CT Application(s) Summary Report

- **Protocol title:**. Efficacy and Safety of M281 in Adults with Warm Autoimmune Hemolytic Anemia: A Multicenter, Randomized, Double-blind, Placebo-controlled Study with a Long-term Open-label Extension
- **Protocol code number:** MOM-M281-006
- ***Public Registry Number:*** 2019-000720-17
- **Version:** Amendment 6
- **Date:**18 August 2022

- **Investigational Medicinal Product being tested:**

Biological ■ **Pharmaceutical** ☐ **Innovative** ☐

Herbal medicine ☐ **Medical device** ☐

- **Sponsor:** Janssen Research & Development, LLC
- **Indication:** Warm Autoimmune Hemolytic Anemia (wAIHA)
- **Investigator's brochure (IB)**
  Version: 8.0
  Date: 12Jun2023
- **Name of all Sites:**
  1. National Cancer Institute
  2. Mansoura University Hospital
  3. Kasr al Eini, Cairo University Hospital
  4. Naser Institute
  5. Alexandria University Hospital, Faculty of Medicine
  6. Ain Shams University Hospital
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- **EDA approval date:**
  1. Initial approval on Protocol version 6 and IB version 7 on **19 July 2023**
  2. Amendment approval: IB version 8 dated 12 June 2023 for all sites on **26 August 2024**, for another one site on **29 October 2024**

- **Summary of pre-clinical studies:**

1. Nonclinical Pharmacology

The pharmacologic evaluation of nipocalimab included **in vitro** and **in vivo** studies to characterize the interaction of nipocalimab with its target, FcRn, elucidate its mechanism of action, evaluate its potential efficacy in animal models of immune-mediated disease, and support GLP-compliant nonclinical toxicology studies.

1.1. Primary Pharmacodynamics

- As nipocalimab does not recognize rodent FcRn, in vivo studies were conducted in human FcRn transgenic mice, which are transgenic for the human FCGRT, hereafter referred to as Tg32 mice.

-Nipocalimab specifically binds to the recombinant extracellular domain of FcRn from human and cynomolgus monkey with high affinity (KD <500 pM) at both pH 6.0 and 7.6, but not to FcRn from mouse or rat.

-Nipocalimab was also selective for binding to FcRn with no cross-reactivity to HLA-A2, which is the closest member in the structurally similar major MHC Class I-like family of antigens and has an extremely low probability of binding to any other MHC Class-I like family member. Binding of nipocalimab to either human or cynomolgus monkey FcRn interfered with binding of IgG. The specificity of nipocalimab for the IgG binding site on FcRn was confirmed by the crystal structure of nipocalimab Fab with FcRn and by the demonstrated interference of IgG binding but not human serum albumin-binding to human FcRn.

-In live cell cultures, nipocalimab was rapidly internalized and saturated total cellular FcRn within 30 to 120 minutes at concentrations from 0.15 to 5 µg/mL (1 to 35 nM). Both the saturation of FcRn occupancy and increases in lysosomal IgG concentrations, a consequence of inhibition of IgG recycling, occurred with IC50 and EC50 values, respectively, of approximately 0.03 to 0.07 µg/mL (0.2 to 0.5 nM) after 18 hours of nipocalimab exposure in primary human endothelial cells or villous trophoblasts. The FcRn protein had a consistently short t1/2 in representative target cell types, ranging from 5 to 11 hours; nipocalimab did not impact the t1/2 of FcRn in any of the cell types tested.

-**In vivo studies** using an experimental **mouse** model (Tg32) that expresses human FcRn showed nipocalimab administered IV resulted in a rapid induction of full FcRn occupancy (Observable within 2 hours) and increased IgG clearance (observable within a day). Similar results were observed in **cynomolgus monkeys** following single doses up to 340 mg/kg and repeated doses up to 300 mg/kg/week for 26 weeks. IV nipocalimab also induced serum IgG decreases in human FcRn transgenic rodents or nonhuman primates and ameliorated disease pathology in animal models of pathogenic IgG-driven autoimmune diseases (CAIA model and ITP mouse model).

-Nipocalimab did not inhibit presentation of antibody-antigen immune complexes to CD4+ T cells and cross-presentation to CD8+ T cells in vitro suggesting FcRn blockade may not impair antigen-mediated IgG production.
-Studies in an **ex vivo** dual-perfused human placental cotyledon model demonstrated minimal maternal to fetal transfer of nipocalimab, but also a significant inhibition of transfer of a representative IgG from maternal to fetal circulation

1.2. Safety Pharmacology

Safety pharmacology assessments incorporated into the design of the repeat-dose toxicity studies.

2. Pharmacokinetics and Metabolism in Animals

-The PK of nipocalimab were characterized in repeat-dose studies in cynomolgus monkeys after IV bolus injection or IV infusion.
-The TK of nipocalimab were determined in GLP repeat-dose toxicity studies of up to 26 weeks duration in cynomolgus monkeys in which nipocalimab was typically administered qw by IV bolus or infusion.
-A specific and reliable indirect ELISA method for the determination of nipocalimab concentrations in cynomolgus monkey serum was established and validated to support GLP toxicity studies of nipocalimab.

2.1. Absorption and Pharmacokinetics

- **Single-dose IV PK/PD Studies in Cynomolgus Monkeys (Study 20070695 & 20081504)**

-Two single-dose IV studies were conducted in cynomolgus monkeys to characterize the relationship between the PK of nipocalimab and PD effects (RO, IgG suppression).
-**In the first IV study (Study 20070695)**, naïve male cynomolgus monkeys were given single IV infusions of nipocalimab at doses of 0 (vehicle control), 0.2, 2, 20, 50, and 100 mg/kg followed by a 36-day observation period. -As shown in following figure, nipocalimab was detected in all nipocalimab-dosed animals at dose levels >0.2 mg/kg. Serum nipocalimab concentrations were detectable at 192 hours (8 days) post-dose only at the 100 mg/kg dose level. Consistent with the mechanism of action of nipocalimab, full RO was observed on monocytes and granulocytes beginning 4 hours post-dose at all nipocalimab dose levels except the lowest(0.2 mg/kg). FcRn occupancy levels gradually returned to baseline levels over time in a dose-dependent manner, with full RO maintained for up to 144 and 192 hours (6 and 8 days) post-dose at the 50 and 100 mg/kg dose levels, respectively. -Nipocalimab also caused dose-dependent decreases in serum IgG concentrations at all nipocalimab dose levels except the lowest. Maximum reductions in IgG occurred at doses of 20 to 100 mg/kg between 96 and 240 hours (4 and 10 days) post-dose, followed by a gradual return toward baseline concentrations over time. A transient and unexpected decrease in IgG concentrations was observed in most animals administered 2, 20, 50, and 100 mg/kg at 864 hours (36 days) post-dose. This transient, unexpected decrease in IgG concentration was not observed in the other single-dose PK study(Study 20081504), nor in any of the repeat-dose TK studies.
-**In the second study (Study 20081504)**, naïve male cynomolgus monkeys were given single IV boluses of nipocalimab at doses of 0 (vehicle control), 20, or 340 mg/kg followed by a 58-day observation period. Consistent with the results of the first study, dose-dependent increases in nipocalimab concentrations were

observed in both the 20 and 340 mg/kg dose groups (see following figure). FcRn occupancy by nipocalimab was maintained for up to 96 hours (4 days) post-dose at 20 mg/kg and for up to 240 hours (10 days) post-dose at 340 mg/kg.

-As expected, animals in the 20 mg/kg nipocalimab group showed consistent reductions in IgG concentrations from 4 hours through 144 hours (6 days) post-dose, followed by a gradual return to baseline concentrations by 528 hours (22 days) post-dose.

-In animals given 340 mg/kg nipocalimab, IgG concentrations showed consistent reductions from 4 hours through 360 hours (15 days) post-dose, followed by a gradual trend toward recovery by Day 58. There were no unexpected decreases in IgG concentrations during the recovery period for either dose group.

- **Single-dose SC/IV PK Study in Cynomolgus Monkeys (Study 20227166)**

-It should be noted that the 150 mg/mL SC formulation used in this non-clinical study contained some different excipients to those included in the 150 mg/mL SC formulation to be used in the first SC clinical study. The clinical formulation contains the excipients, histidine, arginine, trehalose, and polysorbate-80, while the nonclinical formulation contains the excipients acetate, sorbitol, and polysorbate-80. However, all excipients are GRAS and within concentration and amounts that are commonly accepted as safe. Additionally, the difference in excipients is not anticipated to affect the PK or PD of the SC drug.

-As summarized in Table below, following a single dose to female cynomolgus monkeys, nipocalimab exposure was lower with the SC route when compared to the IV bolus injection and the estimated SC bioavailability was 68.7% at the tested 42 mg/kg dose. Serum concentrations of nipocalimab were generally quantifiable up to 144 hours (6 days) post-dose.

- All nipocalimab-treated animals developed detectable ADAs by Day 16 after dosing, with no consistent trends observed between the titers and the systemic exposure to nipocalimab.

Route	C_0 (µg/mL)	t_{max}[a] (hr)	C_{max} (µg/mL)	t_{last}[a] (hr)	C_{last} (µg/mL)	$AUC_{0\text{-}last}$ (hr*µg/mL)	$t_{1/2}$ (hr)	Cl (mL/hr/kg)	V_z (mL/kg)
SC	NC	48 (8-48)	290 ± 80.9	144 (144-192)	16.7 ± 15.6	23500 ± 3910	21.2 ± ID	NC	NC
IV Bolus	1060 ± 54.9	1 (1-1)	979 ± 77.0	144 (96-144)	24.5 ± 31.1	34200 ± 6460	22.7 ± 2.68	1.22 ± 0.182	40.3 ± 10.1

-After SC dosing, the maximum reduction from baseline in serum IgG was slightly greater (71.3% vs 63.6%), and the time to maximum reduction was longer (8 days vs 6 days) as compared with IV dosing. A trend toward recovery was observed starting at 288 hours (12 days) post-dose and continuing through the last time point evaluated (360 hours [15 days] post-dose).

-Fluctuations in serum IgG concentrations were present in some animals between 1 and 24 hours post-dose, which were potentially due to detection of nipocalimab by the total serum IgG assay and were not considered to be related to the pharmacology of nipocalimab.

- **Repeat-dose TK Studies in Cynomolgus Monkeys**

-Serum concentrations of nipocalimab and the formation of ADA were determined in the repeat-dose toxicity, immunotoxicity, and reproductive toxicity studies to characterize the TK and serum exposures associated with qw IV administration in cynomolgus monkeys.
-In general, serum exposures increased in a dose-proportional or slightly greater than dose-proportional manner, and no gender differences in exposure were observed.
-Toxicokinetic assessments after repeated dosing with nipocalimab were hindered by formation of ADA to nipocalimab, which reduced serum exposures in several animals. However, high serum nipocalimab concentrations were observed after repeated administration of high doses suggesting that the impact of ADA on exposure could
be overcome by administering adequately high nipocalimab doses.

2.2. *Distribution* (Study 50999041)

-Biodistribution was investigated in Tg32 mice. Six days after a single IV dose of ~10 mg/kg in Tg32D mice, the tissue distribution of nipocalimab was found to be comparable to that of a human monoclonal IgG1 control antibody. A significant fraction of both antibodies distributed primarily to the liver and exhibited minimal accumulation in kidney or excretion in urine.
-The two-compartment blood PK observed for both nipocalimab and the human IgG1 control antibody was also typical of a mAb. Nipocalimab exhibited a subtle trend toward higher liver distribution within the first 5 hours after dosing and a more rapid alpha elimination phase in circulation compared to the control antibody.

2.3. Metabolism

No drug metabolism studies have been conducted for nipocalimab. As an IgG-based mAb, nipocalimab is expected to be catabolized and eliminated by processes involved in the turnover and degradation of endogenous proteins. Because they are expected to be degraded into amino acids, no generation of reactive metabolites is expected. Therefore, classical biotransformation studies as performed for small molecules are not required.

2.4.Excretion

Similar to other IgG-based mAbs, nipocalimab is presumably eliminated via catabolic pathways that are typically associated with endogenous IgG. Thus, routine studies that attempt to assess mass balance are not expected to be informative, and no specific studies to evaluate the excretion of nipocalimab have been conducted.

2.5. Pharmacokinetic Drug Interactions

No non-clinical drug interaction studies have been conducted.

3. Toxicology

3.1. Single-dose Toxicity

No single-dose toxicity studies have been performed with nipocalimab. Acute toxicity studies designed to evaluate the potential adverse effects of doses causing major (life-threatening) toxicity are not considered appropriate for mAbs that have inherently low toxicity.

3.2. Repeat-dose Toxicity

3.2.1. 14-Day Repeat-dose Toxicity Study of IV Nipocalimab in Cynomolgus Monkeys (Study 529055)

Once weekly IV dosing of 2 doses of 10 or 300 mg/kg nipocalimab (on Days 1 and 8) was well tolerated in male cynomolgus monkeys, with no unscheduled deaths and no evidence of an adverse systemic toxic effect. The only observed effects were expected target and class effects, including binding of WBC FcRn and reductions in IgG concentration at both doses of nipocalimab. Some evidence of recovery in both RO and IgG levels was observed from 5 days after the second dose in animals that received 10 mg/kg/week IV nipocalimab. FcRn occupancy and IgG levels did not recover to baseline levels within the timeframe of this study in animals that received 300 mg/kg/week IV nipocalimab.

3.2.2. 4-Week GLP-compliant Repeat-dose Toxicity Study of IV Nipocalimab in Cynomolgus Monkeys (Study 529060)

-Nipocalimab was well tolerated in a 4-week GLP-compliant repeat-dose toxicity study in male and female cynomolgus monkeys receiving intravenous infusions once weekly (QW) at doses of 0, 20, 100, or 306 mg/kg, followed by a 9-week recovery period. No unscheduled deaths, clinical signs of toxicity, or treatment-related effects on body or organ weights, ophthalmologic, neurologic, electrocardiographic parameters, or clinical and microscopic pathology were observed.

-Dose-related decreases in total protein and albumin were noted at doses ≥20 mg/kg/week, while decreases in the albumin/globulin ratio and increases in cholesterol were observed at doses ≥100 mg/kg/week. These changes were reversible, with no notable differences in clinical chemistry parameters by Weeks 4 and 9 of the recovery period, even at the highest dose.

-Pharmacodynamic evaluation demonstrated rapid FcRn receptor occupancy, with full blockade observed within 2 hours post-dose on Day 1. Recovery of FcRn binding was dose-dependent, occurring approximately 7 days after the last dose at 20 mg/kg/week and around 3 weeks at 306 mg/kg/week. Serum IgG levels initially increased (likely assay-related), followed by reductions that persisted up to one week after the last dose, with recovery to baseline by Day 90 at the highest dose.

-The No Observed Adverse Effect Level (NOAEL) was determined to be 306 mg/kg/week, corresponding to mean $AUC_{0–last}$ values of 746,000 µg·h/mL in males and 827,000 µg·h/mL in females.

3.2.3. 26-Week GLP-compliant Repeat-dose Toxicity Study of IV Nipocalimab in Cynomolgus Monkeys (Study 501555)

-Nipocalimab was well tolerated in a 26-week GLP-compliant repeat-dose toxicity study in male and female cynomolgus monkeys administered intravenously at doses of 0, 20, 100, or 300 mg/kg once weekly, or 50 mg/kg twice weekly, followed by an 8-week recovery period. One male animal in the 300 mg/kg/week group was euthanized due to clinical signs consistent with an exaggerated immune response; this was considered an isolated event likely related to an underlying condition (recrudescence of latent lymphocryptovirus infection) and not treatment-related.

-Nipocalimab administration was associated with infrequent, transient, and self-resolving clinical signs (e.g., swelling, skin reactions, tremors, gastrointestinal symptoms, and scratching) in isolated animals. Dose-

related, non-adverse and reversible changes in clinical chemistry parameters—including reductions in total protein, albumin, globulin, albumin/globulin ratio, and calcium, along with increases in cholesterol—were observed at Weeks 8, 13, and 26, with full recovery by the end of the recovery period. No treatment-related effects were observed on body weight, organ weight, gross or microscopic pathology, or ophthalmologic, electrocardiographic, hematologic, coagulation, or urinalysis parameters.

-Pharmacodynamic assessments demonstrated rapid and sustained FcRn receptor occupancy (RO) across all dose levels, with maximum occupancy observed within 2 hours post-dose. RO duration was dose-dependent, persisting up to Day 15 at higher doses, with delayed return to baseline at ≥100 mg/kg/week. Despite a relatively short half-life, nipocalimab activity persisted due to plasma concentrations exceeding the threshold required for full FcRn saturation (~25 nM).

-Consistent, reversible reductions in serum IgG levels were observed in all treated groups following an initial assay-related increase. IgG levels decreased and stabilized during treatment, with recovery to baseline during the recovery period, including at the highest dose.

-Based on the absence of adverse findings and the reversibility of observed effects, the NOAEL was determined to be 300 mg/kg/week, corresponding to mean AUC_{0}–last values of 503,000 ± 181,000 µg·h/mL in males and 563,000 ± 76,700 µg·h/mL in females.

3.3. Genotoxicity

Genotoxicity studies have not been conducted with nipocalimab. Genotoxicity studies routinely conducted for pharmaceuticals are not appropriate for biotechnology-derived pharmaceuticals such as mAbs. Because of their large molecular size, mAbs, such as nipocalimab (approximately 142 kilodaltons), are not expected to pass through the nuclear membranes and are not expected to interact with DNA or other chromosomal material.

3.4.Carcinogenicity

No carcinogenicity studies are planned. Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals, such as mAbs, and nipocalimab does not bind to rodent FcRn.

3.5. *Reproduction and Developmental Toxicity*

3.5.1. GLP-compliant Embryo-fetal, Prenatal and Postnatal Development (ePPND) Study of IV Nipocalimab in Female Cynomolgus Monkeys (Study 20091416)

A GLP-compliant, two-phase reproductive toxicity study was conducted to evaluate intravenous nipocalimab (0, 100, or 300 mg/kg/week) in pregnant cynomolgus monkeys and their offspring. In Phase 1 (EFD), dosing began on approximately gestation day (GD) 45, with subgroups undergoing C-section on GD100 or GD140 or proceeding to natural delivery. Phase 2 (ePPND) was a live-birth study in which pregnant females were dosed weekly from GD45 to parturition.

Nipocalimab was well tolerated in dams, with no treatment-related clinical signs or histopathological findings. Toxicokinetic and pharmacodynamic assessments demonstrated high systemic exposure and sustained FcRn receptor occupancy, particularly at 300 mg/kg/week, despite the presence of anti-drug antibodies (ADA) and neutralizing antibodies (NAbs). Placental transfer of nipocalimab was low, and the

drug was not detected in infant serum; however, reduced IgG levels in infants suggested a pharmacodynamic effect likely due to decreased maternal IgG transfer rather than direct exposure.
No evidence of nipocalimab-related developmental toxicity was observed. Fetal evaluations showed no effects on growth or teratogenicity, and infants demonstrated normal growth, immune function, and neurobehavioral development up to 6 months postpartum. Offspring loss rates were comparable across all groups and within expected historical ranges.
Placental infarcts were observed at a slightly higher incidence in treated animals compared to controls; however, their toxicological and clinical relevance remains uncertain due to limited historical data, high background rates of pregnancy loss in this species, and the unclear mechanism. A potential association with immunogenicity and hypercoagulability cannot be excluded.
Although ADA and NAbs were detected in most treated dams and in fetuses/infants, these findings are consistent with species-specific immunogenicity and FcRn-mediated transfer. Importantly, high systemic exposure and sustained pharmacodynamic activity were maintained throughout the study.
Overall, there was no evidence of maternal or developmental toxicity attributable to nipocalimab at doses up to 300 mg/kg/week.

3.6. Local Tolerance

3.6.1. Rabbits (Study 500436)

No signs of local irritation at the injection site based on dermal and histopathological assessments were observed in male New Zealand white rabbits after IV (0 or 100 mg/kg) or paravenous (0 and 3.06 mg/kg) injection of nipocalimab into the rabbit ear, when given as either a single dose (Day 1) or 2 weekly doses (Days 1 and 8) in a GLP-compliant local tolerance study.

3.6.2. Cynomolgus Monkeys (Study 20227166)

-Single SC or IV injection of nipocalimab (42 mg/kg; dose volume of 0.2703 and 1.4018 mL/kg, respectively) in female cynomolgus monkeys was well tolerated with no evidence of local or systemic toxicity, in a PK/PD study.
-In repeat-dose toxicity studies in cynomolgus monkeys, nipocalimab at an IV dose volume of 10 mL/kg was well tolerated following weekly injections at up to 300 mg/kg or twice weekly injection at 50 mg/kg for 26 weeks, with no signs of local irritation based on histopathological examination.

3.7. Other Toxicity Studies

3.7.1. *Immunotoxicity* (Study 20104942)

An 8-week GLP-compliant repeat-dose study was conducted in male and female cynomolgus monkeys to evaluate the potential immunotoxicity of intravenously administered nipocalimab at doses of 0, 10, 100, or 300 mg/kg/week, followed by an 8-week recovery period.
Nipocalimab was well tolerated at all dose levels, with only isolated emesis observed in one animal per dose group. No unscheduled deaths or treatment-related effects on body weight, food consumption, organ weights, or gross and microscopic pathology were identified.

Comprehensive immunological assessments showed no adverse effects on peripheral immune cell populations, including T-helper, T-cytotoxic, natural killer, and B-lymphocytes, nor on activation markers (CD69+, CD25+). Additionally, no effects were observed on serum cytokines, cytotoxic T-cell or natural killer cell activity, or granulocyte/monocyte phagocytic and oxidative burst functions.
Reductions in serum IgG levels were observed during dosing, consistent with the pharmacological mechanism of action of nipocalimab, without affecting IgM responses or antigen-specific antibody production (e.g., anti-tetanus IgM and IgG) during recovery.
Pharmacodynamic assessments demonstrated FcRn receptor occupancy in monocytes and granulocytes at Week 4 in the 100 and 300 mg/kg/week groups, with dose-dependent recovery to baseline levels by Week 8 (100 mg/kg/week) and by the end of the recovery period (Week 16) for the 300 mg/kg/week group. Serum IgG levels showed a similar reversible trend, returning to baseline by Week 16.
Based on these findings, the NOAEL was determined to be 300 mg/kg/week, corresponding to mean $AUC_{0–96h}$ values of 407,000 ± 99,000 µg·h/mL in males and 307,000 ± 61,800 µg·h/mL in females following the final dose.

3.7.2. *Hemolytic Potential* (Study 6000286)

No evidence of hemolysis, flocculation or abnormal RBC morphology was observed after spiking of human or cynomolgus monkey whole blood samples with nipocalimab at concentrations up to 15.3 mg/mL, in a GLP-compliant study.

3.7.3. *Cross-reactivity in Adult and Fetal Tissue* (Study 20108517)

-In a GLP-compliant study that evaluated the potential cross-reactivity of nipocalimab with cryosections of normal adult and fetal/neonatal tissue from humans and cynomolgus monkeys, positive-specific staining by nipocalimab was detected in 23 of the 38 adult human tissues, 10 of 14 fetal/neonatal human tissues, 17 of 38 adult cynomolgus monkey tissues, and 6 of 33 fetal cynomolgus monkey tissues evaluated.
-Positive staining was most common in stromal cells in the adventitia, capsule, or connective tissue stroma. Notably, the lymphocytes in the spleen (white pulp), lymph node, thymus, and tonsil parenchymal epithelium and myofibers in smooth and striated (including heart) muscle were not stained by nipocalimab. All observed staining was cytoplasmic; mAb binding to cytoplasmic structures is generally considered of little or no toxicological concern because mAb test articles are not expected to cross cell membranes.

4. Conclusions for Nonclinical Studies

-Nipocalimab binds with high affinity to FcRn, which leads to internalization and catabolism of IgG that may facilitate the removal of pathogenic IgG in various diseases. This potential therapeutic mechanism and benefit were demonstrated in both in vitro and in vivo models of autoimmune diseases.
-PK, TK, and PD evaluations of FcRn occupancy and serum IgG concentrations indicated similar nipocalimab dose-, exposure-, and time-dependent relationships for the PD effects of nipocalimab in cynomolgus monkeys and human FcRn transgenic (Tg32D) mice.
-In the 14-day, and 4- and 26-week GLP-compliant repeat-dose IV toxicity studies in cynomolgus monkeys, no adverse effects were observed after repeated qw administration at doses up to 300 mg/kg/week

nipocalimab. Dose-related decreases in albumin and dose-related increases in cholesterol ≥100 mg/kg/week in the 4- and 26-week studies were reversible and considered non-adverse.
-In the 8-week IV immunotoxicity study, 300 mg/kg/week nipocalimab specifically decreased IgG without affecting non-IgG immunoglobulins, immune cell populations, innate or adaptive immune cell functions, or the ability to mount T-cell-dependent antibody responses. In a GLP-compliant reproductive toxicity study in which pregnant cynomolgus monkeys received IV nipocalimab at doses of up to 300 mg/kg/week from the early second trimester (ie, GD45) through parturition, serum IgG in dams, fetuses, and newborns was decreased with no evidence of nipocalimab-related developmental toxicity or impact on fetal or infant survival. The mechanism of placental infarction and causal relationship with offspring losses has not been firmly established but may be related to nipocalimab species-specific immunogenicity and hypercoagulability in pregnant monkeys.

- **Summary of previous clinical studies:**

****Overview****

-The clinical development program for nipocalimab includes studies in participants with gMG (generalized myasthenia gravis), pSD (1ry Sjogren's disease), RA (rheumatoid arthritis), SLE (systemic lupus erythematous), wAIHA (warm autoimmune hemolytic anemia), IIM (idiopathic Inflammatory Myopathies), CIDP (Chronic Inflammatory Demyelinating Polyneuropathy) and pregnant women at high risk for HDFN (hemolytic disease of the fetus and newborn), as well as in healthy participants.
-Overall, approximately 757 participants have been exposed to nipocalimab in the clinical development program.
-As of the data cutoff date for this IB (28 April 2023), 19 clinical studies of nipocalimab have been completed (7) or are ongoing (12).

- Seven clinical studies have been completed: **MOM-M281-001**, **MOM-M281-004**, **MOM-M281-005**, **MOM-M281-007**, **MOM-M281-008**, **MOM-M281-010**, and **80202135ARA2001**.
- The following 12 studies are ongoing:**MOM-M281-003**, **MOM-M281-011**, **80202135SLE2001**, **80202135SJS2001**, **80202135EDI1001**, **80202135EDI1002**, **80202135EDI1003**, **80202135EDI1009**, **80202135IIM2001**, **80202135MYG2001**, and **80202135CDP3001**.

Study Status	Study Number	Study Design	Primary and secondary Objectives
Phase 1(Healthy participants) Study Start - End Dates: 9 May 2016 - 8 Aug 2017	MOM-M281-001	A Phase 1, single-center, randomized, double-blind, placebo-controlled, single (Part 1) and multiple (Part 2) ascending dose study to evaluate the safety, tolerability, PK, and PD of	**Primary Objectives** • To evaluate the safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of nipocalimab

		nipocalimab administered to healthy participants. **Treatment groups:** Part 1 (SAD): single IV infusions of placebo or escalating doses of nipocalimab: • Cohort 1: 0.3 mg/kg nipocalimab (n=3). • Cohort 2: 3 mg/kg nipocalimab (n=3). • Cohort 3: 10 mg/kg nipocalimab (n=6). • Cohort 4: 30 mg/kg nipocalimab (n=6). • Cohort 5: 60 mg/kg nipocalimab (n=6). • Placebo (n=10). Part 2 (MAD): 4 weekly IV infusions of nipocalimab or placebo: • Cohort 1: 30 mg/kg nipocalimab (n=6). • Cohort 2: 15 mg/kg nipocalimab (n=6). • o Placebo (n=4).	administered intravenously in healthy participants. **secondary Objectives** • To characterize the pharmacokinetics (PK) of nipocalimab following single and multiple intravenous administrations. • To assess the pharmacodynamics (PD) effects of nipocalimab after single and repeated dosing.
Phase 1 (Healthy participants) Study Start - End Dates: 5 Mar 2019 - 2 Aug 2019	MOM-M281-007	A Phase 1, single-dose, sequential, randomized, double-blind (sponsor-open), placebo-controlled, escalating dose and escalating infusion rate study to assess the safety and tolerability of escalating infusion rates of nipocalimab in healthy adult participants. **Treatment groups:** • Cohort 1: 30 mg/kg nipocalimab IV over 60 min (n=6). • Cohort 2: 30 mg/kg nipocalimab IV over 30 min (n=6).	**Primary objectives:** •To evaluate the safety and tolerability of escalating infusion rates of intravenously administered nipocalimab in healthy adult participants. **Secondary Objectives:** •To characterize the pharmacokinetics (PK) of nipocalimab at different infusion rates and dose levels. •To assess the impact of infusion rate on PK

		• Cohort 3: 30 mg/kg nipocalimab IV over 15 min (n=6). • Cohort 4: 30 mg/kg nipocalimab IV over 7.5 min (n=6). • Cohort 5: 60 mg/kg nipocalimab IV over 15 min (n=6). • Placebo IV (n=10)	parameters (e.g., Cmax, Tmax, AUC). To evaluate the pharmacodynamic (PD) effects of nipocalimab across the studied infusion rates.
Phase 1(Healthy participants) **Study Start - End Dates:** 23 Oct 2020 - 16 Mar 2021	MOM-M281-008	A Phase 1, open-label, parallel, three-treatment, PK drug interaction study of the effects of nipocalimab single-dose IV administration on the PK of single-dose fremanezumab in healthy adult participants. **Treatment groups**: • Group A: 225 mg fremanezumab SC on Day 1 (n=8). • Group B: 225 mg fremanezumab SC on Day 1 co administered with 30 mg/kg nipocalimab IV (n=8). • Group C: 225 mg fremanezumab SC on Day 1 and 30 mg/kg nipocalimab IV on Day 15 (n=8)	**Primary objective:** • To determine the effect of nipocalimab coadministration or offset-administration on fremanezumab PK in healthy adult participants. **Secondary objectives:** • To characterize the PK of nipocalimab after coadministration or offset-administration with fremanezumab in healthy adult participants. • To assess the safety and tolerability of single-dose fremanezumab when administered with a single dose of nipocalimab in healthy adult participants.
Phase 1 (Healthy participants) Study Start - End Dates: 18 Sep 2019 - 6 Dec 2019	MOM-M281-010	A Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, PK and PD of nipocalimab administered to adults with gMG **Treatment groups:** • Group 1: placebo IV q2w (n=14).	**Primary objectives:** • To evaluate the efficacy of nipocalimab for gMG as measured by the change in MG-ADL score. • To evaluate the safety and tolerability of treatment with nipocalimab in participants with gMG who have an insufficient clinical response

		• Group 2: 5 mg/kg nipocalimab IV q4w (n=14). • Group 3: 30 mg/kg nipocalimab IV q4w (n=13). • Group 4: 60 mg/kg nipocalimab IV as a single dose (n=13). • Group 5: 60 mg/kg nipocalimab IV q2w (n=14)	to ongoing, stable standard-of-care therapy. **Secondary objectives:** • To evaluate the efficacy of nipocalimab as measured by changes in the QMG score and the MG-QoL15r. • To evaluate the PK of nipocalimab. • To evaluate the PD activity of nipocalimab as measured by effects on total serum IgG concentrations.
Phase 1 (Healthy participants) Study Start - End Dates: 25 May 2021 - Ongoing	80202135EDI1001	A Phase 1, double-blind, placebo-controlled, single- and multiple-dose study to evaluate the safety, tolerability, PK, and PD of SC nipocalimab in healthy male and female participants **Treatment groups**: Part 1 will include a single SC or IV administration of study intervention: • Cohort 1: Dose 1 SC (6 active:2 placebo). • Cohort 2: Dose 2 SC (6 active:2 placebo). • Cohort 3: Dose 3 SC (6 active:2 placebo). • Cohort 4: Dose 4 SC (6 active:2 placebo). • Cohort 5: Dose 1 IV (6 active:2 placebo). • Cohort 6: Dose 2 IV (6 active:2 placebo). • Optional Cohorts 7 and 8 (6 active:2 placebo) to be determined from Part 1 data. Part 2 (10 active:2 placebo) will include up to 4 weekly or 4	**Primary objective:** • To evaluate the safety and tolerability of single and multiple doses of nipocalimab following SC administration compared with IV administration in healthy participants. **Secondary objectives:** • **To evaluate the PK of** single and multiple doses of nipocalimab following SC administration compared with IV administration in healthy participants. • To evaluate the PD effect of nipocalimab on IgG following SC administration compared with IV administration in healthy participants. • To evaluate the antidrug antibody response of nipocalimab following SC administration compared with IV administration in healthy participants

		biweekly SC administrations of study intervention. Additional cohorts and dose levels to be determined from Part 1 data.	
Phase 1 (Healthy participants) Study Start - End Dates: 30 May 2022 - Ongoing	80202135EDI1002	A Phase 1, open-label, sequential-cohort, single-dose study to evaluate the PK, safety, and tolerability of IV nipocalimab in healthy Chinese adult participants. **Treatment groups:** Participants (planned=30) will be enrolled in 3 sequential treatment cohorts: • Cohort 1: single IV dose 15 mg/kg (planned n=10). • Cohort 2: single IV dose 30 mg/kg (planned n=10). • Cohort 3: single IV dose 45 mg/kg (planned n=10). Escalation to the next dose level will not take place until the principal investigator consider that adequate safety and tolerability from the previous cohort has been demonstrated to permit proceeding to the next cohort. Subsequent cohort dosing will be staggered to permit a safety review of AEs, vital signs, ECGs, and laboratory measurements through at least Day 2 of the prior cohort.	**Primary objective:** • To assess the PK of nipocalimab following single IV administration in healthy Chinese participants. **Secondary objective**: • To assess the safety, tolerability, immunogenicity, and PD of nipocalimab following single IV administration in healthy Chinese participants.
Phase 1 (Healthy participants) Study Start - End Dates: 31 Aug 2021 - Ongoing	80202135EDI1003	A Phase 1, open-label study to investigate DDI potential of nipocalimab with coadministration of etanercept (Part 1) or HCQ (Part 2) in healthy participants. **Treatment groups:** In Part 1, participants (planned n=16) will receive a single SC	**Primary objectives**: **Part 1:** • To assess the effect of nipocalimab on the PK of etanercept in healthy participants. **Part 2:** • To assess the effect of HCQ on total serum IgG reduction

		dose of 50 mg etanercept on Day 1, a single IV dose of 15 mg/kg nipocalimab on Day 29, a single SC dose of 50 mg etanercept followed by a single IV dose of 15 mg/kg nipocalimab on Day 43, a single IV dose of 15 mg/kg nipocalimab on Day 57. Part 2 (planned n=32) will include 2 cohorts. In Cohort 1, participants will be administered a single IV dose of 15 mg/kg nipocalimab on Day 1. In Cohort 2, participants will be administered a single oral dose of 400 mg HCQ qd from Day 1 to Day 22 and a single IV dose of 15 mg/kg nipocalimab on Day 8	of or by nipocalimab in healthy participants. **Secondary objectives:** **Part 1:** • To assess the safety and tolerability of nipocalimab following coadministration of etanercept in healthy participants. • To assess the PK of nipocalimab following coadministration of etanercept in healthy participants. • To assess the immunogenicity of nipocalimab following coadministration of etanercept in healthy participants **Part 2:** • To assess and compare the PK of nipocalimab with and without coadministration of HCQ in healthy participants. • To assess the effect of HCQ on nipocalimab PD in healthy participants.
Phase 1 (Healthy participants) Study Start - End Dates: 12 Apr 2023 - Ongoing	80202135EDI1009	A Phase 1, randomized, open-label, parallel, single-center, interventional study in healthy adult participants to investigate the effect of nipocalimab administration on the extent and kinetics of humoral response to the clinically relevant Tdap and PPSV®23 vaccines. **Treatment groups**: Participants (planned n=30) will be randomly assigned in a 1:1 ratio to 1 of 2 arms:	**Primary objective**: • To evaluate the effect of nipocalimab treatment on the antibody response following Tdap vaccination in healthy participants at Week 4. **Secondary objectives:** • To evaluate the effect of nipocalimab treatment on antibody responses following Tdap vaccination in healthy participants through Week 16.

		• Active Arm: nipocalimab 30 mg/kg IV loading dose on Day 1 followed by 15 mg/kg IV at Week 2 and Week 4. A single dose of PPSV®23 and Tdap will be administered on Day 3. • Control Arm: Single dose of PPSV®23 and Tdap administered IM on Day 3 only.	• To evaluate the effect of nipocalimab treatment on the antibody response following PPSV®23 vaccination in healthy participants. • To evaluate the safety and tolerability of nipocalimab treatment following administration with vaccines in healthy participants. • To evaluate the serum PK and immunogenicity of nipocalimab following administration of vaccines in healthy participants. • To evaluate the PD effect of nipocalimab treatment on IgG in healthy participants.
phase 2 (Generalized Myasthenia Gravis) Study Start - End Dates: 2 Jul 2019 - 22 Jun 2020	MOM-M281-005	A Phase 2, OLE study of MOM-M281-004 to evaluate the safety, tolerability, and efficacy of nipocalimab administered to participants with gMG. **Treatment groups**: Participants received 30 mg/kg nipocalimab IV q4w initially.	**Primary objective:** • To evaluate the long-term safety and tolerability of nipocalimab in participants with gMG. **Secondary objectives**: • To evaluate the long-term efficacy of nipocalimab. • To evaluate the long-term immunogenicity of nipocalimab. • To evaluate the long-term PD activity of nipocalimab.
Phase 2/3 (Generalized Myasthenia Gravis) Study Start - End Dates: 20 July 2022 - Ongoing	80202135MYG2001	A Phase 2/3, open-label, uncontrolled, interventional study to evaluate the PK, PD, safety, and activity of IV nipocalimab, administered in addition to protocol-allowed, stable, standard-of-care therapy for the treatment of gMG in pediatric	**Primary objectives:** □ To evaluate the effect of nipocalimab on total serum IgG in pediatric participants 2 to <18 years of age with gMG who have an insufficient clinical response to ongoing, stable standard-of-care therapy.

			participants (from 2 to <18 years of age). **Treatment groups**: -The study consists of a screening period (up to 4 weeks), a 24-week active treatment phase, and a long-term extension phase that will be of variable duration per participating country/territory. The active treatment phase is comprised of 2 cohorts. Cohort 1 (at least n=6) will include adolescent gMG participants aged 12 to <18 years of age receiving IV nipocalimab (30 mg/kg for first infusion, 15 mg/kg thereafter) q2w. -After the active treatment phase is completed for Cohort 1, Cohort 2 (participant children with gMG aged 2 to <12 years of age; at least n=6) will be enrolled and receive nipocalimab for 24 weeks. Dosing for Cohort 2 will be modeled based on all extant PK and PD data available (including adult data from Phase 1 to Phase 3 studies and adolescent data from Cohort 1 of this study) at the time of the interim analysis. After completion of the active treatment phase, all participants from both cohorts will have the option to enroll in a long-term extension phase	The safety and tolerability of treatment with nipocalimab in children and adolescents (2 to <12 years, and 12 years to <18 years of age) with gMG who have an insufficient clinical response to ongoing, stable standard-of-care therapy. To evaluate the PK of nipocalimab in children and adolescents (2 to <12 years, and 12 years to <18 years of age) with gMG who have an insufficient clinical response to ongoing, stable standard-of-care therapy. **Secondary objectives:** To evaluate the treatment response to nipocalimab. To evaluate the effect on health-related quality of life. To evaluate the effect on fatigue. Safety assessments.

Phase 2 (Early Onset Severe Hemolytic Disease of the Fetus and Newborn) Study Start - End Dates: 23 Apr 2019 - Ongoing	MOM-M281-003	A Phase 2, multicenter, open-label study to evaluate the safety, efficacy, PK, and PD of nipocalimab administered to pregnant women at high risk for EOS-HDFN. **Treatment groups**: Participants will receive 30 mg/kg and/or 45 mg/kg nipocalimab IV qw for approximately 20 prenatal infusions (planned n=~15), starting at GA Week 14 through GA Week 35. Doses vary according to the protocol amendment the participant was enrolled under. Dose groups include 30 mg/kg IV qw BLW (ie, total dose at each visit was based on participant's weight at baseline visit]), 45 mg/kg IV qw BLW, and 45 mg/kg IV qw TAW (ie, total dose based on participant's weight measured every 2 weeks over the course of the pregnancy). (Note: Three participants received nipocalimab 30 mg/kg BLW. Two participants began treatment at the 30 mg/kg BLW dose and then received 45 mg/kg BLW (counted in the 30-45 mg/kg BLW dose group). Four participants received 45 mg/kg BLW. Four participants were included in the 45 mg/kg TAW; 2 of the 4 participants included in the 45 mg/kg TAW dose group began treatment at 45 mg/kg BLW.).	**Primary objective:** • To evaluate the safety in mother and neonate/infant of nipocalimab administered to pregnant women at high risk for EOS-HDFN. • To evaluate the efficacy of nipocalimab as measured by the proportion of participants with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy. **Secondary objectives:** • To evaluate the efficacy of nipocalimab on antenatal management and outcome as measured by GA at first fetal IUT, frequency of fetal IUT, and frequency of live birth. • To evaluate the efficacy of nipocalimab on postnatal management and outcome as measured by severity of hyperbilirubinemia, phototherapy, exchange transfusions, and simple transfusions in the first 12 weeks of life. • To evaluate the PD activity of nipocalimab as measured by effects on maternal FcRn occupancy, and maternal and neonatal/infant levels of total IgG and alloantibodies. • To evaluate the PK of nipocalimab.
Phase 2(Primary Sjögren's Disease)	80202135SJS2001	A Phase 2, randomized, placebo-controlled, double-blind, multicenter study to assess the	**Primary objective:**

Study Start - End Dates: 21 Sep 2021 - Ongoing		efficacy and safety of nipocalimab in adult participants with pSD **Treatment groups:** • Group 1: placebo IV q2w (planned n=50). • Group 2: nipocalimab 5 mg/kg IV q2w (planned n=50). • Group 3: nipocalimab 15 mg/kg IV q2w (planned n=50)	• To evaluate the efficacy of nipocalimab in participants with pSD vs placebo. **Secondary objectives:** • To evaluate the safety of nipocalimab treatment vs placebo in participants with pSD. • To evaluate the PK and immunogenicity of nipocalimab in participants with pSD. • To evaluate the effect of nipocalimab vs placebo on levels of serum biomarkers related to pSD.
Phase 2 a (Rheumatoid Arthritis) Study Start - End Dates: 14 Oct 2021 - 10 Aug 2022	80202135ARA2001	A Phase 2a, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of nipocalimab in participants with active RA despite standard therapy **Treatment groups**: • Group 1: placebo IV q2w (n=20). • Group 2: nipocalimab IV q2w (planned n=33)	**Primary objective**: • To evaluate the efficacy of nipocalimab vs placebo in participants with moderate to severe active RA. **Secondary objectives:** • To evaluate the safety and tolerability of nipocalimab vs placebo in participants with moderate to severe active RA. • To evaluate the PK and immunogenicity of IV nipocalimab in participants with moderate to severe active RA
Phase 2 (Systemic Lupus Erythematosus) Study Start - End Dates: 20 Aug 2021 - Ongoing	80202135SLE2001	A Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy of nipocalimab in adult participants with active SLE. **Treatment groups**: Participants will be randomly assigned into 3 treatment groups with a 1:1:1 ratio.	**Primary objective:** • To evaluate the efficacy of nipocalimab vs placebo in participants with active SLE. **Secondary objectives**: • To evaluate the safety and tolerability of nipocalimab vs placebo in participants with active SLE.

		• Group 1: placebo IV q2w (planned n=75) . • Group 2: nipocalimab 5 mg/kg IV q2w (planned n=75). • Group 3: nipocalimab IV q2w (planned n=75).	• To evaluate the PK and immunogenicity of nipocalimab in participants with active SLE
Phase 2/3 (Warm Autoimmune Hemolytic Anemia) Study Start - End Dates: 5 Nov 2019 - Ongoing	MOM-M281-006	An adaptive Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study with a long-term OLE to evaluate the efficacy, safety, tolerability, PK, and PD of nipocalimab in adults with wAIHA. **Treatment groups:** • Group 1: placebo IV infusion q2w (planned n=37). • Group 2: 30 mg/kg nipocalimab IV infusion q4w (planned n=37). • Group 3: 15 mg/kg nipocalimab IV infusion q2w (planned n=37). The OLE treatment: nipocalimab IV infusion q4w	**Primary objective:** • To evaluate the efficacy of nipocalimab in participants with wAIHA. **Secondary objectives:** • To evaluate the impact of nipocalimab treatment on fatigue. • To evaluate the impact of nipocalimab on corticosteroid use.
Phase 2 (Idiopathic Inflammatory Myopathies) Study Start - End Dates: 5 Jul 2022 - Ongoing	80202135IIM2001	A Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose, interventional study to evaluate the efficacy, safety, tolerability, PK, PD, and immunogenicity of nipocalimab in adult participants with active IIM. **Treatment groups:** -Participants will have to be serologically positive and have clinically active disease while receiving at least 1 standard-of-care treatment within at least 6 weeks prior to the first administration of the study intervention. Participants (planned	**Primary objective**: • To evaluate the efficacy of nipocalimab vs placebo in participants with active IIM. **Secondary objectives**: • To further evaluate the efficacy of nipocalimab vs placebo across a range of outcome measures in participants with active IIM. • To evaluate the efficacy of nipocalimab vs placebo in oral glucocorticoid reduction in participants with active IIM. • To evaluate the efficacy of nipocalimab vs placebo in disease activity improvement

		n=200) will be randomly assigned into 1 of 2 treatment groups (IV nipocalimab q2w or placebo) and will be stratified by MSA (DM, IMNM, ASyS) profile and disease severity. -The total duration of this study is up to 112 weeks, consisting of 4 study periods: a ≤6-week screening period), a 52-week double-blind period, a 48-week long-term extension, and a safety follow-up 8 weeks post last administration of study intervention. A 20-week mandatory protocol defined oral glucocorticoid taper will be applied to both study groups from Week 24 to Week 44, for those participants on oral glucocorticoid (>5 mg/day of prednisone or equivalent) at baseline. At Week 52, participants will be assessed by the investigator for eligibility to continue into the long-term extension	over time in participants with active IIM. • DM participants only: To evaluate the efficacy of nipocalimab vs placebo in cutaneous disease activity improvement in participants with active IIM. • To evaluate the safety and tolerability of nipocalimab vs placebo in participants with active IIM. • To evaluate the impact of nipocalimab on PROs in participants with active IIM. • To evaluate the PK and immunogenicity of nipocalimab in participants with active IIM.
Phase 2/3 (Chronic Inflammatory Demyelinating Polyneuropathy) Study Start - End Dates: 23 Sept 2022 - Ongoing	80202135CDP3001	A Phase 2/3, multistage, multicenter, randomized, double-blind, placebo-controlled, parallel-group, withdrawal study to evaluate treatment with nipocalimab in participants diagnosed with active CIDP according to the EAN/PNS 2021 criteria. **Treatment groups:** The study will consist of the following periods: identification of participants with active CIDP (including screening and Run-in);	**Primary objective**: • To evaluate the efficacy of nipocalimab compared to placebo in delaying relapse in participants with CIDP who initially respond to nipocalimab in Stage A. **Secondary objectives**: **Stage A:** • To assess improvement of symptoms on nipocalimab. • To assess improvement in disease severity and progression on nipocalimab.

		open-label treatment with nipocalimab (Stage A); double-blind, placebo-controlled, randomized withdrawal (Stage B); and an OLE. Participants (planned n=121) will be randomized in 1:1 ratio in the 2 treatment groups (IV nipocalimab or placebo in Stage A) before entering Stage B (double-blind placebo-controlled period) of the study. The randomization will be stratified by prior treatment status at study entry, region, and Stage A responder based on adjusted INCAT disability score	**Stage B:** • To evaluate the efficacy of nipocalimab compared to placebo on time to CIDP disease progression from Stage B baseline. • To evaluate the efficacy of nipocalimab compared to placebo on improved functional level compared to Stage B baseline. • To assess the safety and tolerability of nipocalimab compared to placebo. • To assess the PK and immunogenicity of nipocalimab. • To evaluate the PD of nipocalimab.
Phase 3 (Generalized Myasthenia Gravis) Study Start - End Dates: 15 Jul 2021 - Ongoing	MOM-M281-011	A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, PK, and PD of nipocalimab administered to adults with gMG. **Treatment groups:** Participants will receive either placebo or nipocalimab (30 mg/kg IV for first infusion, 15 mg/kg thereafter) q2w, for 24 weeks. Participants who complete the double-blind placebo-controlled phase or participants impacted by the study hold and subsequent termination of the Study MOM-M281-005 have the option to receive open-label treatment of nipocalimab	**Primary objective**: • To evaluate the efficacy of nipocalimab compared to placebo based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed. **Secondary objectives:** • To evaluate the efficacy of nipocalimab compared to placebo based on the QMG scale, in seropositive gMG participants when treatment is taken as directed. • To evaluate the effect of nipocalimab compared to placebo in achieving the MCID or better based on the MG-ADL scale, in seropositive gMG participants

			when treatment is taken as directed. • To evaluate the efficacy of nipocalimab loading dose compared to placebo based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed. • To evaluate sustainability of therapeutic response of nipocalimab compared to placebo based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed. • To evaluate the effect of nipocalimab compared to placebo on the percentage of participants achieving ≥50% symptom improvement based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed

**** Studies on healthy participants****

1. Study MOM-M281-001

1.1. PK

1.1.1. FIH SAD

Across nipocalimab SAD dose groups (0.3 to 60 mg/kg), C_{max} increased in a dose-proportional manner while AUC increased in a greater than dose-proportional manner Clearance decreased with increasing doses of nipocalimab while $t_{1/2}$ increased with increasing dose, from approximately 7.36 hours at 3 mg/kg, 23.8 hours at 10 mg/kg, 30.5 hours at 30 mg/kg, and 32.2 hours at 60 mg/kg.

1.1.2. FIH MAD

-The PK samples were collected during the multiple-dose portion of the Study, which included 6 nipocalimab-treated participants in the 30 mg/kg group (3 received all 4 doses, 1 received 3 doses, and 2

received 2 doses) and 6 nipocalimab-treated participants in the 15 mg/kg group (3 received 4 doses and 3 received 3 doses).

-The PK of nipocalimab following multiple-dose administrations was consistent with the PK of nipocalimab following a single-dose administration. Similar to single-dose PK, serum concentrations appeared to decline rapidly at serum nipocalimab concentrations <10 µg/mL. With repeated weekly dosing of 30 mg/kg, C_{trough} appeared to reach steady state within the 4-dose period and the steady state C_{trough} ranged from approximately 100 to 200 µg/mL. Note: One participant, who received 4 doses, had a predose baseline (time 0) value between 0.1 and 0.4 µg/mL (approximately 0.05% of C_{max} and approximately 0.2% of C_{trough}).

1.2. Efficacy/ PD

1.2.1. FIH SAD

-Reductions in serum IgG concentrations occurred within 1 day of dose initiation at all dose levels; however, the magnitude of the reduction and the duration at minimum concentrations were dose-dependent. The lowest IgG value was 44.5%, 26.0%, and 19.6% of baseline and returned to 87.3%, 81.0%, and 65.3% of baseline on Day 43 following a single IV administration of 10 mg/kg, 30 mg/kg, and 60 mg/kg nipocalimab, respectively. A maximum reduction in IgG concentrations of approximately 75% to 80% from baseline was observed at single doses of 30 and 60 mg/kg, and the durability of the response at the 60 mg/kg dose (~14 days) was longer than that of the 30 mg/kg dose (~10 days).

-Single doses of nipocalimab were also associated with transient and relatively small reductions from baseline in serum albumin concentrations. Mean albumin concentrations decreased by 17% on Day 8 (168 hours) in the 30 mg/kg cohort and by 22% on Day 15 (336 hours) in the 60 mg/kg cohort. Small reductions in albumin concentrations of approximately 7% were also observed at lower doses of nipocalimab (0.3 to 10 mg/kg) as well as in the placebo group. Mean serum albumin concentrations returned rapidly to baseline values after reaching nadirs on Day 8 (~168 hours) in the 30 mg/kg cohort and Day 15 (~336 hours) in the 60 mg/kg cohort, at a similar time to nipocalimab serum concentrations reaching values ≤10 µg/mL.

1.2.2. FIH MAD

-Similar to what was seen in the SAD portion of the study, multiple qw doses of either 30 or 15 mg/kg nipocalimab resulted in IgG reductions from Day 1. Importantly, at both dose levels, reductions in IgG concentrations were self-limited to a maximum of approximately 15% to 20% of baseline values (corresponding to a decrease from baseline of 80% to 85%), regardless of the number of doses administered.

-In the 30 mg/kg MAD cohort, serum IgG concentrations reached their nadir by Days 21 to 28 in the various 30 mg/kg subgroups. The rate of IgG decline was similar among the subgroups and, as in the SAD study, IgG concentrations showed a similar rate of recovery beginning approximately 14 days after the last 30

mg/kg dose of nipocalimab, recovering to approximately 80% of baseline values within 37 to 70 days after the last dose.

-In the 15 mg/kg MAD cohort, the nadir was reached after 3 doses in both subgroups (ie, those who received 3 and those who received 4 doses). The rate of IgG recovery was similar in both subgroups, beginning approximately 7 days after the last 15 mg/kg dose of nipocalimab, and recovering to approximately 80% of baseline within 38 to 54 days after the last dose.

-Multiple doses of nipocalimab were also associated with relatively small and variable reductions from baseline in serum albumin concentrations. Mean albumin concentrations decreased to nadirs of 75% to 80% of baseline values (a decrease from baseline of 20% to 25%) in both the 30 and 15 mg/kg MAD cohorts at varying time points after initiation of study drug administration. Recovery of serum albumin concentration to baseline occurred within

4 to 5 weeks after the last 30 mg/kg infusion. Albumin levels for participants in the 15 mg/kg group recovered to baseline levels in 3 to 4 weeks after the last dose.

-As in the SAD portion of the study, all IgG subclasses (IgG1, IgG2, IgG3, IgG4) and antigen-specific IgG showed similar decreases and recoveries following multiple doses of nipocalimab, similar to total serum IgG. In contrast, no nipocalimab-related changes in total IgM, IgA, IgE, CH50, C3, C4, or cytokine or the inflammatory markers were observed following multiple doses of 30 or 15 mg/kg nipocalimab.

1.3. Safety and tolerability

1.3.1. TEAEs

1.3.1.1. In the **SAD** portion of the study, TEAEs were reported for 18 (75.0%) nipocalimab-treated participants and 7 (70%) participants in the placebo group. There was no apparent relationship between the percentage of participants reporting TEAEs or number of TEAEs reported and the dose administered. The most frequently reported TEAEs by preferred term (reported by at least 3 participants overall) in decreasing order were: headache, oropharyngeal pain, viral upper respiratory tract infection, catheter site hematoma, fatigue, and nausea. These TEAEs were reported in both the nipocalimab and placebo groups, except for catheter site hematoma and oropharyngeal pain, which were reported in the nipocalimab groups only.

1.3.1.2. In the **MAD** portion of the study, TEAEs were reported for 11 (91.7%) nipocalimab-treated participants and 4 (100%) participants in the placebo group. There was no apparent relationship between the percentage of participants reporting TEAEs and the nipocalimab dose administered. The most frequently reported TEAEs by preferred term (reported by at least 3 participants overall) and in decreasing order were: viral upper respiratory tract infection, headache, myalgia, oropharyngeal pain, paresthesia, and blood creatine phosphokinase increased. These TEAEs were reported in both the nipocalimab and placebo groups, except for increased CK, which was reported in the 15 mg/kg nipocalimab group only.

1.3.2. Deaths, SAEs

There were no SAEs, severe AEs, or deaths during this study.

1.3.3. Study Drug Discontinuations

- No participants in the SAD portion of the study experienced TEAEs leading to discontinuation of the study drug.

-In the 15 mg/kg MAD cohort, three participants discontinued treatment after receiving three doses of nipocalimab due to transient, asymptomatic elevations in creatine kinase (CK), which were assessed by the investigator as mild and treatment-related adverse events. One of these participants also experienced a mild, asymptomatic elevation in ALT. Notably, CK elevations were not observed in the higher 30 mg/kg MAD cohort, indicating no apparent dose–response relationship. It is also worth noting that one of the affected participants reported engaging in exercise 96 hours prior to the observed CK elevation. CK elevations of skeletal muscle origin may be associated with increased liver enzyme levels, as these enzymes can be partially derived from muscle tissue.

-In the 30 mg/kg MAD cohort, two participants discontinued treatment after three doses due to asymptomatic decreases in serum IgG levels below 200 mg/dL. An additional participant discontinued after two doses due to a reduction in *Haemophilus influenzae* antibody titer to below 0.15 µg/mL. As this was an initial MAD cohort expected to result in low absolute IgG levels, a conservative alert threshold of 200 mg/dL was predefined based on literature and clinical practice in severe primary immunodeficiency conditions (e.g., common variable immunodeficiency and X-linked agammaglobulinemia). These conditions differ mechanistically from nipocalimab, which selectively reduces the half-life of IgG rather than impairing immunoglobulin production.

-Decreases in tetanus toxoid and *H. influenzae* antibody titers below protective thresholds were also defined as alert criteria. Importantly, IgG levels as well as tetanus toxoid and *H. influenzae* antibody titers returned to normal following discontinuation of treatment in all affected participants. Only one participant subsequently experienced adverse events attributable to nipocalimab (mild nausea and trembling), as assessed by the investigator.

1.3.4. Adverse Events Related to Infection

-As nipocalimab is expected to cause a decrease in serum IgG concentrations, which could theoretically increase the risk for infections, AEs related to infection were of special interest in this study.

-In the **SAD** portion of the study, TEAEs in the SOC of Infections and Infestations included 5 events of viral upper respiratory tract infection and 1 event of influenza. These events were reported in both the placebo and nipocalimab dose groups, without any observed relationship between dosing frequency and dose level. All

of these events were of limited duration, did not require anti-infective treatment, resolved without change or interruption of study drug (placebo or nipocalimab), and the majority were assessed by the investigator as unrelated to study drug and mild in severity.

1.3.5. Laboratory results evaluation

-Clinically relevant decrease in total protein and albumin levels were noted in the 60 mg/kg single-dose group, 30 mg/kg multiple-dose group, and 15 mg/kg multiple-dose group. The decrease in total protein levels was due to the decrease in IgG levels and, to a lesser extent, decrease in albumin levels; protein was not found in the urine samples for the urinalysis assessments, indicating the decrease in serum protein levels was not due to loss in urine. No clinical signs or symptoms associated with hypoalbuminemia were observed.

-There were also mild, asymptomatic reductions in total calcium concentrations noted in some of the higher SAD (30 and 60 mg/kg) and **MAD** (15 and 30 mg/kg) groups that were observed during treatment with a return to normal concentrations shortly after treatment was discontinued. The pattern of reduction and return to normal was similar to what was observed for albumin. Calcium is known to bind to albumin, so the finding of mild reduction in calcium can be explained by the reduction in albumin.

-In this study, total cholesterol and triglycerides, but not HDL and LDL, were assessed. Most of the samples were collected in non-fasting conditions. Asymptomatic, dose-dependent, reversible elevations in total cholesterol were observed in both the SAD and MAD portions of the MOM-M281-001 study. There were no reported AEs of lipid elevation or relevant cardiovascular events.

1.4. Immunogenicity

-In the **SAD** portion of the study, 4 of 24 participants (17%) following a single IV dose of 0.3 to 60 mg/kg were positive for antibodies to nipocalimab, with low titers (highest titer was 1:8). None of the SAD participants was confirmed positive for NAbs.

-In the **MAD** portion of the study, 4 of 12 participants (33%) following qw dosing of either 15 or 30 mg/kg nipocalimab were positive for antibodies to nipocalimab, with low titers (highest titer was 1:128). The 4 ADA-positive participants (all in the 15 mg/kg dose group) were confirmed positive for NAbs.

While ADA and NAbs were detectable in some SAD and MAD participants, no determination of the effect of ADA or NAbs on nipocalimab PK could be made as antibodies to nipocalimab developed after PK had decreased below the level of quantification (ie, <0.15 µg/mL).

2. Study MOM-M281-007

In this placebo-controlled study of various infusion rates (Study MOM-M281-007), 8 participants in each of 5 cohorts were randomized to receive nipocalimab and placebo in a 3:1 ratio.

2.1. PK

-Different infusion rates (ie, 0.5 mg/kg/min to 4 mg/kg/min) were evaluated in healthy participants following a single IV administration of 30 mg/kg (given over 7.5-minute to 60-minute infusions). Mean serum nipocalimab concentration-time profiles were similar following all nipocalimab 30 mg/kg doses regardless of the infusion rates. Following a 60 mg/kg infusion given over 15 minutes, mean nipocalimab concentrations through Hour 168 (Week 1) were approximately 2 times higher than those observed following the 30 mg/kg infusions.

-Geometric mean C_{max} and AUCs of nipocalimab were overall similar when nipocalimab was administered at 30 mg/kg regardless of infusion rate. At slower infusion rates (30- and 60-minute infusions), C_{max} was reached approximately at the EOI, whereas at faster infusion rates (7.5- and 15-minute infusions), median C_{max} was reached approximately 1 hour after the EOI for the 7.5-minute infusion and approximately 11 minutes after the EOI for the 15-minute infusion. Mean $t_{1/2}$ values (ranging from 49.3 to 58.0 hours) were similar in all 30 mg/kg treatment groups. Following the 60 mg/kg (15-minute) infusion, geometric mean overall nipocalimab exposure, as

measured by AUCs, was 2.4 to 2.8 times higher, and mean maximum exposure, as measured by C_{max}, was 2.0 to 2.2 times higher than the exposures observed following 30 mg/kg infusions. Median time to maximum serum concentration was approximately at the EOI and mean $t_{1/2}$ was similar to that of the 30 mg/kg treatment groups.

2.2. Efficacy/PD

-Individual serum IgG values ranged from 1,020 to 1,640 mg/dL at screening among participants in all cohorts. Mean IgG was below reference range (768 to 1,632 mg/dL) among all active treatment cohorts on Days 8 and 15, with mean values ranging from 271.5 mg/dL (Day 15 following 60 mg/kg [15-minute]) to 496.5 mg/dL (Day 8, 30 mg/kg [30-minute]). On Day 29, mean IgG was within the normal range except for the 30 mg/kg (30-minute), 30 mg/kg (7.5-minute), and 60 mg/kg (15-minute) cohorts. In comparison, mean serum IgG values following

placebo administration were relatively stable over time and remained within normal range.

The greatest mean percent reduction from baseline was 79.0% for nipocalimab g/kg (15-minute) on Day 15.

2.3. Safety and tolerability

2.3.1. TEAEs

A total of 12 (40%) participants experienced TEAEs following nipocalimab overall and 1 (10%) participant experienced TEAEs following placebo. Of the participants who received active treatment, there were 3 (50%) participants each with at least 1 TEAE following nipocalimab 30 mg/kg (60-minute infusion), 30 mg/kg (7.5-minute infusion), and 60 mg/kg (15-minute infusion), 2 (33%) participants with at least 1 TEAE following

30 mg/kg (15-minute infusion), and 1 (17%) participant with at least 1 TEAE following 30 mg/kg (30-minute infusion). The most commonly reported TEAE was headache, reported by 6 (20%) participants in the active treatment groups and 1 (10%) participant receiving placebo. Nausea was reported by 3 (10%) participants receiving active treatment. All AEs were mild (grade 1) or moderate (grade 2) severity.

An apparent relationship was observed between rate of infusion and number of AEs, with participants receiving 30 mg/kg nipocalimab at faster infusion rates (infusion duration of 7.5 minutes, 4 mg/kg/minute), and 60 mg/kg administered over 15 minutes (4 mg/kg/minute) reporting more AEs than at slower infusion rates.

2.3.2. Deaths, SAEs

There were no deaths, SAEs, or participant discontinuations due to AEs in this study.

2.3.3. Laboratory evaluation

Creatine kinase excursions greater than 2 times above the upper limit of the normal range (reference: 34 to 329 IU/L) were observed at a single time point in 3 participants in different infusion rate and dose groups. There was no clear relationship with infusion time, rate or dose and all individual CK elevations were deemed not clinically significant and unrelated.

2.4. Immunogenicity

Eight out of 30 participants (8/30, 26.7%) following a single IV infusion of nipocalimab were confirmed positive for antibodies to nipocalimab at Day 29. Among these 8 participants, 2 were confirmed positive for NAbs.

There was no correlation between the nipocalimab dose level or infusion rate and the proportion of participants with confirmed positive ADA detection.

3. Study MOM-M281-008

This was an open-label, single-dose, parallel, three-treatment arms, drug interaction study in 24 healthy adult participants, with the primary objective to determine the effect of nipocalimab coadministration (30 mg/kg nipocalimab IV on Day 1) or offset-administration (30 mg/kg nipocalimab IV on Day 15) on fremanezumab PK. Participants (n=24) were randomized into 1 of 3 treatment arms, in a total of 8 participants per treatment arm. All participants received 225 mg fremanezumab SC on Day 1; participants in Treatment B received 30 mg/kg nipocalimab IV on Day 1; and participants in Treatment C received 30 mg/kg nipocalimab IV on Day 15.

3.1. PK

The DDI observed in this Study MOM-M281-008 was consistent with nipocalimab mechanism of action, and confirmed the hypothesis that nipocalimab could reduce the PK of IgG-based mAbs via FcRn-mediated

recycling. Of note, PK profiles and parameters of nipocalimab (30 mg/kg IV dose) in this study seemed consistent and comparable with historical data of Study MOM-M281-001.

3.2. Efficacy/PD

Following coadministration of fremanezumab and nipocalimab on Day 1, lowest percent of baseline values of serum IgG ranged from 24.81% to 42.14% (Days 8 and 22), returning to 93.75% of baseline by Day 120. Following administration of fremanezumab on Day 1 with offset-administration of nipocalimab on Day 15, lowest percent of baseline values of serum IgG ranged from 25.27% to 48.84% (Days 20 and 36), returning to 93.28% of baseline by Day 120. Ratios of serum IgG for Day 15/Baseline and Day 29/Day 15 were similar following fremanezumab alone, and were low following coadministration of fremanezumab and nipocalimab on Day 1 (Day 15/Baseline), and administration of fremanezumab on Day 1 with offset-administration of nipocalimab on Day 15
(Day 29/Day 15). There were no remarkable trends noted in serum albumin levels and percent of baseline values following any of the treatments.

3.3. Safety and tolerability

There were no deaths or SAEs, and no participants discontinued due to AEs during this study. There were no documented injection site or infusion reactions following administration of study treatments. Overall, a total of 21 TEAEs were reported by 9 (38%) participants, with 2 (25%) participants each reporting AEs following fremanezumab alone (Treatment A) and coadministration of fremanezumab and nipocalimab on Day 1 (Treatment B). Following Treatment C, 4 (50%) participants reported AEs after fremanezumab alone prior to nipocalimab
administration on Day 15 (Treatment C1), and 3 (43%) participants reported AEs following administration of fremanezumab on Day 1 with offset-administration of nipocalimab on Day 15 (Treatment C2). Headache was the most frequently reported TEAE, occurring in 5 (21%) participants. All TEAEs were mild in severity, with the exception of 1 headache AE in 1 participant following fremanezumab alone (Treatment C1) that was moderate in severity.
There were no AESIs in this study. Despite the effects of study treatment on IgG antibodies, there were no trends observed in participants infections during this study. There were no AEs related to vital signs or ECGs during this study and no remarkable trends noted in the clinical laboratory, physical examinations, vital signs, or ECG parameters.

3.4. Immunogenicity

With coadministration of 225 mg fremanezumab SC on Day 1 with 30 mg/kg nipocalimab IV, only 1 of 8 participants (13%) was confirmed positive for antibodies to nipocalimab (titer of 1:240) at the postdose

sample (Day 29). No participants were confirmed positive for antibodies to nipocalimab with staggered administration of 225 mg fremanezumab SC on Day 1 and 30 mg/kg nipocalimab IV on Day 15. Due to the limited observations no meaningful interpretation of nipocalimab immunogenicity could be made.

4. Study MOM-M281-010

This is a placebo-controlled, single-dose, dose-escalating study in healthy participants of Japanese descent, 24 participants were enrolled and completed the study.

4.1. PK

The PK of nipocalimab has been evaluated in Japanese healthy participants following a single IV administration of nipocalimab 10, 30, or 60 mg/kg. Similar to single-dose PK observed in FIH, serum nipocalimab concentrations appeared to decline rapidly at serum concentrations <10 µg/mL in the Japanese healthy participants.

Overall, the PK data are considered comparable beteen Japanese and non-Japanese healthy participants when comparing data from this study (MOM-M281-010; Japanese participants) and those from the FIH study (MOM-281-001; mostly Caucasian participants).

4.2. Efficacy/PD

Slight decreases from baseline in albumin values were shown in Japanese participants in this study, consistent with the observations in non-Japanese participants (MOM-M281-001). No participant had a serum albumin value below the LLN (3.5 g/dL) at any time during the study.

4.3. Safety and tolerability

TEAEs were reported for 3 (17%) participants who received a single IV dose of nipocalimab 30 or 60 mg/kg, and none were reported for participants who received IV nipocalimab 10 mg/kg or placebo. Dizziness was the most common TEAE and was reported for 2 participants who received nipocalimab. There was no apparent relationship between the proportion of participants reporting TEAEs and the nipocalimab dose administered. One participant in the nipocalimab 30 mg/kg group did not receive the full dose of nipocalimab because of a moderate infusion-related reaction; the infusion was discontinued, the event resolved after anti-histaminic administration, and the event was considered by the investigator as related to nipocalimab. All TEAEs were mild or moderate.

4.4. Immunogenicity

One out of 18 participants (1/18, 6%) had confirmed positive for antibodies to nipocalimab on Day 15 following the single IV nipocalimab infusion; this participant received a single 60 mg/kg dose and was subsequently confirmed negative for the NAb assay.

****Studies on** generalized myasthenia gravis **patients****

5. Study MOM-M281-004

Study MOM-M281-004 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, efficacy, PK, PD, and immunogenicity of nipocalimab compared with placebo when administered by IV infusion to participants with gMG. Participants were randomized into 1 of 5 treatment groups (nipocalimab 5 mg/kg q4w, 60 mg/kg single dose, or placebo q2w) and received a total of 5 infusions ver an 8-week treatment period. as enrollment had been fully completed and the study was nearing completion, further dosing with nipocalimab was stopped in the spring of 2020 due to the COVID-19 pandemic out of concern that the act of attending in-person study visits could potentially expose participants to the virus. As a consequence, 7 participants did not receive their last planned dose at the Day 57 visit. Participant follow-up visits for data collection continued either remotely or in person until study conduct was completed.

5.1. PK

The PK profiles of nipocalimab in participants with gMG were generally consistent with those in healthy participants in Phase 1 studies. Mean or median C_{eoi} were approximately dose proportional across the dose regimens tested and were generally consistent with maximum concentrations in healthy participants following similar doses in Phase 1 studies. Mean or median pre-infusion serum nipocalimab concentrations 2 weeks after the infusion (ie, C_{trough} for q2w dosing) were not dose proportional, demonstrating nonlinear PK of nipocalimab. Median C_{trough} were BLQ all below or equal to the LLOQ of the assay (≤0.01µg/mL) for the 5 mg/kg q4w and 30 mg/kgq4w dose groups. However, median C_{trough} ranged from 6.08 to 34.60 µg/mL for q2w group. No accumulations in serum nipocalimab concentrations over time were observed across all nipocalimab treatment groups based on mean or median C_{trough} and C_{eoi} values.

5.2. PD

Consistent with its mechanism of action, nipocalimab produced dose-dependent, reversible decreases in mean total IgG value. Rapid onset of IgG reduction was observed as early as 1 week after the first dose at all dose levels studied and ranged from 30% to 70% of baseline at Week 1. The mean IgG reductions over time were dose level and dosing frequency dependent. The highest dose, which was expected to saturate the FcRn target for the full dosing interval (thereby minimizing total serum IgG concentration), provided a sustained and maximum (approximately 80%) reduction in mean total serum IgG. The lowest dose of 5 mg/kg q4w showed separation in IgG lowering from placebo at most of the trough time points.

The q2w dosing regimen provided a sustained reduction in mean serum IgG, while the q4w dosing regimen provided variable reduction in mean serum IgG levels, with nadir approximately 2 weeks after nipocalimab administration and peak approximately 4 weeks after administration.

Similar results for albumin were observed to those seen in healthy participants with dose-related, self-limiting reductions. Maximum albumin reduction was observed with the administration of 60 mg/kg nipocalimab q2w, which was 81% of baseline on Day 57. Mean albumin values remained within normal limits in all groups at all time points.

5.3. Efficacy

the primary efficacy endpoint was the change from baseline to Day 57 in the total score on the MG-ADL. Administration of study drug reduced MG-ADL scores over time in all treatment groups, including placebo. Importantly, at the primary efficacy time point (before the last dose on Day 57), the greatest and most consistent reductions were observed in participants in the nipocalimab treatment groups (LS mean change from baseline: -3.7 for both 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 groups). Single-dose administration of nipocalimab 60 mg/kg also produced large reductions in MG-ADL scores through Day 29 (Week 4; mean change from baseline: -3.9), but scores increased thereafter (mean change from baseline at Day 57: -1.5) in apparent concert with recovery of IgG concentrations, indicating that the clinically relevant effect of a single dose may not extend beyond 1 month. Statistically significant linear trends were observed for the change from baseline in MG-ADL at Day 57 ($p=0.0310$) as well as the rank of the change from baseline at Day 57 ($p=0.0042$) for the placebo, 5 mg/kg q4w groups.

Consistent with these findings, the percentage of participants achieving clinically meaningful (decrease from baseline of ≥2 points) and durable (≥4 consecutive weeks) response on the MG-ADL through Day 57 was consistently greater in the nipocalimab groups than in the placebo-treated group, with statistically significant differences between placebo and nipocalimab observed at nipocalimab doses of 60 mg/kg (administered as a single dose or q2w). In addition, the percentage of participants with rapid onset of a clinically meaningful and durable response, ie, onset within the first 17 days of dosing, was consistently greater in the nipocalimab groups than in the placebo-treated group.

5.3.1. Relationship of IgG Lowering and MG-ADL Change From baseline

The study included a secondary endpoint to understand the relationship of IgG lowering and MG-ADL change from baseline over time via a pharmacometrics model (MNTA-2020-001-MODELS). While the study was not powered based on the modeling endpoint, the intent of that endpoint was to describe the efficacy of nipocalimab on MG-ADL over time, through the full range of IgG lowering, and with varying

dosing frequencies tested to support Phase 3 dose selection with both dose amount and frequency. The model was developed using all data from completed studies on nipocalimab dosing and IgG lowering, the latter of which has been similar across healthy participant studies and the Phase 2 study in gMG participants. The model includes covariates of body weight, implicitly baseline IgG, and baseline MG-ADL. Additional covariates including race were visually examined and were not found to have an apparent effect.The model estimates the efficacy of the tested nipocalimab doses against placebo to adjust for placebo effects over the course of treatment. Consistent with the raw data, the model predicts that clinically meaningful changes in MG-ADL are obtained at dose levels of nipocalimab ≥30 mg/kg. The model also predicts that an improved and sustained efficacy is obtained when nipocalimab is administered q2w as opposed to q4w.

5.4. Safety and tolerability

The overall incidence of TEAEs was similar between the combined nipocalimab group (83.3%) and the placebo (78.6%) group. No apparent relationship between nipocalimab dose level/regimen was observed across the 4 nipocalimab groups in the overall incidence of TEAEs or for any individually reported preferred term. The most common TEAEs by preferred term in the combined nipocalimab group included diarrhea, headache, and nasopharyngitis (occurring in 6 [11.1%] participants each), rash (in 4 [7.4%] participants), and back pain, dizziness, hypertension, musculoskeletal pain, and oedema peripheral (in 3 [5.6%] participants each). In the
placebo group, all TEAEs occurred as single incidences (7.1%), except for the TEAEs of MG orsening which occurred in 2 participants (14.3%).

5.4.1. Laboratory evaluation

-Asymptomatic, dose-dependent, reversible elevations in non-fasting mean total cholesterol and LDLc were observed. Elevations in HDL were also observed: The maximum mean percent change from baseline was 7.0% in the 5 mg/kg q4w group (Day 43, n=14); and 23.3% in the 60 mg/kg single dose group (Day 15, n=12).

-Thyroid laboratory evaluations included values and changes from baseline for triiodothyronine, free (T3); thyroxine, free (T4); and thyrotropin (TSH). Larger and more consistent decreases were observed in the median change from baseline for T3 levels compared to placebo and other nipocalimab doses. Consistent increases in median change from baseline TSH levels were observed compared to placebo Minimal to no changes were observed in median change from baseline T4 levels.

5.5. Immunogenicity

Five (20%) of the 25 participants who were positive for antibodies to nipocalimab had antibodies that were able to neutralize the bioactivity of nipocalimab in vitro. The presence of antibodies to nipocalimab did not

impact the PK or PD (ie, IgG lowering) of nipocalimab based on comparisons of median serum nipocalimab concentrations or median serum IgG concentrations over time between participants who were positive for antibodies to nipocalimab and participants who were negative for antibodies to nipocalimab. The development of antibodies to nipocalimab did not appear to be associated with a reduced clinical efficacy of nipocalimab, or the occurrence of infusion-site reactions.

6. Phase 2 Study MOM-M281-005

Study MOM-M281-005 was a Phase 2 OLE study of MOM-M281-004 designed to collect long-term safety, efficacy, PD, and immunogenicity data on nipocalimab in participants with gMG. Participants initially received nipocalimab by IV infusion. After at least 8 weeks of treatment on a stable dose of nipocalimab, the dose and/or dosing frequency of nipocalimab could be individually adjusted for a given participant 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 individually adjusted dose could not exceed 60 mg/kg and the dosing frequency could not exceed q2w. Study MOM-M281-005 was paused due to the COVID-19 pandemic. A decision was subsequently taken to close this study and add an OLE arm to the gMG Phase 3 study (MOM-M281-011).

6.1. Efficacy

Myasthenia gravis efficacy measures, including MG-ADL change from baseline, QMG change from baseline, and MG-QoL-15r change from baseline, overall showed a gradual improvement over time following dosing with nipocalimab. Mean change from baseline for MG-ADL 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. 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. For MG-QoL-15r scores, the mean change from
baseline in score values was -1.6, -1.6, -2.9, -3.7, and -0.2 for Weeks 4, 8, 12, end of treatment, and follow-up, respectively.

6.2. Safety and tolerability

Twenty-two participants (59.5%) reported 1 or more TEAEs and the most commonly reported AEs (≥10% participants) were blood IgG decreased (5 participants [13.5%]) and edema peripheral (4 participants [10.8%]). None of the participants who experienced TEAEs of peripheral edema had abnormal serum albumin. Notably, only 2 participants (5.4%) reported mild headaches. Twelve (32.4%) participants in the All Nipocalimab group reported AEs that were related to the study drug.

6.2.1. Deaths/SAEs

-One AE (grade 4 gliosarcoma) leading to death was reported in this study, which was considered a SUSAR and assessed by the Investigator to be related to nipocalimab. Based on PK, the nipocalimab mechanism of action, and the timing of event onset relative to drug exposure, the sponsor assessed the event as not related to nipocalimab.

-Overall, 5 participants (13.5%) experienced SAEs (1 in the Placebo-Nipocalimab group; 4 in the Nipocalimab-Nipocalimab group), with only 1 of the SAEs assessed as treatment-related in the Nipocalimab-Nipocalimab group. Two participants (5.4%) in the All Nipocalimab group reported 1 or more AESIs: 1 participant had PTs COVID-19 pneumonia and hepatic enzyme increased and 1 participant had Coronavirus infection. There were no reports of TEAEs leading to discontinuation of the study treatment/drug.

6.2.2. Laboratory evaluation

-Asymptomatic, reversible elevations in non-fasting mean total cholesterol up to 14.77% were observed at timepoints with values for at least 10 participants. Twenty-eight (77.8%) of the 36 participants had cholesterol values above the ULN (5.18 mmol/L) at some time point post-baseline, including 17 of 23 participants who were within the normal limits at baseline. Individual participant profiles of cholesterol for all 37 participants showed that elevations in

-Cholesterol outside the reference range were transient and returned within reference values.Based on the mechanism of action of nipocalimab, a decrease in albumin can be observed following treatment. Two (5.6%) of 36 participants with at least 1 post-baseline value had a shift from within normal limits at baseline to below the LLN (35 g/L) at a post-baseline visit however, albumin values remained ≥20 g/L for all participants.

6.3. Immunogenicity

The incidence of antibodies to nipocalimab tested with the new sensitive and drug-tolerant ECLIA method through the end of the study was 14.3% (n=5/35). . Peak titers of antibodies to nipocalimab were generally low (4 of 5 had peak titer levels ≤1:40). One (20.0%) of the 5 ADA-positive participants was positive for NAb to nipocalimab. When comparing the peak titers in this study with those in Study MOM-M281-004, only 2 participants newly developed antibodies to nipocalimab with a peak titer of 1:10 and 1:1,280, respectively, in this study. None of the participants who were positive for ADA to nipocalimab experienced any infusion-site reactions during the MOM-M281-005 study period

****Studies on Rheumatoid Arthritis patients****

7. Phase 2a Study 80202135ARA2001

3.1. PK

Trough PK samples after q2w dosing were below LLOQ as nipocalimab exhibits nonlinear PK and accelerated clearance due to its mechanism of action. Median post-dose serum nipocalimab concentrations after 15 mg/kg nipocalimab IV q2w ranged from 411 to 426 µg/mL across Weeks 0, 2 and 8. Overall, the range of concentrations across the CRP categories substantially overlapped and was generally similar (Week 0 postdose) but was unevaluable at later time points due to low participant numbers. Median postdose serum nipocalimab concentrations were similar across age categories (<65, ≥65) and body-weight quartiles.
The median postdose nipocalimab concentrations were comparable in participants receiving methotrexate only or leflunomide at baseline

3.2. PD/efficacy

Study 80202135ARA2001 was a Phase 2a, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of nipocalimab in participants with active RA despite standard therapy.

-At Week 12, participants in the nipocalimab group achieved a numerically greater mean (SD) change from baseline in DAS28 (CRP) score (-1.17 [1.344]) compared with participants in the placebo group (-0.62 [0.964]); the LS mean difference between nipocalimab and placebo groups was -0.45 (95% CI: -1.17; 0.28; p=0.224). (nipocalimab)

- At Week 12, a numerically higher proportion of participants in the nipocalimab group achieved ACR20(15 [45.5%]), ACR50 (5 [15.2%]), ACR70 (4 [12.1%]), and ACR90 (2 [6.1%]) responses compared with participants in the placebo group (4 [20.0%], 1 [5.0%], 0, 0, respectively). The treatment difference between the nipocalimab group and the placebo group based on the main composite estimand was 27.0% (95% CI: 3.2%; 50.9%) (nominal p=0.055) for ACR20, 8.6% (95% CI: -6.7%; 23.8%) (nominal p=0.390) for ACR50, 11.6% (95% CI: 0.9%; 22.3%) (nominal p=0.285) for ACR70, and 5.8% (95% CI: -2.0%; 13.6%) (nominal p=0.521) for ACR90.

-At Week 12, a numerically higher proportion of participants in the nipocalimab group achieved DAS28 (CRP) remission (7 [21.2%]) compared with participants in the placebo group (2 [10.0%]). The treatment difference between the nipocalimab group and the placebo group based on the main composite estimand was 9.9% (95% CI: -9.5%; 29.3%) (nominal p=0.456). A numerically higher proportion of participants in the nipocalimab group achieved DAS28 (CRP) LDA (7 [21.2%]) compared with participants in the placebo group (2 [10.0%]); nominal p=0.456).

- At Week 12, participants in the nipocalimab group had a numerically greater mean (SD) improvement from baseline in HAQ-DI score (-0.27 [0.550]) compared with participants in the placebo group (-0.11 [0.363]). The LS mean difference was -0.22 (95% CI: -0.49; 0.05; nominal p=0.108).

-Nipocalimab treatment exerted PD effects consistent with its mechanism of action, including reduction in total IgG and IgG subclasses, anti-CCP2 IgG autoantibody and total circulating immune complexes. Through Week 12, the placebo group-maintained IgG levels from baseline, whereas decreases from baseline were observed in the nipocalimab group. The median percent change from baseline in total IgG at Week 12 was 2.40% for the placebo group and -53.94% for the nipocalimab group. Changes for all IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were similar to the changes observed for total IgG values. Both treatment groups maintained the IgA, IgE, and IgM levels from baseline

3.3 Safety and Tolerability

3.3.1 TEAEs

-The number and proportion of participants who experienced 1 or more TEAEs were 27 (81.8%) and 12 (60.0%) in the nipocalimab group and the placebo group, respectively. Through Week 18/Final safety follow-up, SAEs were reported for 3 (9.1%) participants in the nipocalimab group and 0 participants in the placebo group. The reported PTs were deep vein thrombosis, infusion related reaction , and burn infection (Table 16). A greater percentage of participants discontinued study intervention due to AEs through Week 18 in the placebo group (30.0%) compared with the nipocalimab group (18.2%)

3.3.2 SAEs and Deaths

-There were no deaths and no AEs of opportunistic infections, anaphylactic reactions, MACE, or malignancies. An AESI of severe burn infection was reported for 1 participant in the nipocalimab group during the study.

3.4 laboratory evaluations

Laboratory Evaluations There were no clinically meaningful effects of nipocalimab on hematology, chemistry, lipid, coagulation, or urinalysis laboratory evaluations.

Mean values of percent change from baseline in triglycerides were numerically higher in the nipocalimab group compared with the placebo group at Week 12 (23.44% in the nipocalimab group and 16.95% in the placebo) and Week 18 (20.31% in the nipocalimab group and -4.04% in the placebo). No treatment-related cardiovascular AEs were reported in participants with increased triglycerides

3.5 immunogenicity

overall incidence of antibodies to nipocalimab through Week 18 was 63.6% (21/33). The titers of anti-drug antibodies were generally low (all of the participants had peak titers<1:1,000 with the exception of one participant having a peak titer of 1:2,560). Seven of these 21 ADA-positive participants were positive for neutralizing antibodies (21.2%). Predose trough serum nipocalimab. concentrations were below LLOQ as

expected based on the nonlinear PK of nipocalimab which precluded evaluating the impact of ADA on nipocalimab concentrations.

8. Phase 2/3 Study 80202135MYG2001 Study

-Study 80202135MYG2001 is an ongoing Phase 2/3, multicenter, open-label, uncontrolled, interventional study to evaluate the PK, PD, safety, and activity of IV nipocalimab, administered in addition to protocol-allowed, stable, standard-of-care therapy for the treatment of gMG in pediatric participants (from 2 to <18 years of age). The study population will be comprised of boys and girls who have had a diagnosis of gMG, who have an insufficient clinical response to ongoing, stable standard-of-care 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 will have a positive serologic test for a gMG-related pathogenic autoantibody (anti-AChR and/or anti-MuSK).

-The study consists of a screening period (up to 4 weeks), a 24-week active treatment phase, and a long-term extension phase that will be of variable duration per participating country/territory. The active treatment phase is comprised of 2 cohorts. Cohort 1 (at least n=6) will include adolescent gMG participants aged 12 to <18 years of age receiving IV nipocalimab (30 mg/kg for first infusion, 15 mg/kg thereafter) q2w. After the active treatment phase is completed for Cohort 1, Cohort 2 (participant children with gMG aged 2 to <12 years of age; at least n=6) will be enrolled and receive nipocalimab for 24 weeks. Dosing for Cohort 2 will be modeled based on all extant PK and PD data available (including adult data from Phase 1 to Phase 3 studies and adolescent data from Cohort 1 of this study) at the time of the interim analysis. After completion of the active treatment phase, all participants from both cohorts will have the option to enroll in a long-term extension phase.

8.1. Efficacy

Efficacy results are not yet available

9. Phase 3 Study MOM-M281-011

Study MOM-M281-011 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-c
ontrolled study to evaluate the safety, efficacy, PK, and PD of nipocalimab administered to adults with gMG who are inadequately controlled with standard-of-care therapy or discontinued standard-of-care therapy due to intolerance or lack of efficacy. Enrolled participants will be randomly assigned in a 1:1 ratio to receive either placebo or nipocalimab (30 mg/kg for first IV infusion, 15 mg/kg thereafter) q2w for 24 weeks. Participants who complete the double-blind placebo-controlled phase of the study or participants impacted by the study hold and subsequent termination of the Study MOM-M281-005 have the option to receive open-label treatment of nipocalimab to evaluate long-term safety and efficacy of

nipocalimab.

9.1. Efficacy

Efficacy results are not yet available.

9.2. Safety and tolerability

-A total of 21 participants in the double-blind period and 11 participants in the OLE , had 1 or more treatment-emergent SAEs reported

-Three of the treatment-emergent SAEs were also AESIs and were assessed as 'related' to the study drug. by the investigators, meeting SUSAR reporting criteria. These SUSARs include Ramsay-Hunt syndrome left side and appendicitis in the double-blind phase and left lower lobe pneumonia in the OLE phase. Sponsor/Company causality assessments based on mechanism of action, temporal relationship, and the participant's other possible past medical history as well as concomitant medications used were 'not related' for the Ramsay-Hunt syndrome, left lower lobe pneumonia and 'related' for the event of appendicitis

9.2.1.Deaths

- Overall, from both phases of the study, 4 deaths have occurred : myocardial infarction, cardiac arrest, respiratory failure, and cardio-respiratory arrest. All these fatal events were assessed as not related to the study drug. by both the investigator and the sponsor. There were 14 AESIs reported in 11 participants across the double-blind and OLE phases of study, of which 12 events were also SAEs.

**** Studies on hemolytic disease of the fetus and newborn (HDFN) patients****

10.Phase 2 Study MOM-M281-003

Study MOM-M281-003 is a single arm Phase 2, multicenter, open-label study to evaluate the safety, efficacy, PD and PK of nipocalimab in pregnant women at high risk for EOS-HDFN. Enrolled participants receive qw IV infusions of nipocalimab at a dose of 30 mg/kg and/or 45 mg/kg starting at GA Week 14 (±6 days), which is prior to the earliest time at which placental transport of maternal IgG reaches a level generally associated with risk of fetal anemia, through GA Week 35.

10.1. Efficacy

Finalized efficacy results are not yet available.

10.2. Laboratory evaluation

-Available shows increases in total cholesterol higher than published reference values during pregnancy for the respective trimesters in some participants at some time points.

-There were ,AEs of hypercholesterolemia, hyperlipidemia, or hypertriglyceridemia reported and no MACE. Overall, asymptomatic elevations in total cholesterol, LDL cholesterol, and triglycerides were observed that trended toward baseline values postpartum. None of the participants required concomitant medication for

treatment of elevated cholesterol. It was recommended per protocol that investigators monitor and take appropriate actions for dyslipidemia during pregnancy as per local health guidelines. One participant had cholesterol values meeting the criteria for additional investigator monitoring; the participant had cholesterol values >10.34 mmol/L at GA weeks 26-36 (fasting measurements at GA weeks 26 and 30) and was advised to implement dietary modifications.

- Interpretation of treatment-emergent elevations in total cholesterol, LDL cholesterol, triglycerides is confounded by pregnancy-related increases in total cholesterol and triglycerides with increasing GA. Of the participants who discontinued study treatment prematurely, none were due to elevation in lipids.

10.3. Safety and tolerability

10.3.1. Maternal safety

-Two participants had SAEs of fetal anemia that required IUT (considered not related to study drug by the investigator). One participant received nipocalimab 30 mg/kg weekly based on her baseline weight; the other received nipocalimab 45 mg/kg weekly, based on her weight measured every other week.

-One participant (30 mg/kg dose) had SAEs of subchorionic hematoma (suspected Breus mole on ultrasound considered by the investigator as probably related to study drug), and of fetal growth restriction, abnormal Doppler ultrasound, and subsequent fetal heart rate decelerations, which were considered by the investigator as possibly related to study drug and study drug was withdrawn because of the fetal growth restriction and subchronic hematoma . The neonate was delivered at 29 weeks GA by C- section due to the fetal heart rate decelerations, treated in the neonatal intensive care unit for anemia, hyperbilirubinemia, hyponatremia, respiratory distress syndrome, retinopathy of prematurity and small for gestational age, all of which recovered except small for gestational age.

-One participant (45 mg/kg dose) had an SAE of placental abruption which was considered by the investigator as possibly related to study drug. At 34 Weeks GA,the participant developed polyhydramnios and was subsequently hospitalized for induction of labor. Amniotomy and induction of labor were followed by placental abruption and C-section.The baby was born at 37 weeks GA and was healthy.

-One participant (45 mg/kg; weight-adjusted dose for last 2 doses) had SAEs of fetal demise and manual removal of placenta (both considered not related to study drug by the investigator). She underwent an IUT for fetal anemia at 22 weeks. It was determined that the transfusion went into the wall of the umbilical cord (rather than the lumen) and caused anumbilical vein tamponade resulting in a terminal fetal bradycardia and fetal demise. The participant experienced retained placenta and under went manual removal. The event of fetal death was protocol-procedure related (complication of the IUT).

10.3.2. Infant safety

Serious Adverse Events

- A total of 6 (50.0%) liveborn neonates/infants had 1 or more SAEs. Preferred terms of SAEs were anemia neonatal, jaundice, upper respiratory tract infection, and neonatal respiratory distress syndrome in 2 neonates each, and hyperbilirubinaemia neonatal in 1 neonate. Serious adverse events in neonates were considered by the investigator to be related to maternal exposure to nipocalimab in 2 (16.7%) neonates: hyperbilirubinaemia neonatal and neonatal respiratory distress syndrome. Hyperbilirubinemia neonatal had missing data for attribution and was considered related per the statistical analysis plan. Both neonates with SAEs of respiratory distress syndrome were delivered pre-term at GA. Week 29 2/7 and Week 33 1/7. Anemia neonatal, jaundice, and hyperbilirubinemia neonatal are consistent with symptoms of the underlying disease of HDFN

-Overall, in neonates/infants with maternal nipocalimab exposure, no unusual or unexpected childhood illnesses (per investigator judgement) were reported. Infections reported in neonates/infants were generally those that are commonly seen during the usual neonatal period through infancy. Infant follow-up is ongoing.

Low serum IgG

-Low serum concentration of IgG in infants at birth is expected due to nipocalimab's blockade of placental IgG transfer. Overall, 9/10 neonates had IgG values at birth that were below the normal range and the extent of low birth IgG values was associated with the proximity of nipocalimab treatment to delivery. All neonates were observed to follow the normal trend for physiological nadir between 4 and 24 weeks, and the 2 neonates with values at 48 or 96 weeks showed increases from nadir (one above and one just below the LLN for their age). Starting at the Week 4 study visit, a majority of infants had IgG values in the normal range (7 of 10 neonates at Week 4; 7 of 8 infants at Week 24; 1 of 2 infants at Week 48; and 1 of 1 at Week 96)

-A relationship between nipocalimab and low infant serum IgG concentrations at 6 months and beyond cannot be excluded. The contribution of the infant's underlying disease condition or disease treatments to the low infant serum IgG levels is also unknown. However, there is no known mechanistic relationship between nipocalimab and the observed low serum IgG at 6 months and 1 year following birth.

** Studies on Warm Autoimmune Hemolytic Anemia patients**

11. Phase 2/3 Study MOM-M281-006

Study MOM-M281-006 is an ongoing adaptive Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study in participants with wAIHA to evaluate the efficacy, safety, tolerability, PK, and PD of nipocalimab compared with placebo, followed by an OLE period. In the double-blind period, participants are randomized to 1 of 3 treatment groups (placebo IV infusion q2w, 30 mg/kg nipocalimab IV infusion q4w, or 15 mg/kg nipocalimab IV infusion q2w). Upon completion of or early termination from the double-

blind period, participants may enroll in the OLE period if they meet the OLE eligibility criteria to continue treatment with nipocalimab for an additional 144 weeks.

11.1. Efficacy

Efficacy results are not yet available.

11.2. Safety and tolerability

Preliminary data indicate that a total of 7 participants experienced 1 or more treatment-emergent SAEs reported during double-blind period and 7 participants reported 1 or more treatment-emergent SAEs during the OLE phase respectively. The most common SAE was worsening wAIHA. In addition, there were 4 unrelated, serious infections reported: 1 (COVID-19) and 3 (pneumonia, anal abscess, and spontaneous bacterial peritonitis) cases of serious infections were reported in the double-blind period and open-label extension respectively. All of these serious infection events were assessed as Grade 3 infections and were considered as AESIs.

Studies on 1ry Sjögren's Disease patients

12. Phase 2 Study 80202135SJS2001

Study 80202135SJS2001 is an ongoing Phase 2, randomized, placebo-controlled, double-blind, multicenter study to assess the efficacy and safety of nipocalimab in adult participants with active, autoantibody-positive pSD. Enrolled participants will be randomly assigned to 1 of 3 treatment groups (placebo IV q2w [planned n=50], nipocalimab 5 mg/kg IV q2w [planned n=50], nipocalimab q2w [planned n=50]). This is the first study conducted in participants with pSD.

12.1. Efficacy

Efficacy results are not yet available.

12.2. Safety and tolerability

As of the data cutoff date, a total of 5 participants with 1 or more SAEs have been reported in the ongoing Study 80202135SJS2001. including one serious anaphylactic reaction leading to discontinuation of study intervention. The SAEs reported in the remaining 4 participants included acute sinusitis, COVID-19, genital herpes, and anembryonic gestation.

studies on SLE patients

13. Phase 2 Study 80202135SLE2001

Study 80202135SLE2001 is an ongoing Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy of nipocalimab in adult participants with active SLE. A target of approximately 225 participants will be randomly assigned into 3 treatment groups (placebo IV q2w,

nipocalimab 5 mg/kg IV q2w, with a 1:1:1 ratio with approximately 75 participants planned per intervention group.

13.1. Efficacy

Efficacy results are not yet available.

13.2. Safety and tolerability

As of the data cutoff date, 1 or more SAEs were reported in 6 participants in the ongoing study 80202135SLE2001 . There were SUSARs of pyrexia and pneumonia (AER 20221109522 and 20230371622), which were confounded by use of concomitant medications (steroids and methotrexate). In addition, there were SAEs considered not related by the investigator of acute myocardial infarction, deep vein thrombosis, SLE, worsening leukopenia, and pneumonia.

****studies on Idiopathic Inflammatory Myopathy patients****

14.Phase 2 Study 80202135IIM2001

Study 80202135IIM2001 is an ongoing Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose, interventional study to evaluate the efficacy, safety, tolerability, PK, PD, and immunogenicity of nipocalimab in adult participants with active IIM, despite being on standard-of-care treatments. Participants will have to be serologically positive and have clinically active disease while receiving at least 1standard-of-care treatment within at least 6 weeks prior to the first administration of the study intervention. Participants (planned n=200) will be randomly assigned into 1 of 2 treatment groups (nipocalimab q2w or placebo) and will be stratified by MSA (DM, IMNM, ASyS) profile and disease severity. JNJ-80202135 (nipocalimab) Investigator's Brochure - Edition 78 The total duration of this study is up to 112 weeks, consisting of 4 study periods: a ≤6-week screening period), a 52-week double-blind period, a 48-week long-term extension, and a safety follow-up 8 weeks post last administration of study intervention. A 20-week mandatory protocol-defined oral glucocorticoid taper will be applied to both study groups from Week 24 to Week 44, for those participants on oral glucocorticoid (>5 mg/day of prednisone or equivalent) at baseline. At Week 52, participants will be assessed by the investigator for eligibility to continue into the long-term extension.

10.1 Efficacy

Efficacy results are not yet available.

10.2. Safety and tolerability

As of the data cutoff date, no SAEs have been reported in the ongoing Study 80202135IIM2001

****studies on chronic Inflammatory Demyelinating Polyneuropathy patients****

15.Phase 2/3 Study 80202135CDP3001

Study 80202135CDP3001 is an ongoing Phase 2/3, multistage, multicenter, randomized, double-blind, placebo-controlled, parallel-group, withdrawal study to evaluate treatment with nipocalimab in participants diagnosed with active CIDP according to the EAN/PNS 2021 (Van den Bergh 2021) criteria. The study will consist of the following periods: identification of participants with active CIDP (including screening and Run-in); open-label treatment with nipocalimab (Stage A); double-blind, placebo-controlled, randomized withdrawal (Stage B); and an OLE. Participants (planned n=121) will be randomized in 1:1 ratio in the 2 treatment groups (IV nipocalimab thereafter] or placebo in Stage A) before entering Stage B (double-blind placebo-controlled period) of the study. The randomization will be stratified by prior treatment status at study entry, region, and Stage A responder based on adjusted INCAT disability score.

11.1 Efficacy

Efficacy results are not yet available.

11.2. safety and tolerability

Phase 2/3 Study 80202135CDP3001 As of the data cutoff date, 1 participant had 1 SAE(COVID-19) reported during the open-label treatment period .No SAEs have been observed during the double-blind period in the ongoing Study 80202135CDP3001

**** Pregnancy****

Pregnancy Pregnant women are excluded from nipocalimab clinical studies except for the clinical studies conducted during pregnancy. Non-pregnancy study participants must agree to use highly effective methods of contraception and pregnancy tests are conducted throughout the study. Study medication is discontinued in participants who become pregnant during the study. These participants are followed up until delivery or pregnancy termination.

As of 28 April 2023, 2 reports of pregnancy were identified in the ongoing Study 80202135SJS2001:

- A 31-year-old female participant with Sjögren's disease had a positive pregnancy test at the Week4 study visit, 2weeks after having tested negative for pregnancy and having received administration of blinded study drug at the Week 2 study visit (and also at the Week 0 study visit). The participant discontinued study participation and no study drug was administered at the visit when pregnancy was discovered. The pregnancy was later confirmed by ultrasound to be an anembryonic gestation and was terminated. The investigator determined that this event was unrelated to study intervention, and the sponsor and investigator remain blinded to study intervention.

- A 24-year-old female participant with Sjögren's disease had a positive pregnancy test at the Week 2 study visit, 2weeks after having tested negative for pregnancy and having received one blinded administration of study drug at the Week 0 study visit. The participant discontinued study participation and no study drug was administered at the visit when pregnancy was discovered. The participant later elected to terminate the pregnancy due to personal reasons. The sponsor and investigator remain blinded to study intervention.

- **Protocol:** Efficacy and Safety of M281 in Adults with Warm Autoimmune Hemolytic Anemia: A Multicenter, Randomized, Double-blind, Placebo-controlled Study with a Long-term Open-label Extension

- Nipocalimab (also referred to as JNJ-80202135, M281, and N027) is a fully human aglycosylated IgG1 mAb designed to selectively bind, saturate, and block the IgG binding site on endogenous FcRn. It contains human-derived heavy and light chain variable regions and human IgG1 constant regions engineered with no terminal lysines. It also contains a mutation at Asn position 296 to Ala 296 resulting in a non-glycosylated, effector less Fc region that inhibits Fc gamma receptor and complement interaction and, thus, immune effector cell activation.

Phase: III

Objective(s):

Objectives	**Endpoints**
Primary efficacy objective	
Efficacy of Nipocalimab in participants with warm autoimmune hemolytic anemia (wAIHA)	Durable response in improvement in hemoglobin (Hgb) in the double-blind period, without the need of rescue therapy: • Hgb concentration ≥10 g/dL • An increase from baseline in Hgb ≥2 g/dL
Key secondary efficacy objective	
Impact of nipocalimab treatment on fatigue	• Change from baseline in the total score from the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale at the time of durable response • Change from baseline in the total score from the FACIT-Fatigue Scale at the end of the double-blind period (Week 24)
Impact of nipocalimab on corticosteroid use	Percent reduction from baseline in average daily dose of prednisone or equivalent at Week 24 among participants on prednisone or equivalent at baseline
Other secondary efficacy objectives	

Effects of nipocalimab on normalization of hemolytic markers	• Simultaneously attain normal lactate dehydrogenase (LDH), and normal haptoglobin, and normal indirect bilirubin levels after baseline • Attainment of the following at any time during the study: – An increase from baseline in Hgb of 2 g/dL and normal LDH, haptoglobin, and indirect bilirubin levels • Attainment of the above
Effect of nipocalimab on maintaining response in Hgb	The proportion of participants who achieve the durable response in improvement of Hgb during the double-blind period and maintain that response for up to 24 weeks, without the need of rescue therapy
Effects of nipocalimab on normalization of hematologic and hemolytic parameters	• Hgb, reticulocyte count, hemolytic markers, and change from baseline in these parameters at the double-blind period • Hgb, reticulocyte count, hemolytic markers, and change from baseline throughout the study
Effects of nipocalimab on the time to, and the duration of, Hgb response	• Time to response defined as the first time point at which the criteria for the primary efficacy endpoint are met • Duration from the first time point at which the durable response criteria for the primary efficacy endpoint are met until the time point at which it is no longer met
Impact of nipocalimab treatment on fatigue improvement	Change from baseline in the total score, item scores, and impact and experience domains from the FACIT-Fatigue Scale through Week 24 of the double-blind period
Effects of nipocalimab on health-related quality of life and health status	EuroQol 5-dimension, 5-level (EQ-5D-5L) quality of life questionnaire, Medical Outcomes Study Short Form 36- Item health survey (SF-36v2), patient global impression of severity (PGIS), and patient global impression of change (PGIC)
Association between immunoglobulin G (IgG) reduction and Hgb/hemolysis parameters	Hgb range at steady state (estimated using a model-based longitudinal analysis of Hgb/hemolysis parameters in relationship to IgG level and dose regimen)
Impact of nipocalimab on the reduction of corticosteroid dose	• Absolute reduction from baseline in average daily dose of prednisone or equivalent at Week 24 of the double-blind period among all participants

	• The proportion of participants who achieve corticosteroid reduction to ≤7.5 mg/day of oral prednisone (or equivalent) at Week 24 of the double-blind period, among participants with prednisone or equivalent > 7.5 mg/day at baseline
Exploratory objectives	
Occurrence of total anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NAb) in participants with wAIHA	Total ADA and NAb
Pharmacokinetics (PK) and pharmacodynamic (PD) activity of nipocalimab, including total IgG and direct antiglobulin test (DAT)	• Serum concentrations of nipocalimab • Total serum IgG concentrations and DAT
Impact of nipocalimab on the need for rescue therapy	• The change in number of transfusions reported for the 6-month period prior to screening to the number of transfusions required between randomization and the end of the double-blind period • Proportion of participants who received any type of rescue therapy for wAIHA (corticosteroids, transfusion, intravenous immunoglobulin [IVIg])
Effect of nipocalimab on fatigue based on the meaningful change threshold (MCT) of the FACIT-Fatigue Scale	• Proportion of participants who meet the MCT using anchor-based, and distribution-based approaches • Cumulative Distribution curves of change from baseline in FACIT-Fatigue Scale over time
Evaluate nipocalimab treatment satisfaction	TSQM-9 domain scores at the end of the double-blind period
Long-term efficacy of nipocalimab	Secondary efficacy outcome measures listed above, over time, during the OLE, if applicable
Safety objective	
Safety and tolerability (short- and long-term) of nipocalimab in participants with wAIHA	• Incidence and severity of adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation of nipocalimab, and AEs of special interest (AESIs) • Physical examinations, vital signs, safety laboratory tests, and electrocardiograms (ECGs)

Rationale:

This study will enroll adult participants who have active primary or secondary wAIHA, based on clinical and laboratory findings of hemolysis and serologic evidence of IgG autoantibodies to RBCs. Considering the intended effect of nipocalimab on IgG levels and the role of pathogenic autoantibodies in wAIHA, these participants are likely to benefit from treatment with nipocalimab and are likely to represent the target

population. A randomized, double-blind, placebo-controlled, parallel group study design was chosen because it is the most robust study design.
- A placebo comparator arm was chosen for this study as it provides the most valid comparison versus active treatment for the analyses of safety, efficacy, PK, and PD. A placebo arm is warranted because participants in this study are not required to stop their current medications for wAIHA.
-The parallel group design allows recruitment of participants for all treatment arms within the same time frame, thus avoiding the potential problem of imbalance when cohorts are recruited sequentially.
-An open-label extension period was included in this study to enable evaluation of long-term effects of nipocalimab treatment.

Design:

This is a **Phase 2/3** multicenter, randomized, **double-blind**, placebo-controlled study in participants with wAIHA **to evaluate the efficacy, safety, tolerability, PK, and PD** of nipocalimab compared with placebo, **followed by an OLE period**.
-The duration of the double-blind period will be 24 weeks (with end-of-treatment assessments at Week 24/early termination [ET] for all participants, and post-treatment assessments at Week 30 of the double-blind period only for participants not enrolled in the OLE period).At the Week 24/ET visit of the double-blind period, participants may enroll in the OLE period if they meet the OLE eligibility criteria to continue treatment with nipocalimab for an additional 144 weeks (with end-of-treatment assessments at Week 144/ET and post-treatment assessments at 8 weeks after the last infusion in the OLE).
-**In the double-blind period**, approximately 111 eligible participants will be enrolled and randomized 1:1:1 to 1 of 3 treatment groups:

- Group 1 (n=37): Placebo intravenous (IV) infusion
- Group 2 (n=37): 30 mg/kg nipocalimab IV infusion every 4 weeks (Q4W)
- Group 3 (n=37): 15 mg/kg nipocalimab IV infusion Q2W

- A Screening Period of ~2 weeks will precede the double-blind period.
-At randomization, participants will be stratified by 3 factors:

- Concurrent treatment for wAIHA: No treatment or corticosteroids at dose ≤20mg/day of prednisone or equivalent with no immunosuppressants o Immunosuppressants or corticosteroids at dose >20mg/day of prednisone or equivalent
- Primary or secondary wAIHA
- Screening Hgb value (ie, the most recent screening value: ≤8.5 g/dL or >8.5 g/dL).

-During the double-blind period, study drug infusions begin with Baseline (Day 1, Week 0) and continue thereafter for 24 weeks for safety, efficacy, PK, and PD assessments. Study drug will be administered during study visits by IV infusion. No infusion will be given at the Week 1 visit. To maintain the study blind, all participants will receive an IV infusion of nipocalimab or placebo, depending on their assigned study group.
-Participants who meet predefined failure criteria (ie, failure to demonstrate an increase from baseline in Hgb ≥1 g/dL and are symptomatic) at or after Week 16 of the double-blind period, or participants who need

rescue therapy at or after, Week 4 may, at the Investigator's discretion, discontinue double-blinded treatment and may be assessed for eligibility for the OLE period.

- At the Week 24/ET visit of the double-blind period, no blinded study drug will be administered, but study assessments will be conducted. As each participant completes or discontinues from the double-blind period, the Investigator will access the IRT to answer questions regarding participant disposition and participant eligibility for the OLE.

-**The post-treatment follow-up** after Week 24/ET through Week 30 after the end of the double-blind treatment does not apply to participants enrolling in the OLE.

-For participants who are eligible for the **OLE**, the Week 24/ET visit of the double-blind period serves as the first visit (Week 0) of the OLE; participants enrolled in the OLE will received their first open-label infusion of nipocalimab at that visit. The OLE treatment assignment for each participant with nipocalimab doses.

-During the OLE period, the nipocalimab dosing regimen for a given participant may be increased or decreased once based on prespecified criteria. In addition, corticosteroids, and if necessary other concomitant medications, including immunosuppressants, for wAIHA, may be altered during the OLE period as per the Investigator's usual clinical practice.

-At or following Week 144 of the OLE period, the participant may be eligible to enroll in another nipocalimab protocol if available or have the option to continue nipocalimab through other access programs if available per local regulations.

Trial intervention:

The trial interventions (treatments) to be administered during the trial are displayed in the table below:

Group	Product	Route of administration	No. of participants to be treated
1 (Test)	Nipocalimab	IV infusion	Approximately 111 participants are planned
2	Placebo		

Benefit/risk assessment

- **Pregnancy**

-Any pregnancy (including the pregnancy of the partner of a male study participant) occurring from the time the participant signed the ICF until 30 days for female participants or 90 days for the female partner of a male participant after the last dose of study drug must be reported.

-The pregnancy should be followed to determine outcome (including premature termination) and status of mother and child.

-Any participant who becomes pregnant during the study must discontinue from further study drug administration.

-While pregnancy itself is not an AE/SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
-An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly birth defect in a child born to a participant exposed to the study drug should be reported as an SAE.

- ***Recommendation &/ or*** **Questions & Answers: NA**

- **Abbreviation**

AChR: acetylcholine receptor
ACPA: anti-citrullinated protein antibody
ADA: anti-drug antibody
ADR: adverse drug reaction
AE: adverse event
AESI: adverse event of special interest
AIHA: autoimmune hemolytic anemia
Ala: alanine
ALT: alanine aminotransferase
ANOVA: analysis of variance
Asn: asparagine
AST: aspartate aminotransferase
AUC: area under the serum concentration-time curve
AUC0-inf: area under the serum concentration-time curve from time zero to infinity
AUC0-last: area under the serum concentration-time curve from time zero to time of last quantifiable concentration AUC0-xh: area under the serum concentration-time curve from time zero to time
BD: birth day
BLQ: below the limit of quantification
CAIA: collagen antibody-induced arthritis
CHO: Chinese hamster ovary
CK: creatine kinase
Cmax: maximum serum concentration
COVID-19: coronavirus 2019
CTCAE: Common Terminology Criteria for Adverse Events
Ctrough: trough serum concentration
DAT: direct antiglobulin test
EFD: embryo-fetal development
ELISA: enzyme-linked immunosorbent assay

EOI: end of infusion
EOS: early onset severe
ePPND: enhanced pre- and postnatal development
Fab: antigen-binding fragment
Fc: fragment crystallizable region
FCGRT: Fc fragment of IgG receptor transporter
FIH: first-in-human
FMH: feto-maternal hemorrhage
GA: gestational age
GD: gestational day
GLP: Good Laboratory Practiceg
HDFN: hemolytic disease of the fetus and newborn
HLA: human leukocyte antigen
IC: immune complex
IC50: half-maximal inhibitory concentration
IgA: immunoglobulin A
IMP: investigational medicinal product
IV: intravenous
IVIg: intravenous immunoglobulin
KD: dissociation constant
LDA: low disease activity
LDH: lactate dehydrogenase
LDL: low-density lipoprotein
M281: nipocalimab
mAb: monoclonal antibody
MAD: multiple ascending dose
MCA: middle cerebral artery
MG: generalized myasthenia gravis
MHC: major histocompatibility complex
Nab: neutralizing antibody
NOAEL: no-observed-adverse-effect level
OLE: Open-label extension
PD: pharmacodynamic(s)
PK: pharmacokinetic(s)
q2w: every 2 weeks
q4w: every 4 weeks
Qd: once daily

qw: once weekly
RA: rheumatoid arthritis
RBC: red blood cell
RF: rheumatoid factor
RO: receptor occupancy
SAD: single ascending dose
SAE: serious adverse event
SAR: serious adverse reaction
SC: subcutaneous
SLE: systemic lupus erythematosus
SOC: system organ class
sSD: secondary Sjögren's disease
SUSAR: suspected unexpected serious adverse reaction
t1/2: half-life
TEAE: treatment-emergent adverse event
Tg: transgenic
TK: toxicokinetic(s)
Tlast: time to last quantifiable serum concentration
Tmax: time to maximum serum concentration
ULN: upper limit of normal
wAIHA: warm autoimmune hemolytic anemia
WBC: white blood cel