IgG to FcRn and thus increases its degradation rate, finally leading to the reduction of circulating IgG, including pathogenic IgG auto-abs. Based on its mechanism of action, nipocalimab is anticipated to be effective in gMG patients who are seropositive for auto-abs directed against AChR or MuSK or LRP4.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority Health Canada (see section 2.1 Applicant’s request / Work-sharing procedure).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority Health Canada (see section 2.1 Applicant's request / Work-sharing procedure).

6 Clinical aspects

6.1 Clinical pharmacology

The clinical pharmacology information included in this submission is based on the 9 Phase 1 studies in healthy volunteers, 2 Phase 2 studies in adult patients with gMG, 1 Phase 3 study in adult patients with gMG and 1 Phase 2/3 study in adolescent patients with gMG. For all studies with PK and immunogenicity assessments, bioanalytical methods were adequately validated; bioanalytical reports detailing the analytical performance of the respective assays were included and were found to be acceptable.

Absorption
Not applicable due to the IV administration.

Distribution
Mean V_z values ranged from approximately 0.477 to 3.09 L, suggesting that nipocalimab is primarily confined in the circulatory system with limited extravascular tissue distribution.

Elimination
Nipocalimab exhibited a dual elimination pathway, consisting of both a linear catabolic pathway and a nonlinear FcRn-mediated pathway, resulting in a nonlinear and concentration-dependent clearance. Following nipocalimab IV dosing at 15 and 30 mg/kg, the linear elimination phase was predicted to last 4.6 days and 7.6 days, respectively. During this period, the nipocalimab clearance (CL), estimated to be 0.692 L/day, was dominant. After the linear elimination phase, the nonlinear concentration-dependent CL (up to 532 L/day) dominated the elimination of nipocalimab.

Based on noncompartmental analyses, mean CL values were approximately 0.032 to 0.241 L/h, and mean terminal half-life ($T_{1/2}$) values ranged from 7 to 40 hours in healthy participants.

Following a nipocalimab IV dose of 15 or 30 mg/kg, it is estimated to take approximately 10.5 and 13.4 days, respectively, to completely wash out nipocalimab from the serum.

Metabolism
The exact pathway through which nipocalimab is metabolised has not been characterised. As a fully human IgG1 mAb, nipocalimab is expected to be metabolised 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.

Linearity
Following single IV infusions of nipocalimab 0.3 mg/kg to 60 mg/kg in healthy participants or participants with gMG, C_{max} increased in a dose-proportional manner, while AUC increased in a greater than dose-proportional manner.

Single dose vs. multiple dose PK
The PK of nipocalimab after multiple-dose IV administrations were consistent with the PK following a single-dose IV administration in healthy participants following 15 mg/kg IV every two weeks (q2w) dosing. Steady-state serum nipocalimab concentrations are achieved without any observed accumulations in serum nipocalimab concentration over time.

Special populations
Dose adjustments are not required for patients with renal or hepatic impairment.

Interactions
In view of the size and nature of the molecule, drug-drug interactions via induction or inhibition of metabolising enzymes are very unlikely to occur.

DDIs related to changes in IgG levels
Nipocalimab is, however, likely to affect the PK of IgG-based therapeutics or Fc fusion proteins because its mode of action results in lowering serum concentrations of IgG. Fremanezumab AUC decreased by approximately 65 to 66%, and C_{max} decreased by 42% with concomitant administration of nipocalimab. The AUC of etanercept decreased by 28% with co-administration of nipocalimab, while etanercept C_{max} remained virtually unchanged. Therefore, the concomitant administration should be avoided if deemed clinically suitable as indicated in the Information for healthcare professionals.

Mechanism of action
Nipocalimab is a fully human mAb that targets the neonatal FcRn IgG binding site, at both acidic and neutral pH, thereby blocking the binding of IgG and thus increasing its degradation rate. This results in a decrease in circulating IgG antibody concentrations. Nipocalimab has demonstrated rapid binding to FcRn in vivo and subsequent IgG reductions in Phase 1 and Phase 2 clinical studies. Nipocalimab further resulted in a reduction in circulating concentrations of pathogenic autoantibodies, such as anti-AChR antibodies that cause MG.

Safety pharmacology
In view of the size and nature of the molecule, QT/QTc interval prolongations are very unlikely.

6.2 Dose finding and dose recommendation

Dose finding – adult gMG
The proposed dose level and dosing regimen for the single pivotal 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 MOM-M281-004 and extensive modelling and simulation of the dose-response relationships for IgG and MG-Activities of Daily Living (MG-ADL).

Dose-finding Phase 2 study MOM-M281-004 (for short: -004)
This study included the following treatment groups: Group 1: placebo (PBO) q2w (14 subjects), Group 2: 5 mg/kg nipocalimab once every 4 weeks (q4w) (14 subjects), Group 3: 30 mg/kg nipocalimab q4w (13 subjects), Group 4: 60 mg/kg nipocalimab as a single dose (13 subjects), and Group 5: 60 mg/kg nipocalimab q2w (14 subjects).
It must be taken into account that study -004 did not include a 15 mg/kg q2w arm. Moreover, it had to be terminated early due to the COVID-19 pandemic and included only few numbers of subjects (13 or 14 subjects per each of the 5 dosing arms and the PBO arms).
Results. Rapid, dose-dependent IgG lowering was observed one week after the initial dose in all dose groups, with maximal IgG lowering achieved at Week 2 in the 60 mg/kg single dose and 60 mg/kg q2w groups. Dose-dependent improvements in MG-ADL scores were also observed. Reductions in MG-ADL from baseline were linearly correlated with reductions in total IgG from baseline ($p<0.001$) and

reductions in anti-AChR autoantibody from baseline (p=0.0002). Total serum IgG lowering has therefore been suggested as a good predictor for efficacy, as assessed using MG-ADL in participants with gMG. Nipocalimab was generally well tolerated across all dose groups.

Population PK/PD/efficacy modelling analyses were conducted using data obtained from nipocalimab Phase 1 and 2 studies to evaluate the relationship between PK, IgG lowering, and MG-ADL, in addition to other efficacy and safety endpoints (including serum albumin and total cholesterol):

Dosing interval. The results indicated that the q2w dosing interval would provide more sustained IgG lowering and MG-ADL reduction at all simulated dose levels when compared with the q4w dosing interval.

Dose. While modelling and simulation suggested numerical differences in IgG lowering and MG-ADL reduction between the 15 and 30 mg/kg q2w dosing regimens (the model-predicted mean IgG lowering is 73.8% versus 79.4%, respectively), the additional 5.6% IgG reduction with 30 mg/kg q2w was expected to produce a minimal additional MG-ADL improvement at steady-state trough beyond the improvement expected with 15 mg/kg q2w.

Dose recommendation
In the light of the adult Phase 2 dosing study result for various dosing intervals and the small added benefit in IgG lowering properties of the 30 mg/kg q2w in PD studies, the 15 mg/kg q2w dose regimen was selected as the single maintenance dose regimen to be studied for the Phase 3 study MOM-M281-011 in gMG (see below).

Dosing in adolescents
Data from Cohort 1 of Study MYG2001 in adolescent participants with gMG, using the adult Phase 3 dosing regimen consisting of an initial 30 mg/kg dose, followed by 15 mg/kg q2w for 24 weeks, were used to conduct population PK-based analyses. A total of 71 serum nipocalimab concentration values from 7 adolescent patients, 45 total serum IgG concentration data from 5 adolescent participants, and 28 serum anti-AChR autoantibody concentration records from 4 adolescent participants were included in this analysis. The $C_{max,ss}$ and $AUC_{tau,ss}$ of serum nipocalimab concentrations in adolescents overlapped with the ranges predicted for adults in the Phase 3 study MOM-M281-011. Similarly, the steady-state pre-dose and nadir total serum IgG reductions from baseline were comparable between adolescents and adults.

6.3 Efficacy

Efficacy
The Applicant has submitted the results of a single pivotal adult Phase 3 gMG study MOM-M281-011 (-011) in adult gMG patients that was further supported by two adult Phase 2 studies and an open-label (OL) paediatric Phase 2/3 study. The international multi-centre Phase 3 trial comprises a completed 24-week double blind (DB) phase and a still ongoing OL phase of variable duration. Efficacy data for both phases refer to a data cut-off of 17.11.2023, while safety data have been provided up to 31.03.2024. Due to the COVID-19 pandemic during the conduct of the study, some of the on-site assessments were not feasible. The Applicant has therefore undertaken additional analyses to evaluate the possible impact of the pandemic on study results. These analyses did not raise specific concerns.

Pivotal Phase 3 study MOM-M281-011 (for short: -011)
Key eligibility criteria included diagnostic criteria meeting the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II a/b, III a/b, or IV a/b for gMG, with an MG-ADL score of ≥6 (without a minimum subscore for extra-ocular symptoms) and an inadequate response to stable MG therapy (e.g. glucocorticoids, AChR inhibitors, or immunosuppressants), or patients who had discontinued corticosteroids and/or immunosuppressants ≥4 weeks prior to screening due to

intolerance or lack of efficacy. Participants were to maintain their current SoC gMG therapy throughout the DB phase. Actually, more than 95% of the subjects in adult pivotal Phase 3 study -011 received nipocalimab as an add-on treatment to stable conventional gMG therapy with acetylcholinesterase inhibitors, glucocorticosteroids, and/or immunosuppressants including azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.
Patient population. The study population included gMG patients who were positive for AChR, MuSK, or LRP4 auto-abs as well as gMG patients who were seronegative for these auto-abs. Marketing authorisation (MA) has been sought for the seropositive gMG population. The number of LRP4-positive gMG patients was limited to three individuals.
Dosing. In the DB phase, a starting dose of 30 mg/kg nipocalimab was followed by 15 mg/kg IV infusions q2w that was also to be continued during the OL. The original study -011 protocol allowed dose changes during the study (and also in the paediatric study -2001). 24 subjects actually switched to 30 mg/kg q4w. After the late Amendment 2 (dated 11.01.2023), these subjects were put back on the original dosing regimen of 15 mg/kg q2w. With its Response to LoQ, the Applicant provided efficacy and safety data for these patients. There was no evidence for a major impact on clinical efficacy or PD. However, safety analyses for patients with a dose switch provided with the Response to LoQ did not consider the actual time-point of the dose switch, but defined the subgroup according to dose switch yes/no over the complete duration of the study. Due to the pooling of safety information across all doses, the specific risk profiles of the 30 mg/kg q4w dose and the 15 mg/kg q2w dose are not fully transparent. The Applicant argued that lower doses would likely result in suboptimal efficacy, while higher doses may not yield much difference in efficacy as predicted for gMG and refers to ‘a great unmet medical need in gMG’. However, the latter argument applies to the condition itself and is not suitable to support a specific dose or dosing regimen.
Overall, the Applicant's rationale regarding dose and dosing regimen does not appear fully conclusive. The rationale for more frequent administration of a lower dose puts a higher burden on the patient and healthcare system. The doubts regarding the dose proposed for MA are further nourished by the limited benefit over PBO in the adult pivotal Phase 3 gMG study (see below).

Statistical analysis. After interacting with health authorities in the US, EU and Japan (PMDA), the Applicant specified three different primary estimands for submission to US/ROW, EU countries, and Japan. The analysis population of the primary estimand in all three regions (US/ROW, US, and Japan) refers to the seropositive patients and is therefore fully supportive of the proposed target population reflected in the indication wording. Estimand 2 (Japan only) refers to AChR+ subjects and Estimand 3 (Japan) to seropositive and seronegative subjects.

The following three different types of intercurrent events (ICE) were pre-specified:
a. Discontinuation of study intervention or stable gMG therapy that is not due to initiation of rescue therapy
b. Discontinuation of study intervention or stable gMG therapy that is due to initiation of rescue therapy
c. Changes in stable gMG therapy (for any reason)

According to the primary estimand EU for the numeric primary and key secondary endpoints, all data collected after ICE a) and c) were addressed with a treatment policy strategy, and data collected after c) were addressed with a hypothetical strategy (according to ICH R1). Missing values under primary estimand EU were imputed by the “Copy Reference” method.
Sensitivity analysis included a Jump to Reference multiple imputation approach. For EU and US/ROW, a fixed sequence (with the sequence of primary and key secondary objectives listed above) testing approach with the hypotheses tested in Primary Efficacy Analysis Set was used.

Clinical assessment tools. The primary and key secondary endpoints refer to validated clinical scales that are widely accepted and used in clinical gMG studies: While the MG-ADL score is exclusively based on the patient’s own evaluation and can be obtained by telephone calls, the Quantitative Myasthenia Gravis (QMG) scale refers to physician-rated semiquantitative and quantitative clinical assessments. For both scales, Minimal Clinically Important Differences (MCID)

have been published, and these were also applied in the nipocalimab clinical development programme to evaluate treatment response. MCIDs are defined as an improvement by 2 points on the MG-ADL scale and 3 points on the QMG scale. Patients with a reduction by the MCID or more were considered as responders.

Efficacy Results
The Full Analysis Set included 98 subjects in each treatment arm. The primary efficacy analysis set (i.e. seropositive subjects) refers to 76 subjects in the PBO and 77 subjects in the nipocalimab-treated arm. Overall, the results for all three approaches yielded confirmatory results.
For the EU approach, nipocalimab met its primary endpoint *change from baseline in MG-ADL scores over Week 22, Week 23 and Week 24* (between group difference vs. PBO (95% CI): -1.45 (-2.38, -0.52) p 0.002). A statistically significant result was also obtained for the key secondary endpoint *change from baseline in QMG total score over Weeks 22 and 24* (between group difference vs. PBO (95% CI): -2.87 (-4.23, -1.50), p <0.001).

Treatment effect size. The difference in mean change between nipocalimab and PBO-treated subjects remained clearly below the MCID for both scales. The limited treatment benefit is also reflected in the results of the responder analyses: the benefit of q2w nipocalimab treatment over PBO corresponds to an increase in responder rates by 16.2% for the MG-ADL score and by 16.6% for the QMG score after 6 months of treatment. Patients have been closely followed during the DB phase of the study. Between DB Week 2 and DB Week 24, MG-ADL responder rates varied between 51.9% and 72.7% for the nipocalimab group and between 39.5% and 61.8% in the PBO group between Weeks 2 and 24. The maximum difference in MG-ADL responder rates between both treatment arms did not exceed 21% across all time-points.
Individual variability of treatment benefit is suggested by the wide range of the change in total MG-ADL or QMG scores across the various assessment time-points including Weeks 22 to 24. While some patients experience a clinically meaningful benefit, others show evidence of clinical worsening as compared to baseline.
Treatment with nipocalimab was administered with no respect to the actual clinical status of the patient. Stopping nipocalimab therapy was only foreseen in case of a severe clinical deterioration with a need for rescue therapy/hospitalisation during the DB phase. However, patients with a need for rescue therapy could later transfer to the OL phase after a nipocalimab-free interval of 4 weeks. Overall, 5.1% of nipocalimab-treated subjects discontinued the DB phase due to the need for rescue therapy (PBO 7.7%). In the OL phase, more than 9% in the nipocalimab/nipocalimab treatment arm required rescue therapy. In the OL phase, patients could continue after receiving rescue therapy, but nonetheless, 8% discontinued from the OL phase due to lack of efficacy (data cut-off: 31.03.2024).

Criteria for lack of efficacy and treatment stopping. Continued nipocalimab treatment with no regard to the actual response of the individual patient may have contributed to the limited efficacy results. The rate of permanent non-responders had not been assessed in the clinical development programme, and the maximum number of administrations to (re-)achieve responder status had been unknown. With its Response to LoQ, the Applicant provided MG-ADL and QMG responder analyses for the DB and OLE Phases. The number of subjects not achieving MG-ADL responder status during the DB period was identical in both DB treatment arms. While all PBO subjects who continued in the OLE achieved responder status, 50% of nipocalimab patients who continued in the OLE on nipocalimab never achieved responder status thereafter. The number of subjects needing more than 6 infusions to achieve responder status is limited to 4/77 patients. For patients with a later response, the relationship to the IMP could not be reliably established as SoC had been continued. It has therefore been considered appropriate to stop nipocalimab treatment if responder status is not achieved with 6 administrations. Almost 60% of QMG responders lost this status again after the first response under continued nipocalimab treatment. 86.7% of patients re-achieved response with 6 or fewer administrations after losing this status. This supports the recommendation to stop treatment with nipocalimab if responder status has been lost and is not re-achieved with 6 additional administrations. This was also demonstrated in subjects after requiring rescue therapy.

In light of the high logistic demands and the safety risks of nipocalimab treatment, recommendations regarding treatment stopping have been implemented in the Information for healthcare professionals. It appears unjustified to continue treatment just because the patient does not require rescue treatment or hospitalisation.

Use in subgroup ≥65 years. The prespecified age subgroup ≥65 years is limited (primary efficacy set: 18 subjects). The numerical difference in the average change in MG-ADL scores from baseline over Weeks 22-24 between PBO- and nipocalimab-treated subjects was 0.0 in this age group. For the physician-rated QMG scores, results imply worse performance than PBO (+1.14). The numbers of subjects treated in the age group ≥45 - 64 years were not considerably higher but yielded more consistent and beneficial results. With its Response to LoQ, the Applicant has presented a very brief discussion of the benefit-risk profile in the age group ≥65 years considered individually, but also compared to younger age groups. The overall low number of subjects ≥65 years included cannot be attributed to a specific low prevalence as late-onset MG represents about 45% of all MG cases. The Applicant's argument that low numbers in the age group >74 years question the robustness of data appears sound. However, this argument also applies to the age group ≥65 to 74 years with 8 subjects in the nipocalimab arm. It must be concluded that the evidence for a robust positive benefit-risk balance is not fully established in the elderly. The lack of information and the interindividual variations in treatment response are now fully covered in the Information for healthcare professionals, including a specific warning for this age group and the need for close clinical follow-up.

6.4 Safety

SAEs. As at 31.03.2024, 8 fatal cases had been reported in patients treated with nipocalimab in DB and OL phases of Phase 2 and 3 gMG studies. One fatal case in the nipocalimab (DB) treatment group was due to MG crisis during the DB phase. Furthermore, AEs related to MG were reported in 12.2% of patients in each DB treatment arm and in more than 15% in the OL phase. SAEs related to MG were reported in 3.1% of nipocalimab-treated subjects during the DB phase and in 5.6% during the OL phase. MG crisis was reported in 1.5% in the OL phase. AEs related to MG were also reported in single patients in the adult Phase 2 studies. So, the finding of AEs related to MG worsening and MG crisis supports the need for defining non-responder and treatment stopping criteria. A recommendation for close clinical follow-up has been implemented in the Information for healthcare professionals. Other AE PTs leading to death refer to hypertensive heart disease, cardiorespiratory arrest, myocardial infarction, haemophagocytic lymphohistiocytosis, and gliosarcoma. No deaths were reported in the paediatric gMG study. Other non-fatal SAEs refer to infections, tumours, pneumothorax, pulmonary embolism, and atrial fibrillation.

ADRs listed in the Swiss Information for healthcare professionals include hypogammaglobulinaemia (total IgG <1g/L), urinary tract infection, bronchitis, pneumonia, herpes zoster, total cholesterol increased, LDL cholesterol increased, insomnia, dizziness, diarrhoea, abdominal pain, nausea, muscle spasms, peripheral oedema, and pyrexia.

Specific safety topics
Increase in total and low-density lipoprotein (LDL) cholesterol and impaired treatment benefit of lipid-modifying agents. Treatment-emergent markedly abnormal fasting LDL cholesterol values were reported in 22.7% of nipocalimab-treated subjects during the DB phase and in 21.5% during the OL phase (PBO 10.3%). Markedly abnormal cholesterol levels were documented for 29.9% of nipocalimab-treated subjects during the DB phase and for 28.7% during the OL phase (PBO 4.1%). The total cholesterol/high-density lipoprotein (HDL) ratio remained below the critical threshold of 4; there was no increased risk for major adverse cardiovascular events (MACE) during the DB and OL phases, but the long-term cardiovascular risk is unknown as the number of subjects treated for more than ≥24 months is limited to 41 subjects. The limited long-term experience with chronic nipocalimab treatment actually

represents a critical issue, especially with respect to the use in the paediatric population. Regarding the longstanding development of MACE/CV risks, the PSUR obligation has been extended.

Immunogenicity. Serum samples collected from Phase 3 gMG study -011 had been analysed for anti-drug antibodies to nipocalimab using a specific, highly sensitive and drug-tolerant electrochemiluminescence immunoassay (ECLIA) method. The respective analyses did not raise specific concerns. The complete dossier, including immunogenicity analyses, refers to nipocalimab manufactured according to PROCESS 2. Meanwhile, the manufacturing process has been changed to PROCESS 3. This PROCESS 3 nipocalimab variant is proposed for the MA. The immunogenic properties of the PROCESS 3 nipocalimab variant are largely unknown. A single-dose immunogenicity study in healthy volunteers for PROCESS 3 nipocalimab yielded a higher prevalence of ADAs and NAbs to nipocalimab. However, the Applicant argued that this does not have an influence on the PK or safety of PROCESS 3 nipocalimab and thus considered these higher incidences of ADA as not clinically meaningful. It should be noted, though, that the submitted comparison of PROCESS 2 and PROCESS 3 nipocalimab-treated healthy subjects with and without ADAs/NAbs is probably not fully robust as the numbers of healthy ADA/NAb-negative subjects exposed to PROCESS 3 nipocalimab were much lower. Another problem arises from the single-dose nature of this Phase 1 study, which is not representative of the risk associated with the chronic use of nipocalimab in gMG patients. Predictions on efficacy cannot be made. Moreover, the analysis presented does not account for the time-point of ADA occurrence. This limitation also accounts for the comparative analysis of infusion-related reactions between seropositive and seronegative healthy volunteers treated with PROCESS 2 and 3 nipocalimab, which did not consider the time-point of ADA and/or NAb occurrence.
The relevant information has therefore been added to the Undesirable Effects section of the Information for healthcare professionals. A potential lack of efficacy for PROCESS 3 nipocalimab due to ADAs and/or NAbs would be difficult to identify after MA. The Applicant will follow potential safety signals of MG worsening and MG crisis from post-market surveillance (PMS) sources, but this might have to remain inconclusive as no routine testing for ADAs and NAbs is available to date. Nevertheless, this approach was finally accepted taking into account that treatment stopping criteria in case of a non-response have been implemented in the Information for healthcare professionals.

Paediatric population - Adolescents ≥12 years

Phase 2/3 study 80202135MYG2001 (study -2001)
The scientific evidence regarding tolerability, efficacy and safety in the adolescent gMG population refers to Cohort 1 (N=7) of the 24-week Active Treatment Phase of the paediatric Phase 2/3 study -2001. Dosing was according to the pivotal adult Phase 3 gMG study. All subjects were seropositive for AChR+, none had MuSK or LRP4 auto-abs. Four out of 5 Active Treatment Phase (ATP) completers continued in the ongoing long-term extension (LTE) of study -2001 with 3 of them transitioning to a 30 mg/kg q4w dose regimen from the 15 mg/kg q2w. At the data cut-off 31.03.2024, 2 out of 4 adolescent subjects in the LTE had been treated for >48 weeks.
Efficacy and safety data therefore do not only relate to a very small number of adolescent subjects but also refer to a more liberal dosing regimen than the one proposed for MA. This limitation cannot be overcome by extrapolating data from adult subjects with lower body weight as the numbers of adult patients with underweight are limited. In addition, the long-term safety profile of nipocalimab is largely unknown. Due to the chronic nature of gMG, the need for longer exposure to nipocalimab has to be anticipated. The risk for infections is increased in the adolescent population and the long-term safety profile of nipocalimab is largely unknown even in adults.
However, according to the ICH E11A guideline (Pediatric Extrapolation, 2022 Draft, ICH 2022), and the EMA reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA 2018), extrapolation from adults to children represents a reasonable approach whenever the response to treatment and course of disease are sufficiently similar.

There are no formal international juvenile myasthenia gravis (jMG) treatment guidelines, and knowledge on treatment patterns and disease burden is limited (Zhou et al., 2025 (Neurology, doi:10.1212/WNL.0000000000213736).
According to the Guidelines of the German Neurological Society (Deutsche Gesellschaft für Neurologie (DGN)) (030087_LL_Myasthenia_gravis_2024_Clean_1732794677869.pdf), current immune treatment recommendations for jMG are derived from established treatment concepts for the adult MG population taking into account the individual autoantibody status and actual disease activity. Overall, robust evidence for the use of immune therapies and thymectomy is limited and mainly based on retrospective studies and empirical experience. Taking together, extrapolation from the adult population was finally accepted for nipocalimab.

6.5 Final clinical benefit risk assessment

Since the variable treatment response overall and the uncertainties related to specific subpopulations are fully reflected in the Information for healthcare professionals, and the criteria for non-responders and stopping treatment have been defined and implemented, the benefit-risk balance for nipocalimab in the following indication:

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

is considered **positive.**

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Imaavy was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

IMAAVY®

Composition

Active substances

Nipocalimab

Excipients

Arginine hydrochloride, Histidine, Histidine monohydrochloride monohydrate, Methionine, Polysorbate 80, Sucrose and Water for Injections.

Pharmaceutical form and active substance quantity per unit

IMAAVY (nipocalimab) is a sterile, colorless to slightly brownish, clear to slightly opalescent concentrate for solution for infusion supplied in a single-dose vial for infusion after dilution.
IMAAVY is available in the following presentation:

- Each 1.62 mL single-use vial contains 300 mg of nipocalimab (1 mL contains 185 mg of nipocalimab).
- Each 6.5 mL single-use vial contains 1200 mg of nipocalimab (1 mL contains 185 mg of nipocalimab).

Indications/Uses

IMAAVY is indicated as an add on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in patients aged 12 years of age and older who are anti-acetylcholine receptor [AChR] or anti-muscle specific tyrosine kinase [MuSK] antibody positive.

Dosage/Administration

Generalized Myasthenia Gravis (gMG)

Intravenous Dosage – adults (≥18 years) and adolescents (12 to < 18 years)

IMAAVY should only be administered by a health care professional and under the supervision of a physician experienced in the treatment of patients with neuromuscular and neuroinflammatory diseases.

Usual dosage

For adults and adolescents 12 years and older with gMG, the recommended initial dose of IMAAVY is 30 mg/kg administered intravenously over approximately 30 minutes, followed by a maintenance dose of 15 mg/kg administered intravenously over approximately 15 minutes every 2 weeks thereafter.

Patients should be monitored for 60 minutes after the first three infusions for signs or symptoms of an infusion-related or hypersensitivity reaction. If no relevant disorders occur during the infusion after the first three doses, the observation period can be reduced to 30 minutes after each subsequent infusion. If an adverse reaction occurs during administration of treatment, the infusion may be slowed or discontinued (see section *Warnings and Precautions*).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

IMAAVY has not been studied in subjects with a bodyweight below 31kg or above 135kg. Patients with Myasthenia Gravis Foundation of America (MGFA) class V have not been studied in the clinical development program for IMAAVY.

Patient status must be documented before starting therapy with nipocalimab and regularly monitored at least every 12 weeks by using the Myasthenia Gravis Activities of Daily Living (MG-ADL) and/or the Quantitative Myasthenia Gravis (QMG) score. If a patient does not achieve responder status (i.e. improvement of at least 3 points on the QMG scale or at least 2 points on the MG-ADL scale) after 24 weeks of treatment (i.e. 12 administrations), treatment with nipocalimab should be discontinued.
If a patient who had previously gained responder status subsequently loses it before Week 24 or at any time-point thereafter, treatment with IMAAVY can be continued for another 12 weeks (i.e. 6 administrations). However, if responder status is not re-achieved with these 6 additional administrations, treatment should be discontinued. If a patient needs rescue therapy, a non-responder status should also be assumed, and the same recommendations apply.

It is recommended to determine IgG levels prior to initiating therapy with IMAAVY.

Patients requiring intravenous immunoglobulins (IVIg) can resume IMAAVY treatment 4 weeks after completion of this rescue therapy (see *Interactions*).

Patients requiring rescue therapy with plasma exchange/immunoadsorption can resume IMAAVY treatment after completion of this rescue treatment; it is recommended that IgG levels exceed the limit of 1g/L before restarting IMAAVY.

Special dosage instructions

Patients with hepatic disorders

The safety and efficacy of IMAAVY have not been established in patients with hepatic impairment (see *Pharmacokinetics*). No dose adjustment is required in patients with hepatic impairment.

Patients with renal disorders

The safety and efficacy of IMAAVY have not been established in patients with renal impairment (see *Pharmacokinetics*). No dose adjustment is required in patients with renal impairment.

Elderly patients (65 years of age and older)

No apparent differences in clearance and volume of distribution were observed in subjects ≥ 65 years of age compared to subjects <65 years of age, suggesting no dose adjustment is needed for elderly subjects (see *Pharmacokinetics*). In the age group ≥ 65 years to 81 years, data are limited (see section Warnings and Precautions). Patients >81 years have not been included in the Clinical Development Programme for IMAAVY.

Children (below 12 years of age)

The safety and efficacy of IMAAVY in children below 12 years of age has not been investigated. No dosing recommendations can be made (see *Pharmacokinetics*).

Delayed administration

If a scheduled infusion appointment is missed, the maintenance dose of IMAAVY should be administered as soon as possible. Thereafter, the dosage should be continued as usual every 2 weeks.

Mode of administration

Intravenous infusion

Dilute IMAAVY prior to administration. Administer via intravenous infusion only. The infusion must be administered through a filter system. For instructions on dilution of the medicinal product before administration and the filters to be used see section *Other Information*, *Instructions for Use* and *Handling and Disposal*.

Contraindications

IMAAVY is contraindicated in patients with a history of severe hypersensitivity to nipocalimab or any of the excipients see section *Warnings and Precautions*.

Warnings and precautions

Temporary or permanent interruption of therapy with IMAAVY

Treatment with nipocalimab must be interrupted in cases of (a) a severe or serious infection that does not respond to anti-infective therapy or worsens under anti-infective therapy, (b) in the event of clinical worsening requiring hospitalization and/or rescue therapy.

Treatment with nipocalimab must be permanently discontinued in cases of (a) a severe allergic and/or severe infusion reaction caused by nipocalimab (e.g., anaphylaxis) and/or (b) recurrent severe and/or serious infection.

Worsening of myasthenia

Patients must be continuously monitored for worsening of their myasthenic symptoms. In the clinical development program, patients treated with IMAAVY (12.2%) and placebo (13.2%) experienced a worsening of their MG symptoms, some requiring rescue therapy such as IVIg or plasmapheresis (IMAAVY 5.1% vs. placebo 7.1%). Rates of myasthenic crisis during the double-blind phase were 1 % for patients treated with IMAAVY and 2 % in the placebo group; in patients who received IMAAVY in the double-blind phase and continued to receive IMAAVY in the open label extension phase the rate was 1.1 %. There was one case of myasthenic crisis under IMAAVY that was fatal, and 2 cases of myasthenic crisis with placebo that were non-fatal.

Myasthenic crisis

The treatment of patients in MGFA Class V (i.e., myasthenic crisis), defined as intubation with or without mechanical ventilation, except as part of routine postoperative care, with nipocalimab has not been studied. The sequence of initiation of established therapies for treating MG crisis and the administration of nipocalimab, as well as their potential interactions, should be considered (see section *Interactions*).
IMAAVY is not approved for the treatment of imminent or manifest myasthenic crisis.

Elderly patients

In the clinical development program, only a few patients with myasthenia gravis aged ≥65 to 81 years were studied. The treatment benefit in this age group was highly variable (see *Clinical Efficacy*). The safety profile for this age range was comparable between the nipocalimab (N=25) and placebo (N=24) arms. More events of myasthenia gravis worsening were observed with nipocalimab, 24% vs. placebo 12.5%; however, fewer events of myasthenic crisis were observed with nipocalimab, 4.0% vs. placebo 8.3%.

Bodyweight <60kg

The clinical development programme included only limited numbers of adult patients <60kg bodyweight.

Other myasthenic syndromes

IMAAVY has not been studied in Lambert-Eaton myasthenic syndrome, drug induced MG, or hereditary forms of myasthenic syndrome

Infections

IMAAVY may increase the risk of infection including the activation of latent viral infections such as herpes zoster (see *Undesirable effects*). Delay IMAAVY administration in patients with an active infection until the infection is resolved. During treatment with IMAAVY, monitor for clinical signs and symptoms of infection. If severe, serious or recurrent infection occurs, check total IgG levels administer appropriate treatment and consider withholding IMAAVY until the infection has resolved (see also *Interruption and permanent stop of IMAAVY*).
In Study 1 (MOM-M281-011), the overall rate of infections was the same between subjects in the IMAAVY group and subjects in the placebo group (42 (42.9%) in each group). Across Study 1 (double blind period) and its extension study (open label-period), out of 186 patients treated with IMAAVY, 132 (71%) patients reported 360 events of infection.
Serious infections were observed in 7% of patients treated with IMAAVY. Most infections were mild to moderate in severity and did not lead to discontinuation of IMAAVY.
Patients with serious infections, including opportunistic infections that required parenteral anti-infective therapy and/or hospitalization within the previous 8 weeks before starting therapy, with a chronic infection (e.g., bronchiectasis, chronic osteomyelitis, chronic pyelonephritis), or those who require ongoing anti-infective treatment, were not studied in the clinical trial program of IMAAVY.

Immunizations

Patients treated with IMAAVY may receive non-live vaccines as needed, according to immunization guidelines. The impact of nipocalimab on a T-cell dependent (Tdap) or a T-cell independent (PPSV23) non-live vaccine response was assessed in healthy volunteers (n=16). Nipocalimab administration with either of these vaccines was well tolerated. Study participants were able to mount adequate IgG response specific to these vaccine agents.
The safety of immunization with live or live-attenuated vaccines and the response to immunization with these vaccines during treatment with IMAAVY are unknown. Immunization with live- or live attenuated vaccines is not recommended during treatment with IMAAVY. Evaluate the need to

administer age-appropriate live and live attenuated immunizations according to immunization guidelines prior to initiation of treatment with IMAAVY.

Hypersensitivity

Administration of IMAAVY may result in hypersensitivity reactions, including rash, urticaria, and eczema. Most hypersensitivity reactions were non-serious, mild or moderate and did not lead to treatment discontinuation. Across the clinical development program of IMAAVY which includes multiple disease areas, an isolated case of anaphylaxis has been reported.
Monitor the patient after each infusion (see *Dosage/Administration*). If a hypersensitivity reaction occurs during administration, discontinue IMAAVY infusion and institute appropriate supportive measures if needed. IMAAVY is contraindicated in patients with a history of serious hypersensitivity to nipocalimab or any of the excipients of IMAAVY (see *Contraindications*).

Infusion-Related Reactions

Administration of IMAAVY may result in infusion-related reactions, including headache, rash, nausea, fatigue, dizziness, chills, and erythema. Most infusion-related reactions observed during the clinical development programme were non-serious, mild to moderate and did not lead to treatment discontinuation. Interrupt IMAAVY infusion and institute appropriate supportive measures if signs of a serious infusion-related reaction occur.

Increased plasma lipid levels

Increases in plasma lipid levels have been observed in adult and adolescent patients treated with nipocalimab (see *Undesirable effects*). Patients with abnormal lipid parameters should be monitored and managed according to the patient's long-term cardiovascular risk and clinical guidelines.

Interactions

Pharmacokinetic interactions

Effect of IMAAVY on other medicinal products

Concomitant use of IMAAVY may reduce systemic exposure of medications that bind to the human neonatal Fc receptor (FcRn) (e.g., immunoglobulin G [IgG] products, IgG-based monoclonal antibodies, antibody derivates containing the human Fc domain of the IgG subclass, or Fc fusion proteins). If patients on treatment with medicinal products that bind to the IgG binding site of the human FcRn receptor (e.g. IVIg) need treatment with nipocalimab, it is recommended to wait for 4 weeks after the last dose of such medicinal products before dosing with nipocalimab. If patients on nipocalimab need treatment with medicinal products that bind to the IgG binding site of the human neonatal Fc receptor, it is recommended these medicinal products are started 2 weeks after the previous dose of nipocalimab, if deemed medically appropriate based on clinical judgment.

In clinical drug interaction studies in healthy participants, nipocalimab reduced the systemic exposures (C_{max} and AUC) of fremanezumab and etanercept.

When concomitant long-term use of such medications is essential for patient care, closely monitor for reduced effectiveness of such medications and consider discontinuing IMAAVY or using alternative therapies (see *Pharmacokinetics*).
When coadministered with fremanezumab in healthy participants, IMAAVY reduced the systemic exposures (C_{max} and AUCs) of fremanezumab by 42% and 66%, respectively. When IMAAVY was administered 14 days after fremanezumab dosing, C_{max} was not altered while AUC was reduced by 53%.
When coadministered with etanercept in healthy participants, IMAAVY reduced etanercept, C_{max} by ~8% and AUC by ~28%.

Effect of other medicinal products on IMAAVY

In a clinical drug interaction study in healthy participants evaluating the effect of hydroxychloroquine (HCQ) on IMAAVY pharmacodynamics, IgG reduction following IMAAVY administration was comparable with and without coadministration of HCQ.

Cytochrome P450 Substrates

Nipocalimab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Pregnancy, lactation

Pregnancy

There are limited amount of data from the use of nipocalimab in pregnant women. There is no available data with nipocalimab use in pregnant women with gMG. Based on available animal data, IMAAVY may cause fetal harm (see *Preclinical data*).

Treatment of pregnant women with IMAAVY should only be considered if the clinical benefit outweighs the risks.
As nipocalimab is expected to reduce maternal IgG antibody levels and is also expected to inhibit the transfer of maternal antibodies to the fetus, reduction in passive protection to the newborn is anticipated. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants from pregnant women exposed to IMAAVY (see *Preclinical data*).

Lactation

There is limited information regarding the presence or absence of nipocalimab in human milk in lactating individuals, the effects on the breastfed infant, or the effects on milk production. Maternal IgGs are known to be excreted in human milk. Very limited data showed that nipocalimab is detectable at low levels for up to 8 days post-partum in the colostrum or breastmilk of women exposed to nipocalimab during the second and third trimester of their pregnancy. A risk to the breastfed newborn/infant cannot be excluded.
The developmental and health benefits of breastfeeding for the child should be considered along with the mother's clinical need for IMAAVY and any potential adverse effects on the breastfed child from IMAAVY or from the underlying maternal condition.

Fertility

There are no data on the effects of nipocalimab on fertility in humans. Animal studies do not indicate harmful effects with respect to fertility (see *Preclinical data*).

Effects on ability to drive and use machines

IMAAVY has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during the double blind and open-label phases in gMG study 1 were total cholesterol increased (29.9%), LDL cholesterol increased (22.7%), muscle spasms (12.2%), ~~and~~ peripheral edema (12.2%), urinary tract infection (10.8%) and blood immunoglobulin G decreased (10.3%).

Tabulated list of adverse reactions

In a placebo-controlled study (gMG Study 1) in adult patients with gMG, 98 patients received IMAAVY 15 mg/kg (after 30 mg/kg initial dose) for up to 24 weeks *(*see *Clinical Efficacy)*.

Adverse reactions from phase 3 gMG Study 1 double-blind placebo-controlled phase and open-label phase are listed below. In MG Study 1 in adult patients, 205 patients received IMAAVY including 98 in the double-blind phase and 195 in the open-label extension. In total, 178 were exposed to the recommended maintenance dose (15 mg/kg every 2 weeks) for at least 6 months, and 132 were exposed for at least 12 months.
Frequency categories refer to the highest incidence rate in either the double blind or open label extension phase of gMG Study 1 (see *Clinical Efficacy*)
The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows: "very common" (≥1/10),"common" (≥1/100, <1/10), "uncommon"

(≥1/1,000, <1/100), "rare" (≥1/10,000, <1/ 1,000), "very rare" (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions

System Organ Class	Adverse Reaction	Frequency
Immune system disorders	Blood Immunoglobulin G decreased (10.3%)[7]	Very common
Infections and infestations	Urinary tract infection (10.8 %)	Very common
	Pneumonia[1]	Common
	Bronchitis	Common
	Herpes zoster[2]	Common
Metabolism and nutrition disorders	Total cholesterol increased (29.9 %)[3]	Very common
	LDL cholesterol increased (22.7 %)[4]	Very common
Psychiatric disorders	Insomnia	Common
Nervous system disorders	Dizziness	Common
Gastrointestinal disorders	Diarrhea	Common
	Abdominal pain[5]	Common
	Nausea	Common
Musculoskeletal and connective tissue disorders	Muscle spasms (12.2 %)	Very common
General disorders and administration site conditions	Peripheral edema (12.2 %)[6]	Very common
	Pyrexia	Common

[1]Includes Pneumonia and Pneumonia bacterial

[2]Includes Herpes zoster and Herpes zoster oticus

[3]Based on the highest proportion of nipocalimab-treated patients who had at least one shift in total cholesterol from <6.2 mmol/L pre-treatment to ≥6.2 mmol/L during any phase of gMG Study 1

[4] Based on the highest proportion of nipocalimab-treated patients who had at least one shift in LDL from <4.1 mmol/L pre-treatment to ≥4.1 mmol/L during any phase of gMG Study 1

[5] Includes abdominal pain and abdominal pain upper

[6] Includes oedema, oedema peripheral, and peripheral swelling

[7]Refers to total IgG <1g/L

Description of specific adverse reactions and additional information

Lipid metabolism

In patients who received nipocalimab in gMG Study 1, increases in fasting total cholesterol, HDL, and LDL were observed. The mean change from baseline peaked at Week 4 (double-blind) then decreased and plateaued by Week 24 (double-blind) to a mean percent increase (SD) of +7.8% (17%) in fasting total cholesterol, +7.0% (21%) in fasting HDL-cholesterol, and +8.3% (23%) in fasting LDL-cholesterol, respectively for patients who received nipocalimab, compared to a decrease of -4.1% (12%), -1.6% (14%) and -3.0% (19%) respectively for patients who received placebo.
In gMG Study 1 (N=98), in adults, significantly elevated fasting cholesterol levels (≥ 240 mg/dl) were observed in 29.9% of subjects treated with IMAAVY during the double-blind phase (placebo: 4.1%) and in 28.7% during the open-label phase. Markedly abnormal fasting LDL cholesterol values (≥160 mg/dl) were reported in 22.7% of IMAAVY treated gMG subjects during the double-blind (placebo 10.3%) and in 21.5% at any point during the open-label phases of Study 1. Potential long term safety risks related to these adverse drug reactions are unknown.

Immunogenicity

In the double-blind placebo-controlled Phase 3 study in adult patients with generalised myasthenia gravis, 83 out of 194 (42.8%) of IMAAVY treated patients developed antidrug antibodies (ADA) and 44 out of 194 (22.7%) patients tested positive for neutralising antibodies (NAb) to nipocalimab.
After completion of pivotal clinical trials, the manufacturing process for nipocalimab was changed.
A Phase 1 study in healthy volunteers compared the incidence of ADA and NAb after a single dose of nipocalimab between nipocalimab from the previous manufacturing process administered in the clinical development programme and nipocalimab produced according to the new process implemented after marketing approval. These analyses yielded higher rates of ADA (82.5% vs. 60%) and NAb (32.5% vs. 25%) after administration of a single dose of nipocalimab from the new manufacturing process. In this single dose trial in healthy volunteers, there was no evidence for an impact on the safety profile or the pharmacokinetic/pharmacodynamic properties of nipocalimab from the new manufacturing process.

Paediatric population with gMG

The safety of IMAAVY was assessed in an open-label study of adolescent patients (12 years and older, n=8) with gMG (Study 2; MYG2001) for up to 24 weeks. Seven of the eight adolescent patients completed the 24-week study phase. The safety profile in adolescent patients was similar to the safety profile from studies in adults with gMG.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Single doses up to 60 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. There are no known specific signs and symptoms of overdose with nipocalimab.

Treatment

Patients should be monitored for adverse reactions, and appropriate symptomatic and supportive treatment should be initiated immediately.

Properties/Effects

ATC code

L04AL03

Mechanism of action

Nipocalimab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (molecular weight approximately 142 kilodaltons (kDa)) that binds with high specificity and high affinity at both neutral (extracellular) and acidic (intracellular) pH to FcRn resulting in the reduction of circulating IgG including pathogenic IgG. Nipocalimab has an aglycosylated Fc region, therefore it lacks effector functions and does not induce cell death, immune pathway activation or tissue damage by these mechanisms. A primary function of FcRn is to serve as a recycling or transcytosis receptor, contributing to the maintenance and homeostasis of circulating serum IgG.

Pharmacodynamics

In Study 1, the pharmacological effect of nipocalimab was assessed by measuring the decrease in serum IgG levels and anti-acetylcholine receptor (AChR) and anti-muscle-specific tyrosine kinase (MuSK) autoantibody levels. Maximum IgG reductions are expected approximately a week after dosing. After the first dose, median observed total IgG reduction change from baseline measured at Week 2 was 75%. With subsequent dosing every 2 weeks, the median of the observed pre-dose total IgG reduction change from baseline was approximately 70% from Week 4-24. Decreases in AChR antibody and MuSK antibody levels followed a similar pattern. Total IgG levels should return to baseline 8 weeks after discontinuation of nipocalimab therapy.
No IMAAVY-related changes were observed in total IgM, IgA, or IgE.

Clinical efficacy

Generalized Myasthenia Gravis (gMG)

Adults

The efficacy of IMAAVY for the treatment of gMG in adults who are antibody AChR, MuSK, or anti-low-density lipoprotein receptor-related protein 4 [LRP4] positive was established in a 24-week, multicenter, randomized, double-blind, placebo-controlled study (gMG Study 1; MOM-M281-011). The study enrolled patients who met the following criteria at screening:

- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV
- MG-Activities of Daily Living (MG-ADL) total score of ≥6 (without a minimum score for non-ocular symptoms)
- On stable dose of standard of care (SOC) therapy prior to baseline, including acetylcholinesterase (AChE) inhibitors, steroids or non-steroidal immunosuppressive therapies (NSISTs), either in combination or alone.

A total of 196 patients (seropositive and seronegative) were randomized and received either IMAAVY plus SOC (n=98) or placebo plus SOC (n=98). Patients were treated with IMAAVY at the recommended dosage regimen *(see Dosage/Administration)*.

There were 153 antibody positive patients: 77 patients were treated with IMAAVY (AChR n=63, MuSK n=12, LRP4 n=2) and 76 patients received placebo (AChR n=71, MuSK n=4, LRP4 n=1). Baseline characteristics were similar between treatment groups. Patients had a median age of 52 years at screening (range 20 to 81 years) and a median time since MG diagnosis of 6 years. 60.1% were female; and 62.7% White; 32.0% Asian. Median MG-ADL total score was 9, and median Quantitative Myasthenia Gravis (QMG) total score was 15.

At baseline, 97% in the IMAAVY group and 100% in the placebo group were on stable background SOC therapy. In the IMAAVY plus SOC treatment group, 83% were on AChE inhibitors, 61% were on steroids, and 53% were on non-steroidal immunosuppressive therapies (NSISTs) at stable doses.

In the placebo plus SOC treatment group, 87% were on AChE inhibitors, 71% were on steroids, and 54% were on NSISTs at stable doses.

The efficacy of IMAAVY was measured using the MG-ADL scale, which is a clinical-administered scale (score range: 0-24) measuring eight daily function items that are typically affected in gMG based on patient recall. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function.

The total score is the sum of the 4 subdomains, including ocular (0 to 6 points), respiratory (0 to 3 points), bulbar (0 to 9 points) and limb/gross motor (0 to 6 points), for a total score ranging from 0 to 24 with the higher scores indicating more severe functional impairment.

The efficacy of IMAAVY was also measured using the QMG total score based on the medical examination. The QMG is a 13-item standardized examination that assesses muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total possible score ranges from 0 to 39, where higher scores indicate more severe impairment.

The primary efficacy endpoint was the mean change in MG-ADL total score from baseline over Weeks 22, 23 and 24 in antibody positive gMG patients. A statistically significant difference favoring IMAAVY was observed in MG-ADL change from baseline (see Table 2).
A key secondary endpoint was the mean change in the QMG score from baseline over Weeks 22 and 24 in antibody positive gMG patients. A statistically significant difference favouring IMAAVY was observed in QMG change from baseline (see Table 2).

Table 2: Mean Change from Baseline in MG-ADL Total Score and QMG Total Score in gMG Study 1

	IMAAVY (n=77) LS mean (SE)	Placebo (n=76) LS mean (SE)	IMAAVY change relative to placebo LS mean difference (95% CI)	P-value
MG-ADL[1]	-4.70 (0.329)	-3.25 (0.335)	-1.45 (-2.38, -0.52)	0.002
QMG[2]	-4.86 (0.504)	-2.05 (0.499)	-2.81 (-4.22, -1.41)	<0.001
MG-ADL = Myasthenia Gravis – Activities of Daily Living QMG = Quantitative Myasthenia Gravis LS mean = Least squares mean SE = standard error CI = confidence interval				

[1] Mean change from baseline over weeks 22, 23, and 24

[2] Mean change from baseline over weeks 22 and 24

Table 3: MG-ADL and QMG responder analyses in gMG Study 1

	Nipocalimab (n=77)	Placebo (n=76)	Nipocalimab - Placebo difference (95% CI)	P-value
MG-ADL responder based on average change over Weeks 22, 23, and 24[1]	68.8%	52.6%	16.2 (0.9, 31.5)	0.021
QMG Responder[2]	46.8%	25%	21.8 (7.0, 36.6)	N/A*

1 Average change over Weeks 22, 23, and 24 is at least a 2-point improvement from baseline.

2 Average change over Weeks 22 and 24 is at least a 3-point improvement from baseline.

*Formal statistical testing was not performed

Response over time (open-label extension phase; ongoing)

Of the 153 antibody positive patients in the double-blind placebo-controlled phase, 137 entered into the open-label extension phase to receive nipocalimab. At the time of the analysis, in patients who initially received nipocalimab during the double-blind phase and continued to receive nipocalimab during the first 48-weeks (n=52) and 84-weeks (n=20) of the open-label extension phase, the mean improvements in MG-ADL and QMG total scores were maintained.

Paediatrics

Adolescents with gMG

The pharmacodynamics, pharmacokinetics, and efficacy of IMAAVY for the treatment of generalized myasthenia gravis (gMG) in adolescents (12 to less than 18 years of age) were evaluated at 24 weeks in an open-label study (gMG Study 2; MYG2001).

The study enrolled patients who met the following criteria at screening:

- MGFA clinical classification class II to IV
- Positive for antibodies to AChR or MuSK
- On stable dose of SOC therapy prior to screening, including AChE inhibitors, steroids or NSISTs, either in combination or alone

Eight adolescent patients received IMAAVY at the recommended dosage regimen (see *Dosage/Administration*) over 24 weeks. Patients had a median age of onset of 10.5 years (range 0.5 to 13.4 years) and a median time since diagnosis of 3.6 years at screening. Seven patients were female; 5 patients were Asian, 1 was Black, and 2 were of unknown race. Their mean (SD) MG-ADL total score was 4.4 (2.26) and mean (SD) QMG-total score was 13.3 (4.13) at baseline. All patients were AChR antibody positive.

At baseline, 4 patients were on AChE inhibitors, 6 were on steroids, and 7 were on NSISTs at stable doses.

The primary endpoint was the effect of IMAAVY on total serum IgG. At Week 24, the median pre-dose, percent reduction in total IgG from baseline (N=7) was 73.3%, consistent with the IgG reduction seen in gMG Study 1 in adults (see *Pharmacodynamics*). For the secondary endpoints, the mean (SD) change at week 24 in MG-ADL was -2.57 (0.535) and in QMG was -4.93 (3.81); the pattern of improvement was consistent with those seen in gMG Study 1 in adults (see *Clinical Efficacy*).

Pharmacokinetics

Absorption

Following a single intravenous infusion of nipocalimab at doses ranging from 0.3 to 60 mg/kg in healthy participants, C_{max} increased in a dose-proportional manner while AUC increased in a greater than dose-proportional manner.

Distribution

The mean volume of distribution was 1.1 to 2.7 L.

Metabolism

Nipocalimab is expected to be degraded by proteolytic enzymes into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Nipocalimab exhibits concentration-dependent pharmacokinetics. Following a single IV administration of 15 mg/kg nipocalimab, the mean clearance is 0.0627 L/h and half-life is 29.3 hours. The pharmacodynamic effect lasts longer relative to the relatively elimination for a monoclonal antibody (see *Pharmacodynamics)*

Linearity

Nipocalimab exhibits non-linear, dose-dependent pharmacokinetics.

Population Pharmacokinetic Analysis

A population pharmacokinetics analysis assessing the effects of age, sex, and race did not suggest any clinically significant impact of these covariates on nipocalimab exposures.

Kinetics in specific patient groups

Hepatic impairment

No dedicated pharmacokinetic study has been performed in patients with hepatic impairment. IMAAVY is not metabolized by cytochrome P450 enzymes, and therefore, hepatic impairment is not expected to affect the pharmacokinetics of IMAAVY. Based on a population pharmacokinetic analysis, which included participants with mild to moderate hepatic impairment, there was no clinically significant effect on nipocalimab clearance. No dose adjustment is required in patients with hepatic impairment.

Renal impairment

No dedicated pharmacokinetic study has been performed in patients with renal impairment. Renal impairment is not expected to affect the pharmacokinetics of nipocalimab. Based on a population pharmacokinetic analysis, which included participants with mild to moderate renal

impairment, renal function (estimated glomerular filtration rate [eGFR] 30–90 mL/min/1.73 m^2) had no clinically significant effect on nipocalimab clearance. No dose adjustment is required in patients with renal impairment.

Elderly patients (≥65 years)

No apparent differences in clearance and volume of distribution were observed in patients ≥65 years of age compared to patients <65 years of age, suggesting no dose adjustment is needed for elderly patients.

Adolescents (12-17 years of age)

Following the recommended IV doses of IMAAVY in adolescent subjects 12 to 17 years of age with gMG (n=5), the observed steady-state serum nipocalimab concentrations were within the range of those observed for adult subjects with gMG.

Preclinical data

Carcinogenicity and Mutagenicity

Carcinogenicity studies have not been conducted with nipocalimab.
The mutagenic potential of nipocalimab has not been evaluated.

Reproductive toxicity

There were no effects of nipocalimab on male and female fertility at doses up to 300 mg/kg/week based on the assessment of reproductive organs (organ weights and histopathology) in monkeys that became sexually mature during the 26-week intravenous study. The doses tested in monkeys achieved exposures that were up to 44 times the expected exposure level in patients on the recommended human maintenance dose for gMG.
No studies have been conducted to assess the potential direct or indirect effects of nipocalimab on implantation, early development, and organogenesis occurring during the first trimester of pregnancy.

In the ePPND study, pregnant cynomolgus monkeys were administered nipocalimab at doses of 100 or 300 mg/kg/week by IV bolus infusion from GD 40 (2nd trimester) until parturition (equal to 5- or 24-times the human exposure at the recommended maintenance dose based on AUC, respectively). Maternal animals developed clinical signs during or shortly after dosing, including emesis, shallow or laboured breathing, salivation, tremors, uncoordinated movement, swelling in one limb, and liquid faeces. The clinical signs developed without apparent dose-response. In the pregnant monkeys administered nipocalimab, four of twenty-five placentas showed large, central placental infarctions. Of these four pregnancies, three were associated with fetal death or stillbirth. A NOAEL cannot be determined for maternal and developmental toxicity. Offspring from treated dams had low levels of IgG at birth. The infant IgG level recovered within 6 months. There was no adverse impact on immune

function of the infants of treated mothers as assessed by a T-cell Dependent Antibody Response (TDAR) assay.

Other information

Incompatibilities

The medicinal product must not be used in combination with dose preparations, infusion bags, infusion sets, or filter materials that have not been tested for compatibility and stability during use. Compatible materials are listed in the section *Instructions for use, handling and disposal*.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Storage Conditions of the Diluted Solution

The diluted infusion preparation is not preserved. Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 °C to 8 °C and an additional 12 hours, including infusion time, at 15 °C to 30 °C. From a microbiological point of view, the prepared diluted solution should be used immediately after preparation. If this is not possible, the expiration time and storage conditions are the responsibility of the user and should normally not exceed 24 hours at 2-8°C, unless the dilution was performed under controlled and validated aseptic conditions.
Do not freeze.

Special precautions for storage

Vial storage

Store in the refrigerator (2-8°C).
Do not freeze. Keep the container in the outer carton in order to protect the contents from light.
Do not shake.
Keep out of the reach of children.

Instructions for use, handling and disposal

Preparation and Administration Instructions
For the IMAAVY solution diluted with 0.9% Sodium Chloride injection solution, infusion containers made of polyolefin, polypropylene, or polyvinyl chloride, as well as infusion sets with tubing made of polybutadiene, polyethylene, polyurethane, polypropylene or polyvinyl chloride can be used. The diluted solution must always be administered together with low protein-binding infusion filters (in-line or add-on) made of polyethersulfone or polysulfone (pore size 0.2 micrometers or less).

Prior to administration, IMAAVY single-dose vials require dilution in 0.9% Sodium Chloride Injection (see *Preparation*).

Preparation

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dosage (mg), total drug volume (mL) of IMAAVY solution required, and the number of IMAAVY vials needed based on the patient's current weight (see *Dosage/Administration*). Each single dose vial of IMAAVY is at a concentration of 185 mg/mL.
- Check that the solution in each vial is colorless to slightly brownish and free of visible particles. Do not use if visible particles are present or if the solution is discolored (other than colorless to slightly brownish).
- Gently withdraw the calculated volume of IMAAVY solution from the vial(s) using syringes (made of polycarbonate or polypropylene) and needles (made of stainless steel). Discard any unused portion of the vials.
- Dilute total volume withdrawn of IMAAVY by adding to an infusion container of:
    - 250 mL 0.9% Sodium Chloride Injection for patients who weigh 40 kg or more
    - 100 mL 0.9% Sodium Chloride Injection for patients who weigh less than 40 kg
    - Only use infusion containers made of polyolefin, polypropylene, or polyvinylchloride.
- Gently invert the infusion container at least ten times to mix the solution. Do not shake.
- Verify that a uniform solution has been achieved by visual inspection. Do not use if particulate matter or discoloration are present. Dispose of the vial appropriately.

Administration

- Administer the diluted solution by intravenous infusion using an infusion set with tubing made of polybutadiene, polyethylene, polyurethane, polypropylene or polyvinylchloride. The administration must always be performed with a sterile, non-pyrogenic, low protein-binding filter made of polyethersulfone or polysulfone (pore size 0.2 micrometer or less).
- Do not infuse IMAAVY concomitantly in the same intravenous line with other agents.
- Administer IMAAVY infusion intravenously over approximately 30 minutes for the initial dose (30 mg/kg) and approximately 15 minutes for subsequent doses (15 mg/kg).
- If an adverse reaction occurs during administration of IMAAVY, the infusion may be slowed or stopped at the discretion of the physician.
- Monitor the patient for 30 minutes after each infusion for signs or symptoms of an infusion-related or hypersensitivity reaction.

Authorisation number

69588

Packs

1 vial with 300 mg/1.62 mL [A]

1 vial with 1200 mg/6.5 mL [A]

Marketing authorisation holder

Janssen-Cilag AG, Zug, ZG.

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