CLINICAL TRIAL PROTOCOL

A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of M281 Administered to Pregnant Women at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN)

Study Number: MOM-M281-003

Study Phase: 2

Product Name: Nipocalimab (M281, or JNJ-80202135)

National Clinical Trial (NCT) Identified Number: NCT03842189

EudraCT Number: 2017-004958-42

Version Number: 11.0

21 March 2022

Sponsor: Janssen Research &Development

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Confidentiality Statement

PROTOCOL APPROVAL SIGNATURE PAGE

Nipocalimab for HDFN
Protocol MOM-M281-003
Version 11.0, 21 March 2022

PROTOCOL APPROVAL SIGNATURE PAGE

Study Title:	A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of M281 Administered to Pregnant Women at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN)
Study Number:	MOM-M281-003
Version:	11.0
Date:	21 March 2022

Authorized Sponsor Representative Signature:

Signature: PPD Date: PPD

Name: PPD

Immunology TA
Janssen Research & Development

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1.1. Synopsis

Name of Sponsor/Company Janssen Research & Development
Name of Investigational Product: Nipocalimab
Name of Active Ingredient: Nipocalimab (M281, or JNJ-80202135)
Title: A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of M281 Administered to Pregnant Women at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN)
Study Description: This is a Phase 2, multicenter, open-label study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of nipocalimab (M281, or JNJ-80202135), a fully human effectorless monoclonal antibody against the neonatal Fc receptor (FcRn), in pregnant women at high risk for early onset severe (EOS)-HDFN. Blockade of FcRn by nipocalimab is intended to reduce the risk and severity of fetal anemia by reducing the transfer of maternal immunoglobulin (Ig)G, including pathogenic alloantibodies, to the fetus, and by blocking FcRn-mediated IgG recycling, thereby reducing pathogenic antibody in maternal circulation. Refer to the Schematic of Study Design Section 1.2 and Schedule of Events (SOE) Section 1.3, for additional details.
Objectives: **Primary Objectives:** • 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 patients with live birth at or after gestational age (GA) Week 32 and without an intrauterine transfusion (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.

Endpoints:

Primary Endpoints:

Safety:

Maternal nipocalimab safety and tolerability will be evaluated in terms of the incidence and severity of adverse events (AEs), serious adverse events (SAEs) and AEs of special interests (AESIs) (ie, infections requiring use of anti-infectives [oral or intravenous (IV) antibacterial/antiviral/antifungal], and hypoalbuminemia ≥ Grade 3 according to the Common Terminology Criteria for Adverse Events v5.0 [CTCAE]) in the mother.

Additional safety assessments will include 12-lead electrocardiogram (ECG) parameters, clinical laboratory tests (chemistry, hematology, urinalysis, lipid panel), analysis of anti-nipocalimab antibody levels, vital signs, physical examinations, and use of concomitant medications and therapies in the mother. Mothers will be followed for safety for 24 weeks post-delivery. Adverse events, SAEs, and AESIs will be analyzed by frequency, severity, and relationship to study therapy. Although nipocalimab is not expected to be transmitted to maternal breast milk in clinically meaningful quantities, colostrum/breast milk samples will be collected for an exploratory analysis to determine if nipocalimab is present. Listings of all maternal participants or their neonates/infants with major adverse cardiovascular events (MACE; non-fatal myocardial infarction, stroke, and cardiovascular death) will be provided.

Fetal health will be assessed by frequent ultrasound assessments (at least every 2 weeks), and umbilical and uterine artery Doppler measurements of flow velocity will be initiated if fetal biometry indicates the potential for intrauterine growth restriction. In addition, surveillance of fetal heart rate before, during, and after nipocalimab infusion will be done.

For the neonates, AEs and concomitant medication/therapies/procedures will be collected from birth through postnatal Month 6 (Week 24). Serious AEs, AESIs (ie, infections requiring use of anti-infectives [oral or IV antibacterial/antiviral/antifungal], unexpected/unusual childhood illnesses, and IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96), and pediatric neurodevelopment will be monitored through Week 96 (~ the first 2 years of age). Other safety assessments include postnatal safety laboratory assessments (chemistry, hematology, and lipid panel); immune development (IgG, lymphocyte phenotyping, vaccine titer to diphtheria/tetanus); vital signs; physical examination findings (including growth); and use of concomitant medications and therapies (including number of intravenous immunoglobulin [IVIG] doses given). Although nipocalimab is not expected to cross the placenta, an analysis of potential effects of exposure to nipocalimab on the neonate/infant will include evaluation of the following: fetal (where possible, if cordocentesis is performed) and neonatal nipocalimab concentrations (from cord blood sample obtained at birth and at Week 4 after birth) and FcRn receptor occupancy (RO).

Efficacy:

The primary efficacy endpoint is the proportion of patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy.

Secondary Endpoints:

Efficacy:

- Percentage of patients with live birth
- Percentage of patients at GA Week 24 without an IUT
- Gestational age at first IUT
- Number of IUTs required
- Gestational age at delivery
- Percentage of patients with fetal hydrops
- Percentage of neonates requiring phototherapy
- Percentage of neonates requiring exchange transfusions
- Number of days of phototherapy required by neonate
- Percentage of neonates requiring simple transfusions in the first 12 weeks of life
- Number of simple transfusions required by neonate in the first 12 weeks of life

PD

- Maternal FcRn RO and levels of IgG and alloantibodies

PK

- Serum PK profile of nipocalimab in maternal patients

Exploratory Endpoints:

- Fetal hemoglobin, hematocrit, and alloantibody levels at first IUT and in subsequent IUTs
- Maternal serum levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE
- Presence of nipocalimab in colostrum/breast milk
- Placental evaluation
- Neonatal bilirubin, direct Coombs, reticulocyte count, hemoglobin, hematocrit, IgG, and alloantibodies, FcRn RO (all measured from cord blood at birth)
- Peak bilirubin levels during the neonatal period
- Number of IVIG doses received by neonate
- Slope of middle cerebral artery peak systolic velocity (MCA-PSV) by Doppler ultrasound

Approximately 15 eligible patients and their offspring will be enrolled.

Inclusion Criteria:

Each patient must meet all of the following criteria to be enrolled in the study:

1. Able to understand and voluntarily provide written informed consent to participate in the study.
2. Female and ≥18 years of age.
3. Pregnant to an estimated GA of 8 to up to 14 weeks.
4. A previous pregnancy with a gestation that included at least one of the following at ≤24 weeks gestation:
    a. Severe fetal anemia, defined as hemoglobin ≤0.55 multiples of the median (MoM) for GA (see table below):

Weeks' gestation	Median hemoglobin (g/dL)	0.55 MoM
16	10.0	5.5
17	10.4	5.7
18	10.6	5.9
19	10.9	6.0
20	11.2	6.1
21	11.4	6.3
22	11.6	6.4
23	11.8	6.5
24	12.0	6.6

Abbreviations: MoM = multiples of the median.
Source: Mari 2000

b. Fetal hydrops (ascites) with an MCA-PSV MoM ≥1.5
c. Stillbirth with fetal or placental pathology indicative of HDFN

5. Maternal alloantibody titers for anti-D of ≥32, or anti-Kell titers ≥4.
6. Free fetal deoxyribonucleic acid (DNA) consistent with an antigen-positive fetus (blood sample drawn from the mother).
7. Maternal evidence for immunity to measles mumps, rubella, and varicella, as documented by serologies performed during Screening. If initial serologies are borderline or negative, they may be repeated at a second lab. Alternatively, vaccination records can be used to support evidence of immunity.
8. Screening IgG and albumin levels within the laboratory normal ranges.
9. Willing to receive standard of care with IUT if clinically indicated.
10. Agree to receive recommended vaccinations per local standard of care for both mother and child throughout the course of the study.
11. Willing to forego collection of cord blood for stem cell storage or other non-study purposes.
12. For mother and neonate, willing to forego participation in another clinical trial of an investigational therapy for the duration of their participation in the current study.
13. Willing to consent to a 24-week safety follow-up period for the patient and a 96-week safety follow-up period for the neonate/infant.
14. It is recommended that patients are up to-date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study patients who received locally-approved (and including emergency use-authorized) Coronavirus Disease 2019 (COVID-19) vaccines recently prior to study entry, follow applicable local vaccine labelling, guidelines, and standards of care for pregnant women receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.6).

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Currently pregnant with multiples (twins or more).
2. Pre-eclampsia in current pregnancy or history of pre-eclampsia in a previous pregnancy.
3. Gestational hypertension in the current pregnancy.
4. Current unstable hypertension.

5. History of severe or recurrent pyelonephritis or 4 or more lower urinary tract infections (UTIs) in the past year or in a previous pregnancy.
6. History of genital herpes infection.
7. History of atypical mycobacterial disease or herpes zoster infection within the last 6 months.
8. History of malignancy (except treated basal cell carcinoma of the skin) with or without systemic cancer chemotherapy.
9. Positive for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C during Screening.
10. Presence of any of the following during Screening: clinically significant abnormal hematologic laboratory values, creatinine >1.5 × upper limit of normal (ULN), or clinically significant abnormal ECG reflective of heart disease.
11. Active infection at Screening or Baseline with Coxsackie, syphilis, cytomegalovirus, toxoplasmosis or herpes simplex 1 or 2, as evidenced by clinical signs and symptoms (evidence for prior infection or exposure, but without clinical signs and symptoms of active infection is acceptable).
12. Active infection with tuberculosis as evidenced by positive QuantiFERON-TB testing.
13. Immunosuppression because of underlying medical condition, including:
    - History of hereditary or congenital immunodeficiencies, cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia
    - History of solid organ or bone marrow transplantation
    - Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject, require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14. Requires treatment with corticosteroids or immunosuppression for disorders unrelated to the pregnancy (use of low-potency topical corticosteroids or intra-articular corticosteroids is permitted).
15. History of drug allergy, hypersensitivity, or intolerance to any drug product that, in the opinion of the Investigator, would compromise the safety of the patient.
16. In the Investigator's opinion, shows evidence of ongoing alcohol/substance abuse/dependence.
17. Smoking during pregnancy.
18. Received plasmapheresis and/or IVIG during the current pregnancy for treatment of HDFN.
19. Criterion modified per Amendment 11.

    19.1. Has received or is expected to receive any live virus or bacterial vaccine within 12 weeks prior to screening or has a known need to receive a live vaccine while receiving nipocalimab, or within 12 weeks after the last administration of nipocalimab in the study or has received Bacille Calmett-Guérin (BCG) vaccine within 1 year prior to the first administration of nipocalimab.

20. Currently receiving an antibody-based drug or an Fc-fusion protein drug.
21. Received an investigational drug and/or device within 30 days or 5 half-lives prior to receiving the first IV infusion of nipocalimab.
22. Received nipocalimab in a prior clinical trial.
23. Criterion modified per Amendment 11.

    23.1. A history or presence of clinically significant cardiovascular, pulmonary, hepatic (eg, viral/alcoholic/autoimmune hepatitis/cirrhosis and/or metabolic liver disease), renal, hematologic, gastrointestinal, endocrine/metabolic, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or severe or recurrent infections (eg, frequent hospitalized pneumonia), or any other condition or issue that, in the opinion of the Investigator, would jeopardize the safety of the patient or fetus/neonate/infant or the validity of the study results.

24. Criterion modified per Amendment 11.

    24.1. History of myocardial infarction, unstable ischemic heart disease, or stroke.

25. Criterion modified per Amendment 11.

    25.1. COVID-19 infection:

    During the 6 weeks prior to baseline (regardless of vaccination status), have had ANY of

    (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), **OR**

    (b) suspected SARS-CoV-2 infection (clinical features without documented test results), **OR**

    (c) close contact with a person with known or suspected SARS-CoV-2 infection

    Exception: may be included with a documented negative result for a validated SARS-CoV-2 test:

    – obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg fever, cough, dyspnea)

      AND

    – with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

    NOTES on COVID-related exclusion:

    - The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.

    Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

Study Population:

Patients will be screened for inclusion between GA Week 8 up to 1 day before the Baseline day (GA Week 14 ±6 days). All screening assessments and confirmation of eligibility must be completed at least 1 day before the Baseline day. To be eligible for the study, patients must have an obstetrical history of severe fetal anemia, hydrops, or stillbirth related to HDFN at GA Week ≤24, have titers for anti-D ≥32 or anti-Kell titers ≥4, and be pregnant with an antigen-positive fetus. The study will include approximately 15 eligible patients and their offspring.

Phase: 2

Description of Sites/Facilities Enrolling Participants:

The study will be carried out at multiple study sites worldwide with expertise in maternal-fetal medicine and the treatment of HDFN. Appropriate measures will be taken to minimize discomfort to the neonate/infant during study procedures.

Description of Study Intervention:

Nipocalimab will be administered once weekly (QW) by IV infusion at a dose of 45 mg/kg. The 45 mg/kg dose will be calculated every 2 weeks using the patient's weight measured at the visits indicated in the SOE rounded to the nearest 0.1 kilogram. The maximum dose amount given in any patient at any dosing visit should not exceed 5.4 grams (ie, assuming a body weight of no greater than 120 kg). Each pregnant woman in the study will receive nipocalimab treatment for approximately 20 weeks (~20 infusions); no reference therapy will be administered. Refer to the SOE Section 1.3, for timing of dose administration. If a patient requires an IUT during the study, nipocalimab administration will be continued weekly until fetal sampling at a subsequent IUT indicates the lack of fetal red blood cells remaining in the fetal circulation; refer to Section 7.1.1.2 for the treatment stopping rule related to IUTs.

Study Duration:

Approximately 40 months

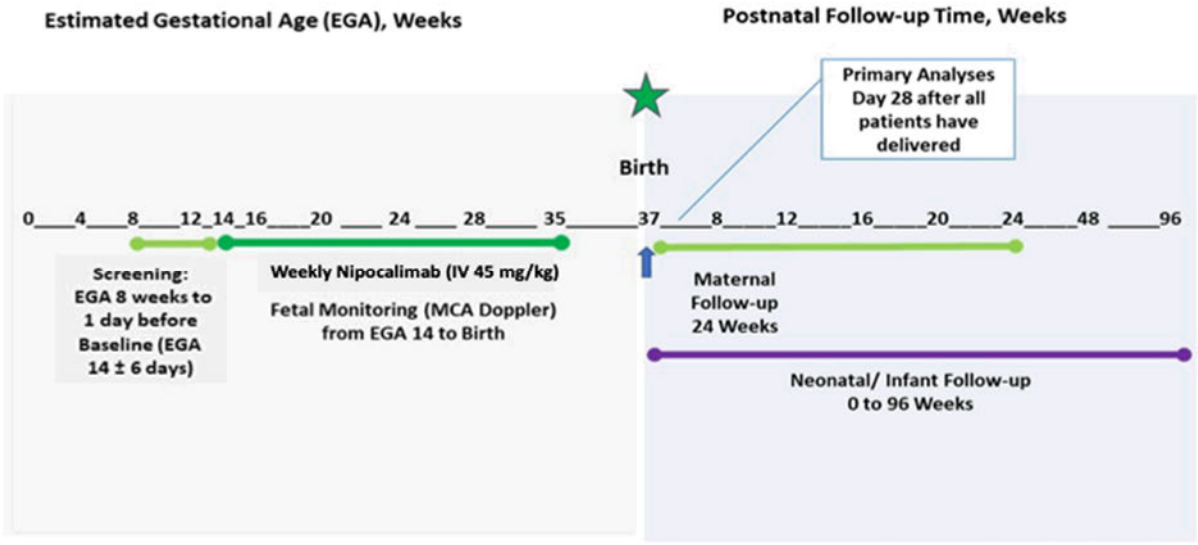
Participant Duration:

Total time on study will be approximately 50 weeks for each pregnant woman entering the study and 96 weeks for each child born during the study. This study includes a maternal screening period of up to approximately 6 weeks, a treatment period of approximately 20 weeks, a 24-week postnatal follow-up period for mothers, and a 96-week follow-up period for all neonates/infants.

Discontinuation of nipocalimab administration does not mean discontinuation from the study. Patients who discontinue nipocalimab treatment for any reason should be actively encouraged to continue in the study to be followed for safety assessments, and also actively encouraged to continue their neonate/infant's participation in the study for safety follow-up (Section 7.1.1).

1.2. Schematic of Study Design

Figure 1: Schematic of Study Design



EGA = estimated gestational age; IV = intravenous; M281 = nipocalimab; MCA = middle cerebral artery

1.3. Schedule of Events

Table 1: Schedule of Events - Part A (Gestation to Birth)

Approximate Trimester	**1st**	**2nd Trimester**												**3rd Trimester**												
Study Period	**Scr**	**Nipocalimab Treatment Period**																								
Estimated Gestational Age (Week) [a]	**Wk 8 up to 1 day before BL**	**BL: 14 ± 6d**	**15 ± 1d**	**16 ± 1d**	**17 ± 1d**	**18 ± 1d**	**19 ± 1d**	**20 ± 1d**	**21 ± 1d**	**22 ± 1d**	**23 ± 1d**	**24 ± 1d**	**25 ± 1d**	**26 ± 1d**	**27 ± 1d**	**28 ± 1d**	**29 ± 1d**	**30 ± 1d**	**31 ± 1d**	**32 ± 1d**	**33 ± 1d**	**34 ± 1d**	**35 ± 1d**	**35B [b] ± 1d**	**36/ EOT [c] ±1d**	**Birth[a] 37**
Patient informed consent	X																								See SOE Part B, Table 2
Parent/ guardian informed consent for neonate/infant	X																								
Placental pathology substudy consent	X																								
Demographics	X																								
Medical/obstetri- cal history[d]	X																								
Entry criteria	X																								
12-lead ECG	X																							X	
Height, weight	X																								
Blood sample for viral serologies[e]	X																								
Blood samples for free fetal DNA and alloantibody titers[f]	X																								

Table 1: Schedule of Events - Part A (Gestation to Birth)

Approximate Trimester	**1st**	**2nd Trimester**												**3rd Trimester**												
Study Period	**Scr**	**Nipocalimab Treatment Period**																								
Estimated Gestational Age (Week) [a]	**Wk 8 up to 1 day before BL**	**BL: 14 ± 6d**	**15 ± 1d**	**16 ± 1d**	**17 ± 1d**	**18 ± 1d**	**19 ± 1d**	**20 ± 1d**	**21 ± 1d**	**22 ± 1d**	**23 ± 1d**	**24 ± 1d**	**25 ± 1d**	**26 ± 1d**	**27 ± 1d**	**28 ± 1d**	**29 ± 1d**	**30 ± 1d**	**31 ± 1d**	**32 ± 1d**	**33 ± 1d**	**34 ± 1d**	**35 ± 1d**	**35B [b] ± 1d**	**36/ EOT [c] ±1d**	**Birth[a] 37**
Blood and urine sample for safety laboratory evaluations (Fasting at BL and GA Wk 26)[g]	X	X[g]				X				X				X[g]				X				X			X	See SOE Part B, Table 2
Blood sample for exploratory PD markers (IgG subclasses, IgM, IgA, IgE)[h]	X	X				X				X				X				X				X			X	
Blood sample for lymphocyte phenotyping[i]		X												X								X				
Blood sample for serum albumin[j], total serum IgG[j], FcRn RO[j], alloantibody titers[j], ADA		X	X	X		X		X		X		X		X		X		X		X		X			X	
Blood sample for PK analyses[k]		X[k]	X[k]	X		X		X		X		X[k]		X[k]		X		X		X		X		X[k]		X	
Physical exam[l], weight[t], vital signs[p], pulse oximetry		X[lt]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X	X	X[l]	

Table 1: Schedule of Events - Part A (Gestation to Birth)

Approximate Trimester	**1st**	**2nd Trimester**												**3rd Trimester**												
Study Period	**Scr**	**Nipocalimab Treatment Period**																								
Estimated Gestational Age (Week) [a]	**Wk 8 up to 1 day before BL**	**BL: 14 ± 6d**	**15 ± 1d**	**16 ± 1d**	**17 ± 1d**	**18 ± 1d**	**19 ± 1d**	**20 ± 1d**	**21 ± 1d**	**22 ± 1d**	**23 ± 1d**	**24 ± 1d**	**25 ± 1d**	**26 ± 1d**	**27 ± 1d**	**28 ± 1d**	**29 ± 1d**	**30 ± 1d**	**31 ± 1d**	**32 ± 1d**	**33 ± 1d**	**34 ± 1d**	**35 ± 1d**	**35B [b] ± 1d**	**36/ EOT [c] ±1d**	**Birth[a] 37**
Influenza and pneumococcal (PPSV23) vaccines[m]			X[m]																						
Fetal MCA Doppler (±cordocentesis)[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See SOE Part B, Table 2
Fetal heart rate by Doppler (prior to the start of nipocalimab infusion, at the end of the infusion, and at the end of the observation period)		X	X	X	X	X	X	X	X	X	X	X	X													
Continuous monitoring of fetal heart rate and uterine activity during the infusion and observation period														X	X	X	X	X	X	X	X	X	X	X		
Ultrasound assessments																										See SOE Part B, Table 2
Fetal viability	X	X		X		X		X		X		X		X		X		X		X		X			X	
Fetal crown-rump length	X	X																								

Table 1: Schedule of Events - Part A (Gestation to Birth)

Approximate Trimester	**1st**	**2nd Trimester**												**3rd Trimester**												
Study Period	**Scr**	**Nipocalimab Treatment Period**																								
Estimated Gestational Age (Week) [a]	**Wk 8 up to 1 day before BL**	**BL: 14 ± 6d**	**15 ± 1d**	**16 ± 1d**	**17 ± 1d**	**18 ± 1d**	**19 ± 1d**	**20 ± 1d**	**21 ± 1d**	**22 ± 1d**	**23 ± 1d**	**24 ± 1d**	**25 ± 1d**	**26 ± 1d**	**27 ± 1d**	**28 ± 1d**	**29 ± 1d**	**30 ± 1d**	**31 ± 1d**	**32 ± 1d**	**33 ± 1d**	**34 ± 1d**	**35 ± 1d**	**35B [b] ± 1d**	**36/ EOT [c] ±1d**	**Birth[a] 37**
Fetal growth biometry (BPD, HC, AC, femur length) and calculate EFW		X		X		X		X		X		X		X		X		X		X		X		X		
Umbilical and uterine arteries flow by Doppler[o]						Only required starting at GA 18 if EFW or AC is below 10th percentile																				
Amniotic fluid maximum vertical pocket		X		X		X		X		X																
Amniotic fluid index												X		X		X		X		X		X				X	
Full anatomical assessment for fetus by ultrasound								X																		
Vaginal microbiome		X																				X				
Group B Streptococcus testing																						X				See SOE Part B, Table 2
Tdap vaccination																		X								
IV nipocalimab[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Table 1: Schedule of Events - Part A (Gestation to Birth)

Approximate Trimester	**1st**	**2nd Trimester**												**3rd Trimester**												
Study Period	**Scr**	**Nipocalimab Treatment Period**																								
Estimated Gestational Age (Week) [a]	**Wk 8 up to 1 day before BL**	**BL: 14 ± 6d**	**15 ± 1d**	**16 ± 1d**	**17 ± 1d**	**18 ± 1d**	**19 ± 1d**	**20 ± 1d**	**21 ± 1d**	**22 ± 1d**	**23 ± 1d**	**24 ± 1d**	**25 ± 1d**	**26 ± 1d**	**27 ± 1d**	**28 ± 1d**	**29 ± 1d**	**30 ± 1d**	**31 ± 1d**	**32 ± 1d**	**33 ± 1d**	**34 ± 1d**	**35 ± 1d**	**35B [b] ± 1d**	**36/ EOT [c] ±1d**	**Birth[a] 37**
Biophysical profile for fetus by ultrasound																								X	
Maternal IVIG administration																								X[q]	
Placental evaluation[r]																									X
AEs/AESIs/SAEs/ Concomitant medications/ther-apies[s]	*Continuous*																								

Abbreviations: AC = abdominal circumference; ADA = antidrug antibodies; AE = adverse event; AESI = adverse event of special interest; BL = Baseline; BPD = biparietal diameter; d= day; ECG = electrocardiogram; EFW = estimated fetal weight; EOT = end of treatment; FcRn = neonatal Fc receptor; GA = gestational age; HC = head circumference; Ig = immunoglobulin; IUGR = intrauterine growth restriction; IUT = intrauterine transfusion; IV = intravenous; IVIG = intravenous immunoglobulin; MCA = middle cerebral artery; PD = pharmacodynamic; PI = pulsatility index; PK = pharmacokinetic; PPSV23 = pneumococcal polysaccharide vaccine 23-valent; PSV = peak systolic velocity; RO = receptor occupancy; SAE = serious adverse event; Scr = screening; SOE = Schedule of Events; Tdap = tetanus diphtheria pertussis; Wk = week.

NOTE: If nipocalimab treatment is prematurely discontinued before GA Week 35 (ie, 2 weeks before delivery), remaining study procedures for the mother and neonate/infant should be completed as indicated by the study protocol (Section 7.1.1).

[a] Screening of patients to be from gestational Week 8 to up to 1 day before the Baseline day (Baseline day = GA Week 14 ±6 days). Study visits during the nipocalimab treatment period should occur at 7-day intervals whenever possible in order to maintain the therapeutic effect. Eg, if a patient receives a nipocalimab infusion earlier than 7 days since her last infusion, the patient's next infusion should occur no more than 7 days after that infusion. The timing of delivery is dependent on Investigator judgment but is anticipated to be at an estimated gestational age of 37 weeks (GA Week 37). Study assessments for the mother and neonate to be performed on the day of birth and the follow-up period are provided in Schedule of Events Part B (see Table 2). Study assessments for patients who deliver prior to GA Week 37 should begin at Day 0 of SOE Part B (Table 2), and all remaining assessments on SOE Part A except for the placental evaluation can be missed.

[b] Week 35B visit is applicable only for those patients who initiated treatment during GA Week 13. Patients who received their first dose at Week GA 13 will receive an additional dose overall but will complete nipocalimab dosing at GA Week 35 to ensure the last nipocalimab infusion occurs approximately two weeks prior to delivery.

[c] Patients who discontinue nipocalimab treatment should be actively encouraged to continue in the study to be followed for safety assessments, and actively encouraged to continue their neonate/infant's participation in the study for safety follow-up (see Table 2: Schedule of Events – B [Birth – Postpartum], and Section 7.1.1). The EOT assessments should be performed at their next clinical visit (ideally within 2 weeks of their last dose of nipocalimab).

[d] Detailed medical/obstetrical history includes medication history and information on all previous pregnancies, including treatment with plasmapheresis, IVIG, and IUTs, fetal blood sampling results, Doppler studies of MCA, and neonatal outcomes (eg, neonatal hemoglobin, bilirubin, alloantibody levels, and IVIG use, simple and exchange transfusions, and phototherapy requirements).

[e] Maternal evidence for immunity to measles, mumps, rubella, and varicella, as documented by serologies performed during Screening. If initial serologies are borderline or negative, they may be repeated at a second lab. Alternatively, vaccination records can be used to support evidence of immunity. Serologies for HIV, syphilis, hepatitis B, hepatitis C, cytomegalovirus (CMV), toxoplasmosis, parvovirus, Coxsackie, herpes simplex 1 and 2, and tuberculosis are also to be performed at Screening.

[f] Blood samples to be taken for free fetal DNA test during Screening to include RhD at ≥ GA Week 10; Kell at ≥ GA Week 13.

[g] Laboratory testing for safety includes chemistry, hematology, lipid panel, and urinalysis at all time points (see Table 7). A fasting lipid panel (fasting for ≥6 hours) should be obtained at Baseline and Week 26; however, if the participant has not fasted, blood samples will still be drawn and it will not be a protocol deviation. Fasting is not required for all other visits. The time of the most recent food intake prior to each lipid sample collection should be recorded.

[h] Blood samples for serum levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE for exploratory PD measures.

[i] Lymphocyte phenotyping to include natural killer (NK), T and B cell counts.

[j] Blood samples for serum albumin, total serum IgG, alloantibody titers and FcRn RO to be collected prior to nipocalimab infusion. If ≥9 days since the last infusion, a blood sample for total serum IgG, alloantibody titers and FcRn RO will be collected prior to nipocalimab infusion (if sample not already scheduled). If a patient requires an IUT or sustains fetal loss in between scheduled collection times, an additional sample will be obtained as soon as possible.

[k] Blood samples for nipocalimab PK will be taken prior to nipocalimab infusion at each indicated time point, and additionally at 45 minutes (±15 minutes) after the end of the nipocalimab infusion (from the opposite arm than the IV infusion line) at GA Weeks 14 and 15 and at GA Weeks 24 or 26 (if missed at GA Week 24), and at GA Week 35. If ≥9 days since the last infusion, a blood sample for nipocalimab PK will be collected prior to nipocalimab infusion (if sample not already scheduled). If a patient requires an IUT or sustains fetal loss in between scheduled collection times, an additional sample will be obtained as soon as possible.

[l] A full physical examination to be performed at Baseline and at GA Week 36 (or EOT as applicable); all other physical examinations are abbreviated and include assessment of heart, lungs, and skin, and assessment of edema.

[m] At the GA Week 15 or the GA Week 16 visit and at least 3 hours after the end of the nipocalimab infusion, patients will receive pneumococcal polysaccharide vaccine 23-valent (PPSV23), and patients who have not already received seasonal influenza vaccine (during routine care) will also be vaccinated for influenza (when vaccine is available). Patients will have the option of visiting the site on a different day during the week before or week after the GA Week 15 or GA Week 16 infusion visit to receive required vaccinations. It is possible that patients should receive a second seasonal influenza vaccination (ie, new season) during their participation in the study, if the new seasonal vaccine becomes available during the study, with timing to be determined by the Investigator. The second influenza vaccine (new season) should be administered no earlier than 4 weeks after the first seasonal influenza vaccine (previous season).

[n] Fetal monitoring by Doppler MCA to determine PSV to be performed weekly. Unscheduled monitoring visits for Doppler MCA are permitted. When clinically indicated cordocentesis is performed, cord blood should be obtained for analysis of fetal hemoglobin, hematocrit, direct Coombs, reticulocyte count, nipocalimab concentration, alloantibodies, FcRn RO, and total IgG where possible.

[o] At GA Week 18 or beyond, if either the estimated fetal weight (calculated from the fetal ultrasound growth measurements) or the abdominal circumference is below the 10th percentile, based on local fetal growth normative standards (see Section 7.1.1.6), weekly Doppler measurements of flow velocity in the

umbilical and uterine arteries will be initiated and the PI for each artery will be calculated. The average of the PI from the left and right uterine arteries will be used for the overall uterine artery PI. The stopping rule for IUGR is depicted graphically in Appendix 2. Additional Doppler measurements of umbilical and uterine arteries may be scheduled as needed at the discretion of the Investigator.

[p] Vital signs to be measured at time 0 (before the start of the nipocalimab infusion), and for the first (60-minute) infusion vital signs measured at 30 minutes, the end of infusion, and 30- and 60-minutes post infusion; fetal heart rate will be measured at 0 minutes, the end of infusion, and 60 minutes post infusion. For all subsequent (30-minute) infusions, vital signs will be measured at start of infusion (0 minutes), at the end of infusion, and at the end of the 30-minute post infusion observation period; fetal heart rate will be measured at 0 minutes, the end of infusion, and 30 minutes post infusion.

[q] IVIG 500 mg/kg to be administered to mothers 48 to 72 hours before delivery (if not contraindicated). If the GA Week 36 visit falls within 48 to 72 hours prior to the estimated time of delivery, then IVIG can be administered at the GA Week 36 visit. If delivery is early/unscheduled (urgent or emergent), IVIG should be given before delivery or as soon as possible after delivery. In case of fetal loss or elective termination of the pregnancy, IVIG should be administered before the procedure or as soon as possible after the procedure. See Section 8.2.1.6 for specific guidelines on maternal IVIG before birth if nipocalimab has been prematurely discontinued.

[r] Whenever possible, the placenta should be examined by the clinical site's pathologist and may be performed in a substudy of the protocol by central reading. Details of the desired placental evaluation are provided in the placental pathology manual.

[s] If maternal IgG concentration falls below 1.0 g/L at any time during the study, the Investigator will contact the patient as soon as possible by phone. The patient will be queried about infection-related symptoms and if the Investigator has any concerns, they will instruct the patient to return to the site for an unscheduled visit. The patient will also be reminded of the steps to prevent contraction of infection (eg, frequent hand washing and good hygiene, avoiding exposure to individuals with upper respiratory or other infections, handling and preparing food safely, etc.

[t] Indicates the weight measured at this visit (rounded to the nearest 0.1 kilogram) should be used to calculate the nipocalimab 45 mg/kg dose for this visit and the following visit.

[u] The 45 mg/kg dose should be calculated every 2 weeks using the patient's weight measured at the visits indicated by footnote t rounded to the nearest 0.1 kilogram. The maximum dose amount given in any patient at any dosing visit should not exceed 5.4 grams (ie, assuming a body weight of no greater than 120 kg).

Table 2: Schedule of Events – Part B (Birth - Postpartum)

Study Period	**Follow-up Period[a]**											
Postpartum Week	**Day 0 (Birth)**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ SF[a]**	**Wk 48**	**Wk 96 EOS**
Visit Window ± Days	0	2	2	2	2	5	5	5	5	5	14	14
Mother												
Site Visit	X	X			X					X[a]		
Assessment by phone call[b]			X	X		X	X	X	X			
Nipocalimab in colostrum/breast milk[c]	X	X										
Safety laboratory evaluations[d]	X				X					X		
Physical examination, weight, vital signs, pulse oximetry[e]	X				X					X[e]		
Blood sample for nipocalimab concentrations,[f] total serum IgG,[f] alloantibody titers,[f] FcRn RO,[f] and ADA	X[f]				X					X		
Blood sample for lymphocyte phenotyping	X				X					X		
Blood sample to test for immunity to rubella (only in women vaccinated postpartum)										X		
AEs/SAEs/AESIs/concomitant medications/therapies	*Continuous*											

Table 2: Schedule of Events – Part B (Birth - Postpartum)

Study Period	**Follow-up Period[a]**											
Postpartum Week	**Day 0 (Birth)**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ SF[a]**	**Wk 48**	**Wk 96 EOS**
Visit Window ± Days	0	2	2	2	2	5	5	5	5	5	14	14
Neonate/Infant/Child[q]												
Site Visit	X	X			X					X[r]	X	X
Demographics	X											
Physical examination (including APGAR score),[g] vital signs	X[g]	X			X					X		
Cord blood sample[h] for safety laboratory evaluations,[i] total serum IgG,[j] and immunoglobulin levels (IgM, IgA, IgE); blood type and antigen status (RhD or Kell); alloantibody titers; nipocalimab concentrations; FcRn RO, and lymphocyte phenotyping	X											
IVIG administration[j,k]	X											
Blood samples (Note: If the total volume of blood to be collected for the below samples at birth, Week 4, Week 24, Week 48, or Week 96 would exceed the allowable amount or cannot be obtained for technical reasons, consult the Laboratory Manual for which blood samples should be prioritized.)												
Blood sample for safety laboratory evaluations [i,l] and nipocalimab concentration					X[m]					X	X	X
Blood sample for total serum IgG, IgM, IgA, and IgE levels		X[n]			X	X[n]		X[n]		X	X	X
Diphtheria/Tetanus antibody panel										X[r]	X	X
Blood sample for lymphocyte phenotyping[o]					X					X	X	X

Table 2: Schedule of Events – Part B (Birth - Postpartum)

Study Period	**Follow-up Period[a]**											
Postpartum Week	**Day 0 (Birth)**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ SF[a]**	**Wk 48**	**Wk 96 EOS**
Visit Window ± Days	0	2	2	2	2	5	5	5	5	5	14	14
ASQ-3										X ASQ-3 6M	X ASQ-3 12M	X ASQ-3 24M
PedsQL												X
Collection of immunization records	*Continuous*											
AEs/Concomitant medications/therapies	*Continuous*											
SAEs/AESIs[p]	*Continuous*											

Abbreviations: ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; APGAR = appearance, pulse, grimace response, activity, respiration score; ASQ-3 = Ages & Stages Questionnaires®, Third Edition; EOS = end of study; FcRn = neonatal Fc receptor; GA = gestational age; Ig = immunoglobulin; IV = intravenous; IVIG = intravenous immunoglobulin; PedsQL=Pediatric Quality of Life Inventory; RO = receptor occupancy; SAE = serious adverse event; SF = safety follow-up visit; Wk = week.

NOTE: If nipocalimab treatment was prematurely discontinued before GA Week 35 (ie, 2 weeks before delivery) per Table 1, the remaining study procedures for the mother and neonate/infant should be completed as indicated by the study protocol (Section 7.1.1).

[a] Week 24 in the Follow-up Period is the End of Study Visit for the mother. For neonates/infants who discontinue prematurely, safety follow-up assessments should be completed for 24 weeks after the last dose of nipocalimab is given to the mother.

[b] Study site to contact mother by phone for assessment of AEs and concomitant medications.

[c] Colostrum/breast milk samples (either is acceptable) should be collected on postpartum Day 1 and Week 1 (±1 day).

[d] Safety laboratory evaluation for the maternal patient includes chemistry, hematology, lipid panel (non-fasting), and urinalysis at all time points (see Table 7).

[e] Physical examination for the mother is abbreviated (includes assessment of heart, lungs, and skin, and assessment of edema on abdomen and lower extremities) at birth and Week 4; and a full physical examination will be performed at Week 24.

[f] In maternal patients who deliver prior to GA Week 37, these assessments should also be performed 2 weeks after the last dose of nipocalimab.

[g] A full physical examination (including APGARs at 1 and 5 minutes after birth) should be performed for the neonate at birth. Thereafter, physical examinations should include length/height, weight, and head circumference, and routine assessment of development.

[h] Cord blood sample from the neonate will be assessed for hemoglobin, hematocrit, total and direct bilirubin, direct Coombs, blood type, antigen positive status (RhD or Kell), reticulocyte count, nipocalimab concentration, total Ig (IgG, IgM, IgA, IgE) and IgG subclasses (IgG1, IgG2, IgG3, IgG4), alloantibody levels, FcRn RO, and chemistry, hematology, and lipid panel safety laboratory evaluations. Lymphocyte phenotyping on cord blood sample will include NK, T and B cell counts.

[i] Safety laboratory assessments (sent to central laboratory) for neonates/infants include chemistry, hematology, and lipid panel (non-fasting). Blood type will also be done if not obtained from cord blood sample.

[j] IgG from cord blood will be assessed at a local laboratory (see Section 8.2.2.1).
[k] IVIG dose of 500 mg/kg may be given (if not contraindicated) within 48 hours of birth according to the neonate's risk of infection and cord blood total IgG concentration assessed at a local laboratory, as described in Section 8.2.2.1
[l] Additionally, laboratory results for hemoglobin, hematocrit, reticulocyte count, direct Coombs, and total and direct bilirubin evaluations performed locally as per standard of care (at any time point) will be recorded.
[m] Nipocalimab concentrations at Week 4 only.
[n] A blood sample at Week 1 for total serum IgG is only required for neonates who receive IVIG at birth; no sample at Week 1 is needed if IVIG was not given at birth. Postnatal Week 8 and Week 16 assessment of total IgG are not required if Week 4 levels of IgG were ≥200 mg/dL. The Week 4, Week 24, Week 48, and Week 96 assessments are required for all babies. Additional ad hoc testing of IgG in the neonate may be done as per investigator judgment if the IgG concentrations remain below age-appropriate levels.
[o] Lymphocyte phenotyping will include natural killer (NK), T and B cell counts.
[p] AESIs for the offspring include infections requiring use of anti-infectives [oral or IV antibacterial/antiviral/antifungal], unexpected/ unusual childhood illnesses, and IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96.
[q] Neonate/infant/child blood draws, clinical assessments, and testing will be done in a child-friendly manner/environment, and by individuals experienced with pediatric care.
[r] A vaccine titer to assess antibody response to diphtheria/tetanus in the infant at the Week 24 visit should be obtained at least 3 weeks after the 2nd vaccination with Diphtheria, Tetanus, and Pertussis (DTaP) as described in Section 8.2.2.2. If necessary, the visit window for the Week 24 visit can be extended up to 30 days to allow for the 3 weeks required from the 2nd vaccination of DTaP.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION OR COMPLETE PHRASE
ACOG	American College of Obstetricians and Gynecologists
ADA	Antidrug Antibody
AE	Adverse Event
AEDF	Absent End Diastolic Flow
AESI	Adverse Event of Special Interest
ALB	Albumin
ALK-P	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APGAR	Appearance, Pulse, Grimace Response, Activity, Respiration score
ASQ-3	Ages & Stages Questionnaires®, Third Edition
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
BCG	Bacille Calmette-Guérin
BLQ	Below the Limit of Quantitation
BUN	Blood Urea Nitrogen
Ca	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
CK	Creatine Kinase
C_{max}	Maximum Plasma Concentration
CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CS	Clinically Significant
C-section	Cesarean Section
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms

ABBREVIATION	DEFINITION OR COMPLETE PHRASE
EFW	Estimated Fetal Weight
EOS-HDFN	Early Onset Severe Hemolytic Disease of the Fetus and Newborn
EOT	End of Treatment
ePPND	Extended Peri- and Postnatal Development Phase
ERC	Ethics Review Committee
FcRn	Neonatal Fc Receptor
FDA	Food and Drug Administration
FIH	First-in-Human
GA	Gestational Age
GBS	Group B Streptococcus
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
Hct	Hematocrit
HDFN	Hemolytic Disease of the Fetus and Newborn
HDL	High-density lipoprotein
HEENT	Head, Eye, Ear, Nose, and Throat
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
Ig	Immunoglobulin
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUGR	Intrauterine Growth Restriction
IUT	Intrauterine Transfusion
IV	Intravenous
IVIG	Intravenous Immunoglobulin
K	Potassium
LDH	Lactate Dehydrogenase
LDL	Low-density lipoprotein
M281	nipocalimab

ABBREVIATION	DEFINITION OR COMPLETE PHRASE
MACE	major adverse cardiovascular event(s)
MAD	Multiple Ascending Dose
MCA	Middle Cerebral Artery
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MoM	Multiples of the Median
Na	Sodium
NCI	National Cancer Institute
NCS	Not Clinically Significant
NCT	National Clinical Trial
NIH	National Institutes of Health
NOAEL	No-Observed-Adverse-Effect-Level
PD	Pharmacodynamic
PI	Pulsatility Index
PK	Pharmacokinetic
PPSV23	Pneumococcal Polysaccharide Vaccine 23-Valent
PedsQL	Pediatric Quality of Life Inventory
PSV	Peak Systolic Velocity
QW	Once Weekly
RBC	Red Blood Cell
REDF	Reversed End Diastolic Flow
RO	Receptor Occupancy
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOE	Schedule of Events
Tdap	Tetanus Diphtheria Pertussis
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal

ABBREVIATION	DEFINITION OR COMPLETE PHRASE
UP	Unanticipated Problem
USA	United States of America
UTI	Urinary Tract Infection
WBC	White Blood Cell

3. INTRODUCTION

3.1. Study Rationale

Affecting approximately 3 in 100,000 to 80 in 100,000 patients per year in countries with well-established health care infrastructure and Rh disease immunoprophylaxis (Koelewijn, 2009; Delaney, 2015), hemolytic disease of the fetus and newborn (HDFN) is a rare and potentially life-threatening condition that occurs when the blood types of the mother and fetus are incompatible. In such cases, maternal alloantibodies cross the placenta during pregnancy and bind to fetal red blood cells (RBCs) possessing the corresponding antigen, thereby causing RBC destruction and anemia in the fetus.

The clinical presentation of HDFN ranges from mild to life threatening. While mildly affected cases may require only postnatal phototherapy for jaundice (Ree, 2017), in more severe cases fetal anemia can result and require intervention to prevent development of fetal hydrops (severe edema in the skin and serous cavities). In such cases, fetal erythropoiesis is unable to compensate for the loss of RBCs, and enlargement of the fetal spleen and liver may occur, along with hyperdynamic circulation, causing cardiomegaly and congestive heart failure. If the anemia is untreated, fetal demise is almost certain unless invasive intervention(s), such as intrauterine transfusions (IUTs) of matched donor blood, are performed in a timely manner (Smits-Wintjens, 2008; Radunovic, 1992; Osanan, 2012). Typically, disease severity increases and gestational age (GA) of onset decreases with every pregnancy with an antigen-positive fetus, due to repeated alloimmunization (Urbaniak, 2000; Lobato, 2008; Jacobs, 1962). The most difficult to treat cases of HDFN are those that develop before 24 weeks GA, when the procedural complication rate and intrauterine fetal demise are markedly higher (Yinon, 2010; Lindenburg, 2013).

In current standard of care practice, HDFN pregnancies at high risk for antenatal anemia are monitored frequently by middle cerebral artery(MCA)-Doppler (Mari, 2000; Oepkes, 2006) and an IUT is performed if the peak systolic velocity (PSV) of blood flow is greater than 1.5 multiples of the median (MoM) for GA and cordocentesis confirms moderate to severe fetal anemia. On average, severe cases of HDFN require 3 (range 1-7) IUTs of donor RBCs followed by postnatal monitoring and, if necessary, postnatal phototherapy or transfusions in the neonatal intensive care unit (Zwiers, 2017b). However, cases of early onset HDFN require an increased number of IUTs (5 IUTs on average [range 1 to 9]), with an increased risk of early fetal demise (Yinon, 2010).

While survival rates following IUT for HDFN generally exceed 90% in specialized centers (Zwiers, 2017a), the technical challenges of performing IUT before 22 weeks of gestation result in a per procedure risk of perinatal loss of 4%, which is more than twice that for HDFN overall (1.6%), and contribute to a 20% rate of fetal loss for early onset severe HDFN (Lindenburg, 2013; Yinon, 2010). Moreover, every IUT performed risks inducing further alloimmunization, potentially increasing disease severity in the current and future pregnancies (Schonewille, 2007). Considering this risk, some clinical centers initiate frequent high dose intravenous immunoglobulin (IVIG) therapy with or without repeated plasmapheresis to delay the onset of anemia and the need for IUT (Ruma, 2007). However, the efficacy of these treatments has not been well established and neither obviate the need for IUT (Ruma, 2007; Schwartz, 2016; Yinon, 2010; Zwiers, 2017a). In addition, these treatments can result in maternal morbidity and quality of life issues (Rossi, 2015).

Thus, there is an unmet medical need for an effective nonsurgical intervention for pregnant mothers with HDFN, especially for those that are likely to require an IUT during early gestation (eg, prior to 24 weeks gestation) when the per procedure risk of fetal loss is relatively high.

The Sponsor plans to initially develop nipocalimab for women at high risk for early onset severe (EOS)-HDFN, defined as women with an obstetrical history (previous pregnancy) of a fetus with severe fetal anemia or HDFN-related stillbirth at ≤24 weeks gestation who have anti-D or anti-Kell immunoglobulin (Ig) G alloantibody titers consistent with disease and are currently pregnant with an antigen-positive fetus. As the fetuses of such pregnancies are at greatest risk for developing severe anemia within the first 24 weeks of gestation, when existing treatment options are less effective and pose a high risk to the fetus, these patients have the greatest unmet medical need.

Nipocalimab is a fully human, aglycosylated immunoglobulin (Ig)G monoclonal antibody that targets the neonatal Fc receptor (FcRn) IgG binding site with high affinity, thereby interfering with the binding of native IgG. In placental syncytiotrophoblasts, FcRn mediates the transfer of maternal IgG and IgG-containing immune complexes to the fetus, transmitting passive immunity. In endothelial cells, FcRn binding of IgG salvages it from degradation and contributes to its long half-life.

In pregnant women at high risk for EOS-HDFN, blockade of FcRn by nipocalimab is intended to reduce the risk and severity of fetal anemia through 2 mechanisms: (1) reducing the placental transfer of maternal IgG, including pathogenic alloantibodies or autoantibodies, to the fetus, thus reducing or eliminating the need for IUT and other existing treatment options that present greater risks to the mother, fetus, and neonate; and (2) reducing pathogenic antibody in maternal circulation by blocking FcRn-mediated recycling.

The primary objectives of the present study, MOM-M281-003, are to evaluate the safety in mother and neonate/infant of nipocalimab administered to pregnant women at high risk for EOS-HDFN, and to evaluate efficacy as measured by the proportion of patients with live birth ≥GA Week 32 and without an IUT throughout their entire pregnancy. Secondary objectives include evaluations of the effect of nipocalimab therapy on antenatal management and outcomes, postnatal management of the neonate/infant, and analyses of nipocalimab pharmacodynamic (PD) parameters and pharmacokinetics (PK) in pregnant women. Secondary efficacy endpoints include the following: percentage of patients with live birth, percentage of patients at GA Week 24 without an IUT, number of IUTs required, percentage of patients with fetal hydrops, and endpoints related to neonatal requirements for simple transfusions, exchange transfusions, and phototherapy.

3.2. Background

3.2.1. Investigational Product: Nipocalimab

The investigational product, nipocalimab, is a fully human, effectorless monoclonal antibody designed to bind, saturate and block the IgG binding site of human neonatal Fc receptor, FcRn. Nipocalimab is an antibody with human-derived heavy and light chain variable regions and human IgG1 constant regions with no terminal Lys and no glycosylation due to a mutation at the Fc glycosylation site. Nipocalimab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system and is purified by a process that includes

specific viral inactivation and removal steps. It consists of 1322 amino acids and has a molecular weight of approximately 142 kilodaltons.

Data from in vitro assays and in vivo animal studies show the expected binding of nipocalimab to the target IgG binding site on FcRn, interfering with and preventing IgG recycling while facilitating an increased rate of IgG catabolism following nipocalimab administration. The data also provide estimates of the degree and duration of binding as a function of dose and/or receptor occupancy (RO) and the related efficacy resulting from these interactions in the in vivo model systems.

3.2.2. Nonclinical Studies

Nonclinical studies of nipocalimab support the potential efficacy of this product for the treatment of HDFN. Nipocalimab blocks FcRn recycling, increasing clearance of circulating IgG in human FcRn transgenic mice and cynomolgus monkeys and is efficacious in murine models of pathogenic IgG-mediated cytopenia (chronic antiplatelet antibody-induced thrombocytopenia) and inflammatory arthritis (collagen antibody-induced arthritis). In addition, an analogous murine anti-FcRn antibody has been reported to protect murine fetuses from thrombocytopenia due to maternal antiplatelet antibodies (Chen, 2010) and from miscarriage due to maternal antibodies inducing placental damage (Li, 2011).

Nipocalimab was generally well tolerated in studies of nonhuman primate toxicology (n = 127 nipocalimab-treated animals), including immunotoxicology (n = 24 nipocalimab-treated animals) and reproductive toxicology (n = 52 nipocalimab-treated animals). Gross abnormal observations in the placenta, characterized microscopically as placental infarcts, were observed in the placentae of 4 cynomolgus monkeys (of 26 evaluable placentae available from nipocalimab-treated dams) dosed with nipocalimab 100 (n = 2) and 300 mg/kg (n = 2) in the extended peri- and postnatal development phase (ePPND) of a reproductive toxicology study. One affected pregnancy ended in live birth and a normal neonate, while two others ended in stillbirth or abortion in late gestation, and one was stillborn in midgestation with evidence of umbilical entrapment. Importantly, there was no difference between the control and nipocalimab-treated groups in terms of fetal or infant loss rates or in the health or number of offspring. While the mechanism of placental infarction in monkeys is unclear, and a causative association of the infarcts with fetal mortality could not be ruled out, it is hypothesized that the abnormal placental infarcts in this sample of monkey placentae may have been caused by cross-species immunogenicity against nipocalimab, a human antibody, and the hypercoagulable state of pregnancy in the monkeys (Kraus, 2004; Mitchell, 2010; Leach, 2010).

Nipocalimab doses and exposures achieved in all pregnant and nonpregnant cynomolgus monkey studies were up to 6.7-fold higher than the anticipated dose in this Phase 2 study. Similar PD effects of nipocalimab were observed in the first-in-human (FIH) study (MOM-M281-001) and the Good Laboratory Practice (GLP) toxicology studies in nonpregnant and pregnant cynomolgus monkeys, with rapid and sustained RO and corresponding self-limited reductions in IgG.

Refer to the Investigator's Brochure for additional details on the nonclinical studies conducted with nipocalimab.

3.2.3. First-in-Human Study: MOM-M281-001

A single ascending dose (SAD)/multiple ascending dose (MAD) study of nipocalimab in healthy normal volunteers, MOM-M281-001, has been completed. In this study, healthy volunteers (28 men; 22 women) received single doses of 0.3, 3, 10, 30, or 60 mg/kg nipocalimab or multiple doses of 15 or 30 mg/kg nipocalimab for up to 4 weeks and were followed for safety and PK for up to 10 weeks. A total of 36 subjects received nipocalimab and 14 subjects received placebo. There were no deaths, serious adverse events (SAEs) including serious infections, or severe adverse events (AEs) in either the SAD or MAD portion of the study, and the majority of treatment-emergent AEs (TEAEs) were transitory, mild, resolved without intervention, and were assessed as unrelated to treatment. Importantly, analyses of serum IgG and FcRn RO confirmed the expected PD effect observed in nonclinical studies of reducing mean circulating total IgG levels by up to 85% from Baseline, as correlated with occupancy of FcRn by nipocalimab and nipocalimab PK. In addition, a moderate decrease in albumin of approximately 25% from Baseline was noted without proteinuria, edema, or any other symptoms or associated change in laboratory values. While nipocalimab does not interfere with albumin binding to FcRn in vitro, the mild albumin decrease may result from some steric hindrance of albumin recycling or transport by nipocalimab. The mild reduction of albumin also correlated with RO by nipocalimab supporting that the effect is mechanistic.

Data from the SAD cohorts demonstrated that nipocalimab exposure increased with increasing dose; the increase in maximum plasma concentration (C_{max}) was dose proportional, while the increase in area under the concentration-time curve (AUC) was greater than dose proportional. Pharmacokinetic data from the MAD cohorts were consistent with the single-dose results, showing increasing exposure with increasing dose. There were no observed differences on exposure, half-life, or systemic clearance related to gender or body weight. Further, there appeared to be a limited accumulation at the trough (pre-next dose) sampling time points, supporting weekly dosing. There were no clinically significant findings with respect to vital signs, electrocardiogram (ECG) findings, physical examinations, body weight, or infusion-related reactions, nor was there any evidence of an increase in the frequency, duration, or severity of infection.

Three subjects in the first MAD cohort (nipocalimab 30 mg/kg) discontinued treatment when two developed predefined alert criteria for low IgG levels (<200 mg/dL) and the third met predefined alert criteria for low *H. influenza* titer (<0.15 µg/mL). The Investigator withdrew the subjects as a precaution even though the findings were not associated with any other laboratory abnormalities, infection, or clinical signs or symptoms. Three subjects in the nipocalimab 15 mg/kg MAD cohort had clinically significant elevations in creatine kinase (CK) levels that were reported as AEs. One of these three subjects also had an increase in alanine aminotransferase (ALT) levels that was reported as an AE. The increased enzyme levels were transitory, asymptomatic, and were normalized before the end of the study. The AEs were considered related to the study drug as judged by the Investigator and led to discontinuation of these subjects from the study. Creatine kinase elevations did not occur in the higher 30 mg/kg MAD group so there was no dose relationship to this finding.

Refer to Section 3.3.1 and the Investigator's Brochure for additional results from Study MOM-M281-001 and other completed and ongoing studies of nipocalimab including the effect of nipocalimab on lipids.

3.3. Risk/Benefit Assessment

3.3.1. Known Potential Risks

Nipocalimab has not been previously administered to pregnant women, thus the risks of nipocalimab exposure are inferred from preclinical toxicology studies and from the FIH study in healthy normal volunteers (Study MOM-M281-001). The FIH study contained a SAD part and a MAD part.

The risk profile of nipocalimab is closely related to its mechanism of action. FcRn binds and mediates intracellular recycling of both IgG and serum albumin. The protective effect of intracellular recycling on IgG and albumin clearance plays an important role in establishing the steady-state concentrations of IgG and albumin. Thus, nipocalimab inhibits FcRn, abolishing recycling and leads to decreases in serum IgG concentrations until the fractional catabolic rate equals IgG synthesis, with sustained FcRn and recycling blockade by nipocalimab, IgG stabilizes at a lower steady-state IgG level. Decreases in IgG levels are an anticipated PD effect of nipocalimab and contribute to its potential benefit in HDFN. It is important to note that the normal immune response to produce IgG in response to a foreign antigen is not affected (Investigator's Brochure for nipocalimab).

3.3.1.1. Nonclinical Placental Findings

Placental infarcts were observed in 4 nipocalimab-treated cynomolgus monkeys in the ePPND phase of a reproductive toxicology study (see Section 3.2.2 and the Investigator's Brochure for further details). The relationship of placental changes in cynomolgus monkeys to nipocalimab administration was uncertain and a direct effect of nipocalimab on the placenta could not be completely excluded. Placental infarction could lead to reduced placental function and, as a result, inadequate fetal growth and development. Monitoring procedures for intrauterine growth restriction (IUGR) and a stopping rule for administration of nipocalimab to individual patients (Section 7.1.1.6), as well as a study stopping rule for IUGR/abnormal growth (Section 7.1.2) are included in this protocol.

3.3.1.2. Reduction in Circulating Maternal IgG

In the FIH study, reduction in circulating IgG was observed in all SAD and MAD nipocalimab-treated healthy volunteers. Reductions from baseline were minimal at single doses of 0.3 to 3 mg/kg and reached a maximum of ~85% following multiple doses of ≥15 mg/kg. The absolute value of serum IgG nadir ranged from 0.86 to 2.85 g/L in MAD cohort subjects (15 and 30 mg/kg) who had Baseline serum IgG levels within the normal range. The rate of reduction in serum IgG was independent of dose, but the duration of reduction was dose dependent. In the 30 mg/kg MAD group, serum IgG concentrations declined to approximately 20% of baseline within 14 days of the first dose. Recovery of IgG from the maximum sustained nadir began approximately 14 days after the last dose. IgG recovery followed an asymptotic approach to within 80% to 100% of baseline approximately 6 to 13 weeks after the last dose. IgG recovery rate correlated to initial baseline serum IgG concentration, where subjects with higher IgG baseline values had faster overall recovery rates.

Concentrations of IgG decline during pregnancy by approximately 40% due to hemodilution, as a result of the increase in plasma volume associated with advanced gestation. Nipocalimab is anticipated to further reduce the IgG concentration when administered in pregnancy.

IgG plays a major role in defense against infections and is involved in other aspects of immune response. The normal concentration of IgG in subjects without immunodeficiency is reported to range between 600 to 1600 mg/dL with a mean of 989 mg/dL (Boyle and Buckley, 2007). Thus, a reduction in IgG may entail an increased risk for infection. However, the degree of risk should take into account the following:

- The primary mechanism by which nipocalimab reduces IgG is increased clearance through reduced intracellular recycling. Other causes of clinical hypogammaglobulinemia due to increased clearance include loss through the gut in severe enteropathies, loss through the kidney in renal amyloidosis, and direct removal from the blood through plasmapheresis or immunoadsorption therapy (Blot, 2014). Among these, immunoadsorption therapy appears most similar in effect to that of nipocalimab, in that it efficiently reduces circulating IgG (Gjörstrup, 1990). However, immunoadsorption is also associated with reductions in IgA, and IgM as well as complement components C3c and C4 (Koll, 1998). Published studies of immunoadsorption without IVIG substitution have not reported any significant risk for infection (0.9-1.3 per patient year), even when circulating IgG levels are maintained between 70% and 95% of baseline over a prolonged period (~ over 1 year) (Furst, 2008; Paglialonga, 2015; Schmaldienst, 2001; Stumvoll, 2004; Stumvoll, 2012). The overall experience in settings of increased IgG clearance leading to reduced circulating IgG levels suggest that, in the context of normal B/T cell function and antibody production, there does not appear to be a clinically significant increased risk for infection (Furst, 2008).
- In contrast, conditions that produce hypogammaglobulinemia due to reduced *production* of immunoglobulins are often reported to have increased risk of infection. These include malignancies such as multiple myeloma and chronic lymphocytic leukemia; infections such as human immunodeficiency virus (HIV), Epstein-Barr virus and cytomegalovirus; chronic immune suppression using medications that deplete or impair B cells, such as rituximab or mycophenolate; and inherited or "primary" abnormalities such as common variable immunodeficiency (Blot, 2014). In a study of 389 patients with a wide variety of secondary causes of hypogammaglobulinemia, the incidence of infection was 22/100/year with no difference observed between those who had total gamma globulin levels (IgG, IgM, and IgA) less than 500 mg/dL compared with those who had levels between 500 and 640 mg/dL (Blot, 2014).

These observations are consistent with a hypothesis that hypogammaglobulinemia from increased clearance is distinct from hypogammaglobulinemia from decreased production; in the former, functional IgG continues to circulate and functional B cells may still upregulate expression depending on immune challenge, while these processes are absent or defective in the latter. This suggests that the risk of increased infections associated with nipocalimab treatment may be low.

3.3.1.3. Reduction in Serum Albumin

Serum albumin decreased from Baseline by 20% to 25% in the FIH study. The mild hypoalbuminemia seen in the FIH study was asymptomatic and self-limited over the duration of dosing and recovered rapidly following dose cessation. In pregnancy, hypoalbuminemia occurs due to hemodilution and is manifested typically by ankle and pedal edema, which is addressed by instructing the patient on elevation of the lower extremities, diet, movement, or the use of compression stockings.

Albumin has several important physiologic functions. Albumin is responsible for maintaining normal plasma colloid oncotic pressure. Edema will develop when oncotic pressure declines significantly. Albumin transports various substances, including bilirubin, fatty acids, metals, ions, hormones, and exogenous drugs. One consequence of hypoalbuminemia is that drugs that are usually protein bound are free in the plasma, allowing for higher drug levels, more rapid hepatic metabolism, or both. Significant alterations in albumin level may affect platelet function.

In the current Phase 2 study, nipocalimab albumin reduction is likely to be self-limited as in the FIH study. The potential development of severe symptoms of hypoalbuminemia with nipocalimab is unlikely for several reasons. Severe hypoalbuminemia in individuals with extremely low albumin levels (less than 1 to 2 g/L) as is seen in congenital analbuminemia is typically associated with mild ankle edema or asymptomatic presentation (Del Ben, 2013; http://albumin.org/register-of-analbuminemia-cases/). Oncotic pressure loss is compensated by increased serum cholesterol, which can occur rapidly in response to large changes in serum albumin (Kaysen, 1987). Albumin also has a high rate of synthesis which unlike IgG is responsive to changes in serum albumin concentration (Kaysen, 1987). In late human pregnancy, intravascular albumin mass increases due to synthesis compensating for hemodilution (Olufemi, 1991). Since the fetus makes its own albumin and albumin is not transported across the placenta, maternal hypoalbuminemia will have no impact on fetal albumin (Gitlin, 1964; van den Akker, 2008). Thus, the potential for development of serious adverse effects of hypoalbuminemia due to nipocalimab treatment are low, monitorable, and manageable.

The potential for hypoalbuminemia during treatment with nipocalimab will be monitored. Refer to Section 7.1.1.4 and Section 8.2.1.1.2 for guidance on further assessments and actions to be taken for hypoalbuminemia.

3.3.1.4. Potential Elevations in Creatine Kinase

As discussed in Section 3.2.3, 3 subjects in the 15 mg/kg MAD cohort of the FIH study discontinued nipocalimab due to asymptomatic CK elevations that were identified as mild, treatment-related AEs and appeared to be of skeletal muscle origin. Creatine kinase elevations did not occur in the higher 30 mg/kg MAD group; thus, no dose relationship was observed for this finding. Transient elevations of CK are often seen in normal populations after sporadic exercise or increased intensity of exercise, minor or major trauma, or drug or alcohol use (Moghadam Kia, 2016). In Phase 1 studies in outpatient healthy volunteers, ALT and CK elevations were the most common deviations from safety parameter reference ranges (Young, 2017). The magnitude of these elevations may be influenced by sex, age, and temperature extremes (Baird, 2012). Creatine kinase levels and subtypes (MB fraction – if CK is elevated) will be monitored as part of ongoing safety laboratory testing in the current study (see Section 3.3.3.3 and Table 7).

3.3.1.5. Potential Reduction in Neonatal Passive Immunity

Transport of IgG across the placenta is mediated by FcRn receptor binding and active transport. Thus, blockage of FcRn by nipocalimab will block placental transfer of IgG. This phenomenon is one of the 2 main mechanisms of potential benefit of nipocalimab in preventing EOS-HDFN by blocking pathologic alloantibodies from crossing the placenta and lysing fetal RBCs. However, the transport of beneficial maternal IgG, which provides initial immunity against environmental antigens during the first months after birth, may also be blocked (newborn IgG production is limited during the first months of life). Family "cocooning" will be recommended.

It is important to note that the fetus and neonate produce IgM endogenously and obtain IgA and other anti-infective proteins through breast milk, while fetal and neonatal IgG up to 4 to 5 months of age is derived primarily from placental transfer of maternal IgG. Therefore, it is anticipated that the neonate will still benefit from protective mechanisms outside of IgG concentrations, including IgM, IgA and other breast milk-derived anti-infective proteins and fully functional humoral and innate immunity including production of IgG.

Otherwise healthy infants born from mothers who received nipocalimab have been found to have immunoglobulin serum concentrations (IgG, IgM, IgA) below normal range or at the lower limit of normal range for up to 1 year (depending on the reference normal range used). It is uncertain whether these low immunoglobulins will persist, and whether they are related to the underlying condition or treatment with nipocalimab. The clinical implications of this finding are not known.

3.3.1.6. Increased Lipids

Elevations in total cholesterol and low-density lipoprotein (LDL) were reported recently with another experimental drug in the same pharmacological class of FcRn antagonists.

In the MOM-M281-001 and MOM M281-004 (a Phase 2 study in myasthenia gravis) studies, asymptomatic, dose dependent, reversible elevations in non-fasting mean total cholesterol were observed up to 25% of baseline. In both studies, elevations in total cholesterol appear to mirror the kinetics of the decreases in albumin observed with nipocalimab.

In pregnant women in the current study MOM-M281-003, a preliminary review suggested a possible treatment-emergent increase in non-fasting total cholesterol higher than published reference values expected during normal pregnancies (ie, physiologic increases for the appropriate gestational age). The cholesterol elevations observed in pregnant women decreased after nipocalimab discontinuation and returned to baseline values after delivery.

3.3.2. Known Potential Benefits

The potential benefit of the current study is prevention of potential complications from severe HDFN including fetal anemia, hydrops, and in some cases, fetal demise or neurodevelopmental deficit or delay (Lindenburg, 2012). At present, the only effective treatment to date for severe HDFN is one or more IUT. Intrauterine transfusion is a complex and resource intensive procedure with procedural complication rates resulting in fetal demise ranging from 20% per case in EOS-HDFN, to an estimated 1% to 5% per case in moderate to severe HDFN (Lindenburg, 2014). Furthermore, the technical challenges of IUT early in pregnancy (GA Week <24) are such that the expertise to perform these procedures is limited to tertiary health

care centers, and as such may not be available to patients unwilling or unable to travel long distances for their care.

3.3.2.1. Immediate Potential Benefits

Nipocalimab may provide a pharmacological alternative to IUT for the treatment of EOS-HDFN for the women in this study through blockage of IgG binding to FcRn receptors in the blood and placenta by a dual mechanism of action:

- Blockage of maternal transfer of IgG through the placenta including pathogenic alloantibodies to the fetal circulation, and
- Lowering of maternal IgG concentrations including pathogenic alloantibody titers that are available to transfer through the placenta to the fetus.

Nipocalimab has demonstrated significant pharmacologic effects in nonhuman primates and healthy human volunteer studies that, if repeated in pregnant patients in the current study, will potentially benefit the pregnant patient by delaying the time of first IUT or eliminating the need for IUT, thus increasing the likelihood of a successful pregnancy/healthy birth. Intrauterine transfusions and other invasive therapies or diagnostic therapies for HDFN increase the risk for further alloimmunization and increase the likelihood of more severe disease in the next pregnancy. Postnatal therapies such as exchange transfusions are also associated with risk to the neonate (Smits-Wintjens, 2013).

The dose and duration of nipocalimab administration selected, 45 mg/kg weekly administered from GA Week 14 to GA Week 35, is predicted to fully block FcRn throughout the critical time period during pregnancy, resulting in reduced or absent placental transfer of pathologic maternal alloantibodies.

3.3.2.2. Long-Range Potential Benefits

Many women with EOS-HDFN choose not to become pregnant again because of the known risks and intensive treatment required to achieve a successful pregnancy and healthy infant. Currently it may not be possible for all women with EOS-HDFN to obtain the best treatment, since IUTs are only performed at a limited number of experienced tertiary health care centers.

Since the technical difficulty of an IUT is reduced if performed later in pregnancy, increasing the GA at first IUT and decreasing the total number of IUTs would provide greater benefit in decreased procedural risk to fetus and mother by decreasing both the early GA-related per procedure risk and the accrued procedure risk associated with multiple IUTs.

Importantly, HDFN is associated with neurodevelopmental deficits (eg, bilateral deafness or blindness, cerebral palsy, severe developmental delay), which occur at an overall rate of 4.8% and with increased risk in cases with decreased fetal hemoglobin, increased number of IUTs, increased neonatal morbidity and gestational age at birth results (Lindenburg, 2012). The ability of nipocalimab to block or greatly decrease alloantibody transfer to the fetus suggests that it can prevent these sequelae of pathogenic alloantibody induced anemia. Also, given that repeated IUTs increase the potential for alloimmunization in the current pregnancy, pharmacologic treatments are needed to address this unmet need and expand access and treatment options for patients with EOS-HDFN.

If nipocalimab is proven to be safe and effective in this and future studies, it could provide a pharmacologic alternative to IUT for the management of EOS-HDFN, with the promise of better outcomes with less invasive treatment and greater access to effective treatment of EOS-HDFN.

3.3.3. Management of Potential Risks

3.3.3.1. Infection

Given the theoretical potential for increased infection risk with reduced circulating IgG levels, procedures have been included in this protocol to reduce the theoretical risk of increased maternal infection:

- Patients at high risk of infection, such as history of pyelonephritis or recurrent lower urinary tract infections (UTIs) in a previous pregnancy will be excluded from the trial. Patients with a history of genital herpes infection will also be excluded. In addition, laboratory evidence of immunity to various viral diseases such as varicella, measles, mumps, and rubella is a required inclusion criterion.
- Patients with a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine/metabolic, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or severe or recurrent infections (eg, frequent hospitalized pneumonia), or any other condition or issue that, in the opinion of the Investigator, would jeopardize the safety of the patient or fetus/neonate/infant will be excluded from the trial.
- Influenza (seasonal) and pneumococcal polysaccharide 23-valent (PPSV23) vaccines will be administered during pregnancy.
- If maternal IgG concentration falls below 1.0 g/L at any time during the study, the Investigator will contact the patient as soon as possible by phone. The patient will be queried about infection-related symptoms and if the Investigator has any concerns, they will instruct the patient to return to the site for an unscheduled visit. The patient will also be reminded of the steps to prevent contraction of infection (eg, frequent hand washing and good hygiene, avoiding exposure to individuals with upper respiratory or other infections, handling and preparing food safely, etc).
- Routine maternal screening for Group B Streptococci will be performed for all patients at GA Week 34 and antibiotic prophylaxis administered for patients with a positive culture (see Section 8.2.1.5).
- In the case of delivery by Cesarean section (C-section), prophylactic antibiotics will be administered in the perioperative delivery period based on assessment of the maternal vaginal microbiome obtained at GA Week 34 (see Section 8.2.1.5).
- Patients will be asked to practice frequent handwashing and avoid crowds and proximity to individuals with known infections, particularly influenza.
- Nipocalimab administration will be stopped at GA Week 35, 2 weeks before delivery at GA Week 37. This will allow time for limited recovery of IgG.

- In addition, IVIG will be administered to the mother (if not contraindicated) 48 to 72 hours prior to delivery to help boost IgG at the time of delivery. For unscheduled (eg, urgent or emergency) delivery, IVIG will be given before delivery or as soon as possible after delivery (see Section 8.2.1.6 for further details on IVIG administration for maternal patients).

Study assessments will include evaluation of maternal safety (AEs, AEs of special interest [AESI], defined for this study as infections requiring treatment with oral or intravenous [IV] antibiotics/antivirals/antifungals and maternal hypoalbuminemia ≥ Grade 3, SAEs, and laboratory assessments), as well as assessment of maternal total IgG levels and subclasses, IgM, IgA, and IgE levels, FcRn RO, and alloantibody levels.

3.3.3.2. Monitoring for Hypoalbuminemia

Risk mitigation strategies for hypoalbuminemia include monitoring of maternal patients for signs and symptoms of edema during the weekly physical examination and biweekly (every 2 weeks) safety laboratory assessments of albumin throughout the gestational period and in early postpartum follow-up. If edema is observed, mitigation strategies for edema in normal pregnancy, such as the use of compression stockings for pedal edema, can be employed. Hypoalbuminemia ≥ Grade 3 (ie, <20 g/L by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0) will be considered an AESI (handled like an SAE and reviewed by the Data Safety Monitoring Board [DSMB]), and individual patient and study stopping criteria related to the co-occurrence of severe hypoalbuminemia with severe edema are included in this protocol (see Section 7.1.1.4 and Section 7.1.2).

3.3.3.3. Monitoring for Potential Elevations in Creatine Kinase

As discussed in Section 3.2.3 and Section 3.3.1.4, 3 subjects in the 15 mg/kg MAD cohort of the Phase 1 study (MOM-M281-001) discontinued nipocalimab due to asymptomatic CK elevations that were identified as mild, treatment-related AEs and appeared to be of skeletal muscle origin. Creatine kinase elevations did not occur in the higher 30 mg/kg MAD group; thus, no dose relationship was observed for this finding.

Monthly monitoring of CK and liver enzymes with reflexive creatine kinase-muscle/brain (CK-MB) isozyme follow-up in case of elevated CK will be done as a precaution in the current study. In addition, weekly physical examination allows for monitoring of clinical signs or symptoms, which may develop in association with elevated CK or any other adverse effects of nipocalimab. Finally, patients are cautioned not to exercise heavily as part of the standard of care for a mother with HDFN, which may help in the interpretation of elevated CK if it occurs during the current study.

3.3.3.4. Fetal Monitoring for Growth

While the potential for nipocalimab to produce placental infarcts in human pregnancy that would negatively impact fetal development is low, frequently monitoring for growth (an adverse consequence of placental infarction) is incorporated as a safety assessment in the current study (see Section 8.2.1.10 and Section 8.2.1.11). Fetal growth monitoring by ultrasound biometry will be conducted every 2 weeks in accordance with clinical management guidelines for suspected

IUGR (McCowan, 2018), and, if estimated fetal growth is below the 10th percentile, weekly fetoplacental vascular monitoring of umbilical and uterine arteries by Doppler will be done, which will inform for associated individual patient and study stopping criteria (see Section 7.1.1.6, Section 7.1.2, and Appendix 2). In the unlikely event that 1) an IUGR stopping rule is met and 2) the condition was caused by a nipocalimab placental infarct, stopping nipocalimab administration may prevent further placental infarction so that the placenta can continue to grow to provide adequate support for the growing fetus.

3.3.3.5. Reduction of Neonatal Immunity

Transport of IgG across the placenta is mediated by FcRn receptor binding and active transport. Thus, blockage of FcRn by nipocalimab will block placental transfer of IgG, which provides immunity to the neonate during early life. Family "cocooning" will be recommended – immunization of direct family contacts with the neonate, per local guidelines. Only placental transfer of the subclass IgG may be blocked by nipocalimab.

Several procedures have been included in this protocol to help reduce the potential risk from blocked transfer of maternal IgG immunity:

- The neonate's risk of infection and total IgG concentration in cord blood will be taken into account to determine whether IVIG is to be administered (see Section 8.2.2.1 for further details). IVIG (500 mg/kg) may be administered (if not contraindicated) within 48 hours according to the neonate's risk of infection and cord blood total IgG concentration assessed at a local laboratory.
- Nipocalimab administration will be discontinued at GA Week 35, 2 weeks before delivery, which will provide some time for IgG recovery and placental transfer of maternal immunity. IVIG will be administered to the mother (if not contraindicated) 48 to 72 hours before delivery to maximize the transfer of IgG to the fetus after nipocalimab administration (and therefore FcRn block) has been discontinued (see Section 8.2.1.6 for further details). In addition, maternal administration of tetanus diphtheria pertussis (Tdap) vaccine will be delayed from GA Week 28 to GA Week 31 so that peak immune response to the vaccine is available for placental transfer at time of delivery.
- All patients will be tested for vaginal microbiome at Baseline, and for Group B Streptococcus (GBS) and vaginal microbiome at GA Week 34. All patients testing positive for GBS will receive GBS antibiotic prophylaxis. Vaginal microbiome results will inform selection of antibiotic prophylaxis for patients who are delivered by C-section (see Section 8.2.1.5).
- Caregivers and family of the neonate/infant will be asked to practice frequent hand washing and to ensure that their vaccinations are up to date as per local medical guidelines.
- Although nipocalimab is not expected to be transmitted to maternal breast milk in clinically meaningful quantities, as a safety precaution colostrum/breast milk samples will be collected on Postnatal Day 1 and 7 to determine if nipocalimab present.

Following delivery, neonates will have cord blood drawn at birth to document antigen positive status as well as to measure nipocalimab concentration, hemoglobin, hematocrit, reticulocyte count, direct Coombs, total and direct bilirubin, alloantibody, FcRn RO, and immunoglobulin levels. Neonates will be followed for evaluation of safety, growth, and general development for a total of 96 weeks from birth. Safety evaluations will include safety laboratory assessments; physical examinations (including APGAR [appearance, pulse, grimace response, activity, respiration] scores at 1 and 5 minutes after birth); reporting of AEs, AESIs (infections requiring treatment with oral or IV antibiotics/antivirals/antifungals unusual/unexpected childhood illnesses/IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96), SAEs, concomitant medications, and assessment of IgG and alloantibody levels as well as lymphocyte phenotyping.

- The occurrence of low concentrations of immunoglobulins in infants will be assessed by monitoring of IgG, IgM, IgA, and IgE concentrations through Week 96 (Section 8.2.2.2). In addition, vaccine titers to diphtheria/tetanus in infants will be assessed at Weeks 24, 48, and 96 to assess immune function. A consult with a pediatric immunologist should be obtained if the total IgG concentrations in the neonate/infant are <200 mg/dL at Week 24 and a vaccine titer is negative for an antibody response to either diphtheria/tetanus. If total IgG concentrations are <300 mg/dL at Weeks 48 and/or 96, consultation with a pediatric immunologist should be obtained if not done previously and regardless of vaccine titer. IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96 will be considered AESIs (Section 8.3.7).

3.3.3.6. Lipids

Patients with a history of myocardial infarction, stroke, or unstable ischemic heart disease will be excluded from participation in the study. Routine laboratory investigations for lipid panel (total cholesterol, LDL, HDL, triglycerides) will be monitored in the study. In patients with elevated lipids (cholesterol >400 mg/dL [10.34 mmol/L] or triglycerides >500 mg/dL [5.65 mmol/L], fasting or non-fasting) at any time during the study, it is recommended that investigators monitor and take appropriate actions for dyslipidemia during pregnancy as per local health guidelines. The lipid panel should be repeated at the subsequent visit (in approximately 1 week) under fasting conditions. If lipid levels remain elevated, investigators are recommended to incorporate changes per local practice such as dietary and lifestyle modifications.

Table 3: Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the safety in mother and neonate/infant of nipocalimab administered to pregnant women at high risk for EOS-HDFN.	• Incidence and severity of AEs, SAEs, and AESIs (ie, infections requiring use of oral or intravenous anti-infectives in the patient; maternal hypoalbuminemia ≥ Grade 3) • Absolute and change from baseline values in ECG, laboratory, and vital sign parameters • Further evaluations will be applied for select variables (ADA, fetal biometry, etc), if warranted	This clinical trial will be the first study of nipocalimab in a pregnant population. A particular focus of the safety evaluation will be to assess the impact of predicted lowering of concentrations of IgG and albumin.
To evaluate the efficacy of nipocalimab as measured by proportion of patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy.	• Proportion of patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy	This is an objective endpoint that is indicative of effective treatment for HDFN.
Secondary		
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.	• Percentage of patients with live birth • Percentage of patients at GA Week 24 without an IUT • GA at first IUT • Number of IUTs required • Gestational age at delivery • Percentage of patients with fetal hydrops • Percentage of neonates requiring phototherapy • Percentage of neonates requiring exchange transfusions • Number of days of phototherapy required by neonate • Percentage of neonates requiring simple transfusions in the first 12 weeks of life • Number of simple transfusions required by neonate in the first 12 weeks of life	The need for IUT, neonatal transfusions, and phototherapy are expected outcomes of EOS-HDFN under standard of care. Reduction of the need for these treatments would be indicative of effective treatment for HDFN. The later in pregnancy a first IUT is needed, the fewer IUTs are needed for the entire pregnancy. In addition, the technical difficulty of an IUT is reduced if performed later in pregnancy. Increasing the GA at first IUT and decreasing the total number of IUTs would provide greater benefit in decreased procedural risk to fetus and mother by decreasing the early GA-related per procedure risk and the accrued procedure risk associated with multiple IUTs. Avoidance of all IUTs would markedly decrease procedural risk of complications and fetal demise. Procedural risk of IUT is highest before GA Week 24.

Table 3: Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		Neonatal transfusions, especially exchange transfusions risk other health consequences and require intensive medical support. Phototherapy requires hospitalization and additional medical resources. Secondary endpoints include decreased neonatal therapies, which reflect decreased disease severity as well as decrease risks associated with exchange transfusions.
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	• Maternal FcRn RO and levels of maternal IgG and alloantibodies	These pharmacodynamic endpoints measure nipocalimab activity through its mechanism of action, ie, blocking FcRn. PD assessments over the course of treatment together with PK are to confirm the projected PK/PD relationship in pregnant women across GA of treatment. Receptor occupancy is a potential biomarker of placental IgG transfer blockade. The anticipated reduction of IgG and alloantibody titers in correspondence with RO will confirm the mechanism of action.
To evaluate the PK of nipocalimab	• Serum PK profile of nipocalimab in maternal patients	The PK profile of nipocalimab has not yet been assessed in pregnant patients. It is necessary to fully interpret the dose selection, safety and efficacy of nipocalimab in pregnant patients. Sparse sampling serum nipocalimab levels will be determined to minimize blood sampling requirements.

Table 3: Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Exploratory		
	• Fetal hemoglobin, hematocrit, and alloantibody levels at first IUT and in subsequent IUTs • Maternal serum levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE • Presence of nipocalimab in colostrum/ breast milk • Placental evaluation • Neonatal bilirubin, direct Coombs, reticulocyte count, hemoglobin, hematocrit, IgG, alloantibodies, and FcRn RO (all measured from cord blood at birth) • Peak bilirubin levels during the neonatal period • Number of IVIG doses received by neonate • Slope of MCA-PSV by Doppler ultrasound.	Selected fetal and neonatal assessments from cord blood help determine whether fetal hemolysis has been prevented. Subclass Ig antibody levels are useful in determining the specific effects of nipocalimab on isotypes of Ig and subclasses of IgG, representing the possible different subclasses of pathogenic IgG. Slope of MCA-PSV prior to first IUT reflects the onset and severity of fetal anemia (Detti, 2002).

ADA = antidrug antibody; AE = adverse event; AESI = adverse events of special interest; ECG = electrocardiogram; EOS = early onset severe; FcRn = neonatal Fc receptor; GA = gestational age; HDFN = hemolytic disease of the fetus and newborn; Ig = immunoglobulin; IUT = intrauterine transfusion; MCA = middle cerebral artery; PD = pharmacodynamic; PK = pharmacokinetic; PSV = peak systolic velocity; RO = receptor occupancy; SAE = serious adverse event.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicenter, open-label study to evaluate the safety, efficacy, PD and PK of nipocalimab, a fully human monoclonal antibody against FcRn, in pregnant women at high risk for EOS-HDFN. Blockade of FcRn by nipocalimab is intended to reduce the risk and severity of fetal anemia by blocking FcRn-mediated IgG recycling, thereby reducing pathogenic antibody in maternal circulation and the transfer of maternal IgG, including pathogenic alloantibodies, to the fetus.

The study will be conducted at centers with expertise in maternal-fetal medicine and the treatment of HDFN. Patients will be screened for inclusion between GA Week 8 up to 1 day before the Baseline day (GA Week 14 ±6 days). All screening assessments and confirmation of eligibility must be completed at least 1 day before the Baseline day. To be eligible for the study, patients must have an obstetrical history of severe fetal anemia, hydrops, or stillbirth related to HDFN at GA Week ≤24, have titers for anti-D ≥32 or anti-Kell titers ≥4, and be pregnant with an antigen-positive fetus. Patients pregnant with multiples, or those with pre-eclampsia in the current pregnancy or history of pre-eclampsia in a previous pregnancy, gestational hypertension in the current pregnancy, current unstable hypertension, severe or recurrent pyelonephritis or >4 lower UTIs in the past year or in a previous pregnancy, or other active infections will be excluded from the study. Also excluded from study participation will be patients who require treatment with corticosteroids or immunosuppression for disorders unrelated to pregnancy, those having a history of drug allergy, hypersensitivity to a drug product that would compromise patient safety, smoking during pregnancy, clinically significant systemic disease, severe or recurrent infections, ongoing alcohol/substance abuse/dependence, or those who received an investigational drug and/or device within 30 days or 5 half-lives prior to receiving the first IV infusion of nipocalimab.

Enrolled patients will receive once weekly IV infusions of nipocalimab 45 mg/kg starting on the Baseline day (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. Patients will be tested for GBS and vaginal microbiome at GA Week 34. Those who test positive for GBS will receive GBS antibiotic prophylaxis. Patients delivering by C-section will have prophylactic antibiotic therapy guided by the vaginal microbiome testing (see Section 8.2.1.5). Patients will receive IVIG (500 mg/kg) 48 to 72 hours before delivery (if not contraindicated); for early/unscheduled (eg, urgent or emergent) delivery, IVIG will be given before delivery or as soon as possible after delivery (see Section 8.2.1.6).

Although nipocalimab is not expected to be transmitted to maternal breast milk in clinically meaningful quantities, colostrum/breast milk samples will be collected on Postnatal Day 1 and 7 for an exploratory analysis to determine if nipocalimab is present. The patients are allowed to breastfeed their infant and should be encouraged and supported by the Investigator and study staff to do so.

During the treatment period, study assessments will include evaluation of maternal safety (including AEs, SAEs, AESIs, physical examinations, vital signs, pulse oximetry, weight, ECG, and clinical laboratory tests including lipid panel), as well as total IgG levels and IgG subclasses,

FcRn RO, anti-nipocalimab antibody levels, and alloantibody titer. Fetal heart rate monitoring will be employed at each nipocalimab infusion to evaluate for abnormalities in heart rhythm and rate. Continuous monitoring of uterine activity will also be employed at each nipocalimab infusion from weeks 26 to the last infusion. Fetal health will be assessed by frequent ultrasound assessments (at least every 2 weeks). If evidence of low fetal weight is detected, weekly Doppler ultrasound monitoring of umbilical and uterine arteries will be instituted to assess utero-placental blood flow and to identify placental insufficiency (see Section 7.1.1.6).

Enrolled patients will be carefully monitored for signs/symptoms of infection throughout the study and treated with anti-infectives as per local medical practice. Patients must have evidence of immunity for measles, mumps, rubella, and varicella as documented by serologies performed during screening to be included in the study, and immunizations to pneumococcus, influenza and diphtheria/tetanus/pertussis will be administered during the pregnancy per the protocol. In addition, patients will be asked to practice frequent handwashing and avoid crowds and proximity to individuals with known infections, particularly influenza. Caregivers and family of the neonate/infant will similarly be asked to practice frequent hand washing and to ensure that all of their vaccinations are up to date. Use of IVIG outside of study-related IVIG administration and/or plasmapheresis therapy for the management of HDFN is prohibited during the study; use of IVIG for the treatment of infection should only be considered if the infection is severe and the patient has been discontinued from treatment with nipocalimab (see Section 7.1.1.3).

The fetus will be monitored for anemia via weekly assessment of PSV of the MCA via Doppler ultrasonography from GA Week 14 (±6 days) to GA Week 36. As per the current standard of care, if the PSV is ≥1.5 times the median PSV for the estimated GA of the fetus, a cordocentesis will be performed to ascertain fetal anemia. If confirmed, fetal anemia will be treated with IUT as per standard of care. If a cordocentesis is required and performed, fetal cord blood will be collected (if possible) for analysis of hemoglobin, hematocrit, direct Coombs, reticulocyte count, nipocalimab concentration, alloantibody, FcRn RO, and IgG levels.

Following delivery, maternal patients will be monitored for 24 weeks for safety (safety laboratory assessments, abbreviated physical examinations, AEs, SAEs, AESIs) as well as for levels of IgG, nipocalimab, antidrug antibody (ADA), and FcRn RO. Patients who discontinue treatment prematurely will complete end of treatment (EOT) assessments within 2 weeks of their last dose of nipocalimab and continue safety follow-up assessments as noted in Section 7.1.1).

Nipocalimab is not expected to cross the placental barrier in clinically meaningful quantities or have any effect on the fetus/neonate. Neonates/infants will be followed for a total of 96 weeks from birth. Evaluations during the first 24 weeks of safety follow-up include safety laboratory assessments, physical examinations (APGAR scores at 1 and 5 minutes after birth; subsequent physical examinations to include length/height, weight, and head circumference), vital signs, AEs, concomitant medications, and assessment of IgG and alloantibody levels, as well as lymphocyte phenotyping and vaccine titer to diphtheria/tetanus. SAEs and AESIs will be collected for 96 weeks (~2 years) from birth.

Neonates will have cord blood drawn at birth to document antigen positive status as well as to measure nipocalimab concentration, hemoglobin, hematocrit, reticulocyte count, direct Coombs, total and direct bilirubin, alloantibody, FcRn RO, and total IgG levels. They may receive IVIG (500 mg/kg) within 48 hours of birth based on their risk of infection and total IgG concentration

in cord blood (criteria for IVIG administration are detailed in Section 8.2.2.1), with measures taken to minimize discomfort

Neonates/infants will receive vaccinations per the standard of care at their location. Infant neurodevelopment will be monitored using the parent-reported developmental assessment, Ages & Stages Questionnaires®, Third Edition (ASQ-3). In addition, the Pediatric Quality of Life Inventory (PedsQL) will be completed by the parent/guardian at Week 96.

Total time on study will be approximately 50 weeks for each pregnant woman entering the study and 96 weeks for each child born during the study. This includes a maternal screening period of up to approximately 6 weeks, a treatment period of approximately 20 weeks, a 24-week postnatal safety follow-up period for mothers, and a 96-week follow-up period for all neonates/infants.

Guidance for study related participant management during the Coronavirus Disease 2019 (COVID-19) pandemic is provided in Appendix 5.

4.2. Scientific Rationale for Study Design

This is a Phase 2 multicenter open-label study to evaluate the safety, efficacy, PD, and PK of nipocalimab, a fully human monoclonal antibody against FcRn, in pregnant women at high risk for early onset severe HDFN. Blockade of FcRn by nipocalimab is intended to reduce the risk and severity of fetal anemia by blocking FcRn-mediated IgG recycling, thereby reducing pathogenic antibody in maternal circulation and reducing the transfer of maternal IgG, including pathogenic alloantibodies to the fetus, thus reducing or eliminating the need for invasive treatments such as IUTs and postpartum care related to HDFN (simple or exchange transfusions, or phototherapy for hyperbilirubinemia).

4.2.1. Justification for Study Design

This study is an open-label, single-arm study in pregnant patients who are at high risk for EOS-HDFN in the current pregnancy and who otherwise are in good general health. Pregnant patients eligible for the current study are women who have already had documented EOS-HDFN in a prior pregnancy (eg, severe fetal anemia, fetal hydrops, or stillbirth at ≤ GA Week 24 and current evidence of disease; see Section 5.1). The target enrollment of approximately 15 patients is appropriate for a rare disease, and recruitment and enrollment will be at multiple centers specializing in maternal-fetal medicine.

The open-label, single-arm design is based on a combination of clinical and scientific considerations. Considering the anticipated efficacy of nipocalimab and the fact that current best standard of care at centers of excellence for EOS-HDFN requires multiple IUTs and still carries an up to 24% risk of fetal demise (Yinon, 2010; Lindenburg, 2013; Poissonnier, 2003; Canlorbe, 2011; Schonewille, 2007; Zwiers, 2017a), patients randomized to a standard of care control group would have no potential for future benefit since, unlike in trials of chronic diseases where control patients can cross over to investigational product after completing the controlled treatment period, the opportunity to provide treatment in a pregnancy study such as MOM-M281-003 essentially ends with either the demise or birth of the offspring.

The expected perinatal outcome in the study population of EOS-HDFN under standard of care is well understood and the primary efficacy endpoint (and key secondary endpoints) are derived from objective criteria. Efficacy will be measured using objective measurements of the need and

timing for IUT (GA), as determined by monitoring for fetal anemia beginning at GA Week 14, and the proportion of patients with live birth at or after GA Week 32.

The expected perinatal outcome in patients receiving standard of care with EOS-HDFN is that all patients would require multiple IUTs during the pregnancy, with approximately 90% of patients requiring their first IUT ≤GA Week 25 (see Section 9.5.4.1). Furthermore, there is approximately a 20% risk of fetal demise during the pregnancy (Lindenberg, 2013; Yinon, 2010). The anticipated perinatal outcome for patients treated with nipocalimab in this study is that all fetuses will survive, the majority of patients will not require any IUTs, and for those who do require an IUT, the timing of the IUT will be much later in pregnancy when there is less of a risk of complications from IUT than when IUT has to be performed earlier in pregnancy (before GA Week 25).

This anticipated large treatment effect of nipocalimab is based on the well-understood etiology of HDFN, the mechanism of action of nipocalimab, and the clinical pharmacology findings in the Phase 1 study of nipocalimab in healthy volunteers. HDFN is caused by the placental transfer to the fetus of maternal alloantibodies that destroy fetal RBCs. FcRn receptors in the placenta are responsible for placental transport of all antibodies from mother to fetus. There are no other physiologic mechanisms aside from FcRn-mediated transport that contribute to placental transport of maternal antibodies to the fetus. Therefore, full blockade of FcRn would prevent placental transport of maternal alloantibodies and thus prevent HDFN. An additional mechanism contributing to the expected efficacy of nipocalimab in HDFN is that FcRn blockade leads to a reduction in circulating maternal IgG concentrations. Key findings from the Phase 1 clinical pharmacology study included the identification of a dose of nipocalimab which blocked 100% of FcRn receptors throughout the dosing period associated with an 85% reduction of circulating IgG concentrations from Baseline, consistent with the pharmacologic outcome of full blockade of FcRn (see Section 3.2.3 and the Investigator's Brochure for study results from Study MOM-M281-001). In addition to the anticipated large treatment effect, many of the methodologic issues in the interpretation of open-label trial results that are compared to historical data are mitigated in this study, as the efficacy outcomes (and how these outcomes are collected) are objective. Key prognostic criteria for these outcomes in EOS-HDFN are well defined and objective, and the standard of care for the diagnosis and treatment of EOS-HDFN has not meaningfully changed in the past decade. Further, data from the current study with nipocalimab-treated patients will be compared with external control data as described in Section 9.5.4.1 and in the statistical analysis plan (SAP).

Although case reports in the literature describe the use of IVIG and plasmapheresis to delay the time to the first IUT (Ruma, 2007), experts in the field who have been consulted on the current study design have indicated that it is medically appropriate to forego administration of IVIG or IVIG + plasmapheresis (an exclusion criterion in this trial) to patients in favor of nipocalimab treatment based upon its mechanism of action, the potential treatment effect of nipocalimab, and the fact that the treatment effect of IVIG or IVIG + plasmapheresis is unproven and quite modest. Neither IVIG nor plasmapheresis obviate the need for IUT (Ruma, 2007; Schwartz, 2016; Yinon, 2010; Zwiers, 2017a). The design of the current study allows for treatment with the investigational product, nipocalimab, beginning at GA Week 14 (±6 days) to GA Week 35, with close monitoring of both the mother and fetus as well as treatment with IUTs if needed (see Section 8).

Safety of both mother and offspring will be monitored closely in this study. Stopping criteria for serious or severe infections and dose withholding rules are defined in Section 7, and safety monitoring of both the mother will continue for 24 weeks after delivery and for 96 weeks for the neonate/infant.

4.3. Justification for Dose

4.3.1. Nipocalimab Dose Selection

Enrolled patients will receive once weekly (QW) IV infusions of nipocalimab 45 mg/kg from Gestational Week 14 ±6 days (which is prior to the earliest time at which transport of maternal IgG reaches a level generally associated with risk of fetal anemia) through Gestational Week 35. Prior to Amendment 7, the dose administered to patients in the trial was 30 mg/kg (using the weight measured at baseline) nipocalimab QW. In Amendment 7, the dose was increased to 45 mg/kg (using the weight measured at baseline) nipocalimab QW to enable the visit window to be longer than 8 days; the dose increase is not anticipated to affect efficacy when ≤7-day visit intervals are maintained. In this amendment (Amendment 10), the 45 mg/kg dose is re-calculated every 2 weeks from baseline based on the weight measurements indicated in the SOE (referred to as "time-adjusted weight based dosing" versus "baseline-weight based dosing" in the prior amendments) to account for weight increases during pregnancy. This is considered necessary in order to maximize the benefit/risk ratio in this rare and potentially life-threatening disease population.

This nipocalimab dose/treatment regimen of 45 mg/kg QW was selected because it is expected to achieve maximum efficacy (blockade of IgG placental transfer and lowering IgG pathologic alloantibodies) by maintaining full RO throughout gestation. A PK/PD model developed using data from the FIH study was used to simulate the dose chosen for this study, taking into account weight changes during pregnancy. The simulation predicted 45 mg/kg with time-adjusted weight dosing can maintain ≥90% participants with full RO (defined at RO ≥90%) at least 1 day longer than a week to ensure that holidays or other unexpected disruptions which may occur do not immediately cause loss of RO or IgG rebound; lower doses did not maintain full RO in this simulation.

Compared to the baseline-weight based dosing (ie, body weight at Gestational Week 14) in the previous amendments, simulations predicted that the mean pre-dose nipocalimab exposure following the time-adjusted weight based dosing approach would be approximately 14.4% higher at Gestational Week 29 and 22.6% higher at Gestational Week 36, respectively. Maintaining sufficient nipocalimab exposure during pregnancy is considered critical for the complete and sustained blockade of IgG placental transfer, including maternal pathologic IgG alloantibodies. It is known that the IgG placental transfer is gestational age dependent, significantly higher at late pregnancy compared to early pregnancy (Malek 1996). Therefore, using time-adjusted weight-based dosing may have a beneficial effect on efficacy while the <25% increase in mean exposure would not result in a safety concern (see below).

In terms of safety, the proposed nipocalimab dose regimen (45 mg/kg IV QW) is expected to have an acceptable safety profile in pregnant women based on the available safety and toxicology findings. Nipocalimab IV doses up to 60 mg/kg were safe and well tolerated in multiple clinical trials of healthy subjects (MOM-M281-001, 007, 010) and patients with

myasthenia gravis (MOM-M281-004). The proposed dose is 6.7 times lower than the no-observed-adverse-effect-level (NOAEL) established in 26-week repeated-dose GLP studies in cynomolgus monkeys (300 mg/kg/week). In addition, in the GLP reproductive toxicology study, in which pregnant cynomolgus monkeys received IV nipocalimab at doses of up to 300 mg/kg/week from the early second trimester through parturition, there was no evidence of nipocalimab-related developmental toxicity. To date, nipocalimab IV doses of 45 mg/kg have been well tolerated in women at high risk for early onset severe HDFN in this ongoing Phase 2 study.

4.3.1.1. Dose Adjustments

Dose adjustments are not anticipated during the trial but were allowed in the previous amendments. Based on the PK, PD, efficacy, and safety data from the existing and ongoing clinical studies of nipocalimab, including the available data from the current Phase 2 study as well as PK/PD simulations, doses higher than 45 mg/kg QW (based on time-adjusted weight measurements) are not considered necessary as they may not provide incremental gain in target engagement and placental IgG transfer inhibition. Therefore, no further dose adjustments will be made.

4.4. End of Study Definition

A patient or neonate/infant are considered to have completed the study if she/he has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events (SOE), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SOE in the trial globally.

5. STUDY POPULATION

5.1. Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

1. Able to understand and voluntarily provide written signed informed consent to participate in the study.
2. Female and ≥18 years of age.
3. Pregnant to an estimated GA of 8 to up to 14 weeks.
4. A previous pregnancy with a gestation that included at least one of the following at ≤24 weeks gestation:
   a. Severe fetal anemia, defined as hemoglobin <0.55 MoM for GA (see table below):

Weeks' Gestation	Median Hemoglobin (g/dL)	0.55 MoM
16	10.0	5.5
17	10.4	5.7
18	10.6	5.9
19	10.9	6.0
20	11.2	6.1
21	11.4	6.3
22	11.6	6.4
23	11.8	6.5
24	12.0	6.6

Abbreviations: MoM = multiples of the median.
Source: Mari 2000

   b. Fetal hydrops (ascites) with MCA-PSV MoM ≥1.5
   c. Stillbirth with fetal or placental pathology indicative of HDFN.
5. Maternal alloantibody titers for anti-D ≥32 or anti-Kell titers ≥4.
6. Free fetal DNA consistent with an antigen-positive fetus (blood sample drawn from the mother).
7. Maternal evidence for immunity to measles, mumps, rubella, and varicella, as documented by serologies performed during Screening. If initial serologies are borderline or negative, they may be repeated at a second lab. Alternatively, vaccination records can be used to support evidence of immunity.
8. Screening IgG and albumin levels within the laboratory normal ranges.
9. Willing to receive standard of care with IUT, if clinically indicated.

10. Agree to receive recommended vaccinations as per local standard of care for both mother and child throughout the course of the study.
11. Willing to forego collection of cord blood for stem cell storage or other non-study purposes.
12. For mother and neonate, willing to forego participation in another clinical trial of an investigational therapy for the duration of their participation in the current study.
13. Willing to consent to a 24-week safety follow-up period for the patient and a 96-week safety follow-up period for the neonate/infant.
14. It is recommended that patients are up-to-date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study patients who received locally-approved (and including emergency use-authorized) COVID-19 vaccines recently prior to study entry, follow applicable local vaccine labelling, guidelines, and standards of care for pregnant women receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.6).

5.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in this study:

1. Currently pregnant with multiples (twins or more).
2. Pre-eclampsia in current pregnancy or history of pre-eclampsia in a previous pregnancy.
3. Gestational hypertension in the current pregnancy.
4. Current unstable hypertension.
5. History of severe or recurrent pyelonephritis or 4 or more lower UTIs in the past year or in a previous pregnancy.
6. History of genital herpes infection.
7. History of atypical mycobacterial disease or herpes zoster infection within the last 6 months.
8. History of malignancy (except treated basal cell carcinoma of the skin) with or without systemic cancer chemotherapy.
9. Positive for HIV, hepatitis B, or hepatitis C during Screening.
10. Presence of any of the following during Screening: clinically significant abnormal hematologic laboratory values, creatinine >1.5 × upper limit of normal (ULN), or clinically significant abnormal ECG reflective of heart disease.
11. Active infection at Screening or Baseline with Coxsackie, syphilis, cytomegalovirus, toxoplasmosis or herpes simplex 1 or 2, as evidenced by clinical signs and symptoms (evidence for prior infection or exposure, but without clinical signs and symptoms of active infection is acceptable).
12. Active infection with tuberculosis as evidenced by positive QuantiFERON-TB testing.

13. Immunosuppression because of underlying medical condition, including:
    - History of hereditary or congenital immunodeficiencies, cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia
    - History of solid organ or bone marrow transplantation
    - Any prior history of other clinically significant immunosuppressive or clinically diagnosed autoimmune disease that may jeopardize the safety of the subject, require therapy that would interfere with study assessments or endpoint evaluation, or otherwise impact the validity of the study results.
14. Requires treatment with corticosteroids or immunosuppression for disorders unrelated to the pregnancy (use of low-potency topical corticosteroids or intra-articular corticosteroids is permitted).
15. History of drug allergy, hypersensitivity, or intolerance to any drug product that, in the opinion of the Investigator, would compromise the safety of the patient.
16. In the Investigator's opinion, shows evidence of ongoing alcohol/substance abuse/dependence.
17. Smoking during pregnancy.
18. Received plasmapheresis and/or IVIG during the current pregnancy for treatment of HDFN.
19. Criterion modified per Amendment 11.

    19.1. Has received or is expected to receive any live virus or bacterial vaccine within 12 weeks prior to screening or has a known need to receive a live vaccine while receiving nipocalimab, or within 12 weeks after the last administration of nipocalimab in the study or has received Bacille Calmett-Guérin (BCG) vaccine within 1 year prior to the first administration of nipocalimab.
20. Currently receiving an antibody-based drug or an Fc-fusion protein drug.
21. Received an investigational drug and/or device within 30 days or 5 half-lives prior to receiving the first IV infusion of nipocalimab.
22. Received nipocalimab in a prior clinical trial.
23. Criterion modified per Amendment 11.

    23.1. A history or presence of clinically significant cardiovascular, pulmonary, hepatic (eg, viral/alcoholic/autoimmune hepatitis/cirrhosis and/or metabolic liver disease), renal, hematologic, gastrointestinal, endocrine/metabolic, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or severe or recurrent infections (eg, frequent hospitalized pneumonia), or any other condition or issue that, in the opinion of the Investigator, would jeopardize the safety of the patient or fetus/neonate/infant or the validity of the study results.
24. Criterion modified per Amendment 11.

    24.1. History of myocardial infarction, unstable ischemic heart disease, or stroke.

25. Criterion modified per Amendment 11.

25.1. COVID-19 infection:

During the 6 weeks prior to baseline (regardless of vaccination status), have had ANY of

(a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), **OR**

(b) suspected SARS-CoV-2 infection (clinical features without documented test results), **OR**

(c) close contact with a person with known or suspected SARS-CoV-2 infection

Exception: may be included with a documented negative result for a validated SARS-CoV-2 test:

– obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg fever, cough, dyspnea)

AND

– with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

NOTES on COVID-related exclusion:

- The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.

Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

5.3. Lifestyle Considerations

During this study through Week 96 after birth, patients and caregivers and family of the neonate/infant will be asked to:

- Avoid crowds and close proximity to individuals with known infections, particularly influenza, during pregnancy and postpartum.
- Practice frequent handwashing.
- Request that their family members and caretakers of the infants be up to date on vaccinations (“family cocooning”).

The patients are allowed to breastfeed their infant and should be encouraged and supported by the Investigator and study staff to do so. Whether or not the infant is breastfed and the duration of breastfeeding will be captured in the electronic case report form (eCRF).

The subject must agree not to receive a live vaccine (including BCG vaccine) during the study while receiving nipocalimab and for 12 weeks after receiving the last dose of nipocalimab.

It is recommended to be up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.6).

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened. The reasons for screen failure will be collected in the eCRF.

6. STUDY INTERVENTIONS

6.1. Study Intervention Description

Nipocalimab is a sterile solution intended for IV infusion. It is supplied in 20-mL glass vials nominally containing 30 mg/mL nipocalimab protein in solution (see Section 6.3.2).

No reference therapy (control product) will be administered during this open-label study.

6.2. Dosing and Administration

Nipocalimab will be administered QW by IV infusion at a dose of 45 mg/kg. The first dose will be administered at 14 weeks ±6 days GA. The 45 mg/kg dose will be calculated every 2 weeks using the patient's weight measurements indicated in the SOE (rounded to the nearest 0.1 kilogram). The maximum dose amount given in any patient at any dosing visit should not exceed 5.4 grams (ie, assuming a body weight of no greater than 120 kg). Note, the reported 90th percentile body weight in females is approximately 105 kg (US EPA 2011) and the median weight gain during pregnancy is approximately 15 kg (Hutcheon 2013). The first infusion of nipocalimab will be administered over 60 minutes, followed by a 60-minute post-infusion observation period. Subsequent infusions will be administered over 30 minutes, followed by a 30-minute post-infusion observation period. Each pregnant woman in the study will receive nipocalimab treatment for approximately 20 weeks (approximately 20 infusions). Refer to the SOE Section 1.3, for the timing of vital signs, fetal monitoring during maternal treatment, and dose administration.

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Acquisition and Accountability

Refer to the pharmacy manual/study-site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Study drug administration must be captured in the source documents and the eCRF.

6.3.2. Formulation, Appearance, Packaging, and Labeling

The investigational drug product nipocalimab is a sterile solution intended for IV infusion. It is supplied in a 20-mL glass vial. Each vial nominally contains 20 mL of nipocalimab solution, containing 600 mg nipocalimab protein.

Nipocalimab is formulated to a target concentration of 30 mg/mL in 25 mM sodium phosphate, 25 mM sodium chloride, 8.7% w/w trehalose, 0.01% w/v Polysorbate 80, pH 6.5.

The nipocalimab primary container is a 20-mL glass vial, with a stopper, and an overseal.

Nipocalimab will be provided open-label as one container per carton. Supplies of nipocalimab will be labeled with the local language.

6.3.3. Product Storage and Stability

Store nipocalimab vials at 2°C to 8°C in a secure, controlled-access location. Nipocalimab should only be administered to maternal patients participating in the study.

6.3.4. Preparation

Nipocalimab is to be administered by IV infusion. Details on the preparation of the study drug for administration can be found in the pharmacy manual/study-site investigational product and procedures manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.5. Study Intervention Compliance

The dates of nipocalimab administration and also the start and stop times of the infusions will be recorded in the eCRF by study personnel. Additional details on study intervention compliance can be found in the pharmacy manual/study-site investigational product and procedures manual.

6.6. Concomitant Therapy

All concomitant medications/therapies, and procedures administered to patients at any time during the study from the time of informed consent are to be recorded in the eCRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and supplements. Any COVID-19 vaccinations and treatments (including authorized for emergency use) at any time in the past must be recorded in the eCRF. Other therapies and procedures are also to be recorded.

Immunizations to pneumococcus, influenza, and diphtheria/tetanus/pertussis will be administered to the patient during the pregnancy, per protocol, and recorded on the eCRF.

When considering use of locally-approved non-live vaccines (and including emergency use-authorized COVID-19 vaccines) in study patients, follow applicable local vaccine labelling, guidelines, and standards of care for pregnant women receiving immune-targeted therapy.

For study patients receiving a locally-approved (and including emergency use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study drug be administered on different days, separated by as large an interval as is practical within the protocol.

Concomitant medications, therapies, and procedures administered to the neonate/infant are to be collected and recorded in the eCRF from birth through postnatal Week 24. Appropriate measures should be taken to minimize discomfort to the neonate/infant during study procedures.

Neonates/infants will receive vaccinations per the standard of care at their location, with vaccinations documented in the eCRF. Inactivated polio vaccine should be used, and oral polio vaccine is not recommended. Refer to the production information/prescribing information and local guidelines for potential interactions between IVIG administration and a specific vaccine if IVIG has been administered to the infants. Infants with low IgG concentrations and negative vaccine titers to either diphtheria/tetanus at Week 24 and beyond (Section 8.2.2.2) are recommended to consult with a pediatric immunologist before receiving live vaccinations beyond 6 months of age.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Investigational Product Stopping Rules for Individual Patients

Unless patient safety precludes doing so, the Sponsor should be consulted prior to stopping or modifying nipocalimab administration.

Discontinuation of nipocalimab administration does not mean discontinuation from the study. Patients who prematurely discontinue nipocalimab treatment for any reason should be actively encouraged to continue in the study to be followed for safety assessments, and actively encouraged to continue their neonate/infant's participation in the study for safety follow-up. The EOT assessments for the mother as described in Table 1 should be performed at their next clinical visit (ideally within 2 weeks of the last dose date of nipocalimab). The remaining study procedures for the mother and neonate/infant should be completed as indicated by the study protocol as specified in the SOE (Section 1.3) with the following modifications:

- Maternal blood draws for determination of nipocalimab concentrations and RO are not required following completion of the EOT assessments
- Maternal blood draws for IgG and albumin should continue every 2 weeks until IgG is greater than 500 mg/dL and albumin is greater than the lower limit of normal (adjusted for trimester as specified at: http://www.perinatology.com/Reference/Reference%20Ranges/Albumin.htm) and monthly thereafter as part of the safety laboratory evaluations in the SOE
- Tdap vaccine may be given at GA week 28 instead of week 31 if maternal IgG is greater than 500 mg/dL at or before GA Week 28.

See Section 8.2.1.6 for specific guidelines on maternal IVIG before birth if nipocalimab has been prematurely discontinued.

If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

7.1.1.1. Elective Termination of the Pregnancy/Fetal Loss

If a patient experiences elective termination of the pregnancy or fetal loss, nipocalimab administration should be stopped and IVIG administered as detailed in Section 8.2.1.6. An autopsy of the fetus and placental evaluation should be performed if possible (see Section 8.3.6.1 and Section 8.2.1.12, respectively). In addition, blood samples for nipocalimab concentration, total serum IgG, alloantibody titers, and FcRn RO will be obtained from the patient at the time of the elective termination/fetal loss or as soon as possible.

7.1.1.2. IUT Stopping Rule

If a patient requires an IUT during the study, nipocalimab will be continued weekly until fetal sampling at a subsequent IUT indicates the lack of fetal red blood cells remaining in the fetal circulation as confirmed by laboratory assessment (eg, Kleihauer-Betke stain <5%, flow cytometry <5%, or mean corpuscular volume < 95 fL). At this point, the infusions of nipocalimab must be discontinued. In addition, nipocalimab may be discontinued at the time of the first IUT, if the IUT occurs later in the 3rd trimester (eg, after 30 weeks GA).

Maternal blood samples for nipocalimab PK, total serum IgG, alloantibody titers and FcRn RO will be obtained at the time of the first IUT and at any subsequent IUTs if nipocalimab infusions are continuing.

7.1.1.3. Infection Stopping Rule

The Investigator will assess patients with infections using NCI CTCAE v5.0 criteria (NCI CTCAE 2017).

Nipocalimab administration must be stopped if any of the following events occur:

- The patient develops a CTCAE Grade 4 infection (eg, sepsis, requiring ventilation assistance, hypotension requiring vasopressors),
- The patient develops a CTCAE Grade 3 infection that is unresponsive or worsens while on anti-infective therapy.

In the event of a CTCAE Grade 3 infection, the Investigator may withhold 1 weekly dose of nipocalimab until the clinical scenario clarifies whether the infection is improving or getting worse.

7.1.1.4. Hypoalbuminemia Stopping Rule

Since edema occurs frequently in pregnancy, only severe edema in combination with NCI CTCAE Grade 3 hypoalbuminemia meets stopping criteria. Asymptomatic hypoalbuminemia is not a criterion for stopping nipocalimab. Hypoalbuminemia associated with a serum albumin of <20 g/L may include bilateral pitting edema (3+ based on pitting depth, duration, and extent) to the feet, legs, arms and face, abdominal wall edema, ascites, pulmonary edema, or pleural effusion (Table 4 and Table 5).

Table 4: Grading of Edema for Hypoalbuminemia Stopping Rule

Pitting Depth and Duration
1+ : ≤2 mm pitting that disappears rapidly
2+ : 2 to 4 mm pitting that disappears in 10-15 seconds
3+ : 4 to 6 mm pitting that may last more than 1 minute; dependent extremity looks fuller
4+ : 6 to 8 mm pitting that may last more than 2 minutes; dependent extremity is grossly distorted
Severity of Bilateral Pitting Edema
1+ (mild): Both feet/ankles
2+ (moderate): Both feet + lower legs, hands or lower arms
3+ (severe): Generalized bilateral pitting edema, including both feet, legs, arms and face

Table 5: NCI CTCAE Grading for Hypoalbuminemia

Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
<LLN to 3 g/dL; <LLN to 30 g/L	<3 to 2 g/dL; <30 to 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated

CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal; NCI = National Cancer Institute
Source: NCI CTCAE v5.0 November 27, 2017;
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

General severe bilateral pitting edema (3+ based on pitting depth and duration) including both feet, legs, arms and face or abdominal wall edema, ascites, pulmonary edema, or pleural effusion in association with a serum albumin of <20 g/L.

If events meeting the stopping criteria occur, weekly nipocalimab infusions will be stopped until signs/symptoms show resolution and serum albumin levels begins to rise. At that point, if the patient has missed ≤2 weekly nipocalimab infusions, weekly infusions can be restarted. If a patient has missed >2 weekly infusions then nipocalimab should be stopped permanently.

7.1.1.5. Pre-eclampsia Stopping Rule

Nipocalimab administration must be stopped if a patient develops pre-eclampsia.

7.1.1.6. Intrauterine Growth Restriction (IUGR) Stopping Rule

The algorithm for stopping nipocalimab due to potential IUGR is based on measurements obtained at GA Week 18 or beyond. The stopping rule is described below and depicted graphically in Appendix 2.

As described in Section 8.2.1.10, fetal biometry by ultrasound to assess for growth and development will be performed at Screening, Baseline, and then every 2 weeks thereafter. A measurement of crown-rump length will be obtained at Screening and again at Baseline to confirm dating. The estimated fetal weight (EFW) will be determined at each ultrasound assessment starting at the Baseline examination.

At GA Week 18 or beyond, if either the EFW or the abdominal circumference is below the 10th percentile based on local fetal growth normative standards, weekly Doppler measurements of flow velocity in the umbilical and uterine arteries will be initiated and the pulsatility index (PI) for each artery will be calculated. The average of the PI from the left and right uterine arteries will be used for the overall uterine artery PI. Additional Doppler measurements of umbilical and uterine arteries may be scheduled as needed at the discretion of the Investigator.

- If absent end diastolic flow (AEDF) or reversed end diastolic flow (REDF) is detected, nipocalimab treatment must be stopped.
- If any PI measurement is >95%, the umbilical artery and uterine artery PIs should be repeated 1 week later. If either the umbilical artery or uterine artery PI is also >95% at this repeat assessment (ie, >95% at 2 consecutive weekly assessments), or if umbilical artery AEDF/REDF is detected, nipocalimab treatment must be stopped.
- If all PI measurements are ≤95%, the umbilical artery and uterine artery PIs should be repeated weekly until the fetus is no longer below the 10th percentile for EFW or abdominal circumference.

7.1.1.7. Hypersensitivity Stopping Rule

Nipocalimab administration must be stopped if a patient develops a severe hypersensitivity reaction such as:

- Anaphylaxis
- Severe infusion-related reaction

7.1.1.8. Clinically Significant Abnormal Hematology Laboratory Result Stopping Rule

Nipocalimab administration must be stopped if a patient develops any of the following clinically significant abnormal hematological laboratory results confirmed on repeat testing:

- White blood cell count (WBC) < 3000/mm^3 (< 3.0 × 10^9/L) or absolute neutrophil count < 1,500/μL
- Hemoglobin < 8 g/μL
- Platelets < 100,000/μL

7.1.1.9. Clinically Significant Abnormal Hepatic Laboratory Result Stopping Rule

If elevated ALT or aspartate aminotransferase (AST) ≥ 3 × ULN occurs then liver tests should be repeated within 3-5 days and include ALT, AST, bilirubin (total and direct), alkaline phosphatase, gamma-glutamyl transferase, and creatine kinase.

Stop administration of nipocalimab if the patient meets one of the following conditions:

- ALT or AST > 5 × ULN
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio > 1.5

- ALT or AST > 3 × ULN sustained for more than 2 weeks (additional testing beyond first retest is required)

7.1.2. Study Stopping Rules

- Following a maternal death*, treatment will not be initiated in new patients, pending sponsor evaluation and DSMB recommendation.
- Following the occurrence of a maternal CTCAE Grade 4* event, treatment with nipocalimab will not be initiated in new patients, pending sponsor evaluation and DSMB recommendation.
- If CTCAE Grade 3 or higher infection occurs in 3 separate patients (including neonates), nipocalimab infusions will not be initiated in new patients, pending Sponsor evaluation and DSMB recommendation.
- If 3 patients have nipocalimab infusions stopped due to edema/hypoalbuminemia, treatment of new patients will be paused pending Sponsor evaluation and DSMB recommendation. Patients currently receiving treatment would be permitted to continue nipocalimab infusions as long as there are no associated hypoalbuminemia AEs.
- If 2 patients have nipocalimab infusions stopped due to IUGR, nipocalimab infusions will not be initiated in new patients pending Sponsor evaluation and DSMB recommendation.

* NOTE: Events that are definitively not related to study treatment (eg, accidents or other external causes) will not trigger study stopping rules.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants are free to discontinue nipocalimab infusions or withdraw from participation in the study at any time upon request.

An investigator may discontinue nipocalimab infusions or withdraw a patient from the study for the following reasons:

- Significant study intervention noncompliance.
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient.
- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for patient discontinuation of nipocalimab infusions or withdrawal from the study will be recorded on the eCRF. Patients who discontinue nipocalimab treatment should be actively encouraged to stay in the study to be followed for safety (see Section 7.1.1).

7.2.1. Replacing Patients in the Study

Patients who sign the informed consent form but do not receive the study intervention or those who receive treatment and withdraw from the study for reasons other than safety may be replaced to a maximum of 3 additional patients. Patients who sign the informed consent form and receive the study intervention, and who withdraw or are discontinued from the study due to AEs will not be replaced.

7.3. Lost to Follow-Up

A patient or neonate/infant will be considered lost to follow-up if the patient or neonate/infant fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site will attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record or study file.

Should the patient continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Efficacy Assessments

8.1.1. Procedures/Assessments for Efficacy (Maternal Patients)

To be eligible for the study, women must have an obstetrical history of severe fetal anemia or stillbirth at ≤24 weeks gestation, have titers for anti-D ≥32 or anti-Kell titers ≥4, and be pregnant with an antigen-positive fetus. Refer to Section 5 for a complete list of inclusion and exclusion criteria.

Patients who provide signed informed consent will be screened for inclusion from GA Week 8 to up to 1 day before the Baseline day (ie, GA Week 14 ±6 days). Refer to SOE, Section 1.3 for procedures to be performed during the screening period.

Procedures to assess the efficacy of nipocalimab in this study include:

8.1.1.1. Determination of Fetal Anemia: Measurement of PSV of the MCA

The fetus will be monitored for anemia via weekly assessment of PSV of the MCA via Doppler ultrasonography from GA Week 14 (±6 days) to birth as per Mari (2000). As per the current standard of care, if the PSV is ≥1.5 MoM PSV for the estimated GA of the fetus, a cordocentesis will be performed to ascertain fetal anemia. If confirmed, fetal anemia will be treated with IUT, as per standard of care (Zwiers 2017a).

The Investigator may postpone the decision to do a cordocentesis when there is a single isolated reading of 1.5 MoM PSV of the MCA without prior readings of a rising PSV value of the MCA and no other ultrasound findings. In such situations, the patient will be asked to return for a follow-up reading. If there are no additional signs of anemia, the patient should return for another reading in 3 or 4 days.

8.1.1.2. Cordocentesis and Intrauterine Transfusion

Cordocentesis will be performed to ascertain fetal anemia as per Section 8.1.1.1. The GA-appropriate volume of fetal cord blood will be collected for analyses of hemoglobin, hematocrit, direct Coombs, reticulocyte count, nipocalimab concentration, alloantibody, FcRn RO, and IgG levels.

Fetal anemia requiring IUT is defined as a hematocrit <30% or hemoglobin <2 standard deviations (SDs) below the mean hemoglobin for GA (approximately 2 g/dL below the mean hemoglobin for GA; Table 6). If a fetus meets the criteria for fetal anemia but no IUT is done, the investigator will explain the rationale for this decision in the eCRF.

If fetal anemia is determined, IUT will be performed and the appropriate amount of blood administered to the fetus, taking into account the extra blood needed for study assessments.

If a patient requires an IUT during the study, nipocalimab will be continued weekly until fetal sampling at a subsequent IUT indicates the lack of fetal red blood cells remaining in the fetal circulation; refer to Section 7.1.1.2 for the treatment stopping rule related to IUT.

Table 6: Normal Mean and <2 SD Values for Fetal Hemoglobin

Gestational Age (weeks)	Mean Hemoglobin (g/dL)	<2 SD Hemoglobin from the Mean (g/dL) [a]
18	11.3	9.3
19	11.5	9.5
20	11.7	9.7
21	11.9	9.9
22	12.1	10.1
23	12.3	10.3
24	12.5	10.5
25	12.7	10.7
26	12.8	10.8
27	13.0	11.0
28	13.2	11.2
29	13.4	11.4
30	13.6	11.6
31	13.8	11.8
32	14.0	12.0
33	14.2	12.2
34	14.4	12.4

Abbreviations: SD = standard deviation.
[a] Two SD below the mean is approximately 2 g/dL below the mean hemoglobin for gestational age.
Source: Nicolaides 1988

8.1.1.3. Pharmacodynamic and Target Engagement Assessments (IgG, Alloantibody Titer, and FcRn RO)

Blood samples for PD analysis of total circulating IgG, FcRn RO, and alloantibody titer will be collected at predetermined time points as outlined in SOE Section 1.3. Blood samples will also be collected for assessment of exploratory PD biomarkers in serum (levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE). Instructions for blood sample collection, processing, storage, and shipping are described in the Laboratory Manual.

If ≥9 days since the last infusion of study drug, a blood sample for total serum IgG, alloantibody titers and FcRn RO will be collected prior to nipocalimab infusion (if sample not already scheduled).

If a patient requires an IUT or sustains fetal loss in between scheduled assessments, blood sampling will be performed for analysis of IgG, FcRn RO, and alloantibody titer as soon as possible.

8.1.1.4. Pharmacokinetic Assessments (Serum Nipocalimab Concentrations)

Patients will undergo blood sampling prior to the beginning of and at the end of each nipocalimab infusion and as specified in the SOE Section 1.3 to determine serum nipocalimab concentration(s). Instructions for blood collection, processing, storage and shipping are described in the Laboratory Manual.

If ≥9 days since the last infusion of study drug, a blood sample for nipocalimab concentration will be collected prior to nipocalimab infusion (if sample not already scheduled).

If a patient requires an IUT or sustains fetal loss between scheduled assessments, blood sampling will be performed as soon as possible.

8.2. Safety and Other Assessments

8.2.1. Procedures/Assessments for Safety - Maternal Patients (Study Start to Week 24 Postpartum)

Safety evaluations for the maternal patients prior to delivery will be performed at intervals detailed in Table 1, SOE Part A, Section 1.3. Adverse events will be collected throughout the study. Following delivery, maternal patients will be monitored for 24 weeks for safety (safety laboratory assessments, abbreviated physical examinations, AEs). Patients who discontinue nipocalimab prematurely will complete EOT assessments within 2 weeks of their last dose of nipocalimab and continue to be followed as per Section 7.1.1.

8.2.1.1. Adverse Events of Special Interest

8.2.1.1.1. Infections Requiring Anti-infective Treatment

The main theoretical risk of nipocalimab is an increased risk of infections due to the PD effect of lowering systemic IgG levels in the maternal circulation. As such, all infections requiring anti-infective (ie, oral or intravenous antibacterial, antiviral, or antifungal) treatment will be considered an AESI. These cases will be handled similar to an SAE and reviewed by the DSMB as they occur.

8.2.1.1.2. Hypoalbuminemia ≥ Grade 3

The potential for hypoalbuminemia during treatment with nipocalimab will be monitored on a weekly basis by physical examination and through biweekly (every other week) monitoring of serum albumin as part of safety laboratory assessments. Hypoalbuminemia ≥ Grade 3 (ie, <20 g/L by NCI CTCAE Version 5.0 criteria) will also be considered an AESI and handled similar to an SAE and reviewed by the DSMB (see also Section 7.1.1.4).

Refer to Section 8.3.6 for additional information regarding reporting of AEs, SAEs, and AESIs.

8.2.1.2. 12-Lead Electrocardiograms

Single 12-lead ECGs will be obtained after the patient has been in the supine position for at least 5 minutes. Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T Wave, and U Wave abnormalities.

The Investigator will determine if the ECG results are clinically significant or not clinically significant. Clinical significance is defined as any variation in assessment results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening value is noted, the clinically significant value and reason for clinical significance will be documented in the eCRF and the ECG will be repeated. The Investigator will continue to monitor the patient with additional assessments until the values have reached either the reference range, the approximate values at screening, or until the Investigator determines that follow-up is no longer medically necessary.

8.2.1.3. Physical Examinations

Height and weight will be measured at Screening. A full physical examination for the mothers will be performed at Baseline and at GA Week 36/EOT, and at postnatal Week 24. These examinations will include vital signs and physical assessment of the following systems: head, eye, ear, nose, and throat (HEENT), skin, heart, lungs, abdomen (gastrointestinal [GI] system, spleen), and extremities. An abbreviated physical examination (heart, lungs, and skin, and assessment of edema) will be performed for the mothers at weekly study visits from GA Week 15 to GA Week 35, and during the follow-up period on the day of birth and also at Week 4. Directed examinations will be performed if indicated based on AE reports or results of safety laboratory assessments.

8.2.1.4. Safety Laboratory Assessments

Patients will be in a seated or supine position during blood collection. Instructions for blood sample collection, processing, storage, and shipping are described in the Laboratory Manual.

Clinical laboratory tests for safety for the maternal patients will include the following (Table 7):

Table 7: Safety Laboratory Assessments for Maternal Patients

Hematology: • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential • Prothrombin time (PT) • Activated partial thromboplastin time (aPTT) **Urinalysis:** • Appearance • Bilirubin • Color • Glucose • Ketones • Microscopic examination of sediment • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen	**Serum Chemistry:** • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine • Creatine kinase and subtypes (MB fraction – if CK is elevated) • Gamma-glutamyl transferase (GGT) • Glucose • Immunoglobulin G • Lactate dehydrogenase (LDH) • Inorganic phosphate • Potassium (K) • Sodium (Na) • Total bilirubin • Direct bilirubin • Total protein • Troponin I • Uric acid **Lipid Panel** • Total cholesterol • High-density lipoprotein (HDL) • Low-density lipoprotein (LDL) • Triglycerides

8.2.1.4.1. Maternal IgG Result Less Than 1.0 g/L

If maternal IgG concentration falls below 1.0 g/L at any time during the study, the Investigator will contact the patient as soon as possible by phone. The patient will be queried about infection-related symptoms and if the Investigator has any concerns, they will instruct the patient to return to the site for an unscheduled visit. The patient will also be reminded of the steps to prevent contraction of infection (eg, frequent hand washing and good hygiene, avoiding exposure to individuals with upper respiratory or other infections, handling and preparing food safely, etc).

8.2.1.4.2. Increased Lipids

Routine laboratory investigations for lipid panel (total cholesterol, LDL, HDL, triglycerides) will be monitored in the study according to the SOE. In patients with elevated lipids (cholesterol >400 mg/dL [10.34 mmol/L] or triglycerides >500 mg/dL [5.65 mmol/L], fasting or non-fasting) at any time during the study, it is recommended that investigators monitor and take appropriate actions for dyslipidemia during pregnancy as per local health guidelines. The lipid panel should be repeated at the subsequent visit (in approximately 1 week) under fasting conditions. If lipid levels remain elevated, investigators are recommended to incorporate changes per local practice such as dietary and lifestyle modifications.

8.2.1.5. Testing for Vaginal Microbiome and Group B Streptococci

Assessments of vaginal bacterial burden/microbiome diversity will be performed at Baseline and at GA Week 34 to assess whether nipocalimab changes the vaginal microbiome and also to guide the selection of appropriate prophylactic antibiotics to be given for C-section (if performed) and inform on treatment of infections, if they occur. The vaginal microbiome test results will be interpreted by a central reviewer and categorized into one of the groups defined in Table 8.

Prophylactic antibiotic therapy should be administered for C-section (if performed) based on results of the vaginal microbiome testing (Table 8).

Table 8: Guidance for Prophylactic Antibiotic Therapy for C-Section Based on Results of Vaginal Microbiome Testing

Vaginal Microbiome Test Result	Antibiotic Prophylaxis
Lactobacillus dominant (normal result)	Standard of Care (usually 1 dose of a cephalosporin prior to incision).
Facultative anaerobes dominant	Standard of Care but given for 3 doses over 24-hour period (usually a cephalosporin, the first dose given before incision and the second and third doses given q8hrs following the first dose).
Anaerobes dominant	Standard of Care (usually a cephalosporin) + metronidazole 500 mg, both ×3 doses. The first dose (both antibiotics) given prior to incision and the second and third doses of both antibiotics given every 8 hours following the first dose.

Maternal patients will be tested for GBS at GA Week 34. Patients testing positive will receive GBS intrapartum antibiotic prophylaxis as per the American College of Obstetricians and Gynecologists (ACOG) guideline for management of positive GBS testing in third trimester (Appendix 3).

8.2.1.6. Use of IVIG

IVIG (500 mg/kg) should be given to mothers 48 to 72 hours prior to delivery (if not contraindicated) as prophylaxis against maternal infection and to allow for placental transfer of IgG (Gitlin, 1964; Ensom, 2011). If delivery is early/unscheduled (urgent or emergent), IVIG should be given before delivery or as soon as possible after delivery.

In case of fetal loss or elective termination of the pregnancy, IVIG should be administered before the procedure or as soon as possible after the procedure (see Section 7.1.1).

Use of IVIG for the treatment of severe infection in maternal patients should only be considered in conjunction with discontinuing nipocalimab treatment, as per stopping rules for individual patients (see Section 7.1.1).

Consultation with the Medical Monitor should be done (time permitting) when considering IVIG in the management of severe infection.

For patients who prematurely discontinue nipocalimab and are continuing in the study for safety follow-up (Section 7.1.1), the need for administration of prophylactic IVIG before delivery will be determined based on the patient's total serum IgG (at the last assessment before delivery). If the total serum IgG is below 200 mg/dL, prophylactic IVIG should be given. If the patient has a risk factor(s) for infection, prophylactic IVIG should be given if the total serum IgG is below 500 mg/dL.

8.2.1.7. Immunogenicity

Maternal blood samples will be taken for anti-nipocalimab antibody levels (immunogenicity). Instructions for blood collection, processing, storage, and shipping are described in the Laboratory Manual:

- ADAs to nipocalimab and,
- For samples positive for ADA, the titer and neutralizing capacity will be determined.

8.2.1.8. Lymphocyte Phenotyping

Maternal blood samples for lymphocyte phenotyping (T cells, B cells and NK cells) will be taken in the prenatal and postnatal periods for an exploratory safety evaluation of the potential effect of nipocalimab on lymphocyte subsets in pregnant women. Instructions for blood collection, processing, storage, and shipping are described in the Laboratory Manual.

8.2.1.9. Monitoring During and After Nipocalimab Infusion

Refer to the SOE Part A, Section 1.3 for details on the timing of maternal and fetal monitoring during nipocalimab infusions.

8.2.1.9.1. Maternal Vital Signs

Vital signs will be measured at time 0 (before the start of the nipocalimab infusion), and for the first (60-minute) infusion vital signs measured at 30 minutes, the end of infusion, and 30- and 60-minutes post infusion; fetal heart rate will be measured at 0 minutes, the end of infusion, and 60 minutes post infusion. For all subsequent (30-minute) infusions, vital signs will be measured at start of infusion (0 minutes), at the end of infusion, and at the end of the 30-minute post infusion observation period; fetal heart rate will be measured at 0 minutes, the end of infusion, and 30 minutes post infusion. Vital signs measurements will include supine blood pressure and pulse rate, respiration rate, and body temperature. The patient will be at rest for a reasonable amount of time before all vital signs are recorded, according to the practices of the investigative site.

The Investigator will determine if any of the vital signs measurements are clinically significant or not clinically significant. Clinical significance is defined as any variation in assessment results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the patient's eCRF. The Investigator will continue to monitor the patient with additional assessments until the values have reached reference range and/or the values at Screening, or until the Investigator determines that follow-up is no longer medically necessary.

8.2.1.9.2. Pulse Oximetry

Continuous monitoring of heart rate and blood oxygen saturation by pulse oximetry will be done throughout the duration of the infusion. Clinically significant changes in heart rate or blood oxygen saturation will be documented on the AE page of the patient's eCRF.

8.2.1.9.3. Fetal Heart Rate

Monitoring of fetal heart rate will be performed by Doppler ultrasound prior to the start of the nipocalimab infusion, at the end of the infusion and at the end of the post infusion observation period from GA Week 14 to GA Week 25. Continuous monitoring of fetal heart rate by ultrasound will be recorded and evaluated for abnormalities in rate or rhythm during the nipocalimab infusion and the post infusion observation period from GA Week 26 until the last infusion (GA Week 35). Abnormalities will be recorded as an AE.

8.2.1.9.4. Uterine Activity

Continuous monitoring of uterine activity by tocodynamometry for premature contractions will be performed during the nipocalimab infusion and the post infusion observation period from GA Week 26 until the last infusion.

8.2.1.10. Fetal Assessments by Ultrasound (Biometry) for Growth and Development

Fetal ultrasound for assessment of fetal viability will be performed at Screening, Baseline (GA Week 14 ±6 days), and every 2 weeks thereafter. A measurement of crown-rump length will be obtained at Screening and again at Baseline to confirm dating. Growth measurements (biometry) including, biparietal diameter, head circumference, abdominal circumference, femur length, and amniotic fluid volume (maximum vertical pocket at <24 weeks and amniotic fluid index ≥24 weeks' gestation) will be obtained at the time points indicated in Table 1, Schedule of Events.

The EFW will be determined at each ultrasound assessment starting at the Baseline examination. At GA Week 18 or beyond, if either the EFW or the abdominal circumference is below the 10th percentile based on local fetal growth normative standards, weekly Doppler measurements of flow velocity in the umbilical and uterine arteries will be initiated (see Section 8.2.1.11).

A full anatomical assessment for the fetus will be done at GA Week 20. A biophysical profile for the fetus will be done at GA Week 36 to evaluate heart rate, breathing movement, tone and body movement, and amniotic fluid volume.

8.2.1.11. Umbilical and Uterine Artery Flow Velocity

If the fetal growth measurements indicate the potential for IUGR (Section 8.2.1.10), weekly Doppler measurements of flow velocity in umbilical and uterine arteries will be initiated and PI for each artery will be calculated and recorded.

The IUGR algorithm for stopping nipocalimab is described in Section 7.1.1.6 and depicted graphically in Appendix 2. Briefly, if AEDF or REDF is detected, or if any PI is >95% for 2 consecutive weeks, nipocalimab treatment must be stopped.

8.2.1.12. Exploratory Placental Evaluation

Whenever possible, the placenta should be examined by the clinical site's pathologist. Additionally, the placenta may be examined as part of a substudy of this protocol by a central reader. Details of the desired placental evaluations (such as placental weight and photographs, and microscopic examination of umbilical cord and placental tissue sections) are provided in the placental pathology manual. Observations related to the presence or absence of placental thrombosis and/or infarction, hemolytic disease, infection, and other significant findings should be documented in the pathology reports.

8.2.1.13. Exploratory Evaluation of Nipocalimab in Breastmilk

Although nipocalimab is not expected to be transmitted to maternal breast milk in clinically meaningful quantities, colostrum/breast milk samples will be collected on Postnatal Days 1 and 7, if available, to determine if nipocalimab is present.

8.2.2. Procedures/Assessments for Safety Follow-up Period – Neonates/Infants (Birth to Week 96)

Appropriate measures should be taken to minimize discomfort to the neonate/infant during study procedures. Safety evaluations for the neonate/infant will be performed at intervals detailed in Table 2, SOE Part B, Section 1.3.

Nipocalimab is not expected to cross the placenta. Safety procedures and assessments for the neonate/infant in the follow-up period will include the following:

- Cord blood sample at birth to document blood type and antigen positive status (ie, RhD or Kell); measure nipocalimab concentration, hemoglobin, hematocrit, reticulocyte count, direct Coombs, total and direct bilirubin, alloantibody titers, FcRn RO, total serum IgG levels (as well as immunoglobulin IgM, IgA, IgE, and IgG subclasses); other chemistry and hematology (including lipid panel) safety laboratory evaluations; and lymphocyte phenotyping
- Neonates may receive IVIG (if not contraindicated) within 48 hours of birth only if required based on their risk of infection and total IgG concentration in cord blood (as described in Section 8.2.2.1).
- Record results of local laboratory testing, if performed, for hemoglobin, hematocrit, total and direct bilirubin, reticulocyte count, and direct Coombs
- Postnatal safety laboratory assessments by the central laboratory (chemistry, hematology, and lipid panel); see Table 9

- Physical examination findings (including growth)
- Vital signs
- Neonatal nipocalimab concentration at Week 4.
- Assessment of IgG, IgM, IgA, IgE levels.
- Lymphocyte phenotyping
- Documentation of standard pediatric vaccinations (scheduled per local guidance).
- AEs to be recorded from birth until Week 24; SAEs and AESIs (infections requiring use of anti-infectives [oral or IV antibacterial/antiviral/antifungal], unexpected/unusual childhood illnesses, and IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96) to be recorded from birth until Week 96.
- Use of concomitant medications and therapies (including the number of IVIG doses given)
- ASQ-3, completed by a parent/guardian at 24, 48, and 96 weeks after birth.

  The ASQ-3 is one of the most widely used and accepted developmental screening tools, and assesses developmental performance of children in the areas of communication, gross motor skills, fine motor skills, problem solving, and personal-social skills (Singh, 2017; Appendix 4).
- PedsQL, completed by a parent/guardian at 96 weeks after birth.

  The PedsQL is a widely used 45-item generic health status instrument for ages 13 to 24 months (Varni, 2011)

If the total volume of blood to be collected for the samples at birth, Week 4, Week 24, Week 48, or Week 96 would exceed the allowable amount or cannot be obtained for technical reasons, consult the Laboratory Manual for which blood samples should be prioritized.

Table 9: Safety Laboratory Assessments for Neonates/Infants

Hematology: • Hematocrit (Hct) [a] • Hemoglobin (Hgb) [a] • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential • Direct Coombs Blood Type and RhD or Kell (if not obtained from cord blood)	**Serum Chemistry:** • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Chloride (Cl) • Creatinine • Creatine kinase and subtypes (MB fraction – if CK is elevated) • Gamma-glutamyl transferase (GGT) • Glucose • Immunoglobulin G (IgG) • Lactate dehydrogenase (LDH) • Inorganic phosphate • Potassium (K) • Sodium (Na) • Total bilirubin [a] • Direct bilirubin [a] • Total protein **Lipid Panel** • Total cholesterol • High-density lipoprotein (HDL) • Low-density lipoprotein (LDL) • Triglycerides

8.2.2.1. Testing for Total Serum IgG in Neonatal Cord Blood and IVIG Administration

Neonatal total IgG concentrations should be measured by a local laboratory from a cord blood sample taken at birth. The neonate's risk of infection and total IgG concentration in cord blood are both to be taken into account to determine whether IVIG is to be administered.

In the following situations, IVIG (500 mg/kg) will be administered (if not contraindicated) within 48 hours after the cord blood total IgG result from the local laboratory is available:

- For neonates without risk factors for infection, IVIG will be administered if the total IgG concentration in cord blood is <200 mg/dL.

- For neonates with risk factors for infection, IVIG will be administered if the total IgG concentration in cord blood is <500 mg/dL. Risk factors for infection in the neonate include:
  - Intrapartum maternal fever (>38°C) or clinical signs of chorioamnionitis;
  - Spontaneous preterm premature rupture of membranes;
  - Maternal GBS colonization, bacteriuria, or UTI;
  - Invasive GBS infection in previous child;
  - Neonate required umbilical artery catheterization, central line, or
  - Other risk factors for infection as identified by the Investigator or study personnel.

If the neonate requires IVIG at birth, a subsequent blood sample for total serum IgG must be obtained at Week 1 for testing by the local laboratory. If total IgG concentrations in the neonate/infant are still <200 mg/dL at Week 1 or any subsequent follow-up assessment through Week 16, additional IVIG should be given until IgG concentrations return to within normal age-appropriate levels and additional ad hoc testing of IgG in the neonate may be done as per investigator judgment if the IgG concentrations remain below age-appropriate levels.

8.2.2.2. Testing for Total Serum IgG and Vaccine Titers to Diphtheria/Tetanus

Blood samples for total serum IgG must be obtained from all infants at Weeks 4, 24, 48, and 96. In addition, vaccine titers to diphtheria/tetanus will be obtained at Weeks 24, 48, and 96 to assess antibody response. The vaccine titer to diphtheria/tetanus at Week 24 should be performed at least 3 weeks after the infant has received the second vaccination with Diphtheria, Tetanus, and Pertussis (DTaP). The result of a positive or negative vaccine titer will be stated in the laboratory report and positive/negative thresholds are found in the Laboratory Manual.

Total serum IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96 will be considered an AESI (Section 8.3.7).

Week 24

A consult with a pediatric immunologist should be obtained if the total IgG concentrations in the neonate/infant are <200 mg/dL at Week 24 and a vaccine titer is negative for an antibody response to either diphtheria/tetanus.

Weeks 48 and 96

If total IgG concentrations are <300 mg/dL at Weeks 48 and/or 96, consultation with a pediatric immunologist should be obtained if not done previously and regardless of vaccine titers. Low IgG (and other clinically significant lab abnormalities) at the end of the study/early withdrawal should be followed by the investigator (including additional lab tests and reporting adverse events) until IgG level is normalized or a stable condition is reached. The additional follow-up information should be recorded in the eCRF.

In addition to the above, a pediatric immunology consultation should be considered if the neonate/infant is presenting with frequent, and/or serious infections. Infants with low IgG concentrations and negative vaccine titers at Week 24 and beyond are recommended to consult with a pediatric immunologist before receiving live vaccinations beyond 6 months of age.

8.3. Adverse Events and Serious Adverse Events

8.3.1. Definition of Adverse Events (AE)

An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can therefore be any unfavorable and unintended sign, symptom, disease, concurrent illness, or clinically significant abnormal laboratory finding that emerges or worsens (ie, aggravated in severity or frequency from the baseline condition) during the study. Clinically significant abnormal results of laboratory tests or diagnostic procedures are to be reported as AEs.

Test results are clinically significant if they result in:

- Treatment or any other therapeutic intervention,
- Additional diagnostic measures, including active surveillance, or
- Discontinuation of the study drug or from the study.

Abnormal clinical laboratory results: All clinically significant (CS) abnormal laboratory results will be reported in the eCRF. Investigators will indicate on the lab report whether abnormal values are CS or not clinically significant (NCS). All CS abnormal laboratory results will be considered as AEs.

The recording of AEs will begin at the time of signing informed consent.

Treatment-emergent AEs are defined as any AE that begins after the start of the first infusion of nipocalimab.

8.3.2. Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Unscheduled obstetrical interventions will be recorded along with the associated diagnosis.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon the Investigator’s judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3. Classification of an Adverse Event

Severity of Event

The severity of an event will be graded by the CTCAE v5.0 criteria. While CTCAE provides specific criteria for grading adverse events as well as laboratory tests, the grades are as follows:

Grade 1, Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2, Moderate: minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.

Grade 3, Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4, Life-threatening consequences; urgent intervention indicated.

Grade 5, Death related to AE.

Relationship to Study Therapy

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the patient based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the patient's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time

after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the patient's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the Reference Safety Information in the Investigator's Brochure for the study intervention.

8.3.4. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review of data by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured and recorded on the appropriate eCRF starting after signing of the informed consent. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship, and all information prompted in the eCRF will be recorded for each AE reported.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator must follow all nonserious AEs until resolution, the condition stabilizes, the event is otherwise explained, or until the participant either withdraws consent, dies, or is lost to follow-up. The status of the AE as of that date will be recorded in the eCRF and AE follow-up will conclude. If the AE has worsened since the end-of-study visit, this will be recorded in the eCRF and the Investigator will continue to either treat the patient until the AE resolves or ensure that the patient receives appropriate care from another health care provider until the AE is resolved.

Selected adverse events (eg, cardiovascular events) may undergo major adverse cardiovascular event (MACE) adjudication by the Event Adjudication Committee (EAC). Investigators will be asked to provide a specific package of information to be submitted for adjudication evaluation that will be provided in a procedural manual. The EAC will assess such events according to the committee's charter and will independently classify the events while blinded to treatment assignment.

8.3.5. Adverse Event Reporting

At each contact with the patient, the Investigator or designee will capture AEs by specific questioning and, as appropriate, by examination. Participants will be asked standard questions to capture medically related changes to their well-being. Participants will also be asked if they have been hospitalized, had any accidents, sought care from a health professional, used any new medications/therapies, or changed concomitant medication regimens (both prescription and over-the-counter) due to an AE.

8.3.6. Serious Adverse Event Reporting

The Investigator will report to the Sponsor any SAE or AESI within 24 hours of becoming aware of the event, whether or not considered study intervention related, including those listed in the protocol or Investigator Brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

The Sponsor will be responsible for notifying the Food and Drug Administration (FDA) and other regulatory authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

It is the responsibility of the Sponsor to determine the reportability of SAEs.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the patient is stable. Other supporting documentation of the event may be requested by the DSMB or Sponsor and should be provided as soon as possible.

An independent DSMB will be responsible for safety oversight of the study. The DSMB will meet and review all available data on a regular basis; ad hoc meetings may be scheduled if needed. The DSMB will review all SAEs and AESIs as they occur.

8.3.6.1. Fetal Loss/Neonatal Death

In the event of fetal loss/neonatal death, an autopsy of the fetus/neonate and placental evaluation should be encouraged (see also Section 7.1.1.1 and Section 8.2.1.12, respectively).

8.3.7. Adverse Events of Special Interest

Participants (both mothers and neonates) in the study will be queried and/or observed for the following AESIs:

- In maternal patients and neonates/infants, infections requiring treatment with oral or intravenous anti-infectives (antibacterial/antiviral/antifungal).
- In maternal patients only, hypoalbuminemia ≥ Grade 3 (ie, <20 g/L by NCI CTCAE Version 5.0).
- In neonates/infants, unexpected/unusual childhood illnesses.

- In infants, IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96.

The Investigator will determine whether individual treatment-emergent AEs meet the criteria of an AESI and will report to the Sponsor any AESI within 24 hours of becoming aware of the event. See Section 8.2.1.1 for additional information on the definition of AESI for maternal patients.

8.3.8. Reporting of Pregnancy

Not applicable.

8.4. Unanticipated Problems

8.4.1. Definition of Unanticipated Problems

An unanticipated problem (UP) meets the following three criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved or Ethics Review Committee (ERC)-approved research protocol and informed consent document; and (b) the characteristics of the patient population being studied;
2. Related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Potential UPs may be based on new information from:

- Manufacturing or clinical supply management
- Nonclinical findings
- Clinical studies
- Other sources, including literature and regulatory assessments.

8.4.2. Unanticipated Problem Evaluation

The Sponsor will evaluate adverse events from clinical studies in a timely manner to determine whether they should be considered as unanticipated problems that must be reported to the IRB/ERC.

8.4.3. Reporting of Unanticipated Problems

Unanticipated problems identified by the Sponsor will be reported to the IRB/ERC and to participating investigators. If an unanticipated problem results in a change to the informed consent document, then participating patients will be informed and should sign the revised document.

9. STATISTICAL CONSIDERATIONS

A detailed SAP will be developed prior to study completion and database lock.

9.1. Sample Size Determination

The sample size of approximately 15 evaluable patients is considered appropriate for analysis of safety, efficacy, PD, and PK data. When the underlying true proportion of patients treated by nipocalimab achieving the primary endpoint (live birth at or after GA 32 weeks and no IUT throughout the pregnancy) is at least 0.4, the chosen sample size of 15 evaluable patients offers at least 78% power for the primary analysis.

9.2. Planned Interim Analyses

An interim analysis of the accrued data may be conducted to support development of nipocalimab for the treatment of HDFN. Details of the interim analysis will be specified in the SAP.

9.3. Analysis Sets

The following analysis sets will be used for analyses:

- Safety Analysis Set includes all patients who have received any amount of nipocalimab.
- Full Analysis Set is the same as the Safety Analysis Set, which includes all patients who have received any amount of nipocalimab.

  The Full Analysis Set will be the primary analysis set for primary efficacy endpoint analysis.
- PK Analysis Set is a subset of the Safety Analysis Set and includes all patients who have at least 1 measured concentration.
- PD Analysis Set is a subset of the Safety Analysis Set and includes all patients who have at least 1 measured PD assessment.

Patients who enroll in the study but do not receive any nipocalimab will not be included in any analysis set. These patients will be reported in a listing including all available recorded data.

9.4. Handling of Missing Data

Missing data will not be imputed.

9.5. Analysis Methods

9.5.1. General Approach

The main analyses (efficacy, safety, PK/PD) will be conducted 28 days after the last maternal patient's delivery. Supplemental safety analysis will be conducted for mothers at 24 weeks after the last patient's delivery, and for neonates, at 96 weeks after delivery of the last neonate.

Descriptive summary statistics will be provided for demographics, disposition and dose exposure. The number and percentage of patients who discontinued from the study, along with reasons for discontinuations, will be tabulated and described in listings.

Continuous data will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) and, where appropriate, coefficient of variation (CV%) and graphic representation. Categorical data will be summarized by sample size and proportions. Graphs of actual values and changes over time may also be created as appropriate.

9.5.2. Baseline Descriptive Statistics

Descriptive summary statistics will be provided for patient disposition and demographics.

9.5.3. Safety Analyses

Descriptive statistics will be computed for safety parameters, as appropriate. The number and percentage of patients who discontinued from the study because of AEs will be tabulated; severity and frequency of AEs, SAEs, and AESIs will also be summarized. Absolute and, where appropriate, change from baseline in clinical laboratory values, vital signs, and ECG results will also be summarized. All safety data will be provided in listings. Further statistical evaluations will be applied for select variables, if warranted.

Adverse events will be coded with Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as any event occurring after the initiation of the first infusion of nipocalimab.

Adverse event overview will include:

- Summary of Adverse Events by System Organ Class and Preferred Term
- Summary of Related Adverse Events by System Organ Class and Preferred Term
- Summary of Serious Adverse Events by System Organ Class and Preferred Term
- Summary of Severe (or Grade ≥3) Adverse Events by System Organ Class and Preferred Term
- Summary of Adverse Events Leading to Discontinuation

The analysis of AEs for neonates/infants will be summarized separately from the mother's AEs.

Analysis of other safety endpoints such as laboratory parameters, vital signs, ECG, etc, will be detailed in the SAP.

Listings of all maternal participants or their neonates/infants with MACE (non-fatal myocardial infarction, stroke, and cardiovascular death) will be provided.

9.5.4. Efficacy Analyses

Because this is a single arm study, statistical analyses and inference of the primary endpoint involve comparisons to a historical benchmark, and statistical analyses and inference of the other endpoints involve comparison to external data sources, including a prospective external concurrent control and historical control. The historical benchmark and external data sources are introduced here. The SAP will establish and discuss the comparability between the treated population and the external data sources.

Where appropriate, select secondary efficacy endpoints may also be compared against each subject's prior pregnancy history. Details on such analyses will be provided in the SAP.

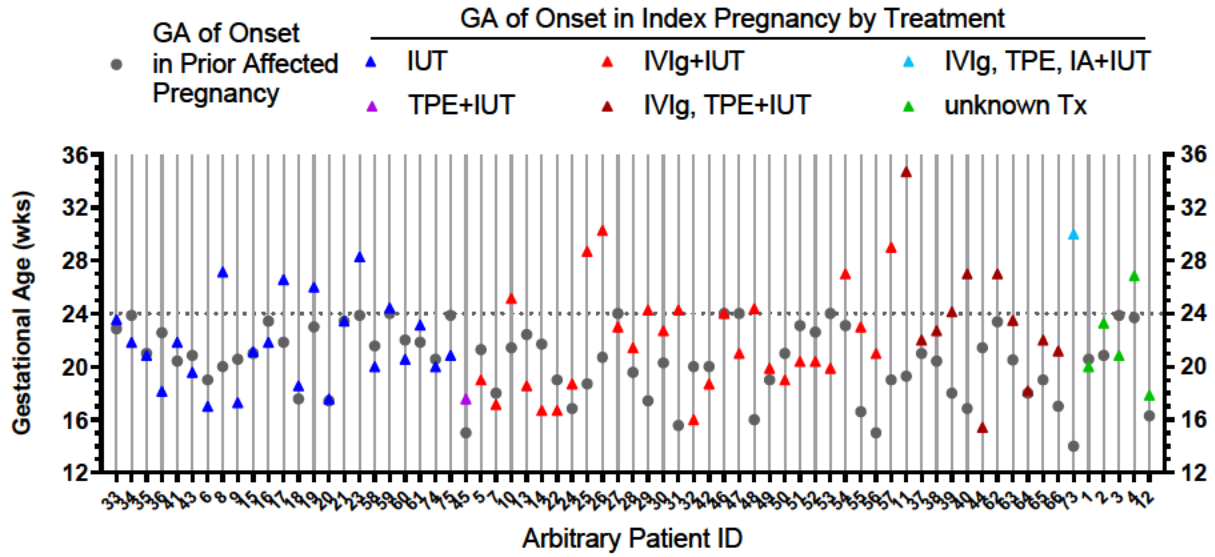
Descriptive statistics will be computed for efficacy parameters, as appropriate. Details will be provided in the SAP.

9.5.4.1. Definition of External Control Groups

Historical Benchmark

For the primary endpoint, it is common understanding based on expert opinion and analysis of available data (see below) that, for any patient with EOS-HDFN as defined in the inclusion/exclusion criteria, under the standard care, the expected probability (P_0) of delivering a live baby at or after GA Week 32 and without an IUT throughout their entire pregnancy for fetal anemia is 0. Data from published studies and other data from global academic medical centers with expertise in managing EOS-HDFN is summarized in Figure 2. All 69 patients with EOS-HDFN in a prior pregnancy required an IUT for fetal anemia in the current pregnancy, as illustrated in the scatter plot. In a recent multinational study with 45 cases showing EOS-HDFN, ie, required the first IUT or had fetal loss due to HDFN <24 weeks GA in the previous pregnancy, all 45 cases required an IUT in the index (current) pregnancy (PETIT Study; Zwiers, 2018). Similar results were observed in several smaller studies of women with EOS-HDFN, as well as in unpublished data from 3 academic research centers (Zwiers, 2018; Colpo, 2017; Ruma, 2007; The Fetal Center at Children's Memorial Hermann Hospital in Houston, Texas; The Department of Maternal Fetal Medicine at Ohio State University in Columbus, Ohio; The University of Toronto Fetal Medicine program at Mount Sinai Hospital in Toronto, Canada). Of the 24 patients from these additional sources who had required their first IUT (or had fetal loss) ≤24 weeks GA in a prior pregnancy, 100% required at least 1 IUT (mean of ~5 IUTs; data on file) in their index pregnancy.

Figure 2: Gestational Age of HDFN Onset in Pregnancies with Prior EOS HDFN (n=69)



Abbreviations: EOS-HDFN = early onset severe hemolytic disease of the fetus and newborn; GA = gestational age; IUT = intrauterine transfusion; IVIG =intravenous immunoglobulin; TPE = therapeutic plasma exchange; Tx=treatment; wks = weeks.

Individual patient data for EOS-HDFN patients with a previous history of IUT or fetal demise ≤24 weeks GA were obtained from the following sources: Zwiers, 2018 (ie, PETIT study; n = 45); Colpo, 2017 (n = 1); Ruma, 2007 (n = 5); The Fetal Center at Children's Memorial Hermann Hospital in Houston, Texas, USA (n = 2); The Department of Maternal Fetal Medicine at Ohio State University in Columbus, Ohio, USA (n = 4); and The University of Toronto Fetal Medicine program at Mount Sinai Hospital in Toronto, Canada (n = 12).

Note: Of the 69 patients included above, 23 patients received IUT only during the index (current) pregnancy. The remaining patients received IUT + TPE (n=1); IUT + IVIG (n = 28); IUT + IVIG + TPE (n = 11); IUT + IVIG + TPE/immunoabsorption (n = 1); IUT + treatment not reported (n=5).

Because 100% of these 69 historical EOS-HDFN cases required IUT during pregnancy, the observed probability of success in the primary endpoint as defined in this protocol is P_0=0, with 95% Clopper-Pearson upper confidence limit of 0.040, and 97.5% upper confidence limit of 0.049. Based on this observation, an a priori criterion is set forth to compare the proportion of nipocalimab-treated patients (P_t) with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy in the Full Analysis Set against a clinical significance margin from P_0 = 0. This margin is chosen to be c=0.1. It corresponds to the critical value of observing 5 or more patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy, out of 15 total patients, with associated lower bound of 95% Clopper-Pearson confidence interval 0.12 >c=0.1.

External Concurrent Control: A Multicenter, Prospective Observational Study to Characterize the Clinical Course of Pregnant Women and Children at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (MOM-M281-103)

A prospective observational (natural history) study (MOM-M281-103) will be conducted concurrently with this study. Patients in the prospective natural history study will receive current standard of care for EOS-HDFN, including frequent Doppler assessment of fetal MCA and IUT

when indicated, with or without IVIG ± plasmapheresis, depending on the clinical site's standard of care. To maximize comparability with the nipocalimab-treated patients in this Phase 2 treatment study, the natural history study (MOM-M281-103) will be conducted during the same timeframe and at the same sites as the current study, and the key inclusion criteria defining the history of EOS-HDFN will be identical to those for this Phase 2 treatment study. In addition, the efficacy endpoints (including the primary endpoint) for study MOM-M281-103 will be nearly identical to this Phase 2 treatment study. Study MOM-M281-103, however, will be open to patients who either declined to participate in this Phase 2 treatment study or who were excluded due to the presence of non-disease-related factors (eg, vaccination titers or infection risk) that have no influence on the course of an HDFN pregnancy and have no impact on pregnancy outcomes.

The data collected from this study will be used to further solidify the historical benchmark for the primary efficacy analysis and may be used as a comparator in analyses of secondary and exploratory endpoints.

External Retrospective Control

Historical data (either existing databases from observational studies, or separate retrospective natural history studies through medical chart review, or a combination of both) will be collected and used as control data to which this single arm study will be compared. Patients from historical data will be selected based on a matching mechanism (such as exact match on a set of criteria, or propensity score) and the selected cohort will be compared to the data observed in this study. The details on patient selection and data collection will be provided in the SAP.

The data collected from this study will be used to further solidify the historical benchmark for the primary efficacy analysis and may be used as a comparator in analyses of secondary and exploratory endpoints.

9.5.4.2. Primary Efficacy Endpoint: Proportion of Patients with Live Birth at or After GA Week 32 and Without an IUT Throughout Their Entire Pregnancy

The analysis will be performed in the Full Analysis Set. All patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy will be counted as meeting the endpoint (success). All patients who have fetal loss, or have IUT before birth, or end of pregnancy before GA Week 32, or patients who discontinued early due to an AE will be counted as not meeting the endpoint (failure). Patients who discontinued early for reasons unrelated to an AE and did not have IUT before discontinuation will also be counted as failure.

The number and percentage of patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy will be presented. The following statistical test will be performed in the Full Analysis Set:

H_0: $P_t \leq c = 0.10$

H_a: $P_t > c = 0.10$

where P_t is the proportion of nipocalimab-treated patients with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy. The value c=0.10 was chosen because it represents a clinically meaningful difference from historical benchmark (0%), and it corresponds to the critical value of 5 out of 15 patients with live birth at or after GA Week 32 and without an

IUT throughout their entire pregnancy. See Section 9.5.4.1 for details. Additional details will be provided in the SAP.

P value will be from one sample exact binomial test. The Clopper-Pearson 95% confidence interval of P_t will be presented. A 2-sided 0.05 significance level will be used for the primary efficacy analysis.

Analysis of the primary efficacy endpoint will be conducted 28 days after the last maternal patient's delivery.

9.5.4.3. Secondary Endpoints

- Percentage of patients with live birth
- Percentage of patients at GA Week 24 without an IUT
- Gestational age at first IUT
- Number of IUTs required
- Gestational age at delivery
- Percentage of patients with fetal hydrops
- Percentage of neonates requiring phototherapy
- Percentage of neonates requiring exchange transfusions
- Number of days of phototherapy required by neonate
- Percentage of neonates requiring simple transfusions in the first 12 weeks of life
- Number of simple transfusions required by neonate in the first 12 weeks of life

Descriptive statistics will be computed for efficacy parameters, as appropriate. Additional details for analyses of study endpoints will be provided in the SAP.

9.5.4.4. Statistical Considerations for Analysis of Secondary Efficacy Endpoints

When suitable, the secondary endpoints defined in this study will be compared against external controls.

Secondary endpoints will be analyzed using descriptive statistics, and when appropriate, statistical comparisons may be performed.

The data from Study MOM-M281-103 will serve as the main source of external control data. As discussed in Section 9.5.4.1, study MOM-M281-103 has been specifically designed to maximize comparability of patients with this proof of concept study through key inclusion and exclusion criteria. The statistical analysis will use all patients from study MOM-M281-103, excluding those who were lost to follow-up prior to first IUT or end of pregnancy.

Other sources of external control data may be used in addition to study MOM-M281-103, including the dataset described under "retrospective historical control" in Section 9.5.4.1. When these are used, the subject selection criteria and statistical methods will be detailed in the SAP.

Where appropriate, select secondary efficacy endpoints may also be compared against each subject's prior pregnancy history. Details on such analyses will be provided in the SAP.

9.5.5. Pharmacodynamic Analyses

Pharmacodynamic endpoints will be summarized by time point. The primary measures of PD will be nipocalimab RO, circulating IgG and alloantibodies.

9.5.6. Pharmacokinetic Analyses

Serum nipocalimab concentrations will be summarized by time points. Descriptive statistics will be presented. No PK noncompartmental parameters will be derived.

9.5.7. Exploratory Analyses

Exploratory endpoints for this study include:

- Fetal hemoglobin, hematocrit, and alloantibody levels at first IUT and in subsequent IUTs
- Maternal serum levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE
- Presence of nipocalimab in colostrum/breast milk
- Placental evaluation
- Neonatal bilirubin, direct Coombs, reticulocyte count, hemoglobin, hematocrit, IgG, alloantibodies, and FcRn RO (from cord blood at birth)
- Peak bilirubin levels during the neonatal period
- Number of IVIG doses received by the neonate
- Slope of MCA-PSV by Doppler ultrasound prior to the first IUT

Details of the exploratory analyses will be provided in the SAP.

9.5.8. Subgroup Analyses

Not applicable.

9.5.9. Tabulation of Individual Participation Data

Individual participant data will be listed by measure and time point.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

Including pregnant women in a clinical trial involves careful scientific and ethical considerations, including the risk-benefit assessment. This clinical trial is designed to enroll a population of pregnant women who have had a previous pregnancy complicated by EOS-HDFN (either severe fetal anemia, fetal hydrops, or stillbirth with fetal or placental pathology indicative of HDFN occurring at ≤24 weeks GA) who are therefore at high risk for developing EOS-HDFN again. Thus, the population who can most benefit from the study intervention.

Risks to the pregnant women, their fetuses, and neonates will be minimized by safety monitoring beginning at study entry and a 24-week follow-up for the mothers and a 96-week follow-up of neonates/infant. Further, adequate nonclinical studies of pregnant animals have been completed, and as described in the Investigator's Brochure, support the potential efficacy of the product for the treatment of HDFN. A low incidence of gross abnormal morphological changes, characterized microscopically as infarcts, were observed in the placentae of 4 monkeys out of 26 evaluable placentae available from nipocalimab-treated dams; 2 monkeys each at 100 and 300 mg/kg in the ePPND study (see Section 3.2.2, Section 3.3.1, and the Investigator's Brochure). The relationship of these placental changes to nipocalimab was uncertain and a direct effect of nipocalimab on the placenta could not be completely excluded, therefore monitoring procedures for IUGR and a stopping rule for administration of nipocalimab to individual patients (Section 7.1.1.6 and Appendix 2) and a study stopping rule for IUGR (Section 7.1.2) are included in this protocol.

This clinical trial is designed as an open-label, single-arm study with comparisons to data from a planned prospective observational study in patients with EOS-HDFN and historical controls, as described further in Section 9.5.4.1. Early onset, severe HDFN can have serious and irreversible consequences to the fetus, including fetal demise (see Section 3.1), and therefore a placebo or other concurrently controlled trial design would offer no potential short-term or long-term benefit for patients and could result in serious and irreversible harm to those subjects randomized to a control arm (see Section 4.2.1, Justification for Study Design). Further, due to the need for timely intervention during gestation in order to prevent consequences of HDFN, concurrently controlled study designs including a placebo group, a standard of care group, or crossover study design with later access to the investigational drug in an extension study are not possible. The current study design allows for treatment with the current standard of care, IUTs, if needed.

This clinical trial will conform to all applicable regulations including those related to human subject/patient protections of the National Health Authorities, and the applicable national, state, or local laws of the jurisdiction in which the clinical trial will be conducted. Additionally, this clinical trial will follow the provisions of the Code of Federal Regulations (CFR) 21 CFR312.120, as well as the FDA Guidance (including the International Council for Harmonisation [ICH] E6), FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions (March 2002). Finally, in the conduct of this clinical trial, efforts will be made when performing clinical examinations, testing, and blood draws on neonates/infants/children to do so in a child-friendly and sensitive environment by investigators experienced in pediatric care.

10.2. Informed Consent Process

Only pregnant women will be recruited for this clinical trial.

Informed consent, in accordance with 21 CFR Part 50, ICH E6 or other applicable national, state, or local laws of the jurisdiction in which the clinical trial will be conducted, will be obtained from the pregnant patient prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research (screening), and for enrollment in the clinical trial itself. Permission from the fetus' father will be obtained in accordance with the requirements of applicable national, state, or local laws of the jurisdiction in which the clinical trial will be conducted.

All patients will be provided a written informed consent form (ICF) describing this study that provides sufficient information to make an informed decision about participation in this study, to facilitate the potential participant's comprehension of the information, to provide adequate opportunity for the potential participant to ask questions and to consider whether to participate, to obtain potential participant's voluntary agreement to participate, and to continue providing information as the clinical trial progresses or as the participant or situation requires.

Voluntary informed consent must be obtained from each eligible patient (and/or legally authorized representative) before any protocol-defined procedures are performed. The patient's signature on the ICF indicates her willingness to participate in this study. Other study personnel (eg, Principal Investigator, Study Nurse) will sign the ICF in accordance with local IRB/ERC procedures.

A template ICF will be provided by the Sponsor or designee. The ICF must be reviewed and approved by the IRB/ERC and must contain all elements required by national or local regulations or requirements, FDA regulations, state and federal laws, and institutional policies. If, during the approval process, the IRB/ERC makes any substantive changes to the ICF, then this altered ICF must be provided to the Sponsor or designee for review before it is implemented.

In addition, parental consent/permission must be provided for the neonate/infant's participation for the 96-week safety follow-up period.

A substudy consent will be provided by the maternal participant for participation in the central pathology substudy.

10.2.1. Consent, Parental Permission, and Other Informational Documents Provided to Participants

10.2.1.1. Parental Permission and Subpart D Considerations for Neonates/Infants

The IRB or the ERC must review this clinical investigation involving neonates/infants under 21 CFR, part 50, Subpart D, and approve it accordingly. It is the sponsor's assessment that this clinical investigation should be considered by the IRB(s) and ERC(s) for approval under 21 CFR 50.52, *Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects*. The following provisions are required under 21 CFR 50.52:

- The risk associated is justified by the anticipated benefits to the subjects;

- The relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches; and,
- Adequate provisions are made for soliciting parental permission, as set forth in 21 CFR 50.55.

The clinical trial interventions or procedures, and the long-term follow up and monitoring activities (eg, postnatal administration of IVIG, immunologic and safety laboratory tests, AE evaluations, developmental assessments) described in the protocol confer direct safety benefits to the pediatric subjects.

According to 21 CFR 50.55(e)(1), the permission of 1 parent is sufficient for clinical trials conducted under 21 CFR 50.52. Procedures for obtaining parental permission will conform to this provision, unless the applicable national, state or local laws require additional permissions.

10.2.2. Consent Procedures and Documentation

The Investigator is responsible for ensuring that a careful and thorough informed consent procedure is implemented before a patient enters the study and at any time during the study when the ICF changes. This includes, but is not limited to: (1) providing a quiet place for the potential participant to read the ICF and allowing ample time for this review; (2) ensuring that qualified medical personnel are available to directly answer questions that a potential participant may have; (3) ensuring that each potential study participant understands that her medical treatment will not be otherwise affected based on the decision or not to participate in the study, that her participation is completely voluntary, and that she can opt to stop participation in the study at any time for any reason; and (4) ensuring a full copy of the signed ICF is given to the study participant to take home for her medical records, to serve as a reminder of the elements of the clinical trial, and to provide contact information in case of additional questions or concerns arise. The process for obtaining informed consent should also be noted in the patient's source documentation.

Pregnant women retain the right to withdraw from the clinical trial themselves or to withdraw their neonates or infants. Should this occur, the clinical investigator(s) will ask the patient who is withdrawing whether she wishes to agree to continued follow-up and further data collection subsequent to her withdrawal (or the withdrawal of her neonate/infant) from the interventional aspects of the clinical trial. Under this circumstance, the discussion will distinguish between study-related administration of the investigational product, continued follow-up of associated clinical outcome and safety information (eg, laboratory results through protocol-scheduled blood tests), and medical course obtained through non-invasive chart review or reporting, or complete withdrawal from the clinical trial.

10.2.3. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigator, Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the IRB/ERC, and

Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/ERC, and/or regulatory authorities.

10.2.4. Confidentiality and Privacy

Patient confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/ERC, regulatory agencies or Sponsor supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/ERC, Institutional policies, Sponsor requirements and regulatory authority requirements.

Participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management vendor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the data management vendor's research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the data management vendor.

10.2.5. Future Use of Stored Specimens and Data

If intended specimens or residual specimens are retained after the study is complete, future uses of specimens will be described in the consent document, with options that are available for the participant to agree to the future use of his/her specimens, images, audio or video recordings as well as her neonate's cord blood. Specify the location(s), if other than the clinical site, where specimens or other data will be maintained, how long specimens or other data will be stored, if the site's IRB/ERC will review future studies, and protections of confidentiality for any future

studies with the stored specimens or data (eg, specimens will be coded, bar-coded, de-identified, identifying information will be redacted from audio recording transcripts). Include a statement that genetic testing will or will not be performed.

See also Section 10.2.4, Confidentiality and Privacy and Section 10.3, Data Handling and Record Keeping, for further information on future use of study records.

10.2.6. Key Roles and Study Governance

Principal Investigator
Kenneth J. Moise, Jr., MD Professor of Obstetrics, Gynecology, Reproductive Sciences, and Pediatric Surgery McGovern School of Medicine University of Texas Health Houston, Texas USA PPD

10.2.7. Safety Oversight: Data Safety Monitoring Board

Safety oversight will be under the direction of an independent DSMB. Members of the DSMB will have knowledge and expertise in the management of HDFN and other conditions of high-risk pregnancy. The DMSB will operate under the specific rules and responsibilities of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study Sponsor.

The DSMB will meet and review all available data, including data from the observational study (MOM-M281-103), on a regular basis; ad hoc meetings may be scheduled if needed. The DSMB will review all SAEs and AESIs (including infections that require treatment with oral or intravenous antibiotics/antivirals/antifungals, maternal hypoalbuminemia ≥ Grade 3, unusual/unexpected childhood illnesses, and IgG concentrations <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96 in the neonate/infant) as they occur.

10.2.8. Clinical Monitoring

Clinical Research Associates (CRAs) representing the Sponsor will routinely visit the study site throughout the study. The Investigator will also ensure that the monitor, or other compliance or quality assurance reviewer, is given access to all study-related documents and study related facilities (eg, pharmacy, diagnostic laboratory, medical records, etc), and has adequate space to conduct the monitoring visit. In addition to the monitoring visits, frequent communications (email, letter, telephone, and/or fax) by the CRA will ensure that the investigation is conducted according to protocol design and regulatory requirements. The Investigator, or appropriate designee, will allocate adequate time for monitoring activities and follow-up correspondences.

The CRA will review ICFs, eCRFs, and laboratory and other diagnostic reports, comparing them with source documents to verify adherence to the protocol, and to ensure complete, accurate, consistent, and timely collection of data. The CRA will record and report any protocol deviations not previously sent to the Sponsor. The CRA will also confirm that AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB/ERC. The Investigator will be asked to provide any missing information or to clarify any discrepancies found by the CRA/monitor. It is expected that the Investigator will be present for a concluding review at the end of each monitoring visit.

10.2.9. Quality Assurance and Quality Control

To assure quality and consistent study data, procedures will only be carried out by the Principal Investigator or trained staff under the direction of the Principal Investigator. Study-related procedures will be carried out in accordance with written materials (eg, study manual, pharmacy manual/study-site investigational product and procedures manual, eCRF completion guidelines, Procedure Manual for MACE Adjudication, etc).

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor or a Sponsor's designee may conduct a quality assurance audit of the study center(s).

10.3. Data Handling and Record Keeping

10.3.1. Data Collection and Management Responsibilities

Sites will enter source data into the eCRFs. The Clinical Monitoring Plan will identify which data should be considered source data. A Data Management Plan will be written by the Sponsor or designee which will be finalized prior to performing any data validation.

Source documents are all original documents, data, and records that pertain to a study participant and can be either electronic or physical in origin. Examples of source documents are: hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files and records kept at the pharmacy, at the laboratories and at technical departments involved in the study. When source document data are shared with originating files (eg, hospital records or other clinic charts), photocopies of specific components of these data can be included as source document provided that these copies are signed and dated by appropriate research site personnel.

CRAs, monitors and auditors must have access to original records (unless copies are certified as authentic copies). Source data must be legible and written concurrently with the patient visit, and no data may be obliterated. If the source document contains a participant's address and phone number, it must be obliterated before it is included as a study document and the participant's name will be obliterated except for the first letters of the first, middle (if present), and last names. The completed eCRF must be reviewed and approved by an authorized Investigator before it can be considered final.

10.3.2. Study Records Retention

The Principal Investigator shall retain all study-related documentation, including source data, source documents, eCRFs, laboratory and diagnostic results, protocol and amendments, study drug accountability records, regulatory documentation and correspondence, ICFs, patient identification lists, and correspondence. These records should be retained in the format they were originally obtained (eg, electronic or paper) unless a quality controlled and authorized complete electronic version is created for long-term storage at the end of the study. The Sponsor will provide an electronic copy of the final eCRF for each study patient within 3 months of study closeout.

The Investigator must retain an organized file with all study-related documentation that is suitable for inspection by the Sponsor and representatives of Regulatory Authorities.

The Investigator must retain essential documents until notified by the Sponsor, and at least for 15 years after study completion.

Documents should be stored in such a way that they can be accessed and data can be retrieved at a later date. Consideration should be given to security and environmental risks.

Documentation retention will generally comply with Section 8 of the ICH consolidated guideline on GCP, Essential Documents for the Conduct of a Clinical Trial.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator or the Research Site should the Investigator leave the institution. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor prior to any actions being taken.

10.4. Protocol Compliance and Amendments

Except for a change intended to eliminate an immediate hazard to a participant, the protocol shall be conducted as described without any changes or deviations. Any change must be reported immediately to the Sponsor and to the IRB/ERC, as required by their regulations.

Protocol amendments will be prepared and approved by the Sponsor or Sponsor's designee and sent to the appropriate IRB/ERC for review and approval. For each amendment to the protocol, the Investigator Protocol Agreement page will be signed by the Principal Investigator. Documentation of IRB/ERC approval must be forwarded to the Sponsor or designee before the procedures associated with the amendment commence.

If an amendment significantly alters the study design, increases potential risk to the patient, or otherwise affects statements in the ICF, the protocol and the ICF must be revised accordingly and submitted to the IRB/ERC and the local/national health authority for review and approval before being implemented, unless the change is made to eliminate hazard to a participant. The approved ICF must be used to obtain informed consent from new patients prior to registration and must be used to re-obtain informed consent from patients already registered if they are affected by the amendment.

10.5. Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Authorship will be guided by the guidelines developed by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and based on the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

10.5.1. Institutional Review Board/Ethics Review Committee

The Principal Investigator will be responsible for obtaining initial IRB/ERC approval and renewal approvals (eg, annual, protocol amendment) throughout the duration of the study. All IRB/ERC correspondences (eg, submission paperwork, IRB/ERC approvals or rejections) will be retained in the study file and made available for review whenever requested. It is also the responsibility of the Principal Investigator to obtain other committee approvals based on local institutional policies.

The Investigator will notify the IRB/ERC of protocol violations and/or SAEs in accordance with local procedures.

10.6. Audits and Inspections

The study may be evaluated by representatives of government agencies, national health agencies, and national health authorities, who also will be allowed access to study documents. The Investigator should promptly notify the Sponsor when any audits are scheduled or on the first day of any unscheduled investigation. The Investigator will share all audit or investigation findings that pertain to this study with the Sponsor. The Investigator will permit study-related monitoring, audits, and inspections by the IRB/ERC, the Sponsor, government regulatory bodies, and compliance and quality assurance groups of all study-related documents (eg, source documents, regulatory documents, data collection instruments, study data, etc). All authorized personnel, including health authority inspector(s), Sponsor and designees, CRAs, Medical Monitor(s), and auditor(s) will be given direct access to source data and documentation (eg, medical records, laboratory results, etc) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

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12. APPENDICES

APPENDIX 1. Investigator Protocol Agreement

APPENDIX 2. Stopping Rule Algorithm for Intrauterine Growth Restriction

APPENDIX 3. American College of Obstetricians and Gynecologists (ACOG) Committee Opinion No. 797: Prevention of Group B Streptococcal Early-onset Disease in Newborns

APPENDIX 4. ASQ-3 Ages and Stages Questionnaires®

6 Month Questionnaire

12 Month Questionnaire

24 Month Questionnaire

APPENDIX 5. Guidance on Study Conduct During the COVID-19 Pandemic