Janssen Research & Development

Statistical Analysis Plan

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)

Protocol MOM-M281-003; Phase 2

80202135 (nipocalimab)

Status:	Approved
Date:	20 December 2022
Prepared by:	Janssen Research & Development, LLC
Document No.:	EDMS-RIM-445988, 3.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	04-JUN-2021	Not Applicable	Initial release
2.0	03-MAY-2022	• Change to the Janssen template • Added Estimand Framework • Changes listed in Appendix 2	Change of Sponsor New ICH E9 Guidance
3.0	20-DEC-2022	• Moved PedsQL and ASQ-3 to secondary endpoints • Moved hemoglobin levels in multiple of medians at time of first IUT and number of IUTs with anemia to exploratory endpoints • Moved number of neonates requiring hospitalization, hemoglobin levels in cord blood for neonates (all and with or without IUT) to exploratory endpoints • Moved concentrations of nipocalimab in colostrum/breast milk, in fetus (cordocentesis), and in neonate to exploratory endpoints • Clarified populations for analysis to align with data presentation needs • Clarified handling data of participant who enrolled twice • Added derivation for duration of phototherapy • Updated participant dispositions summaries • Clarification on tipping point analysis • Added live births prior to GA week 32 and without IUT and live births without IUT to GA at first IUT and delivery summary • Clarified summaries for frequency of IUTs required, percentage of IUTs meeting each anemia severity category, and IUT complications • Clarified summary of GA at delivery • Clarified handling of bilirubin values collected for phototherapy and transfusions; similar updates for hemoglobin values for simple transfusions	Updated after review of data presentation specifications for alignment based on clinical team requests

SAP Version	Approval Date	Change	Rationale
		• Clarified summary of neonatal hospitalizations • Updated mocks for comparisons of prior HDFN qualifying and current pregnancies, as well as specification of graphical displays for these data • Added summaries describing protocol-prohibited IVIG administrations • Added reference lines for MoM values for MCA-PSV plot • Removed description of summary for HR and uterine activity during nipocalimab infusions • Changed display fetal biophysical parameters from a summary to a listing • Removed text about nipocalimab exposure applying to neonates/infants • Added text for summary of prophylactic IVIG exposure as allowed/recommended by protocol • Added text for overall summaries of AEs for both maternal participants and neonates/infants; clarified summaries of AEs to be presented • Clarified handling of local versus central laboratory values • Clarified plotting of laboratory data • Removed text about laboratory toxicity grades • For clinically important thresholds, added SI units parenthetically • Removed text about growth curve percentiles for neonates/infants and other summaries of physical examination data • Removed frequency table of worst ECG outcomes • Added listing for fetal heart rate doppler • Removed summary of abnormal ultrasound results	

SAP Version	Approval Date	Change	Rationale
		• Removed summaries of yes/no for umbilical artery flow doppler and middle cerebral artery doppler being performed • Removed summaries of yes/no for microbiology specimens being collected • Updated summaries for PK and PD analyses • Added derivations for ASQ-3 and PedsQL scoring • Added text for lymphocyte phenotyping • Clarified handling of obstetrical history • Clarified summaries for protocol deviations • Clarified handling of concomitant medications and procedures • Updated handling of medical history data • Clarified derivation of intervention compliance • Removed medications of special interest • Added references • Administrative updates	

STATEMENT OF TRANSPARENCY

At the time of finalization of SAP version 1.0 on 04 June 2021, there were 7 participants enrolled in Study MOM-M281-003.

At the time of preparation of this SAP version 2.0 on 03 May 2022, there were 13 participants enrolled in Study MOM-M281-003.

At the time of preparation of this SAP version 3.0 on 19 December 2022, there were 13 participants enrolled in Study MOM-M281-003 and all participants had completed their pregnancies (ie, delivery outcomes were available).

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analysis methods for evaluation of the primary, secondary and exploratory objectives of this Phase 2, multicenter, open-label study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of M281 (nipocalimab hereinafter) administered to pregnant women at high risk for early onset severe hemolytic disease of the fetus and newborn (HDFN). Nipocalimab is a fully human effectorless monoclonal antibody blocking the neonatal Fc receptor (FcRn).

This study is part of a clinical program that is designed to provide data on nipocalimab treated group as well as an overview of standard of care of the outcomes of pregnant women at high risk for early onset severe HDFN. The latter will be based on an external cohort of participants receiving standard of care (SoC) and will come from the following two studies:

- Study MOM-M281-103: 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.
- Study 80202135EBF0001 (EBF0001): A Historical Cohort, Multicenter Study to Characterize the Management, Clinical Course, and Outcomes of Pregnancies in Women Who Have Experienced a Pregnancy With Early Onset Severe HDFN

EBF0001 is to be conducted at many of the same sites as studies MOM-M281-003 and MOM-M281-103. Data from the EBF0001 will be collected from chart reviews of participants who met similar eligibility criteria as in MOM-M281-003, excluding any participants who would later enroll into either the MOM-M281-003 or MOM-M281-103 studies. The external cohort will be formed by identifying participants from a combined pool of participants from Studies MOM-M281-103 and EBF0001 that meet specified inclusion/exclusion criteria aligned to those used in Study MOM-M281-003.

This document only describes the analyses to be performed on the data from study MOM-M281-003. Analyses to be performed comparing the results of this study versus the external cohort is described in a separate overarching SAP (EDMS-RIM-569268).

This version of the statistical analysis plan was prepared in accordance with the latest protocol MOM-M281-003, version 11.0, dated March 21, 2022.

1.1. Objectives and Endpoints

OBJECTIVES	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 (i.e., ○ infections requiring use of oral or intravenous anti-infectives in the maternal participants and neonates/infants ○ Maternal hypoalbuminemia ≥ CTCAE v5.0 Grade 3, ○ Unexpected/unusual childhood illnesses in the neonate/infant ○ IgG concentrations<200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96) in neonates/infants) • Absolute and change from baseline values in ECG, laboratory, and vital sign parameters • Frequency of Intrauterine Growth Restriction (IUGR) based on ultrasound assessment ○ Estimated Fetal Weight (EFW) <10th percentile • Frequency of abnormal amniotic fluid assessments based on ultrasound assessment ○ For Max vertical pocket <2 cm or >8 cm ○ For Amniotic Fluid Index (AFI) <5 cm or >24 cm • Incidence of Abnormal Physical Examinations and APGAR scores (Infant) • Use of concomitant medications and therapies
• To evaluate the efficacy of nipocalimab as measured by the proportion of participants with live birth at or after gestational age (GA) Week 32 and without IUT throughout their entire pregnancy	• Proportion of participants with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy

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	• Percentage of participants with live birth • Percentage of participants without an IUT before GA Week 24 • GA at first IUT • Number and frequency of IUTs required • Percentage of participants with fetal hydrops in utero or post 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	• Gestational age at delivery • 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 •
• 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	• FcRn RO in mother serum • FcRn RO in fetus (cordocentesis blood) • FcRn RO in cord blood and neonatal samples • Maternal serum levels of total IgG and subclasses (IgG1, IgG2, IgG3, IgG4), IgA, IgM, and IgE, alloantibody titer at baseline and change from baseline at each visit and frequency of positive ADA and Nab • Fetal levels of IgG and Neonatal levels of IgG, IgA, IgM, and IgE, alloantibody titer
• To evaluate the PK of nipocalimab	• Concentration of nipocalimab in mother serum
	• Pediatric neurodevelopment as measured by the total and subscale scores from the Pediatric Quality of Life (PedsQL) and Ages and Stages (ASQ-3) questionnaires

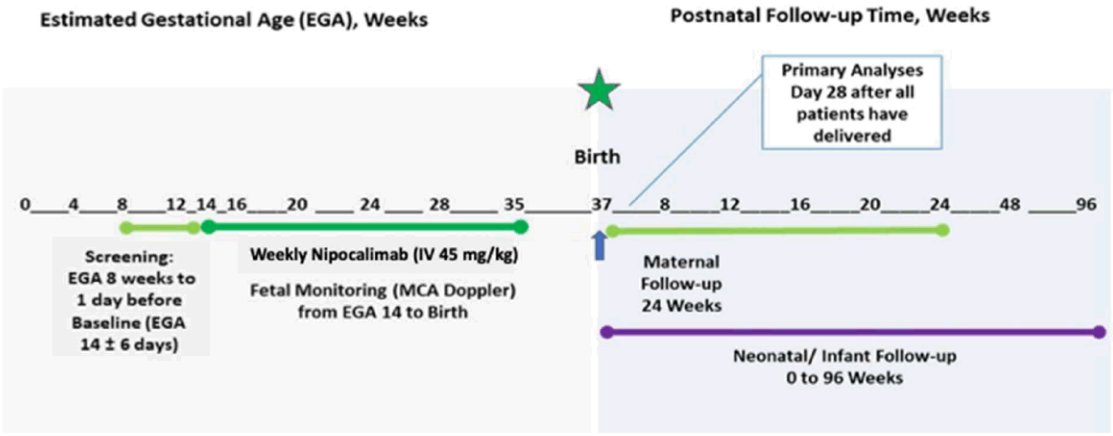
Exploratory	
	• Fetal hemoglobin, hematocrit and alloantibody levels at first IUT and in subsequent IUTs • Listing of observations related to placental evaluation • Absolute values in neonatal bilirubin, direct Coombs, reticulocyte count, hemoglobin, and hematocrit • Peak bilirubin levels during the neonatal period • Number of IVIG doses received by neonate • Proportion of neonates who received IVIG • Proportion of mothers who received IVIG or plasmapheresis prior to delivery • Slope of MCA-PSV by Doppler ultrasound • PSV at the time of first IUT • • Maternal and neonatal/infant lymphocyte phenotyping • Concentration of nipocalimab in fetus (cordocentesis blood) • Concentration of nipocalimab in neonate • Concentration of nipocalimab in colostrum/breast milk • Hemoglobin levels in multiple of medians at the time of first IUT • Number of IUTs with anemia defined as a hematocrit <30% or <2 SD below the mean hemoglobin for GA • Number of neonates requiring hospitalization including NICU and length of stay at NICU • Hemoglobin levels in cord blood for all neonates • Hemoglobin levels in cord blood for neonates with or without IUT
ADA = antidrug antibody; AE = adverse event; SAE = serious adverse event; AESI = adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FcRn = neonatal Fc receptor; GA = gestational age; Ig = immunoglobulin; IUT = intrauterine transfusion; MCA = middle cerebral artery; PD = pharmacodynamic; PK = pharmacokinetic; PSV = peak systolic velocity; RO = receptor occupancy; IVIG = intravenous immunoglobulin; SAE = serious adverse event	

1.2. Study Design

This is a multicenter, open-label phase 2 study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of nipocalimab administered to pregnant women at high risk for early onset severe HDFN. Randomization and blinding are not applicable.

An overview of the design is provided in Figure 1.

Figure 1: Study Design



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

Participants will be screened for inclusion between GA Week 8 up to 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.

Following delivery, maternal participants 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. Participants 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 of the protocol.

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 (Appearance, Pulse, Grimace Response, Activity, Respiration [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. Other data including labs, 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, with measures taken to minimize discomfort. Infant neurodevelopment will be monitored using the parent-reported developmental assessment, Ages & Stages Questionnaires®, Third Edition (ASQ-3™).

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. In addition, the Pediatric Quality of Life Inventory (PedsQL) will be completed by the parent/guardian at Week 96.

Participants 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.

2. STATISTICAL HYPOTHESES

The primary endpoint is the proportion of participants with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy. The hypothesis to be tested is:

H_0: $P_t \leq c = 0.10$

H_a: $P_t > c = 0.10$

where P_t is the proportion of nipocalimab-treated participants 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%), see Section 9.5.4.1 of the protocol illustrating that this endpoint has not been achieved in this population in relevant literature.

The hypothesis test will be performed by constructing a 95% confidence interval using the method of Clopper-Pearson. If this confidence interval excludes the value of 0.10, the null hypothesis will be rejected. This approach is identical to a two-sided exact test at the 0.05 level of significance.

Note that this SAP only describes the analyses to be performed on the data from study MOM-M281-003. Clarification of the historical benchmark based on Real-World Data is provided in the overarching SAP.

3. SAMPLE SIZE DETERMINATION

Given the rarity of the disease, the sample size of approximately 15 evaluable participants is considered appropriate for analysis of safety, efficacy, PD, and PK data. When the underlying true proportion of participants 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, with two-sided type I error <0.05, the chosen sample size of 15 evaluable participants offers at least 78% power to rule out the proportion of success in the primary endpoint is ≤10%.

The historical benchmark 10% was chosen based on data obtained from literature, where 0 out of 69 EOS-HDFN cases had success in the primary endpoint (see Protocol Section 9.5.4.1), with

upper bound of 97.5% Clopper-Pearson confidence interval <10%. Further examination of the historical benchmark will be described in the overarching SAP.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Screened	All maternal participants who sign the ICF.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all maternal participants who received any dose of nipocalimab.
Safety Analysis Set	All maternal participants who have received at least 1 dose of nipocalimab.
Pharmacokinetics (PK) Evaluable Analysis Set	All maternal participants who received at least 1 dose of nipocalimab and have at least 1 valid post-dose blood sample drawn for PK analysis.
Immunogenicity Evaluable Analysis Set	All maternal participants who received at least 1 dose of nipocalimab and have appropriate samples for ADA detection.
Pharmacodynamics (PD) Evaluable Analysis Set	All maternal participants who received at least 1 dose of nipocalimab and have at least 1 valid post-dose PD (RO or IgG) assessment.
Neonates/Infants	All live births to maternal participants who received at least 1 dose of nipocalimab in the study pregnancy. Note that fetal loss is considered as data of the maternal participant.
Pharmacokinetics (PK) Evaluable Analysis Set – Neonates/Infants	All neonate/infant participants who have at least 1 valid blood sample drawn for PK analysis.
Pharmacodynamics (PD) Evaluable Analysis Set – Neonates/Infants	All neonate/infant participants who have at least 1 valid PD (RO or IgG) assessment.

As of 31 July 2022, 13 individuals had enrolled in this study and were dosed with nipocalimab, including 1 individual who enrolled twice due to 2 qualifying pregnancies (she underwent elective termination at GA Week 17 for a fetal familial genetic disorder unrelated to HDFN and re-enrolled during her next pregnancy, which was not affected by this genetic disorder, and she continued in the study through delivery); enrollment was thus closed as of 01 August 2022.

For analysis sets, the maternal participant who enrolled twice (once as ID PPD and once as ID PPD) will be handled in the following manner:

- For the FAS, the maternal participant will be summarized using data from the second pregnancy (ID PPD). For efficacy purposes, the first pregnancy will not be considered (as the decision to terminate the pregnancy was unrelated to HDFN), meaning that it is not considered a success, but also not a failure. For safety data summarized over time, only the second pregnancy will be summarized.
- For the Safety Analysis Set, the participant will be counted once, as only unique participants can be counted. All exposures and any AEs of the same maternal participant will be added as part of a unique participant (for the second pregnancy, AEs observed after treatment

initiation will be considered as on-treatment). Any abnormalities (including those of the first pregnancy during the exposed period) will be tabulated considering the unique participant.
- For PK, PD, and Immunogenicity Evaluable Analysis Sets, the participant will be presented using data from the second pregnancy (ID PPD).

For Individual Patient Listings or Graphs, the data will be presented separately by original participant number.

A footnote will be added to each output to clarify how data from this participant is handled.

Maternal participants who enroll in the study but do not receive any nipocalimab will not be included in any analysis set. The same applies to their fetus/neonate.

5. STATISTICAL ANALYSES

5.1. General Considerations

In this analysis plan, the term 'participant' refers both to the mother (or maternal participant) and her fetus/neonate/infant. Unless otherwise specified, in all the statistical analyses, the data from the maternal participants and neonates/infants will be summarized separately, and the denominator will be based on the number of maternal participants and neonates, respectively (see Section 4 for the datasets considered).

Efficacy endpoints will be presented for all dose levels combined and supporting tabulation by dose level received categorized as 30 mg/kg only, 30 mg/kg to 45 mg/kg, 45 mg/kg based on baseline weight, and 45 mg/kg based on current weight. A participant will only be summarized for 1 treatment group; in case a participant switched during the study, the higher dose group will be taken.

5.1.1. Visit Windows

Section 1.3 of the protocol defines the treatment period (gestation to birth), postpartum week, and corresponding visit structure and visit names. Nominal visits will be used for all *by visit* analyses, unless those visits are weekly or bi-weekly visits and GA provides a more appropriate mapping to visits. In case of ties the nominal visit will prevail. This will be noted in Title and/or footnotes. In individual participant plots, gestation age as defined below will be used as the x-axis instead of the nominal visits. In data listings, both the nominal visit and actual gestation age will be displayed.

5.1.2. General Definitions

Start of Treatment	Date and start time of the first infusion of the study drug
Completion of Study Treatment	A maternal participant is considered to have completed the study treatment if she received all protocol required doses up to the date of first IUT (before Amendment 10) or in compliance with section 7.1.1.2 of the protocol (after Amendment 10), or when no IUT is performed, date of GA week 35 or delivery (whichever comes first).

Study Completion	A maternal participant or neonate is 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, Section 1.3 in the protocol.
Baseline	For maternal participants, baseline represents the procedure or assessments done prior to the administration of study treatment. The Baseline value will be the value obtained closest to and prior to the first administration of study treatment (Day 1). These values can occur on the same day as the first administration of study treatment (or in the Screening visit), as long as they are measured before the study treatment is administered. Additional details for how laboratory data will be handled with respect to central and local laboratories is included in Section 5.6.3.1. For neonates, baseline values, when applicable, represents the measurements taken at birth, such as the cord blood measurements.
Gestational Age (GA)	The gestational age will be taken from the estimated gestation age on the eCRF. The gestational age will be displayed in listings in the format xxWxD (or Week xx x/7) as appropriate. The values for Days are 0 to 6 (or 0/7 to 6/7).
Timing in GA Week	The meaning of *before GA Week 24* is any GA ≤ Week 23 6/7. The meaning of *at or after GA Week 32* is any GA ≥ Week 32 0/7.
Visit based assessments	For statistics of visit-based assessments, such as lab, vital signs, etc., summary statistics can be based on the nominal visits as collected in the CRF. See Section 5.1.1.
Trimester	Trimesters are defined based on the GA. Trimester 1: any time in the pregnancy up to GA Week 13 6/7. Trimester 2: any time from GA Week 14 0/7 to Week 26 6/7. Trimester 3: any time from Week 27 0/7 up to (but not including) delivery.
Delivery	Delivery refers both to cases of a live birth as well as a fetal loss.
Year	Duration of 1 year = 365.25 days. Year is calculated as (days/365.25) and will be rounded up to 1 significant digit (tenths) for purposes of presentation.
Month	Duration of 1 month = 30.4375 days. Month is calculated as (days/30.4375) and will be rounded up to 1 significant digit (tenths) for purposes of presentation.
Pound	0.454 kg. SI units will be used in presentation.
Inch	2.54 cm. SI units will be used in presentation.
Investigational Product	Nipocalimab (Study Drug).
Study Drug Duration	Duration of treatment is defined as the last dose date minus the first dose date of the study treatment plus 1.

Missing data	Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated.
Duration of phototherapy	If both start and end dates are present and both start and end times are present, duration of phototherapy is calculated as End Date/Time – Start Date/Time, in hours. However, if both start and end dates are present, but start time and/or end time are missing, then duration of phototherapy is calculated as End Date – Start Date, in hours (note that this would result in durations in 24-hour increments).

5.2. Participant Dispositions

Participant disposition will be tabulated and listed for the maternal participants and will include:

- Number of maternal participants in each analysis set (Screened, Safety, FAS, PK, PD, and Immunogenicity)
- Number of maternal participants treated with nipocalimab
- Number of maternal participants completing the study treatment, and primary reason for treatment discontinuation
- Number of maternal participants completing the Week 4 (Day 28) post-partum visit
- Number of maternal participants completing the study and the primary reason for study discontinuation

A by-participant data listing of study treatment discontinuation information, including the reason for study treatment withdrawal, will be presented for maternal participants.

Participant disposition will also be tabulated for the neonates based on the dataset Neonates/Infants and will include:

- Number of neonates/infants in each analysis set (Neonates/Infants, PK Evaluable, and PD Evaluable)
- Number of neonates/infants completing the study and the primary reason for study discontinuation
- Number of neonates/infants completing Weeks 4, 24, 48, and 96 follow-up visits

A by-participant data listing of study completion information, including the reason for study withdrawal, will be presented separately for the maternal participants and neonates/infants.

A by-participant data listing of screen failures, including inclusion and exclusion criteria not met, will be presented for maternal participants.

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint(s)

The proportion of nipocalimab-treated participants with live birth at or after GA Week 32 and without an IUT throughout their entire pregnancy. For the primary and secondary endpoints that involve GA, the GA is taken as recorded in the CRF for each pregnancy (as defined in Section 5.1.2). Note that if a live birth occurs and the first IUT occurs after start of GA Week 32 the participant is considered a treatment failure.

5.3.2. Estimand

5.3.2.1. Primary Estimand

Primary Trial Objective: To evaluate the efficacy of nipocalimab as measured by the proportion of participants with live birth at or after gestational age (GA) Week 32 and without IUT throughout their entire pregnancy.

Estimand Scientific Question of Interest: What is the proportion of nipocalimab treated participants considered to have reached the primary endpoint interpreted as treatment success?

Study Intervention	Nipocalimab (30 mg/kg only, 30 mg/kg to 45 mg/kg, 45 mg/kg based on baseline weight, 45 mg/kg based on current weight), all doses combined
Population	Pregnant women with a history of EOS-HDFN
Variable	Live birth at or after GA Week 32 and without an IUT throughout the entire pregnancy (treatment success or failure)
Intercurrent Events (ICE) and Corresponding Strategies	1. Use of IVIG or plasmapheresis during pregnancy (with the exception of treatment with IVIG within 48-72h prior to delivery as per protocol – see Protocol Section 8.2.1.6). 2. Discontinuation of study intervention with less than 50% of treatment exposure versus planned exposure up to GA Week 32 for any reason All ICEs will be handled with the *treatment policy strategy*, estimating the treatment effect regardless of the occurrence of the ICE; all observed data will be used, including data obtained after the occurrence of the ICE.
Population-level summary	Proportion of participants with treatment success

5.3.2.2. Supplementary Estimand (Composite Estimand)

The composite estimand is defined to support the primary estimand. Here the ICEs are handled with the composite strategy, where the use of prohibited medication of IVIG or plasmapheresis during pregnancy is interpreted as a treatment failure. Secondly, insufficient exposure to nipocalimab, defined here as less than 50% of planned exposure, will also be considered as

treatment failure. For pregnancies with sufficient exposure and without rescue medication the treatment policy strategy will be applied; meaning that a success will be counted as such.

Estimand Scientific Question of Interest: What is the proportion of nipocalimab treated participants considered to have reached the primary endpoint interpreted as treatment success without use of prohibited medication and attributable to nipocalimab exposure?

Study Intervention	Nipocalimab (30 mg/kg only, 30 mg/kg to 45 mg/kg, 45 mg/kg based on baseline weight, 45 mg/kg based on current weight), all doses combined
Population	Pregnant women with a history of EOS-HDFN
Variable	Live birth at or after GA Week 32 and without an IUT throughout the entire pregnancy (treatment success or failure)
Intercurrent Events (ICE) and Corresponding Strategies	1. Use of IVIG or plasmapheresis during pregnancy (with the exception of treatment with IVIG within 48-72h prior to delivery as per protocol – see Protocol Section 8.2.1.6). 2. Discontinuation of study intervention with less than 50% of treatment exposure versus planned exposure up to GA Week 32 for any reason The ICEs will be considered as treatment failures.
Population-level summary	Proportion of participants with treatment success

5.3.3. Analysis Methods

Data for primary analysis

Primary analysis is based on the FAS (Section 4). In order to be counted as a success the following data need to be observed in the clinical database:

- Live birth at or after GA Week 32
- Absence of any IUT during the pregnancy

Primary analysis method

The p-value will be from a one sample test using the exact method. The 95% Clopper-Pearson confidence interval will also be presented. Sample code in SAS is provided below.

```
proc freq data=adam;
   tables primary / binomial(exact p=0.1) alpha=.05;
   weight Count;
run;
```

Missing data handling rules for primary estimand

If a participant status of the primary endpoint is unknown due to lost to follow-up, the participant will be included in the analysis and will be considered as failed the primary endpoint. (Note that

this means that there was not already an IUT recorded: only situations are taken into account where treatment success or failure cannot be established due to missing data.)

Tipping point analysis will be used to evaluate the impact of missing data on the analysis results. Assuming m participants with missing primary efficacy endpoint, the analysis will be repeated m times, each time assuming 1, 2, ...m of the missing values are failure and others as success. The results of the m analyses will be summarized to define a breakpoint where the result of the primary efficacy endpoint would change statistical significance.

As an example – suppose that 2 participants have a missing value. In that case 2 additional analyses will be prepared:

- The analysis where the 2 participants are considered failures is the primary analysis
- One analysis will consider 1 participant as failure and 1 as a success
- The second analysis will consider 0 participants as failure and 2 as successes

For both additional analyses the 95% CI and associated p-values will be calculated. If at any stage the conclusion changes, this will be reported as the tipping point, ie., the null hypothesis is not rejected if of the 2 participants with missing data preventing to conclude the primary outcome 1 participant is considered a failure and 1 as a success, but the null hypothesis can be rejected if both are considered as successes.

Analysis	Failure	Success	95% CI	P-value	Significant	Tipping Point
Primary	2	0			Yes/No	
Tipping point m=1	1	1			Yes/No	Yes/No
Tipping point m=2	0	2			Yes/No	Yes/No

If no data are missing, the tipping point analysis will not be performed.

5.3.4. Supplementary Analyses

5.3.4.1. Composite Estimand

This supplementary analysis will be performed according to the Supplementary Estimand (Composite Estimand) as defined in Section 5.3.2.2. Similar analysis and missing data handling as for the primary estimand will be performed.

5.4. Secondary Endpoint(s) Analysis

For the secondary endpoints, estimands will be defined analogous to the primary estimand. Here only a treatment policy strategy towards intercurrent events will be used. No supplementary estimands are planned.

Descriptive statistics or counts with percentage of participants will be presented for the following secondary endpoints, and instructions are provided below each endpoint on derivation details. Analysis will be done on maternal participants using the FAS:

- Percentage of maternal participants with live birth – This will be expressed as a percentage of all FAS participants (ie, participants who discontinue the study early for any reason or are lost to follow-up will still be counted in the denominator. In the unlikely case that the outcome is unknown it will not be counted as a live birth; a footnote will be added).

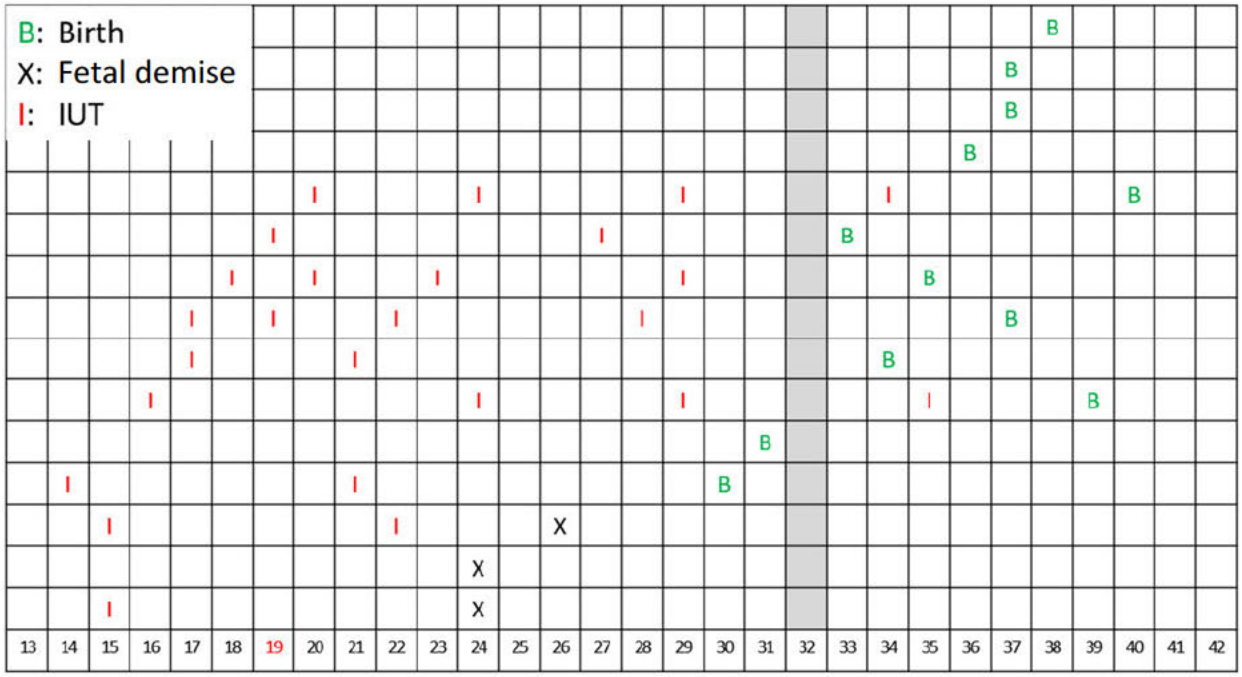
- Percentage of maternal participants without an IUT before GA Week 24 with live birth – Similarly, the number of participants meeting this criterion will be expressed as a percentage of all FAS participants, regardless of their study status (ie, participants who discontinue the study early for any reason or are lost to follow-up will still be counted in the denominator). The endpoint means that the first IUT must be at GA Week 24 0/7 or later (or no IUT), and the fetus is born alive. A footnote will be added noting the number of fetal losses < GA Week 23 6/7 when applicable.

- GA at first IUT and delivery. This variable will be presented based on the FAS, noting also the percentage of participants that had a successful live birth as defined in the primary endpoint. All cases of fetal demise will also be presented separately, if applicable, and separated by having had at least one IUT versus no IUT. Those that did not reach a primary endpoint nor had a fetal demise will be presented showing the n (%) of the FAS, and for the GA at first IUT, mean, median, min and max GA at first IUT and birth, presented as Week with number of days as x/7, rounded to nearest 1/7th.

Outcome	**N (%)**	**GA at first IUT***	**GA at delivery***
Primary Outcome	N (%)	NA	Mean (Week, x/7) Median (Min, Max)
Live births prior to GA week 32 and without IUT	N (%)	NA	Mean (Week, x/7) Median (Min, Max)
Live births without IUT	N (%)	NA	Mean (Week, x/7) Median (Min, Max)
Live births with IUT	N (%)	Mean (Week, x/7)	Mean (Week, x/7)

		Median (Min, Max)	Median (Min, Max)
Fetal demise without IUT	N (%)	NA	Mean (Week, x/7) Median (Min, Max)
Fetal demise with IUT	N (%)	Mean (Week, x/7) Median (Min , Max)	Mean (Week, x/7) Median (Min, Max)

A supporting graphic will be made for all cases in the FAS showing the time of key events by GA week. The key events to be presented are the live births, fetal demise, and IUTs. Note that in this graphic, participant PPD will not be presented; see the explanation of the FAS population; a footnote will be added to this graphic. For a mock see below.



- Percentage of maternal participants with a fetus with fetal hydrops (N, %)

- Number of IUTs required and frequency of IUTs per week for maternal participants, where the frequency of IUTs is calculated as: total number of IUTs divided by ([the date of delivery – date of first IUT + 1] / 7). This table will also show counts and frequencies separate by live births and fetal demise. Statistics include, N, median, and range.

The following endpoints will be defined for all IUTs.

- Number of IUTs with anemia defined as a hematocrit <30% or <2 SD below the mean hemoglobin for GA

The criterion of <2 SD below the mean hemoglobin for GA will be taken from the Table 1 presented below (see protocol Section 8.1.1.2).

Table 1: Normal Mean and < 2 SD Values for Fetal Hemoglobin values by Gestational Age

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

- Hemoglobin levels in multiple of medians at the time of IUT

This endpoint will be calculated using the multiples of the median using the Table below (Mari 2000), and the categorizations defined above.

Definition of fetal anemia using the reference of Mari 2000, presented in Table 2 below.

Table 2: Fetal Anemia Definition

GA (Weeks)	Median Hb (g/dL)
16	10.0
17	10.4
18	10.6

19	10.9
20	11.1
21	11.4
22	11.6
23	11.8
24	12.0
25	12.1
26	12.3
27	12.4
28	12.6
29	12.7
30	12.8
31	12.9
32	13.1
33	13.2
34	13.3
35	13.4
36	13.5
37	13.5
38	13.6

Note that even weeks data taken from Mari 2000, Table 1; uneven weeks were estimated based on Mari 2000.

The degrees of anemia are classified as follows: mild anemia (hemoglobin concentration from 0.84 to 0.65 times the median for gestational age), moderate anemia (hemoglobin concentration from less than 0.65 to 0.55 times the median), and severe anemia (hemoglobin concentration less than 0.55 times the median). Each IUT will be classified using this coding and the fraction of the multiples of the median will also be calculated. Percentage of IUTs meeting each anemia severity category (N, %) will be summarized. A scatter plot of the last available hemoglobin results up to and including the start of first IUT by gestational age will be presented.

Also initial and final fetal hemoglobin and hematocrit values will be summarized for each IUT.

- IUT complications

For each IUT a summary (N only) will be presented for complications captured categorized as: fetal bradycardia, cord bleeding, infection, PPROM, preterm delivery, emergency C-section, and fetal demise; this summary will also include N, % for number of participants who had at least 1 IUT in study pregnancy and experienced any complication at least once due to an IUT, as well as N, % for total number of IUTs with at least 1 complication in study pregnancy and N only for total number of IUTs.

The following secondary endpoints will be presented based on the Neonates/infants set (see Section 4):

- Gestational age at delivery, formatted in GA week and day (i.e., fetal demise or live birth; mean, median, and range and GA week categories [≥37 weeks and <37 weeks, with subcategories of <34 weeks, <32 weeks, and <28 weeks])

- Percentage of neonates requiring phototherapy (N, %)

    - Summary of bilirubin prior to first phototherapy and after last phototherapy.

- Number of hours of phototherapy required by neonate (N requiring, mean [SD], median, and range)

- Percentage of neonates requiring exchange transfusions (N, %)

    - Summary of bilirubin prior to first exchange transfusion and after last exchange transfusion.

- Percentage of neonates requiring simple transfusions in the first 12 weeks of life (N, %)

    - Number of simple transfusions required by neonate in the first 12 weeks of life (N requiring, mean [SD], median, min max)

    - Total volume of simple transfusions required by neonate in the first 12 weeks

    - Summary of hematocrit and hemoglobin before first transfusion and after last transfusion.

Number of neonates requiring NICU and length of stay in NICU (N requiring, mean [SD], median, and range), length of stay for hospitalization for those not requiring NICU (N, mean [SD], median, and range), and overall hospitalization time; hospitalization information (including type of care [NICU or non-NICU], dates of admission and discharge, and any other information) will also be listed

- Hemoglobin levels in cord blood for all neonates (N, mean [SD], median,, and range)

- Hemoglobin levels in cord blood for neonates *with or without IUT* (N, mean [SD], median, and range)

Comparison of HDFN qualifying prior pregnancy and current pregnancy

Using the most recent HDFN qualifying prior pregnancy as a reference, the following obstetrical and HDFN-related endpoints will be compared against the participant's current pregnancy:

- Live Birth (Yes/No)

- Gestational age at delivery (expressed as GA Week and Day)

- Gestational age at time of first IUT (expressed as GA Week and Day)

- Number of IUTs per pregnancy
- Hydrops present (Y/N)
- Antibody type (e.g., D, Kell) and associated peak titer
- Simple blood transfusions required
- Exchange transfusions required
- Phototherapy required

For this analysis the following Table will be presented for each maternal participant (mock):

	Qualifying Pregnancy	Study Pregnancy
Subject xxxx - xxxx		
Alloantibody type: xxx		
Live births	No	Yes
Gestational age at delivery*	NA	35
Gestational age at time of first IUT	18 2/7	22 3/7
Number of IUTs per pregnancy	5	3
Hydrops present	Yes	No
Simple blood transfusions required	Yes (2)	No
Exchange transfusions required	Yes (1)	No
Phototherapy required	Yes (2 hours)	Yes (1 hour)
Peak titer	xxx	xxx

*Delivery can be live birth or fetal demise

A Summary Table will be presented as follows:

Summary	Qualifying Pregnancy	Study Pregnancy
Number of subjects with an IUT		

Number of IUTs per pregnancy (Median, Range)		
Gestational age at first IUT (Median, Range)		
Hydrops present (N, %)		
Live births (N, %)		
Gestational age at delivery (Median, Range)		
Neonates required simple blood transfusion (N, %)		
Neonates required exchange transfusion (N, %)		
Neonates required phototherapy (N, %)		
Antibody type (N, type, %)		

The endpoints below will also be summarized using a graphical display:

Summary	Description
Gestational age at time of first IUT	Frequency plot with two colors side by side for qualifying and current pregnancy, GA weeks
Number of IUTs per pregnancy	Frequency plot with two colors side by side for qualifying and current pregnancy, # IUTs

For prior pregnancies, a summary will be provided for maternal participants that required IVIG presenting the frequency (N, %) for each of the following IVIG complications: headache, flushing, chills, muscle pain, wheezing, abnormally rapid heart rate, lower back pain, nausea, abnormally low blood pressure, venous thrombosis, and fever. This will be done for all prior pregnancies (showing the frequency of maternal participants at least once experiencing the side effect) and will be done limited to the qualifying pregnancy only. IVIG history will also be listed. For study pregnancies, a summary will be provided that will include N, % for number of participants who had at least 1 protocol-prohibited IVIG administration in study pregnancy and experienced any complication at least once due to that IVIG administration, as well as N, % for total number of protocol-prohibited IVIG administrations with at least 1 complication in study pregnancy and N only for total number of protocol-prohibited IVIG administrations.

A summary of IUT complications among patients who received IUTs in prior pregnancies, as well as a summary of IUT complications among patients who received IUTs in current pregnancy will be presented.

5.5. Exploratory Endpoint(s) Analysis

The following exploratory endpoints will be summarized (unless otherwise specified) using descriptive statistics or plots, as specified:

Maternal/Fetal (FAS):

- A plot of MCA-PSV values versus gestation age at first IUT will be presented for each subject with IUT of available MCA-PSV data, with reference lines for MoM values included, as presented in Table 3 below (Mari 2000). Slope of MCA-PSV by Doppler ultrasound from baseline until first IUT will be provided on the plot. Numerical modeling methods may be applied to investigate any underlying trend. Appropriate modeling method, if deemed fruitful, will be based on the observed data. Note that each subject with data will be plotted; data points will not be connected.

Table 3: MCA-PSV by Doppler Ultrasound MoM (cm/sec)

	Multiples of the Median	
GA Week	**Median**	**1.50**
18	23.2	34.8
20	25.5	38.2
22	27.9	41.9
24	30.7	46.0
26	33.6	50.4
28	36.9	55.4
30	40.5	60.7
32	44.4	66.6
34	48.7	73.1
36	53.5	80.2
38	58.7	88.0
40	64.4	96.6

- Fetal hematocrit, hemoglobin, bilirubin (if collected), and alloantibody levels at first IUT and in subsequent IUTs will be listed.

- Observations related to placental evaluation and documented in the pathology report will be listed (which may include placental weight and photographs, microscopic and macroscopic examination of umbilical cord and placental tissue sections, presence or absence of placental thrombosis and/or infarction, hemolytic disease, infection, and other significant findings).

- Incidence of use of protocol-prohibited IVIG by maternal participants (N, %), during pregnancy, as well as number (descriptive statistics) and frequency (N, %, for list of 0, 1, 2, ≥3) of IVIG administrations.

- Incidence of use of plasmapheresis by maternal participants (N, %), during pregnancy.

- Summary of maternal participants receiving Tdap, pneumococcal and influenza vaccines during pregnancy and the FU period.

- Fetal biophysical parameters will be listed. For each maternal participant, NST/reactive FHR, fetal breathing movements, fetal activity/gross body movement, fetal muscle tone, qualitative AFV/AFI), and total score will be provided.

Neonate/Infants:

- Absolute and change from baseline values in neonatal bilirubin, direct Coombs, reticulocyte count, hemoglobin, hematocrit, IgG, alloantibodies

- Peak bilirubin levels during the 4-week (28-day) and 12-week post-birth neonatal/infant period

- Lowest hematocrit and hemoglobin levels during the 4-week (28-day) and 12-week post-birth neonatal/infant period

- Incidence of IVIG doses received (N, %), number of IVIG doses received (descriptive statistics), and frequency (N, %, for list of 0, 1, 2, ≥3) of IVIG doses received by neonate

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

Nipocalimab will be administered once weekly (QW) by IV infusion at a dose of 30 (protocol versions 1-6) and/or 45 mg/kg (protocol versions after 6.0) based on body weight at Baseline. After Amendment 10 implementation, Nipocalimab will be administered at 45 mg/kg based on time-adjusted weight-based dosing, i.e., based on current weight measured bi-weekly. Study drug exposure will be determined by duration, and number of infusions will be summarized using descriptive statistics.

Duration of study drug exposure will be calculated by the number of days participants were administered study drug, as determined below.

Duration of Study Drug Exposure = (Date of last dose – Date of first dose) + 1

For participant PPD who was treated for two pregnancies, the duration of study drug exposure equals:

Exposure as PPD [(Date of last dose – Date of first dose) + 1] +

Exposure as PPD [(Date of last dose – Date of first dose) + 1]

Study drug administration data for each maternal participant will also be presented in data listing.

The proportion of participants receiving protocol-allowed prophylactic IVIG ≤72 hours prior to delivery and within 7 days after delivery will be summarized. Maternal and neonatal protocol-allowed IVIG administrations will be listed.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs for maternal participants will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention is considered to be treatment-emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment-emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent AEs will be included in the analysis. For neonates/infants all AEs will be considered as treatment-emergent. For each AE, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

AEs will be classified by the investigator as related or not related to study drug for AEs experienced by maternal participants. In case of a missing relationship the AE will be considered as related to study intervention. For neonates/infants the relationship of an AE to phototherapy is reported and will be summarized.

An overall summary (by dose group and overall) of treatment-emergent AEs will be provided for maternal participants with 1 or more AE (overall) in the following parameters:

- AEs
  - AEs related to nipocalimab
  - AEs related to cordocentesis
  - AEs related to IUT
- Serious AEs (SAEs)
  - SAEs related to nipocalimab
- Fetal loss
- AEs leading to death
  - Related AEs leading to death
- AEs leading to dose interruption to nipocalimab
- AEs leading to discontinuation of nipocalimab
- Grade ≥3 AEs
- Adverse events of special interest (AESIs)

An overall summary (by maternal dose group and overall) of treatment-emergent AEs will be provided for neonates/infants with 1 or more AE in the following parameters:

- AEs
  - AEs related to nipocalimab
  - AEs related to phototherapy
- SAEs
  - SAEs related to nipocalimab
  - SAEs related to phototherapy
- AEs leading to death
- Grade ≥3 AEs
- AESIs

Summary tables will be provided for treatment-emergent AEs by SOC and PT for maternal participants and for neonates/infants:

- AEs
- SAEs
  - SAEs considered *at least possibly related* to nipocalimab treatment by the investigator
  - SAEs considered *at least possibly related* to phototherapy by the investigator (for neonates/infants only)
- AEs leading to discontinuation of nipocalimab treatment (for maternal participants only)
- AEs leading to discontinuation of nipocalimab treatment that are considered *at least possibly related* to nipocalimab (for maternal participants only)
- AESIs (cf. Section 5.6.2.1)
  - AESIs considered *at least possibly related* to nipocalimab treatment
  - AESIs considered *at least possibly related* to phototherapy (neonates/infants only)
- AEs with NCI-CTCAE toxicity grade ≥ 3
  - AEs with NCI-CTCAE toxicity grade ≥ 3 considered *at least possibly related* to nipocalimab treatment
  - AEs with NCI-CTCAE toxicity grade ≥ 3 considered *at least possibly related* to phototherapy (neonates/infants only)
- AEs considered *at least possibly related* to nipocalimab treatment by the investigator
- AEs leading to dose interruption of nipocalimab treatment (for maternal participants only)
- AEs *at least possibly related* to phototherapy (for neonates/infants only)

In addition to the summary tables, listings will be provided for maternal participants and neonates/infants who had:

- SAEs

- AEs leading to death (excluding the pregnancy termination for maternal participant 1031)
- AEs leading to discontinuation of nipocalimab treatment (for maternal participants only)

5.6.2.1. Adverse Events of Special Interest

Incidence of other treatment-emergent adverse events of special interest will be summarized by the appropriate data set. Adverse Events of Special Interest (AESI) are defined as follows:

- In maternal patients and neonates/infants, infections requiring treatment with oral or intravenous anti-infectives (antibacterial/antiviral/antifungal).
- In maternal patients only, hypoalbuminemia <20 g/L.
- In neonates/infants, unexpected/unusual childhood illnesses.
- In infants, IgG concentration <200 mg/dL at Week 24 through Week 47 or <300 mg/dL at Week 48 through Week 96.

See Section 8.3 of the study protocol for more details on definitions. Investigators will note if an AE is of special interest. Categorization of AESIs will be based by medical review. AESIs will be summarized by category and overall, for maternal participants and neonates/infants.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the maternal participants included in the FAS and for neonates and infants based on the Neonates/infants set.

In some cases, both local and central laboratory draws exist at the same time point. In that case, the following logic will be applied to summary tables and graphs, with an appropriate footnote added to the relevant output:

- If both local and central laboratory results exist at the same time point for a subject, the central labs will be favored over local labs (ie, only central laboratory results will be displayed for that subject/time point). This holds true for baseline as well (even if the local lab is closer in time to first dose, the central laboratory result will be used).
- If only local laboratory results exist at a time point, then local laboratory results will be summarized.
- If only central laboratory results exist at a time point, then central laboratory results will be summarized.

Descriptive statistics and change from baseline will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points for maternal participants (FAS) and neonates/infants. Urinalysis results are only available for maternal participants.

Abnormality criteria using pregnancy-related reference ranges will be applied to baseline and postbaseline values for maternal participants while they are pregnant.

Figures (spaghetti plots) for the actual values and change from baseline in maternal albumin and lipids (HDL, LDL, and total cholesterol and triglycerides), and fetal/neonatal/infant hemoglobin, total bilirubin, and direct bilirubin over time will also be presented. Other parameters of interest may also be included.

For neonates, abnormality criteria using appropriate reference ranges will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- FFor abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered treatment-emergent. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as treatment-emergent.

A listing of maternal and neonatal/fetal abnormal laboratory values will be provided.

Proportion of maternal patients with at least 1 treatment-emergent occurrence of the following clinically important laboratory thresholds will be summarized by dose group and overall (FAS). Note that any value at the day of birth itself are considered to be during pregnancy:

- Number/proportion of maternal participants with at least one total cholesterol value >349 mg/dL (>9.025 mmol/L) (ULN for 3rd trimester based on Abbassi) during pregnancy.
- Number/proportion of maternal participants with at least one total cholesterol value >200 mg/dL (>5.172 mmol/L) (ULN for non-pregnant based on Abbassi) post birth.
- Number/proportion of maternal participants with at least one LDL value >224 mg/dL (>5.793 mmol/L) (ULN for 3rd trimester based on Abbassi) during pregnancy.
- Number/proportion of maternal participants with at least one LDL value >100 mg/dL (>2.586 mmol/L) (ULN for non-pregnant based on Abbassi) post birth.
- Number/proportion of maternal participants with at least one HDL value <48 mg/dL (<1.2413 mmol/L) (LLN for 3rd trimester based on Abbassi) during pregnancy.
- Number/proportion of maternal participants with at least one HDL value <40 mg/dL (<1.0344 mmol/L) (LLN for non-pregnant based on Abbassi) post birth.
- Number/proportion of maternal participants with at least one triglyceride value >453 mg/dL (>5.114 mmol/L) (ULN for 3rd trimester based on Abbassi) during pregnancy.
- Number/proportion of maternal participants with at least one triglyceride value >150 mg/dL (>1.6935 mmol/L) (ULN for non-pregnant based on Abbassi) post birth.
- Number/proportion of maternal participants with at least one albumin value <2 g/dL (<20 g/L) during pregnancy.

- Number/proportion of maternal participants with at least one albumin value <2 g/dL (<20 g/L) post birth.
- Number/proportion of maternal participants with at least one IgG value <100 mg/dL (<1 g/L) during pregnancy.
- Number/proportion of maternal participants with at least one IgG value <100 mg/dL (<1 g/L) post birth.

A listing of maternal clinically important laboratory values will be provided.

Proportion of neonates with at least one occurrence of the following clinically important thresholds will be summarized (Neonates/infants set):

- Number/proportion of neonates with at least one IgG value <100 mg/dL (<1 g/L)
- Number/proportion of neonates with at least one IgG value <200 mg/dL (<2 g/L)
- Number/proportion of neonates with at least one total bilirubin >8 mg/dL (>136.8 µmol/L)

A listing of neonatal/infant clinically important laboratory values will be provided.

5.6.3.2. Vital Signs

Vital sign parameters will be summarized for maternal participants (safety analysis set) and neonates/infants (neonates/infants set).

Maternal participants

Continuous vital sign parameters including temperature, respiratory rate, weight, pulse, and blood pressure (systolic and diastolic) will be summarized at each assessment time point (pre/start of infusion, end of infusion, and 30 minutes after end of infusion).

Abnormality criteria (based on criteria defined below in Table 4) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied. A listing of maternal participants with abnormal vital signs will be presented.

Table 4: Abnormal Vital Signs for Maternal Participants

Vital Sign	Abnormal
Pulse	>120 bpm with >30 bpm increase from baseline
	<50 bpm with >20 bpm decrease from baseline
Systolic blood pressure	>140 mm Hg
Diastolic blood pressure	>90 mm Hg
Temperature	>38°C

Neonates/Infants

Continuous vital sign parameters including temperature, respiratory rate (RR), pulse rate, and blood pressure (systolic and diastolic) will be summarized at each assessment time point.

Neonate/infants with abnormal vital signs, as defined in Table 5, will be listed. The actual age of the neonate/infant at time of measurement will be used for the age category for determining

whether abnormality has occurred. Actual age is calculated by comparing the day of the month to the date of birth (ie, if an infant was born on May 5th, it will be considered 1 month old on June 5th).

Table 5: Age Adjusted Abnormal Vital Signs for Neonate/Infants

Age	Low Temp	High Temp	Low SysBP	High SysBP	Low DiaBP	High DiaBP	Low RR	High RR	Low Pulse	High Pulse
0-1 month	36.5	37.5	60	90	40	60	25	68	110	180
1-3 months	36	38	60	95	40	60	25	60	110	170
3-12 months	36	38	70	105	40	60	25	50	100	150
1-2 years	36	38	70	110	40	70	20	40	90	140

Vital sign limits are considered within the normal range. Age ranges are inclusive for the lower range, so 1 month is included in 0-1 months.

5.6.3.3. Physical Examination Findings

Full physical examinations for the maternal participants will be performed at Baseline, GA Week 36, and postnatal Week 24. An abbreviated physical examination will be performed for the maternal participants at weekly study visits from GA Week 15 to GA Week 35, and during the follow-up period on the day of birth and at Week 4. Any clinically significant findings are recorded on Medical History or Adverse Event CRF page, as appropriate. No summaries will be presented for physical examinations of maternal participants.

For the neonates/infants, a full physical examination (including APGARs at 1, 5 and 10 minutes after birth) will be performed at birth (Neonates/Infants). Thereafter, physical exams performed at Weeks 0, 4 and 24 will include length/height, weight, and head circumference, and routine assessment of development. Physical examination values will be listed. See Appendix 6.3.1 for details on summarization of Apgar data.

5.6.3.4. Electrocardiogram

Electrocardiograms (ECG) will be collected at Screening and GA Week 36 for maternal participants (FAS). Mean ventricular rate will be summarized using descriptive statistics for the actual value and change from baseline to GA Week 36.

Listings will be produced for all ECG data including unscheduled visit data for abnormal ECG based on clinical interpretation will be provided.

5.6.4. Other Safety Parameters

5.6.4.1. Fetal Heart Rate Doppler

Fetal heart rate results (bpm) will be summarized relative to the infusion (pre-infusion, end of infusion, 1 hour after infusion or post-infusion) by visit or GA, using descriptive statistics for maternal participants (safety analysis set). A listing of these results will also be provided.

5.6.4.2. Fetal Growth and Development Monitoring

A listing of maternal participants with abnormal ultrasound will be provided, with all data recorded.

Continuous parameters for fetal growth including estimated fetal weight (grams) and weight percentile (%) as well as crown rump length (cm), head circumference (mm), femur length (mm), biparietal diameter (mm), abdominal circumference (mm), and femur length (cm) will be summarized by GA using descriptive statistics (mean, standard deviation, median, minimum and maximum).

The frequency of Intrauterine Growth Restriction (IUGR) based on the estimated fetal weight (EFW) of $<10^{th}$ percentile based on ultrasound assessments will be summarized by gestational age and overall (safety analysis set).

Biophysical profile will be listed by gestational age.

5.6.4.3. Amniotic Fluid Assessments

The amniotic fluid volume will be summarized at each assessment time point as normal or as abnormal categorized by the investigator as *increased, moderately decreased*, *oligohydramnios,* or *anhydramnios* for each maternal participant (safety analysis set).

The amniotic fluid index as well as the maximum vertical pocket (cm) will be summarized, as well as change from baseline. The baseline for the maximum vertical pocket will be based on the last measurement prior to first dose of study intervention, while the baseline for the amniotic fluid index will be based on the first measurement using amniotic fluid index.

Number and percent of maternal participants with amniotic fluid volume meeting the following abnormal criteria will also be summarized at each assessment time point and by overall:

- For Max vertical pocket <2 cm or >8 cm
- For Amniotic Fluid Index (AFI) <5 cm or >24 cm

5.6.4.4. Umbilical Artery Flow Doppler

When performed, results (systolic peak, diastolic flow [present, absent, reversed], cord S/D ratio, mean velocity, pulsatility index, and resistance index) will be listed.

5.6.4.5. Middle Cerebral Artery Doppler

When performed, results of fetal peak systolic velocity (cm/sec, MoM) and if cordocentesis/IUT was required will be listed. MCA Doppler results will be plotted by as described in Section 5.5.

5.6.4.6. Microbiology Specimen

Group B strep and vaginal microbiome information will be provided in separate listings.

5.7. Other Analyses

5.7.1. Pharmacokinetics

PK samples for measuring serum nipocalimab concentrations will be collected from all participants at the specified visits as shown in the Schedule of Activities. All PK evaluations will be performed on the PK analysis set defined as patients who have received at least 1 administration of nipocalimab and have at least one post-dose sample collection.

Descriptive statistics (N, mean, SD, median, range, and interquartile [IQ] range) will be used to summarize nipocalimab serum concentrations at each sampling time point. PK data may be displayed graphically, such as median ± IQ range PK concentrations over time by dose group. Geometric mean and CV (%) may be presented as appropriate. Individual line plots may be added. The following analyses will be performed as appropriate:

Maternal Serum PK:

- Summary of maternal serum nipocalimab concentrations at each visit and by dose group ; additionally, this analysis will be repeated by baseline body weight (kg) categories (< median, ≥ median).

- Number of participants with maternal serum nipocalimab concentrations below the lower limit of quantification x minimum required dilution (LLOQ) by dose group and overall at each visit.

- Plot of median +/- IQ range as well as individual maternal serum nipocalimab concentrations over time (linear and semi-log scales).

Maternal Milk PK:

- Summary of maternal milk nipocalimab concentrations at each visit by milk type (colostrum or mature breast milk) by dose group

- Proportion of participants without detectable maternal milk nipocalimab concentrations (below the LLOQ) by dose group and overall, at each visit

Neonate/Infant Serum PK:

- Summary of neonate/infant serum nipocalimab concentrations at each visit

- Proportion of participants without detectable infant serum nipocalimab concentrations (below the LLOQ) at each visit

Cord blood PK:

- Listing of cord blood nipocalimab concentrations by subject

Listing of maternal serum, maternal milk, and infant serum/cord blood nipocalimab concentrations will be presented.

If sufficient data are available, then population PK analysis using maternal and infant serum nipocalimab concentration-time data as well as milk nipocalimab concentration-time data will be performed using nonlinear mixed-effects modeling to estimate typical population PK parameters. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

Unless otherwise specified, the following data handling guideline will apply to PK analyses:

- All serum (maternal and infant) and milk concentration summaries for a particular time point will include data obtained from treated patients at the time point of interest without imputing any missing data

- A concentration not quantifiable (below LLOQ) will be treated as 0.5*LLOQ in geometric mean and 0 in other summary statistics and shown as the lower limit of quantification (<LLOQ) in the data listings

- The data from a patient who meets one of the following dosing deviation criteria will be excluded from the by-visit data analyses and from that point onwards:

    - Discontinue nipocalimab administrations
    - Skipped a nipocalimab administration
    - Received incomplete/incorrect dose
    - Received incorrect study agent
    - Received additional dose

Of note, serum or milk nipocalimab concentrations prior to the first of any event as described above will be included in the summaries. In addition, if a participant has an administration outside of dosing window, the concentration data collected at and after that will be excluded from the by-visit data analyses. Additional exclusions for PK data to be implemented based on TV-GDL-00362. All patients and samples excluded from analysis will be documented in the Clinical Study Report.

5.7.2. Immunogenicity Analysis

Blood samples will be collected to examine the formation of antibodies to nipocalimab at the specified visits as shown in the Schedule of Activities of the protocol.

“Sample ADA status” and sample titer as well as the cumulative “subject ADA status” and peak titer through the visit will be coded and provided by the bioanalytical group.

Patient ADA Classifications

Patients evaluable for immunogenicity are defined as having at least one postdose ADA time point collected for antibody to nipocalimab detection.

1. Patients with treatment-emergent antibodies to nipocalimab include patients with treatment-induced antibodies to nipocalimab and treatment-boosted antibodies to nipocalimab.

2. Patients with treatment-induced antibodies to nipocalimab have a sample negative in antibodies to nipocalimab prior to nipocalimab administration and at least one sample positive in antibodies to nipocalimab after the first nipocalimab administration.

3. Patients with treatment-boosted anti- nipocalimab antibodies have an antibodies to nipocalimab positive sample prior to nipocalimab administration and at least one anti-nipocalimab antibodies positive sample after nipocalimab with a [2]-fold increase in titer over baseline (the fold difference, referred to as the baseline multiplier, could be greater than [2] for some assays).

If titer remains the same after intervention or if ADA titer reduces or ADA disappears, the patient is classified as "treatment-emergent ADA negative". Patients that are unavailable for treatment-emergent ADA following intervention will be classified as "patients with baseline samples only", ie, no appropriate sample is available after intervention.

The summary and evaluation of antibodies to nipocalimab will be based on the observed data; therefore no imputation of missing data will be performed. Note: participant status is through each visit, thus, participant status and peak titers may change as the study progresses over time. Therefore, the 'subject ADA status' at a visit represents the cumulative ADA status through that visit. For example, if a study has a database lock at Week 24, datasets through Week 24 will have patient level status (eg, negative) but at Week 58, they may have developed ADA and the patient status becomes "treatment-emergent ADA positive" from the interim to the final DBL. Peak titers can also change (increase) if a higher titer occurs after an initial DBL.

The summary of participants with baseline positive samples is taken from the sample status at baseline. There is no participant level status at baseline.

The data analysis of maternal antibodies to nipocalimab includes the following:

- Incidence of maternal antibody (evaluable, treatment-emergent ADA positive, ADA positive at baseline and treatment-boosted, ADA positive at baseline but not treatment-boosted, and treatment-emergent ADA negative) status, peak titers and neutralizing antibodies (NAb) to nipocalimab will be summarized.

- Descriptive statistics (N, mean, SD, median, range, and IQ range) and incidence (N, %) of the relationship between maternal treatment-emergent antibodies to nipocalimab status (positive or negative) and PK concentration will be assessed.

- Incidence (N, %) between maternal treatment-emergent antibodies to nipocalimab status (positive or negative) and infusion-related reactions will be assessed:
  - Patients evaluable for immunogenicity
  - Patients with infusion-related reaction
  - Patients with severe infusion-related reaction
  - Patients with serious infusion-related reaction
  - Patients with infusion-related reaction leading to discontinuation
  - Nipocalimab infusions with infusion-related reactions (out of total number of nipocalimab infusions)
- In addition, listings of maternal patients with baseline positive ADA samples, patients who are classified as positive for treatment-emergent antibodies to nipocalimab, and patients who discontinue the study by antibodies to nipocalimab status, as well as graphical representation of median serum nipocalimab concentrations by antibody status, will be presented.

5.7.3. Pharmacodynamics

Absolute values and change from baseline in unoccupied maternal FcRn RO (monocytes) will be summarized by visit using descriptive statistics. Similarly, levels of unoccupied FcRn RO (monocytes) will be summarized descriptively by visit for neonates as well.

Absolute values for maternal levels for albumin, maternal and fetal FcRn RO percentage unoccupied-by-nipocalimab receptor (monocytes) and maternal/fetal/neonatal alloantibodies will be plotted over time. Listings of maternal and neonatal FcRn RO percentage of monocytes and neutrophils unoccupied by nipocalimab and maternal and neonatal pathogenic alloantibodies and titer will be provided.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Exploratory PK-PD analyses, including graphical exploration of PK-PD data, may be performed for mother (for example maternal serum PK with FcRn RO, total IgG, alloantibodies, albumin, and lipids, if feasible), infant (for example infant serum PK with FcRn RO, total IgG, and alloantibodies, if feasible) and between mother and infant, as applicable. The primary measures of PD will be nipocalimab RO, circulating IgG and alloantibodies. Exploratory PK-PD analyses, including graphical exploration of PK-PD data, may be performed.

If deemed feasible and necessary, exposure-response analyses may be performed. The analysis methods may be summarized in a separate analysis plan. Results of such analyses may be presented in a separate technical report.

5.7.5. Biomarkers

PD biomarkers in serum are levels of IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE in maternal and neonatal/infant participants (where all are exploratory except for IgG). Levels of these biomarkers will be presented by descriptive statistics, including percent change from baseline

where applicable. Additionally, spaghetti plots of IgG, IgA, IgM, and IgE for maternal and neonatal/infant participants will be provided. If deemed of interest further analyses will be reported in a separate Biomarker report.

5.7.5.1. Health Economics

Not applicable

5.7.6. Other Variables and/or Parameters

5.7.6.1. Pregnancy Outcomes

Pregnancy outcomes will be displayed for maternal participants summarizing the method of delivery (vaginal or caesarean section) and if antibiotics were received (Yes/No).

Outcomes will be summarized as live birth versus fetal demise, categorized as spontaneous miscarriage, therapeutic abortion, or still birth. Additional delivery information will be listed.

Data in placental evaluation (Yes/No) will be listed, as well if photos were taken (fetal side, maternal side, materials sent to central pathologist).

5.7.6.2. ASQ-3

Infant neurodevelopment will be monitored using ASQ-3 at Months 6, 12, and 24. The total score will be calculated for each area of five areas of child development: communication, gross motor, fine motor, problem solving, and personal-social. There are 6 questions in each area. If the response is missing for up to 2 questions, the missing response(s) will be imputed with the average score from the non-missing responses in calculating the adjusted total area score as follows:

1. Calculate adjusted total area score: total area score ÷ number of items answered in that area = average total score for that area.

2. Add adjusted item score to the other item scores, to produce a total area score: average total score + scores for other items = adjusted total area score. Note, if 2 items were omitted, the adjusted score is added twice to the other item scores.

If more than 2 questions are unanswered within an area, the total area score cannot be calculated and is left missing for the entire area.

Five total area scores will be summarized on the Neonates/infants set using descriptive statistics.

5.7.6.3. PedsQL

To assess the health-related quality of life of children born during this study, the PedsQL, version 4.0 Generic Core Scales, will be completed at week 96. The PedsQL is a widely used a 45-item generic health status instrument with parent and child forms that assesses four domains: physical, emotional, social, and school functioning in children and adolescents ages 2 to 18 (Varni, 2001). In addition, there is a separate summary score for psychosocial health (sum of all items over the number of items answered in the emotional, social, and cognitive functioning scales) and physical

health summary score (sum of the items over the number of items answered in the physical functioning and physical symptoms scales), as well as a Total score (sum of all the items over the number of items answered on all the scales.). Items will be reverse-scored and linearly transformed to a 0-100 scale (ie, where 0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate a better quality of life.

Missing items will be handled as described in the PedsQL scaling and scoring manual. If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: impute the mean of the completed items in a scale.

All domain, summary, and total scores will be summarized using descriptive statistics on the Neonates/infants set.

5.7.6.4. TDAP Vaccination

If a TDAP vaccination was performed (Yes/No) will be summarized for each maternal participant (safety analysis set). It will be summarized when the vaccination was performed (GA Week 28 or Week 31) or if it was not done.

For influenza and pneumococcal vaccination, it will be summarized if it was performed (Yes/No) for each maternal participant (safety analysis set).

5.7.6.5. Lymphocyte Phenotyping

The following lymphocyte parameters as absolute cell counts and percentages, will be listed for maternal and neonatal/infant participants separately: Total T cells (CD3+), Helper T cells (CD3+, CD4+), Cytotoxic T cells (CD3+, CD8+), B cells (CD3-, CD19+), NK cells (CD3-, CD16+, CD56+), and the ratio of absolute counts for Helper T cells/Cytotoxic T cells (CD3+, CD4+ T cells/CD3+, CD8+ T cells).

5.7.7. Definition of Subgroups

Not applicable.

5.8. Interim Analyses

An interim analysis of the accrued data may be conducted to support development of nipocalimab for the treatment of HDFN at the discretion of the Sponsor. If this interim analysis is conducted the following outputs will be generated:

Analysis	Description	Comments
Primary safety endpoint	Incidence and severity of AEs, SAEs, and AESIs (i.e., infections requiring use of oral or intravenous anti-infectives in the mother/neonate/infant; maternal hypoalbuminemia ≥ CTCAE v5.0 ≥	See Section 5.6.2

	Grade 3, unexpected/unusual childhood illnesses in the neonates/infant)	
Primary efficacy endpoint	Live birth at or after GA Week 32 and without an IUT throughout the entire pregnancy (treatment success or failure)	Using the primary estimand and supporting outputs (Section 5.3.2.1)
Selected Secondary endpoints	Percentage of participants with live birth	See Section 5.4
	Percentage of maternal participants without an IUT before or at GA Week 24	See Section 5.4
	GA at first IUT	See Section 5.4
	Gestational age at delivery	See Section 5.4
	Percentage of maternal participants with a fetus with fetal hydrops	See Section 5.4
	Percentage of neonates requiring phototherapy	See Section 5.4
	Percentage of neonates requiring exchange transfusions	See Section 5.4
	Number of days of phototherapy required by neonate	See Section 5.4
	Percentage of neonates requiring simple transfusions in the first 12 weeks of life	See Section 5.4
	Number of simple transfusions required by neonate in the first 12 weeks of life	See Section 5.4
PK	Key analyses will be performed	See Section 5.7.1
ADA	Key analyses will be performed	See Section 5.7.2

In case of a formal interim analysis, a database lock will be performed; the status at the time of the interim database lock will be presented. For example, if data on a neonate at the time of database lock has only been recorded up to 4 weeks after birth, only data up to that point will be analyzed.

Note that interim summaries of the data can be made during the study to support the DSMB and HA interactions.

5.9. Data Monitoring Committee (DMC) or Other Review Board

During the course of the trial, accrued data were reviewed by the sponsor personnel and DSMB to evaluate participant safety, and to inform phase III study design.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFI	Amniotic Fluid Index
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
ATC	Anatomical Class (from WHODRUG dictionary)
BLQ	Below the Limit of Quantification
CRF	Case Report Form
CI	Confidence Interval
COVID-19	Corona virus disease 2019
C-section	Cesarean Section
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of Variation
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
EFW	Estimated Fetal Weight
EOS-HDFN	Early Onset Severe Hemolytic Disease of the Fetus and Newborn
EOT	End of Treatment
FAS	Full Analysis Set
FcRn	Fc Receptor
GA	Gestational Age
GBS	Group B Streptococcus
GCO	Global Clinical Outcome
GCP	Good Clinical Practices
HDFN	Hemolytic Disease of the Fetus and Newborn
ICE	Intercurrent Event
ICH	International Committee for Harmonization
Ig	Immunoglobulin
IQ	Interquartile
IUGR	Intrauterine Growth Restriction
IUT	Intrauterine Transfusion
IV	Intravenous
IVIG	Intravenous Immunoglobulin
LLOQ	Lower Limit of Quantification
MCA	Middle Cerebral Artery
MedDRA	Medical Dictionary for Regulatory Affairs
MRD	Minimum Required Dilution
NICU	Neonatal Intensive Care Unit
PD	Pharmacodynamics
PK	Pharmacokinetics

PSV	Peak Systolic Velocity
QW	once weekly
RO	Receptor Occupancy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHODRUG	World Health Organization Drug

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Changes from V1.0 compared to V2.0

Change	Justification
Template changed from Momenta to Janssen	Change of Sponsorship
Test in Section specifies analyses to be performed in case of an Interim Analysis	Based on Protocol Amendment 11 the possibility of an interim analysis has been added
The PP dataset and analysis has been removed	This analysis was not in the protocol and was removed
Hypothetical Estimand replaced by a composite estimand	The composite estimand was considered to be a simplification. With so few participants a hypothetical approach was considered questionable.
Various minor updates based on the CRF	Some assessments that were part of the CRF have been described that were not part of v1.0

Changes from V2.0 compared to V3.0

Change	Justification
Added PedsQL and ASQ-3 as secondary endpoints	This was collected per the protocol but not listed as an endpoint. This was added as a secondary endpoint per clinical request.
Updated/added analysis sets	To clarify the exact populations that are being used in the data outputs beyond what is in the protocol, especially differentiating between maternal participants and neonates/infants.

6.3. Appendix 3 Demographics and Baseline Characteristics

6.3.1. Demographics

The number of maternal participants and neonates/infants in each analysis set will be summarized and listed.

Table 6 presents a list of the demographic variables that will be summarized for the FAS, Safety Analysis set, PK, Immunogenicity, and PD analysis set(s) for maternal participants. Note that only if the datasets are different, different demographics tables will be produced; otherwise the variables will be summarized on the FAS.

Table 6: Demographic Variables for Maternal Participants

Continuous Variables:	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median ,and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Gestational age at Informed Consent and Baseline (Week, Day)	
Categorical Variables:	**Summary Type**
Age ([18-34 years, ≥35 years])	Frequency distribution with the number and percentage of participants in each category.
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Country (based on site)	
Antibody type (D, C, c, E, e, Kell)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 7 presents a list of the demographic variables that will be summarized for Neonates/ infants.

Table 7: Demographic Variables for Neonates/infants

Continuous Variables:	**Summary Type**
Weight at Birth (kg)	Descriptive statistics (N, mean, median, and range [minimum and maximum]).
Length at Birth (cm)	
Head Circumference at Birth (cm)	
Gestational age at Birth (Weeks)	
Categorical Variables:	**Summary Type**
	Counts (%)
Sex	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Country	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Apgar scores will be summarized by time point (1, 5, and 10 minutes). For each time point (and worst) also the frequency (N, %) will be presented for Apgar scores <5, 5-7, and 8-10.

6.3.2. Obstetrical History (Current Pregnancy and Prior Pregnancies)

Current ("study") pregnancy

Information on the current pregnancy, such as method of conception, gestational age at the time of consent, cycle length (days) and type (regular or irregular), contraception type last used, as well as baseline alloantibody type will be summarized (FAS). All (other) relevant data will be presented in a data listing. Note that here data of participant 1041 will be summarized and data of participant 1031 will be omitted from summaries, but all data will be listed.

Prior Pregnancies

All information collected on all prior HDFN-affected pregnancies will be presented in the data listings. Information collected includes pregnancy number, whether HDFN affected, number of IUTs performed, complications from IUT, pregnancy outcome, delivery methods, and neonatal outcomes. Number of prior pregnancies will be summarized descriptively and categorically (FAS). Prior pregnancy antibody titer information will be listed.

Qualifying Pregnancy

Patients were required to have had a qualifying pregnancy, defined as meeting one or more of the following criteria at ≤24 weeks gestation during a previous pregnancy prior to study entry:

1. Severe fetal anemia (as defined in the protocol)
2. Fetal hydrops with MCA-PSV MoM ≥1.5
3. Stillbirth with fetal or placental pathology indicative of HDFN

If a patient had more than one qualifying pregnancy, the latest one before the current pregnancy will be used. A summary of the prior qualifying pregnancy will be presented; data will be summarized as captured on the CRF.

The following obstetrical and HDFN-related parameters will be summarized for both qualifying and current pregnancies using descriptive statistics or number and percentages, as appropriate, based on the FAS (see Section 5.4):

- Number of participants with an IUT
- Number of IUTs
- Gestational age at time of first IUT
- Hydrops present (Y/N)Live Birth
- Gestational age at delivery
- Simple blood transfusions required (Y/N)
- Exchange transfusions required (Y/N)
- Phototherapy required (Y/N)
- Alloantibody type (e.g., D, Kell)

The above parameters will also be presented by participant. In case of simple blood transfusions and exchange transfusions, the number of respective transfusions required will be provided; in

case of phototherapy, the number of banks for qualifying pregnancy and number of hours for study pregnancy will be provided. For alloantibody type, the peak titer will be listed.

The qualifying pregnancy will be identified on the data listings for prior and HDFN affected pregnancies.

6.4. Appendix 4 Protocol Deviations

Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized (maternal and neonates/infants will be summarized separately). Maternal participants will be summarized using the Safety Analysis Set.

The following descriptions *may* be used to categorize major protocol deviations:

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

For major protocol deviations, as well as COVID-related deviations, a listing will be presented (maternal and neonates/infants will be listed separately). Maternal participants will be listed using the Safety Analysis Set.

6.5. Appendix 5 Prior and Concomitant Medications/Procedures

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC terms (level 2 and level 4), and dose group and overall for maternal participants and by overall for neonates/infants. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior (maternal) and concomitant medications and procedures (maternal and neonates/infants) will be listed.

6.6. Appendix 6 Medical History

General maternal medical history will be listed.

6.7. Appendix 7 Intervention Compliance

Compliance will be summarized descriptively by dose group and overall, calculated as follows:

> Compliance (%) = (actual number of IV treatments / number of IV treatments supposed to be taken) x100.

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.

Number of IV treatments supposed to be taken is defined based on the last treatment that was taken based on early discontinuation or study intervention completion date (i.e., Week 35 or delivery, whichever comes earlier).

The number and percentage of participants who have at least 50% compliance and at least 90% compliance will be summarized.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined in Section 5.6.2.1. Categorization of AESIs will be provided as based on Medical Review.

6.9. Appendix 9 Medications of Special Interest

Not applicable.

6.10. Appendix 10 Laboratory Reference Ranges

In addition to any ranges that come from the lab vendors, analytes for which ranges are provided by the following sources will be applied in lab post-processing:

- Pregnant mothers - Abbassi reference ranges
- Post-partum mothers - Standard ranges for healthy adults as delivered by vendor
- Neonates/ Infants:
  - The Jolliff references includes normal infant reference ranges for IgG, IgA, and IgM.
  - The Kjellman reference includes normal infant ranges for IgE levels.
  - Harriett Lane ranges will be used for normal lymphocyte levels
  - Preterm assessments and birth and subsequent results have reference ranges based on Fanaroff, when available
- For pregnant mothers and neonates/infants, when there is a specialized range provided, any vendor range provided will be post-processed to supplemental qualifiers in SUPPLB, and the specialize range will be processed into the main LB domain.
- When there is no specialized range for any specific analyte for one of the populations, the vendor range will be maintained.
- A flag will be derived for each record to identify the source of the range that is applied in the dataset.

7. REFERENCES

Abbassi-Ghanavati M, Greer LG, Cunningham, FG. Pregnancy and Laboratory Studies A Reference Table for Clinicians. Obstet Gynecol 2009; 114,6. 1326-1331.

American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. ACOG Practice Bulletin No. 222. Obstet Gynecol 2020; 135:e237-260.

Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001 Aug;39(8):800-12.

Johns Hopkins Hospital, Kleinman K, McDaniel L, Molloy M. The Harriet Lane Handbook, 22nd Edition – E-Book. Philadelphia, PA: Elsevier Health Sciences; 2020.

Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization.

Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med. 2000 Jan 6;342(1):9-14.

Millman GC. Fanaroff and Martin's neonatal-perinatal medicine diseases of the fetus and infant, 8th edn, Vols I and II. Arch Dis Child Fetal Neonatal Ed. 2006 Nov;91(6): F468. PMCID: PMC2672777.