

Quantitative Assessment of Anti-RhD Alloantibody Lowering by Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn: Phase 2 UNITY Study

Leona E. Ling,^{1*} Ashley Orillion,² John Smoleniec,³ Mark D. Kilby,⁴ R. Katie Morris,⁴ Kenneth J. Moise, Jr.,⁵ Masja de Haas,^{6,7} Claudia C. Folman,⁶ Shumyla Saeed-Khawaja,¹ Yosuke Komatsu⁸ for the UNITY Study Group

¹Johnson & Johnson, Cambridge, MA, USA; ²Johnson & Johnson, Horsham, PA, USA; ³Liverpool Hospital, Liverpool, NSW, Australia; ⁴Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham, UK; ⁵University of Texas at Austin and Dell Children’s Medical Center, Austin, TX, USA; ⁶Sanquin Diagnostic Services, Sanquin, Amsterdam, The Netherlands; ⁷Leiden University Medical Center, Leiden, The Netherlands; ⁸Johnson & Johnson, Spring House, PA, USA

**Presenting author*

Background

- High prenatal levels of RhD alloantibodies (anti-D) are associated with severe hemolytic disease of the fetus and newborn (HDFN) due to neonatal Fc receptor (FcRn)-mediated placental transfer of maternal immunoglobulin G (IgG) alloantibodies to the fetus resulting in fetal anemia¹
- Nipocalimab, a FcRn blocker, reduced maternal IgG by 80–85% and alloantibody titers by 4- to 32-fold while decreasing transplacental IgG and alloantibody transfer in the phase 2, open-label UNITY study of pregnant individuals with prior early-onset severe (EOS)-HDFN (NCT03842189)¹⁻³
 - Reductions in maternal IgG and alloantibody titers were well-tolerated
 - 54% of participants (pts) avoiding intrauterine transfusions (IUTs) with live births after 32 weeks gestation and no antenatal or neonatal transfusions in 46%¹⁻³
- These findings led to the ongoing phase 3 AZALEA study in severe HDFN⁴
- However, the absolute concentrations and percent reduction from baseline of anti-D could not be determined from semiquantitative titers

Objective

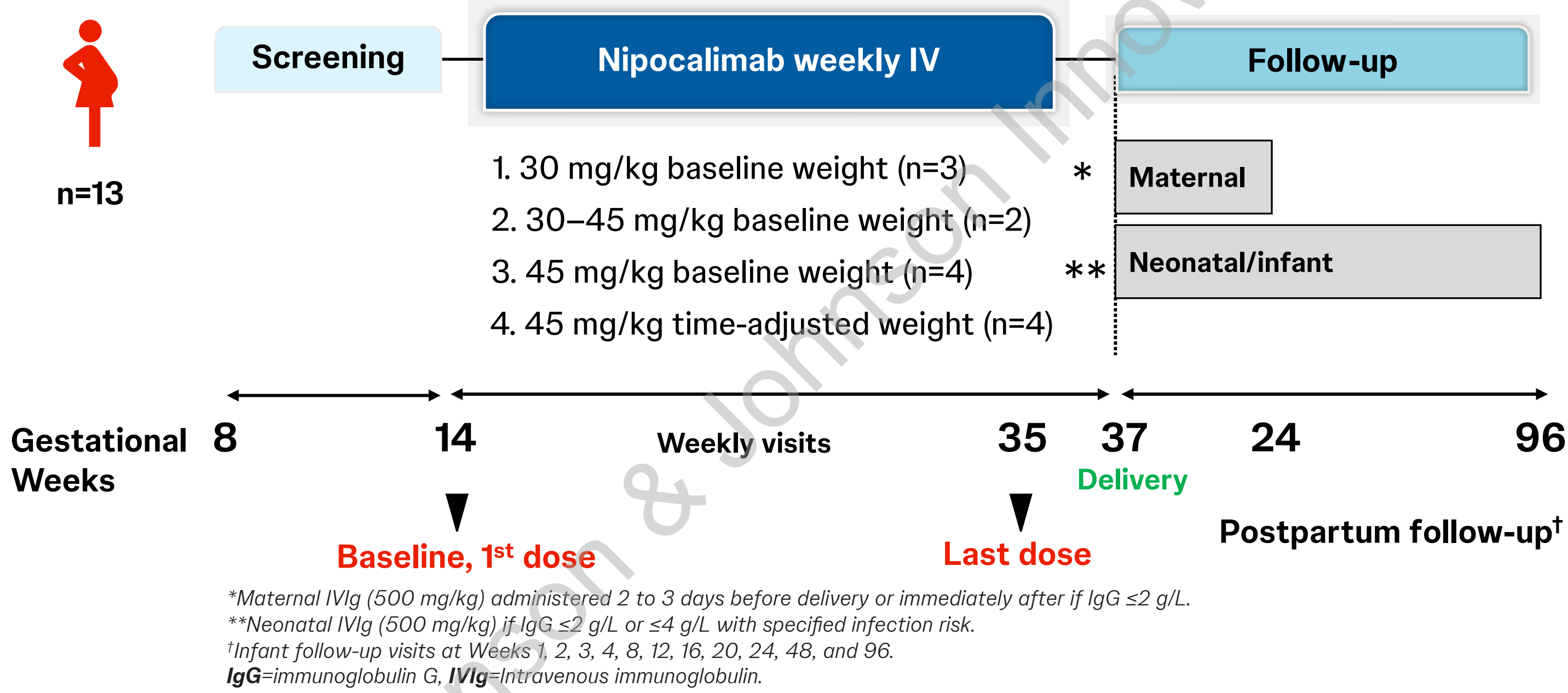
- To descriptively characterize the depth and consistency of anti-D reductions during nipocalimab treatment in individual participants with available anti-D concentrations and explore their relationship with serum IgG, anti-D titers, and HDFN outcomes

Methods

- The phase 2 UNITY study enrolled 13 pts with at least one previous anti-D or anti-Kell alloimmunized EOS-HDFN pregnancy* and a current pregnancy with a fetal antigen-positive fetus (by cell-free fetal DNA testing) and anti-D or anti-Kell above critical titer
- Nipocalimab (30 or 45 mg/kg, intravenous [IV]) was administered from 14 to 35 weeks of gestation unless discontinued for fetal anemia requiring IUT or safety-related stopping criteria
- Doses were escalated over the study to achieve consistent pharmacokinetics and pharmacodynamics. Planned delivery was at 37 weeks with administration of 500 mg/kg IV immunoglobulin (IVIg) 2–3 days prior to delivery per protocol
- Maternal anti-D titers and serum IgG concentrations were evaluated every 2 weeks
- Anti-D alloantibody concentrations measured by a continuous flow analyzer⁵ were obtained locally for management in 4 pts and evaluated along with IgG and anti-D titers

*Prior EOS-HDFN pregnancy was documented as at least one of the following: fetal hemoglobin <0.55 multiple of the median (MoM), hydrops and peak systolic velocity MoM >1.5, or stillbirth with fetal or placental pathology indicative of HDFN.

Figure 1. Study design

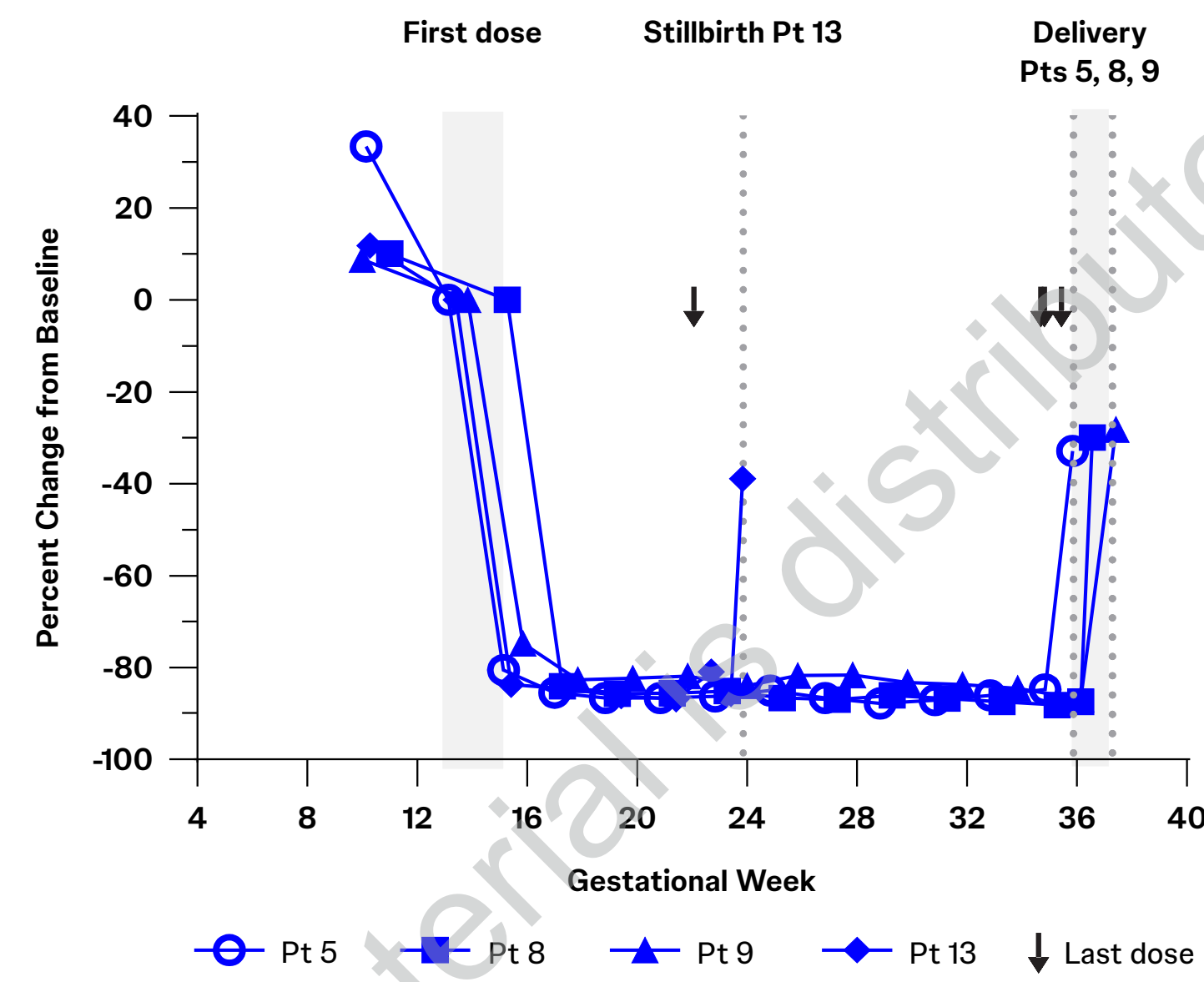


Results

Change from baseline in serum IgG levels

- Serum IgG decreased rapidly with treatment and was maintained at a median (range) of 85 (74–88)% or mean (SD) of 83 (2)% reduction from baseline during the dosing period. At delivery, IgG was increased due to IVIg just prior to delivery per protocol (Figure 2)

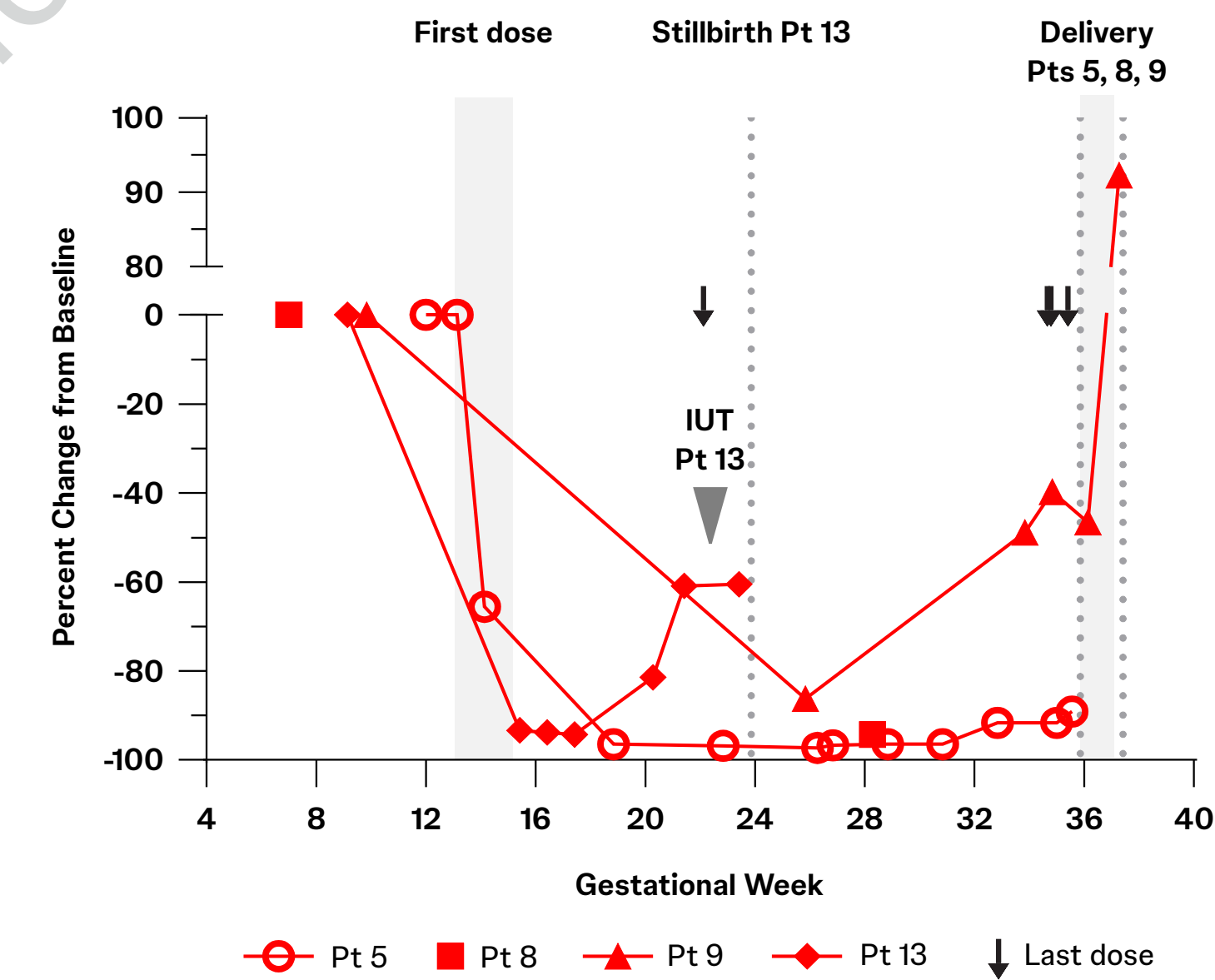
Figure 2. Change from baseline in serum IgG



Change from baseline in anti-D concentration

- Anti-D concentration decreased by >80% from baseline after treatment initiation (Figure 3)
 - Three pts required no IUTs and delivered at ≥36 weeks gestation (Pts 5, 8, 9)
- Pt 13 had complications from an IUT, with stillbirth and delivery in the following week (Figure 3)

Figure 3. Change from baseline in anti-D concentration



Reduction in anti-D level and titer from baseline: Individual participants and overall

- Anti-D concentrations substantially decreased from baseline during treatment (observations following the first dose and up to last dose) (Table 1, Table 2)
- Anti-D titers were decreased at nadir between 8–32 fold from baseline in all 4 pts similar to the range observed in the remaining study pts¹ (Table 1, Figure 4)

Table 1. Individual anti-D antibody and titers at baseline and during treatment

Individual Identifier	Pt 5	Pt 8	Pt 9	Pt 13
Anti-D concentration				
Baseline, IU/mL	95	54	13	266
Percent decrease from baseline, Median (range)	96 (66–97)	94	49 (40–86)	87 (61–94)
Observations during treatment, n	8	1	3	4
Anti-D Titer				
Baseline titer	2048	1024	64	8192
Observations during treatment, n	11	10	10	4
Fold decrease range	8–32	16–32	1–8	0.5–32

Table 2. Overall anti-D concentration percent decrease from baseline during treatment

Pts (N)	4
Observations, (n)	16
Mean (SD) percent decrease	83.5 (19.0)
Median (range) percent decrease	93.6 (39.7–97.3)

Key Takeaways

- Substantial reductions in anti-D concentrations were observed in the 4 pts with available anti-D concentration data, broadly consistent with their total IgG reductions
- The preliminary data from these 4 pts suggest the potential for consistent nipocalimab-mediated reductions in anti-D and merit further evaluation
- Anti-D increases following treatment-mediated reductions in some individuals were consistent with immunoselective targeting of IgG recycling without suppression of antibody production by nipocalimab

Change in anti-D concentration and titer by individual participant

- Both anti-D titers and concentrations rose after 30 weeks gestation in Pt 9 and minimally in Pt 5 without fetal anemia. A large rise in both measures preceded the first IUT in Pt 13 (Figure 4)
 - However, no rise in titers was observed in the remaining 5 Pts in UNITY prior to the first IUT (data not shown). These increases in anti-D occurred in a minority of UNITY pts across dose groups¹ and could be due to anamnestic responses to feto-maternal hemorrhage unaffected by FcRn inhibition

Figure 4. Change in anti-D concentration and titer for each participant

