Hemolytic disease of the fetus and newborn: awareness precedes change

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CHAPTER
11

Infant Immunity after Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn

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ABSTRACT

Background: Antenatal treatment with nipocalimab, a neonatal Fc receptor (FcRn) blocker, delayed or prevented fetal anemia, as compared with a historical benchmark, in a phase 2 study of early-onset severe hemolytic disease of the fetus and newborn (HDFN). We report on the fetal and neonatal pharmacokinetics of nipocalimab and infant immunity through 96 weeks after birth.

Methods: The UNITY study was a single-group, open-label study assessing pregnant individuals at high risk of early-onset severe HDFN treated with weekly intravenous nipocalimab (30 or 45 mg/kg) from 14 to 35 weeks' gestation, unless discontinued for safety-related stopping criteria or intrauterine transfusion initiation. Pharmacokinetics were assessed in maternal, fetal, and infant blood and colostrum/or breast milk; FcRn receptor occupancy and immunoglobulin G (IgG) were measured in neonatal and maternal blood; and infant IgG and safety were monitored through 96 weeks after birth.

Results: Safety analysis included 12 live-born infants from 13 pregnancies (one fetal loss occurred following intrauterine transfusion complications). Nipocalimab concentrations were maintained in maternal participants at pharmacologically active concentrations (greater than 10 μg/ml) during the weekly dosing intervals, but were observed at low concentrations (10 μg/ml or less) in one of four fetal cordocenteses (0.04 μg/ml), one of 11 cord blood samples (0.7 μg/ml), three of seven colostrum samples (less than 4 μg/ml), and two of nine breast milk samples (less than 2 μg/ml). Low infant IgG at birth (cord blood median, 175 mg/dl; range, 92-941) reached levels consistent with a physiologic nadir by 24 weeks after birth (median, 273 mg/dl; range, 153-429) and recovered to normal range (with one exception) between 16 and 96 weeks (median, 762 mg/dl; range, 407-925). Infectious adverse events were primarily mild to moderate and typical for early childhood. Protective titers to age-appropriate vaccinations (diphtheria and tetanus) were observed in six of seven infants at or before 96 weeks.

Conclusions: In this cohort of 12 live-born infants, antenatal treatment with nipocalimab resulted in low levels of detectable drug in fetal, neonatal, and infant samples. Treatment was associated with low IgG levels at birth; however, unusual or unexpected childhood illnesses or impaired vaccine responses were not observed. (Funded by Johnson & Johnson; ClinicalTrials.gov number, NCT03842189.).

INTRODUCTION

Hemolytic disease of the fetus and newborn (HDFN) is a rare disorder in which maternal alloantibodies against paternally-inherited fetal blood group antigens are transferred across the placenta, where they cause fetal and/or neonatal anemia.[1-3] Early-onset severe HDFN, where fetal anemia develops at 24 weeks' gestation or earlier,[4-9] is the most severe presentation, resulting in the need for intrauterine transfusions at an early gestational age, multiple intrauterine transfusions, increased risk of fetal loss, and high recurrence rates in subsequent incompatible pregnancies.[5-8,10-13]

Serum concentrations of immunoglobulin G (IgG), including alloantibodies, are maintained in the maternal circulation and transported across the placenta by the neonatal Fc receptor (FcRn). Nipocalimab, a fully human IgG1 monoclonal antibody, blocks IgG-FcRn interaction to prevent transplacental alloantibody transfer and decrease circulating maternal alloantibodies available for transfer to the fetus.[14,15] In a recent phase 2 study of nipocalimab in early-onset severe HDFN (UNITY) by Moise et al. in which nipocalimab was administered to 13 pregnant participants at high risk of early-onset severe HDFN with anti-D or -K alloantibodies[16], 54% (7/13) of participants achieved the primary endpoint of live birth at 32 weeks' gestation or later without intrauterine transfusion(s) as compared with a 10% historical benchmark ($P<0.001$).[16] Additionally, 6 of these 7 infants did not receive any postnatal transfusions. No unusual maternal or pediatric infections were observed, and serious adverse events were generally consistent with HDFN, pregnancy, or prematurity.[16]

Nipocalimab reduces the transfer of both pathogenic and beneficial IgG and, if transferred across the placenta, may inhibit infant FcRn-mediated IgG recycling, thereby decreasing infant IgG levels. Therefore, nipocalimab treatment may decrease infant IgG levels and subsequently affect infant passive immunity. Although minimal transfer of nipocalimab was observed in the *ex vivo* human placental perfusion model,[14] neonatal nipocalimab concentrations from the UNITY study have not been previously reported.[16] Herein, we present fetal and infant results from UNITY as well as key neonatal and pediatric immune safety up to 96 weeks after birth.

METHODS

Study Oversight

The study was conducted in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and applicable local regulations. The pregnant study participants provided written consent prior to enrollment. The protocol,

available at www.evidence.nejm.org, was approved by the institutional review board or independent review board for each site. Study oversight was provided by a data and safety monitoring board. Study design, data compilation and analysis, and manuscript development involved investigators, Johnson & Johnson personnel, and a medical writing agency, as previously described.[16] An author (SSK) employed by the sponsor assures completeness, accuracy, and adherence to the study protocol.

Study Design and Treatment

As previously reported, UNITY was a multicenter, open-label, single-arm, phase 2 study assessing the safety, efficacy, pharmacokinetics, and pharmacodynamics of intravenous nipocalimab in anti-D or -K alloimmunized and incompatible pregnancies at high risk for recurrent early-onset severe HDFN.[16] Details of the study design were described previously[16] and are provided in the protocol. Treatment was administered weekly from 14 to 35 weeks' gestation. Dosing was initiated at 30 mg/kg baseline weight but was subsequently increased to 45 mg/kg baseline weight for all participants per protocol amendment to ensure FcRn receptor occupancy. It was then modified again to 45 mg/kg weight assessed every 2 weeks, based on modeling to ensure full FcRn receptor occupancy (i.e., complete FcRn blockade in whole blood monocytes[17]) across a large population, accounting for pregnancy-associated weight gain.[16] Intravenous immunoglobulin (IVIG; 500 mg/kg administered as a single bolus) was given 48 to 72 hours before delivery to maternal participants who had completed nipocalimab treatment and at birth to infants who had an IgG concentration less than 200 mg/dL on cord blood analysis, a threshold for risk of inadequate endogenous antibodies.[18]

Nipocalimab Concentrations

Fetal serum nipocalimab concentration was assessed in cordocentesis samples immediately prior to intrauterine transfusion. Neonatal serum nipocalimab concentration was assessed in cord blood samples at birth and in venous blood samples collected at 4 weeks after birth. Nipocalimab concentration was assessed in colostrum samples between days 0 and 3 and in breast milk samples between days 5 and 8 after birth.

Receptor Occupancy Assessments to Estimate FcRn Saturation

Receptor occupancy measures the percentage of FcRn not occupied by nipocalimab (free FcRn). Receptor occupancy was assessed in circulating monocytes as a surrogate for systemic receptor occupancy, including in the placenta. Free FcRn was quantified with a fluorescence-labeled nipocalimab in permeabilized monocytes from

maternal or neonatal blood and quantified by flow cytometry. Receptor occupancy was expressed as a percentage of the total free FcRn present at maternal baseline (14 weeks' gestation) before treatment, as previously described.[19] FcRn saturation was defined as 90% or more bound FcRn (based on 10% nonspecific background signal), while values less than 90% were considered equivalent to the absence of receptor occupancy. A nipocalimab concentration greater than 10 μg/mL was considered the threshold for pharmacologic activity based on previous evidence demonstrating its ability to achieve FcRn saturation in vivo and in vitro.[17,19]

Immune Adverse Events

The comprehensive adverse event profile from the primary analysis was previously described.[16] In this report, adverse events, including infections and those observed alongside IgG concentrations in neonatal/infant blood, are reported. Adverse events of special interest included infections requiring oral or intravenous antibacterial/antiviral/antifungal treatment (nontopical), unexpected or unusual illnesses throughout the first 96 weeks after birth, and IgG concentrations below age-specified thresholds (IgG less than 200 mg/dL from 24 to 47 weeks after birth or less than 300 mg/dL from 48 to 96 weeks after birth[18]). Adverse event severity was based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.[20]

Serum Immunoglobulins

Total serum concentrations of IgG in infants were determined by a central laboratory, except in rare instances where a central laboratory was not available and values from local laboratories reported by the investigator were used. Local and central laboratory total IgG values were similar in the cases when both were available. Serum concentrations were assessed at the central laboratory by immunoturbidimetry (Roche) for IgG, IgA, and IgM, and by chemiluminescence immunoassay (Siemens Centaur) for IgE. They were measured in cord blood (at birth) and in venous blood samples at 1 week after delivery in neonates supplemented with IVIG and at the 4-, 24-, 48-, or 96-week visits (approximately 4, 24, 48, or 96 weeks after birth).

Vaccination Response

Vaccinations per local standard of care were recommended for study infants per protocol. Diphtheria and tetanus IgG antibody titers (EUROIMMUN enzyme-linked immunosorbent assays) were assessed at the 24-, 48-, or 96-week visit (approximately 24, 48, or 96 weeks after birth). At week 24, vaccine titers were scheduled to be

assessed at 3 weeks or more after the second inoculation with the combination diphtheria/tetanus/pertussis vaccine.

Statistical Analyses

All outcomes in this analysis are presented descriptively. Continuous data are reported as median (range) and categorical data as proportions. Sample size determination was previously described.[16] The same identification numbers are used to describe maternal participants and their infants reported in this study. Additional details are provided in the statistical analysis plan (available with the protocol).

RESULTS

Participants

In the UNITY study, 13 pregnant participants delivered 12 liveborn infants and 1 stillborn, a fetal loss due to intrauterine complications (**Figure 1**).[16] Baseline characteristics of the maternal participants and neonates have been previously reported.[16] The median gestation at birth for liveborn infants was 36 weeks and 5 days (range, 29 weeks and 2 days to 37 weeks and 3 days), and median birth weight was 2825 g (range, 860 to 4000; **Table 1**). Complete follow-up through 96 weeks occurred in 92% (11/12) of infants. One infant was lost to follow-up after completing the 24-week visit. Among 9 maternal participants who received nipocalimab less than 3 weeks before delivery, 8 were supplemented with IVIG before delivery to promote IgG transfer to the fetus and 1 received IVIG within 7 days of delivery. The 3 maternal participants who discontinued nipocalimab more than 7 weeks before delivery had IgG levels greater than 200 mg/dL and therefore did not receive IVIG before delivery (**Figure 1A**).

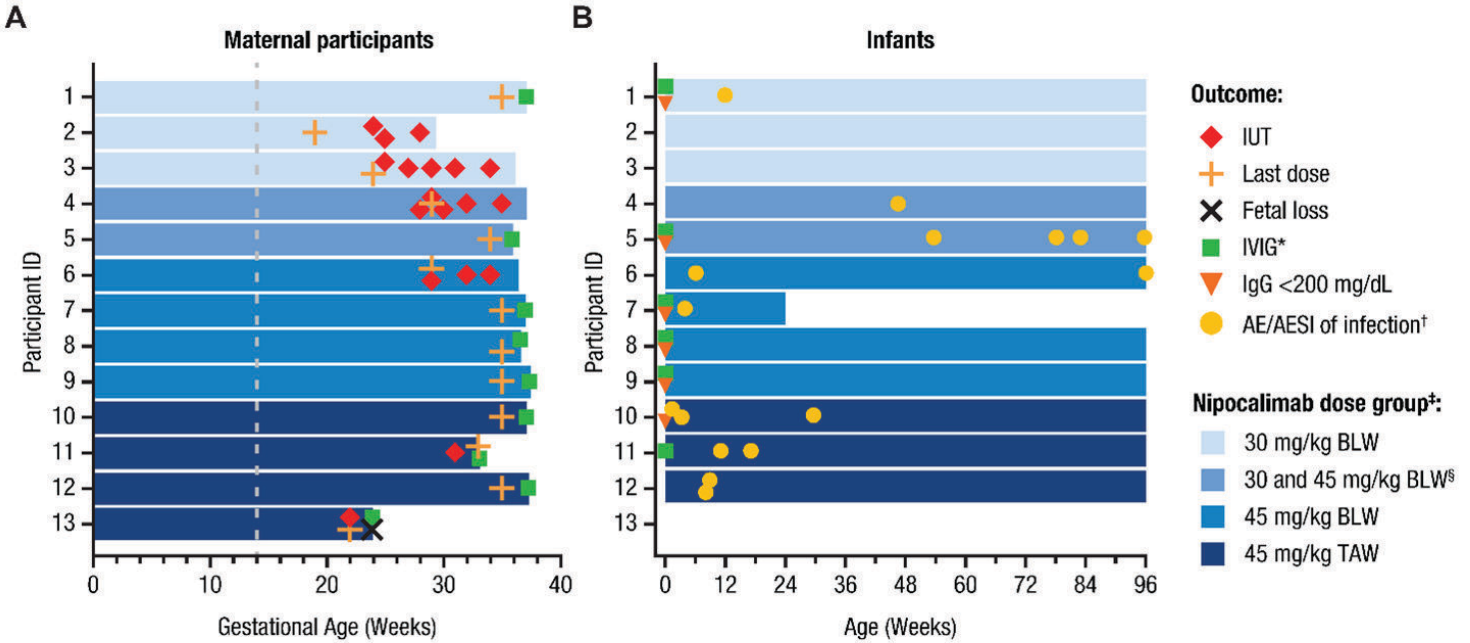

Figure 1. (A) Antenatal Treatment And Outcomes In Maternal Participants And (B) Postnatal Treatment And Outcomes In Infants.
AE, adverse event; AESI, adverse event of special interest; BLW, baseline weight (total dose calculated on baseline weight); IgG, immunoglobulin G; IUT, intrauterine transfusion; IVIG, intravenous immunoglobulin; TAW, time-adjusted weight (total dose calculated on current weight assessed every 2 weeks).
Dotted line indicates start of weekly nipocalimab administration.
*A single IVIG dose (500 mg/kg) was prophylactically supplemented in maternal participants with serum IgG <200 mg/dL or with risk factors for infection at 48 to 72 hours before a scheduled delivery, and in infants with cord blood or serum IgG <200 mg/dL at birth. Infant 10 received <5% of the 500 mg/kg dose due to an IVIG AE.
†For infant 6, the actual date of an AE of infection at 96 weeks after birth was not reported.
‡Bars for maternal participants extended to gestational age at delivery, and bars for infants extended to the last follow-up visit.
§The 30 and 45 mg/kg BLW group consists of a transitional cohort where participants 4 and 5 initially received 30 mg/kg of baseline body weight, and the dose was escalated to 45 mg/kg of baseline body weight later during pregnancy (at gestational age of 27 and 30 weeks, respectively) in accordance with a protocol amendment.

Table 1. Baseline Characteristics Of Maternal Participants And Infants At Birth.

	Maternal participants (N=13)
Age at enrollment, mean (SD), years	35.8 (4.8)
BMI at enrollment, mean (SD), kg/m^2	26.4 (6.2)
Nipocalimab treatment duration, median (range), weeks	20 (5-22)
Number of nipocalimab administrations, median (range)	21 (6-23)
Delivery type, n (%)	
Vaginal	6 (46.2)
Cesarean	7 (53.8)
	Infants (N=12)
Female, n (%)	4 (33.3)
Gestational age at birth, median (range)	36 wk 5 days (29 wk 2 days to 37 wk 3 days)
Gestational age at birth, n (%)	
Very preterm (28 to <32 weeks' gestation)*	1 (8.3)
Preterm (32 to <37 weeks' gestation)	5 (41.7)
Early term (37 to <38 weeks' gestation)	6 (50.0)
Birth weight, median (range), g	2825 (860-4000)
Length at birth,† median (range), cm	46.0 (32.0-57.0)
Head circumference at birth, median (range), cm	34.4 (24.5-36.0)

BMI, body mass index; SD, standard deviation.
*Infant 2 was delivered preterm at gestational 29 weeks and 2 days from a maternal participant who had a previous pregnancy with fetal growth restriction. Infant 2 had a birth weight of 0.86 kg (~12th percentile for gestational age[32]), head circumference of 24.5 cm (~11th percentile for gestational age), and length at birth of 32 cm (3rd percentile for gestational age). The infant's weight was 1.42 kg at week 4 and 5.0 kg at week 24 (~10th percentile for gestational age); head circumference at week 24 was 38.5 cm (~10th percentile for gestational age) and length was 56.0 cm (~2nd-3rd percentile for gestational age).
†Calculated based on available samples (n=11).

Nipocalimab Concentrations and FcRn Receptor Occupancy

Fetal Exposure During Maternal Treatment

Fetal cordocentesis samples from the first intrauterine transfusion were available in 4 participants. These maternal participants were dosed 1 week or less before the first intrauterine transfusion, with the most recent serum maternal drug concentrations before the first intrauterine transfusion between 110 and 572 µg/mL. One participant had a fetal cordocentesis nipocalimab concentration of 0.04 µg/mL at 31 weeks' gestation while the remaining participants had undetectable concentrations at the time of cordocenteses, which were performed between 25 and 29 weeks' gestation. The only first intrauterine transfusion cordocentesis sample available for receptor occupancy assessment indicated no receptor occupancy (unoccupied FcRn: 32%).

Neonatal Exposure

Cord blood at birth was available from 11 of 12 infants (**Table 2**). In the 3 infants who were delivered more than 7 weeks after the last nipocalimab dose, nipocalimab concentrations were undetectable in both maternal and cord blood at delivery (participants 3, 4, 6). Nipocalimab was also undetectable in 7 of the 8 remaining infants who were delivered less than 3 weeks after the last maternal nipocalimab dose. In 6 of 8 infants, nipocalimab was undetectable in cord blood although the maternal nipocalimab concentrations at birth were measurable in all except 1 (range, 0.02 to 100 µg/mL). The remaining 1 infant, who was delivered 8 days after the last maternal nipocalimab dose, had a cord blood concentration of 0.7 µg/mL in conjunction with a maternal serum concentration of 100 µg/mL. No receptor occupancy was observed in the cord blood from 8 infants, including the 1 infant with a detectable nipocalimab concentration (**Table 2**). Nipocalimab was not detected in any of the 8 infants with available values at 4 weeks after birth.

Colostrum and Breast Milk

All 12 maternal participants were sampled for colostrum between 0 and 3 days after birth and/or for breast milk between 6 and 8 days after birth (**Table 3**). Nine of the 12 infants were breastfed. Nipocalimab was detected in 4 of 7 (57%) colostrum samples and 2 of 9 (22%) breast milk samples. In the 4 colostrum samples with detectable nipocalimab, 3 (75%) had concentrations less than 4 µg/mL, below the threshold of 10 µg/mL considered to be pharmacologically active, and 1 (25%) had a concentration of 68.4 µg/mL, above this threshold. All breast milk samples with detectable nipocalimab (n=2) had concentrations less than 4 µg/mL, with none above the threshold.

When comparing colostrum versus breast milk samples across 4 maternal participants with both available colostrum and breast milk samples, 2 showed low, pharmacologically inactive drug concentrations (1.35 and 3.66 µg/mL) in colostrum and undetectable concentrations (below the 0.01 µg/mL lower limit of quantitation [LLOQ]) in breast milk. One maternal participant had an undetectable drug concentration (below LLOQ) in colostrum, but a low drug concentration (1.27 µg/mL) in breast milk. One additional maternal participant was found to have a drug concentration of 68.4 µg/mL in colostrum 2 days after delivery, which decreased to 0.58 µg/mL in breast milk 8 days after delivery. This maternal participant delivered on the day of the last nipocalimab administration and had a serum nipocalimab concentration of 1100 µg/mL at delivery. All samples with detectable nipocalimab were collected from maternal participants who discontinued treatment less than 3 weeks before delivery (n=5), whereas no nipocalimab was observed in colostrum or breast milk from participants who discontinued treatment more than 7 weeks before delivery (n=7). At week 4 after

birth, none of the 5 breastfed infants (including 2 who were breastfed by the maternal participants with the 2 highest colostrum nipocalimab concentrations) had detectable serum nipocalimab concentrations (below LLOQ).

Table 2. Nipocalimab Concentrations and FcRn Receptor Occupancy in Neonatal Cord/Venous Blood and Maternal Blood

	30 mg/kg BLW						30 and 45 mg/kg BLW*			
Participant ID	**1**		**2**		**3**		**4**		**5**	
Visit – wk	0†	4	0†	4	0†	4	0†	4	0†	4
Neonatal concentration – µg/mL	<LLOQ	<LLOQ	-	-	<LLOQ	-	<LLOQ	-	0.7	-
Neonatal unoccupied FcRn – %	-	-	-	-	118.2	-	57	-	84.2	-
Maternal concentration – µg/mL	0.03	<LLOQ	-	<LLOQ	<LLOQ	-	-	-	100	-
Maternal unoccupied FcRn RO – %	121.9	156.3	-	-	131.6	103.2	36.9	109.4	5.1	87.5
Time since last dose – wk	1.4	5.3	6.1	14.2	11.4	-	7.9	-	1.1	-

BLW, baseline weight (total dose calculated on baseline weight); <LLOQ, below lower limit of quantitation (0.01 µg/mL); NR, not reported; TAW, time-adjusted weight (total dose calculated on current weight assessed every 2 weeks).
*The 30 and 45 mg/kg BLW group consists of a transitional cohort where participants 4 and 5 initially received 30 mg/kg of baseline body weight, and the dose was escalated to 45 mg/kg of baseline body weight later during pregnancy (at gestational age of 27 and 30 weeks, respectively) in accordance with a protocol amendment.
†0 weeks indicates at birth.
- indicates not reported

Table 3. Nipocalimab Concentrations in Colostrum, Breast Milk, and Maternal Blood at Birth

	30 mg/kg BLW			30 and 45 mg/kg BLW*		
Participant ID	**1**		**2**	**3**	**4**	**5**
Sample type	**COL**	**BM**	**BM**	**COL**	**BM**	**COL**
Milk concentration –µg/mL	<LLOQ	1.27	<LLOQ	<LLOQ	<LLOQ	3.6
Maternal concentration at birth – µg/mL	0.03	-	-	-	-	100
Time since last dose – wk	1.6	2.4	11.1	11.6	8.9	1.3
Infant breastfeeding	No	No	Yes	Yes	Yes	Yes
Infant breastfeeding period – wk†	-	-	0† to 24	0† to 24	0† to 33	0.3 to 1

BLW, baseline weight (total dose calculated on baseline weight); BM, breast milk; COL, colostrum; <LLOQ, below lower limit of quantitation (0.01 µg/mL); TAW, time-adjusted weight (total dose calculated on current weight assessed every 2 weeks).
- indicates not reported.
*The 30 and 45 mg/kg BLW group consists of a transitional cohort where participants 4 and 5 initially received 30 mg/kg of baseline body weight, and the dose was escalated to 45 mg/kg of baseline body weight later during pregnancy (at gestational age of 27 and 30 weeks, respectively) in accordance with a protocol amendment.†0 weeks indicates at birth.

45 mg/kg BLW								45 mg/kg TAW					
6		7		8		9		10		11		12	
0†	4	0†	4	0†	4	0†	4	0†	4	0†	4	0†	4
<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	-	<LLOQ	<LLOQ	<LLOQ
60.8	-	-	-	86.1	-	95.7	-	51.1	-	-	-	97.9	-
<LLOQ	<LLOQ	0.03	<LLOQ	43.6	<LLOQ	<LLOQ	<LLOQ	0.03	<LLOQ	1100	<LLOQ	0.02	<LLOQ
87.9	97.8	88.7	204.3	4.1	101.7	94.6	119.3	64.3	77.7	6.9	76.9	88.1	144.4
7.3	11.1	1.9	5.9	1.3	5.1	2.6	6.6	2.1	6.3	0	4.1	2.3	6.3

45 mg/kg BLW						45 mg/kg TAW			
6	7		8		9	10	11		12
COL	COL	BM	COL	BM	BM	BM	COL	BM	BM
<LLOQ	1.35	<LLOQ	3.66	<LLOQ	<LLOQ	<LLOQ	68.4	0.577	<LLOQ
-	0.03	-	43.6	-	-	-	1100	-	-
7.3	2.1	2.7	1.4	2.3	3.3	3.0	0.3	1.1	3.1
Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
0† to 24	-	-	0† to 16	0† to 16	0† to 24	0† to 23	0† to 24	0† to 24	-

Infant IgG and Infant Immune Safety Outcomes

Infant IgG at Birth and over Time

Cord blood IgG concentration at birth measured in 10 of the 12 live births was overall below normal (636 mg/dL[21]) at a median of 175 mg/dL (range, 92 to 941; **Table S1**). In the plot of time from last dose to birth vs cord blood IgG concentrations (**Figure S1A**), individual cord blood IgG concentrations were observed to be higher with greater time since birth. Individual cord blood IgG concentrations were observed to trend with the duration between the end of nipocalimab treatment and delivery, but less so with maternal IgG concentrations at delivery (**Figure S1B**). Cord blood IgG concentrations were greater than 400 mg/dL in infants delivered more than 7 weeks after the last dose, but less than 400 mg/dL in infants delivered less than 3 weeks after the last dose (**Figure 2A** and **Table S1**). Maternal IVIG supplementation 2 to 3 days prior to delivery normalized maternal IgG in 7 of 8 individuals but did not normalize neonatal IgG at birth (6 infants had cord blood IgG concentrations less than 200 mg/dL and 1 below the lower limit of normal at 306 mg/dL).

Serum IgG across all infants were observed to nadir during 4 to 24 weeks after birth and rose thereafter (**Figure 2**). The median serum IgG was 305 mg/dL (range, 134 to 553) and 273 mg/dL (range, 153 to 429) at the week 4 and 24 visits, respectively. These values were near or just below the lower limit of normal and followed the normal trend for physiological nadir between weeks 4 and 24 across dose groups (**Figure 2B** and **Table S1**). Total serum IgG concentrations for 8 of 9 infants were above the **lower limit of normal** at the week 24 visit. Total serum IgG concentrations at week 48 or 96 visits were within the normal range for age in 6 of 7 infants, while the remaining infant recovered to 12% below the lower limit of normal at week 48.

Six infants who received 500 mg/kg IVIG (for cord blood IgG less than 200 mg/dL) showed initial increases into the normal range for IgG at weeks 1 and/or 4 followed by nadirs at approximately week 24. In contrast, 2 infants with low IgG at birth, who did not receive IVIG supplementation, showed subnormal nadirs at 4 weeks with normalization of IgG by 16 weeks.

IgA, IgM, and IgE concentrations were generally within normal range in available infant samples. IgA, IgM, and IgE increased over time (**Table S2**).[21,22]

Infant Infections

During the first 24 weeks after birth when the potential impact of nipocalimab-associated low IgG at birth was most apparent, 6 infants experienced 8 infections (**Table 4**). Seven of the 8 infections were mild or moderate in severity with a typical

duration; these were an upper respiratory infection, pyrexia, bacterial conjunctivitis, and 2 episodes each of uncomplicated oral candidiasis/thrush and nasopharyngitis. Both infants with oral candidiasis were treated with topical/oral nystatin, during which 1 infant also had nasopharyngitis for 8 days. The remaining infection was a severe respiratory syncytial virus (RSV) infection, which required a 5-day hospitalization and transitioned to moderate severity without the need for antiviral treatment. This infection started at 8 weeks after birth during a time of severe RSV season in the region, late in the COVID pandemic.[23]

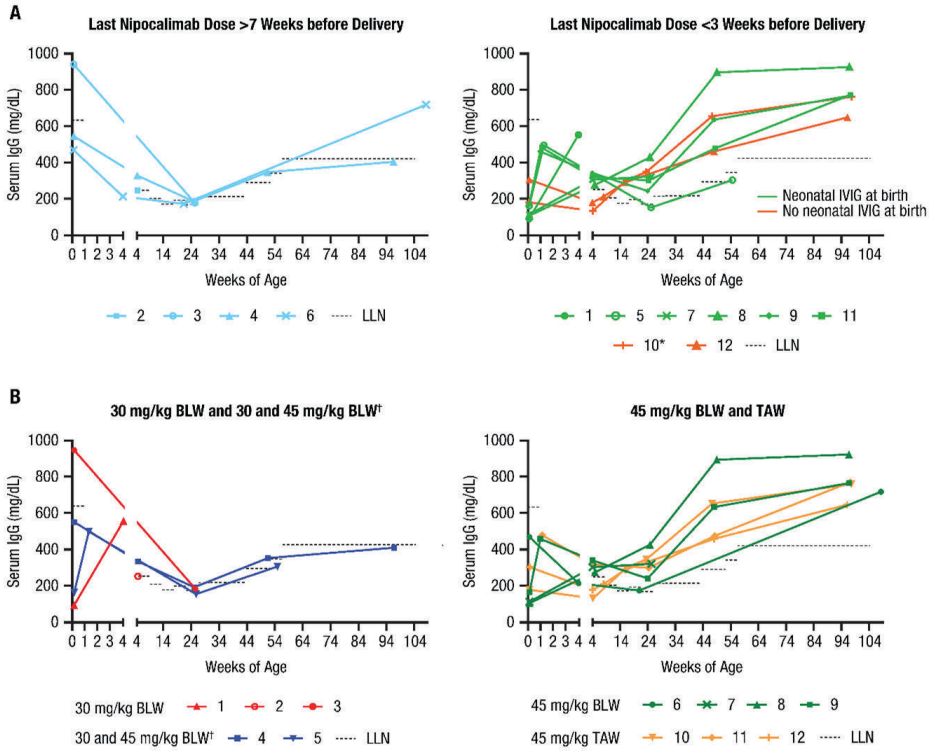

Figure 2. Infant Serum IgG Concentration over Time by (A) Weeks from Last Maternal Nipocalimab Dose to Birth and Neonatal IVIG in the First 5 Days after Birth, and (B) Nipocalimab Dose Group.
BLW, baseline weight (total dose calculated on baseline weight); IgG, immunoglobulin G; LLN, lower limit of normal; TAW, time-adjusted weight (total dose calculated on current weight assessed every 2 weeks).
*Infant 10 received less than 5% of the 500 mg/kg IVIG dose due to an IVIG adverse event.
†The 30 and 45 mg/kg BLW group consists of a transitional cohort where participants 4 and 5 initially received 30 mg/kg of baseline body weight, and the dose was escalated to 45 mg/kg of baseline body weight later during pregnancy (at gestational age of 27 and 30 weeks, respectively) in accordance with a protocol amendment.

Table 4. Infant Infectious Adverse Events

Infant ID	Infectious adverse event	Severity*	Onset – day (wk after birth)	Duration – days	Treatment†
1	Candida infection/thrush	Mild	83 (11.9)	21	Nystatin (oral)
4	Pyrexia/fever‡	Mild	331 (47.3)	9	Paracetamol (oral)
5	Ear infection	Mild	375 (53.6)	13	Amoxicillin (oral)
	Ear infection	Mild	547 (78.1)	23	Amoxicillin (oral) Prednisolone (oral)
	Otorrhea	Mild	580 (82.9)	19	Amoxicillin (oral)
	COVID-19	Mild	670 (95.7)	2	-
6	Nasopharyngitis	Mild	43 (6.1)	9	-
	Varicella	Moderate	742 (106.0)§	<30§	-
7	Bacterial conjunctivitis	Moderate	27 (3.9)	8	Fusidic acid/ tobramycin (ophthalmic)
10	Candida infection/thrush	Moderate	10 (1.4)	27	Nystatin (oral)
	Nasopharyngitis	Mild	23 (3.3)	8	-
	Otitis media acute	Moderate	207 (29.6)	<37‖	Amoxicillin (oral) Paracetamol (rectal)
11	Upper respiratory infection	Moderate¶	78 (11.1)	3	Jonosteril (intravenous)
	Pyrexia/fever‡	Mild	120 (17.1)	4	Ibuprofen (rectal)
12	RSV	Severe**	57 (8.1)	5	Paracetamol (rectal)
		Moderate	62 (8.9)	20	Paracetamol (rectal)

RSV, respiratory syncytial virus.
- indicates not reported.
*Severity per investigator based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 and coded using the *Medical Dictionary for Regulatory Activities Version 26.0* (mild, grade 1; moderate, grade 2; severe, grade 3; life-threatening, grade 4).
†Dose and duration for treatments were: nystatin 3 to 4 times daily for 20 to 22 days; amoxicillin 125 or 150 mg, 3 times daily for 5 to 16 days or <4 weeks (only the month and year were provided for end of treatment for 1 instance); 1% fusidic acid/tobramycin 1 drop daily for 8 days; prednisolone 5 mg twice daily for 6 days; jonosteril (an infusion solution for hydration) 10 mL/h for ≤2 days; ibuprofen rectal 60 mg once daily for 4 days; paracetamol rectal 75 or 240 mg, 3 times a day for 3 days to <4 weeks; paracetamol oral 100 mg as needed for 9 days.
‡Marked "yes" by the investigator in the case report form selection for the question "Is this event an infection?"
§Estimated start day and duration based on the case report form entry indicating no specific days for start and end, but that both occurred within the same month. Day 742 corresponded to the 96-week visit for this infant.
‖Estimated duration based on the case report form entry indicating the specific start date and the month of adverse event end.
¶Infant 11 was hospitalized for 3 days in accordance with the mother's request.[16]
**Infant 12 required 5 days of hospitalization and transitioned to moderate severity without the need for antiviral treatment.

After 24 weeks, infections were reported in 4 infants, at a time when their IgG concentrations were within or near the normal range. One infant developed otitis media treated with oral amoxicillin (**Table 4** and **Figure 2B**). Another infant who had not been vaccinated against varicella was reported to have a moderate varicella infection

at 106 weeks after birth (96-week visit). The only infant with IgG outside the normal range (12% below lower limit of normal) had 2 episodes of acute otitis media and 1 of otorrhea requiring oral amoxicillin. This infant later had a mild COVID-19 infection occurring at 96 weeks after birth, which did not require any treatment and resolved within 2 days. One additional infant had grade 1 pyrexia for 9 days. All were of mild or moderate severity, except for the RSV case discussed above.

Vaccine Responses to Diphtheria and Tetanus

Vaccinations administered per local guidelines to infants on study included diphtheria, tetanus, and pneumococcal vaccines in 92% (11 infants) for each and rotavirus vaccine (live-attenuated) in 6 infants (50%) between birth and 93 weeks after birth. Assessment of anti-diphtheria and tetanus IgG response was available in 7 infants who were assessed at the 24-, 48-, or 96-week visit (**Table S3**). Six infants achieved protective titers at or before the 96-week visit. The exception was 1 infant who had a single assessment at 96 weeks after birth with protective tetanus titers, but a subthreshold diphtheria titer (0.03 IU/mL) approximately 20 months after last vaccination.

DISCUSSION

This analysis of the completed UNITY study included nipocalimab exposure during or after maternal antenatal treatment in fetuses or neonates, colostrum, and breast milk as well as infant IgG concentrations, vaccine responses, and clinical infant infections from birth to 96 weeks after birth. Fetal and neonatal nipocalimab concentrations were observed to be below the pharmacologically active threshold, and detectable concentrations in some colostrum samples decreased to below this threshold in breast milk collected within 8 days after birth. Despite low neonatal IgG at birth, 8 infants experienced 15 infections in the 96 weeks after birth, with 14/15 mild or moderate and one severe, all largely consistent with typical illnesses of this age. Similarly, 6/7 infants assessed for IgG vaccine responses achieved protective titers at or before 96 weeks.

Maternal serum nipocalimab concentration was maintained in the pharmacologically active range (greater than 10 µg/mL) for all but 1 sample (at the 30 mg/kg dose), with no concomitant loss of receptor occupancy (**Figure S2**). However, only 1 of 10 infants had detectable nipocalimab in cord blood, which was at a pharmacologically inactive concentration of 0.7 µg/mL and considerably lower than the maternal nipocalimab concentration of 100 µg/mL at delivery. When detectable, the ratio of nipocalimab cord to maternal blood concentration (0.7:100) was much lower than the ratios (near 1) observed for other IgG therapeutics or endogenous IgG at birth.[24,25] In utero transfer of nipocalimab was detectable in only 1 of the 4 cordocentesis samples at a concentration

of 0.04 µg/mL, which constituted less than 0.1% of the maternal concentration at time of cordocentesis. While fetal concentrations of other IgG therapeutics have not been reported, normal fetal IgG concentrations are observed to be approximately 50% of maternal blood, which is higher than the less than 0.01% observed for nipocalimab.[24] These results suggest limited, but not zero, potential for fetal and neonatal drug exposure due to transplacental transfer during maternal nipocalimab treatment from 14 to 35 weeks' gestation.

We speculate that low transplacental transfer of nipocalimab may be due to its molecular and physicochemical characteristics including pH-independent, high-binding affinity to FcRn, which may prevent its release into fetal circulation.[14,17] The absence of pharmacologically active nipocalimab in fetal blood or cord blood also suggests that the primary mechanism for the low neonatal IgG at birth may be related to the inhibition of transplacental maternal IgG transfer rather than direct inhibition of fetal or infant FcRn-mediated IgG recycling.

The presence of nipocalimab in colostrum and breast milk appears to be related to the time of drug discontinuation and is consistent with its pharmacokinetics and mechanism of action. Nipocalimab was detected only in maternal participants who received treatment until less than 3 weeks before delivery, but not in those who discontinued more than 7 weeks before delivery, consistent with the shorter half-life of nipocalimab versus other IgG therapeutics.[19] Nipocalimab was observed in some participants' colostrum, but the breast milk collected less than 1 week later contained little to no concentration of nipocalimab. Additionally, no apparent difference in neonatal IgG samples at 1 week after birth was observed between those who were breastfed colostrum that did or did not contain pharmacologically active nipocalimab concentrations, though this small study was not designed to definitively evaluate such comparisons. Additional studies are ongoing to assess exposure in the first week after birth when nipocalimab may be present in colostrum.[26,27]

Maternal nipocalimab treatment appeared to be associated with low cord blood IgG concentrations; graphical representation of the data suggests the extent of the decrease may be correlated with the proximity of the last dose to delivery. Notably, maternal IVIG supplementation 48 to 72 hours before delivery did not seem to improve low neonatal IgG. We speculate that the drug-free interval between the last maternal nipocalimab infusion and delivery was insufficient to allow uninhibited FcRn-mediated transplacental transfer of maternal IgG. The observed decreases in IgG to nadir concentrations between 4 to 24 weeks after birth mirror the normal process of maternal IgG clearance in infancy, which is typically completed by approximately 24 weeks

after birth and followed by significant endogenous IgG production.[21,28] Neonatal IVIG administration did increase serum IgG concentrations and may help mitigate the risk of decreased passive immunity. However, the impact of neonatal IVIG administration on infection rates due to low IgG in the first months after birth cannot be determined from these limited numbers of participants.

Of 15 infant infections, 14 were mild or moderate through 96 weeks, including during the first 24 weeks when the impact of nipocalimab was most apparent. Infants recovered from all infections with or without treatment. One severe episode of RSV requiring hospitalization occurred in the period when infant IgG concentration was below the normal range, although it was rising from an early nadir observed 4 weeks prior. One varicella infection occurred in an infant who was not administered varicella vaccination. The live-attenuated rotavirus vaccine was administered to 6 infants during the period of IgG nadir, without complications or evidence of diarrheal symptoms.

Vaccine responses that achieved protective titers to tetanus and diphtheria were observed in response to routine infant immunizations, except for one subthreshold diphtheria titer at 96 weeks after birth (~20 months after the last vaccination). These findings align with preclinical evidence and a phase 1 study of healthy volunteers, where nipocalimab did not affect the IgG response to T-cell–dependent and independent vaccines.[17,29] However, specific recommendations on vaccinations for pregnant individuals treated with nipocalimab and their infants cannot be made based on this phase 2 study. Phase 3 studies are ongoing to further evaluate humoral responses to vaccinations in a larger sample of pregnant individuals with severe HDFN (ClinicalTrials.gov identifier: NCT05912517) or fetal/neonatal alloimmune thrombocytopenia (FNAIT; NCT06449651, NCT06533098).[27,30,31]

Although reassuring, these findings are preliminary given the limitations of small numbers, lack of a control group, and incomplete representation of all populations (**Table S4**). The evidence supports further evaluation of nipocalimab in patients at risk of severe HDFN,[27,30] which will provide more information on the immune-related and overall safety of nipocalimab in infants after antenatal treatment.

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SUPPLEMENTAL FILES

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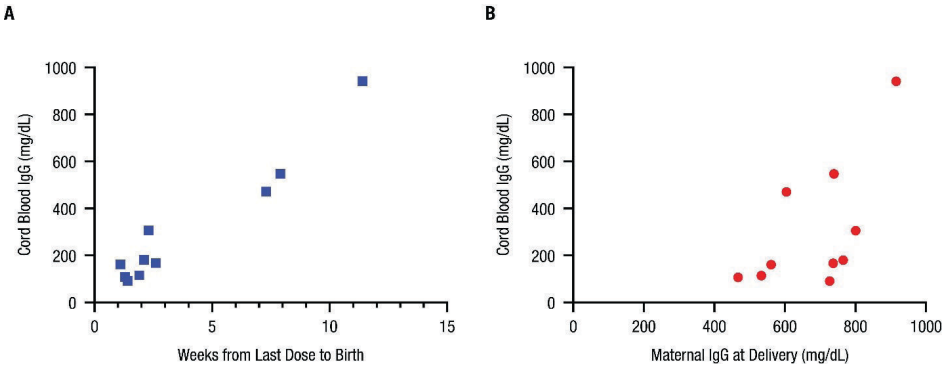

Figure S1. Relationship Between Cord Blood IgG Concentration at Birth and (A) Weeks from Last Dose to Birth and (B) Maternal IgG at Delivery.*
IgG, immunoglobulin G.
*All maternal-infant pairs are represented, except for maternal-infant pairs 2 and 11 where cord blood samples were not collected at birth.

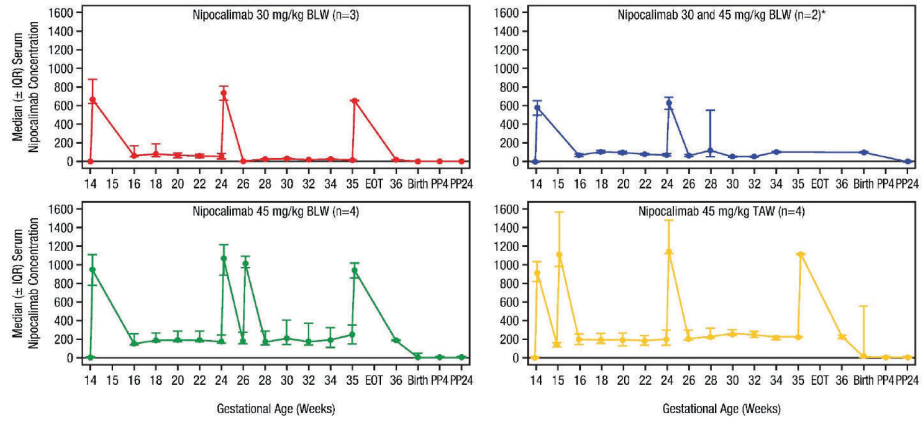

Figure S2. Maternal Serum Nipocalimab Concentrations.
BLW, baseline weight (total dose calculated on baseline weight); EOT, end of treatment; IQR, interquartile range; PK, pharmacokinetic; PP, postpartum; TAW, time-adjusted weight (total dose calculated on current weight assessed every 2 weeks).
Data from blood samples assessed pre-dose at baseline and during treatment, at birth, and at postpartum weeks 4 and 24 are plotted. Data were not included from blood samples assessed during pregnancy after dose discontinuation or after incomplete dose administration (which only occurred in the last dose in 2 participants). At gestational weeks 14, 15, 24, 26 and 35, post-dose (45 minutes after the infusion) blood samples were drawn in addition to pre-dose blood samples for the assessment of serum nipocalimab concentrations. Notably, 1 participant in the 30 and 45 mg/kg BLW dose group had 2 pre-dose PK samples attributed to gestational week 28, 1 of which was 554 µg/mL. This sample was included but considered discordant due to missing collection date and time.
*The 30 and 45 mg/kg BLW group consists of a transitional cohort where participants 4 and 5 initially received 30 mg/kg of baseline body weight, and the dose was escalated to 45 mg/kg of baseline body weight later during pregnancy (at gestational age of 27 and 30 weeks, respectively) in accordance with a protocol amendment.

Table S1. Summary Of Serum Igg Concentrations In Infants Through 96 Weeks After Birth By The Time Of Drug Discontinuation.

Time Of Drug Discontinuation	Infant Igg, Median (Range), Mg/Dl [N]				
	At Birth	4 Weeks	24 Weeks	48 Weeks	96 Weeks
Overall	175 (92-941) [N=10]	305 (134-553) [N=10]	273 (153-429) [N=8]	636 (461-896) [N=5]	762 (407-925) [N=7]
<3 Weeks Before Delivery	162 (92-306) [N=7]	305 (134-553) [N=7]	302 (153-429) [N=5]	636 (461-896) [N=5]	768 (649-925) [N=5]
>7 Weeks Before Delivery	548 (471-941) [N=3]	250 (217-332) [N=3]	182 (177-190) [N=3]	–	564 (407-720) [N=2]
Lower Limit Of Normal Value*	636	251	215	294	424

Igg, Immunoglobulin G; N, Represents Number Of Unique Participant Values.
*Lower Limit Of Normal Value Is Based On Jolliff Cr, Et Al. Clin Chem 1982;28:126-8.

Table S2. Serum IgA, IgM, and IgE Concentrations in Infants through 96 Weeks after Birth.

	IgA – g/L	IgM – g/L	IgE – IU/mL
At birth, N	9	9	10
Median (range)	0.04 (0.0-0.0)†	0.05 (0.0-0.1)†	1.4 (1.4-2.4)
Reference range*	0.014-0.36	0.063-0.25	<0.1-1.5
4 weeks after birth, n	6	7	7
Median (range)	0.05 (0.0-0.2)	0.32 (0.1-0.5)	1.4 (1.4-5.7)
Reference range*	0.013-0.53	0.20-0.87	<0.1-2.8
24 weeks after birth, n	8	8	7
Median (range)	0.17 (0.1-0.4)	0.54 (0.3-0.9)	1.9 (1.4-43.3)
Reference range*	0.081-0.84	0.33-1.08	0.9-28.0
48 weeks after birth, n	5	5	5
Median (range)	0.23 (0.2-1.0)	1.12 (0.6-1.3)	2.9 (1.4-220.7)
Reference Range*	0.16-0.84	0.41-1.49	1.1-10.2
96 weeks after birth, n	6	6	6
Median (range)	0.31 (0.3-0.7)	1.11 (0.6-1.5)	11.3 (6.3-22.2)
Reference range*	0.14-1.23	0.48-1.68	1.1-49.0

IgA, immunoglobulin A; IgE, immunoglobulin E; IgM, immunoglobulin M.
*Lower limit of normal values for IgA and IgM are based on jolliff CR, et al. Clin Chem 1982;28:126-8; lower limit of normal values for IgE are based on Kjellman N-I M, et al. Clin Allergy 1976;6:51-9.
**Lower limit of quantification for IgA and IgM was <0.05 g/L. For statistical analysis, all values <0.05 g/L were considered to be 0.04 g/L.

Table S3. Tetanus and Diphtheria Vaccine Responses.

Infant ID	Vaccine administration – scheduled visit	Weeks after birth	Diphtheria IgG antibody – IU/mL (results – category)*	Tetanus IgG antibody – IU/mL (results – category)†
4	1	13		
	2	23		
		51.1	0.56* (negative)	>0.5 (negative)
	3	51.4		
		96	>1 (positive)	1.13 (positive)
6	1	9		
	2	13		
	3	21		
		108	0.03 (equivocal)	1.16 (positive)
8	1	9		
	2	20		
		24	0.87 (positive)	0.27 (equivocal)
	3	32		
		49	0.64 (positive)	0.27 (equivocal)
	4	78		
		96	>1 (positive)	0.71 (positive)
9	1	6		
		24	0.09 (equivocal)	0.16 (equivocal)
	2	27		
	3	47		
		48	0.29 (positive)	0.51 (positive)
		96	0.69 (positive)	1.5 (positive)
10	1	15		
	2	23	0.19 (positive)	0.12 (equivocal)
		47	0.31 (positive)	0.11 (positive)
	3	53		
	4	93		
		97	>1 (positive)	>2.24 (positive)
11	1	17		
	2	22		
	3	27		
		28	0.98 (positive)	0.87 (positive)
		48	0.63 (positive)	0.86 (positive)
		97	>1 (positive)	0.59 (positive)

Infant ID	Vaccine administration – scheduled visit	Weeks after birth	Diphtheria IgG antibody – IU/mL (results – category)*	Tetanus IgG antibody – IU/mL (results – category)†
12	1	9		
	2	14		
		48	0.07 (equivocal)	0.08 (equivocal)
	3	79		
		95	>1 (positive)	>2.24 (positive)

Infant vaccinations, including diphtheria/tetanus/pertussis and inactivated polio vaccines, per local standard of care were recommended.
*Diphtheria IgG antibody titers were categorized as follows: negative (less than 0.01 IU/mL), equivocal (0.01 to less than 0.1 IU/mL), and positive (0.1 IU/mL or greater).
†Tetanus IgG antibody titers were categorized as follows: negative (less than 0.01 IU/mL), equivocal (0.01 to 0.5 IU/mL), and positive (greater than 0.5 IU/mL).

Table S4. Representativeness of Study Participants (Moise KJ Jr, et al. N Engl J Med 2024;391:526-37).

Category	Description
Disease	Severe hemolytic disease of the fetus and newborn (HDFN) including early-onset severe HDFN.
Special considerations related to:	
Sex and gender	HDFN is a condition of pregnancy and affects female individuals, including transgender men with childbearing potential.
Age	Severe HDFN and especially early-onset severe HDFN may be more common at more advanced childbearing years due to potential for increased alloimmunization associated with each maternal-fetal erythrocyte antigen incompatible pregnancy, a characteristic related to gravidity.
Race or ethnicity	Race and ethnicity are poorly documented in studies of severe HDFN or early-onset severe HDFN. Susceptibility to RhD alloimmunization comprising the large majority of severe HDFN cases is greater in White, non-Hispanic, based on RhD negative prevalence of 15% in White compared to 5-8% in African and African Americans, but lower in Asian and Native Americans.
Other considerations	RhD, K and Rhc alloantibody types comprise the majority of severe HDFN and early-onset severe HDFN cases reported across the literature. Disparities in access to prenatal care and RhD prophylaxis in some countries may result in higher rates of severe HDFN in certain racial/ethnic groups, which may be represented in immigrant populations in countries with more developed healthcare systems. This is supported by global estimates of HDFN and alloimmunization, as well as the one available report with race and ethnicity data in severe HDFN at a single center (Pegoraro V, et al. 2020, Schwab ME, et al. 2021).

Category	Description
Overall representativeness	The participants in the UNITY study were pregnant women (female sex assigned at birth) of unknown gender (not asked), with a median (range) age of 37 (2843) years, which is similar to median maternal ages ranging from 30-36 years for other study populations in severe or early-onset severe HDFN ([a]Zwiers C, et al, 2018; [b]Zwiers C, et al. 2018; Maisonneuve E, et al. 2021; Yinon Y, et al. 2010; Canlorbe G, et al. 2011; Nwogu LC, et al. 2018; Ruma MS, et al. 2007; Schwab ME, et al. 2021; Vlachodimitropoulou E, et al. 2023). The median gravidity of UNITY participants was 4, which is similar to the reported median (range) gravidity of 3 to 5 that has been reported in retrospective studies in severe HDFN populations (Maisonneuve E, et al. 2021; Schwab ME, et al. 2021; Canlorbe G, et al. 2011; Nwogu LC, et al. 2018; Ruma MS, et al. 2007; Vlachodimitropoulou E, et al. 2023). UNITY participants were predominantly anti-D (85%) and a minority anti-K (15%) alloimmunized representative of the EOS-HDFN population and a large proportion of the broader severe HDFN population (Castleman JS, et al. 2020). Participants were asked what term best described their race (White, Black, Asian, Native American, undefined or prefer not to report) and if they were of Hispanic ethnicity. The majority were white, non-Hispanic (92%) and minority, Hispanic (8%) with no reported Black, Asian or Native American participants. A similar trend of the majority White, non-Hispanic (44%) and next most common, Latina (23%) was reported by Schwab (Schwab ME, et al. 2021). However, both UNITY and the study by Schwab, et al. involved very small sample sizes. The UNITY cohort also included participants originating from countries in less developed healthcare systems who may be at greater risk of HDFN alloimmunization and severe disease. Five UNITY participants had a country of origin different from the country of study site. Of these, at least 3 (23%) were from countries with less access to prenatal care and RhD prophylaxis than is typical in the US. Similarly, the study by Schwab et al. reported 20% of participants with English as a second language and 21% with pregnancies or miscarriages occurring prior to immigration to the United States. The available data suggest that the UNITY cohort is representative of majority populations from previously studied cohorts and includes representation of severe HDFN populations in immigrant populations. Minority populations including Black, Asian/Pacific Islander and Alaskan or Native Americans were not represented in this small study. The pharmacology of nipocalimab (ie, pharmacokinetics, FcRn occupancy, IgG levels, and safety profile) observed in UNITY is similar to that reported in larger studies of non-pregnant male and female individuals that included minoritized races and ethnicities.

Supplemental References

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