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Safety and efficacy of Nipocalimab in early-onset severe hemolytic disease of the fetus and wewborn

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Objective

The UNITY phase 2 study evaluates the efficacy and safety of nipocalimab, a neonatal Fc receptor (FcRn) blocking monoclonal antibody, to reduce the risk of fetal anemia, intrauterine transfusions (IUT), and poor outcomes for pregnancies at high risk of early-onset severe hemolytic disease of the fetus and newborn (EOS-HDFN). Nipocalimab aims to inhibit placental transfer of HDFN-associated alloantibodies from mother to fetus and to lower circulating maternal alloantibody levels.

Methods

This open-label, single-arm study (NCT03842189) enrolled RhD (D) or Kell (K) alloimmunized pregnant individuals with singleton pregnancies at high risk for EOS-HDFN based on a prior obstetric history of fetal loss, fetal hydrops, severe fetal anemia, or need for IUT at ≤24 wks gestational age (GA) due to HDFN. The previous qualifying EOS-HDFN–affected pregnancies resulted in 38% (5/13) live births, with median GA at delivery of 23 6/7 wks (18 3/7 to 36 6/7); 85% received an IUT, with a median GA at first IUT of 20 4/7 wks (17 1/7 to 23 5/7) and median of 3 (1-11) IUTs. In UNITY, confirmation of positive fetal D or K genotype and critical maternal titer (anti-D ≥32, anti-K ≥4) were completed during the screening period (8-14 wks GA). Weekly 30 mg/kg or 45 mg/kg intravenous nipocalimab was administered between 14-35 wks GA, with delivery targeted for 37 wks GA. Follow-up was 24 wks postpartum for mothers and 96 wks postnatal for infants. Primary analysis of efficacy, safety, pharmacokinetics, and pharmacodynamics of nipocalimab are evaluated through Day 28 postpartum of the last participant for this ongoing study. The primary efficacy endpoint is the proportion of participants with a live birth at ≥32 wks GA without an IUT. Secondary endpoints for antenatal and postnatal management are reported.

Results

Fourteen D or K alloimmunized singleton pregnancies at high risk for EOS-HDFN were enrolled. One pregnancy was not included due to early elective abortion for an unrelated reason. In this study, 54% (7/13) of participants achieved the primary efficacy endpoint of a live birth at >32 wks GA without IUTs, with a median GA at delivery of 37 1/7 wks (35 6/7 to 37 3/7). Twelve of 13 (92.3%) pregnancies resulted in a live birth with a median GA at delivery of 36 5/7 wks (29 2/7 to 37 3/7). One pregnancy resulted in fetal demise following complications of an IUT at 22 5/7 wks GA. Of the 5 participants who had a live birth and IUTs, none of the IUTs were initiated before 24 wks GA and the median GA at the first IUT was 28 3/7 wks (24 1/7 to 31 5/7). A median number of 3 (1 to 5) IUTs per fetus were performed in these 5 participants. None of the 13 pregnancies developed fetal hydrops. Of 12 live births, 11 (92%) neonates received phototherapy for median 87.0 hours (12 to 301). 50% (6/12) of neonates/infants received ≥1 simple transfusion in the first 12 weeks of life. The median number of simple transfusions was 2 (1 to 6), with 5 of 6 in pregnancies that received IUTs including 1 exchange transfusion. In 7 cases without an IUT, 1 infant had 1 simple transfusion. No maternal or neonatal/infant deaths occurred. Four serious adverse events (SAEs) possibly related to nipocalimab occurred: fetal growth restriction, subchorionic hematoma, and fetal heart rate deceleration abnormality in one participant and placental abruption at delivery in another. One neonate delivered at 29 weeks developed an SAE of respiratory distress which the investigator attributed as possibly related to nipocalimab. Five maternal participants experienced mild to moderate infections that required anti-infective treatment. Consistent with the mechanism of action of nipocalimab, 11 of 12 neonates/infants had serum IgG <200 mg/dL at some point during the study. Neonatal and infant serum IgG approximated normal physiological nadirs at 24 wks of age; levels rose by 96 wks although most neonates showed IgG concentrations near or just below the lower limit of normal. Four infants had IgG concentration <200 mg/dL at 24 wks of age; one experienced 3 ear infections requiring antibiotics across 4 separate 4–7-day periods between 1-2 years of age (IgG was within normal range at 1 year of age in this infant). No other infectious complications occurred.

Conclusion

This first prospective interventional study demonstrates the potential for nipocalimab, an FcRn blocking antibody, to alter the underlying disease mechanism impacting the antenatal and postnatal management of fetal anemia in pregnancies at high risk for EOS-HDFN. These findings support a favorable benefit–risk profile of nipocalimab and warrant further evaluation of this drug in a phase 3 trial in pregnant individuals at risk for severe HDFN.