DESIGN OF A PHASE 3 STUDY OF NIPOCALIMAB IN PREGNANCIES AT RISK FOR SEVERE HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN (HDFN)

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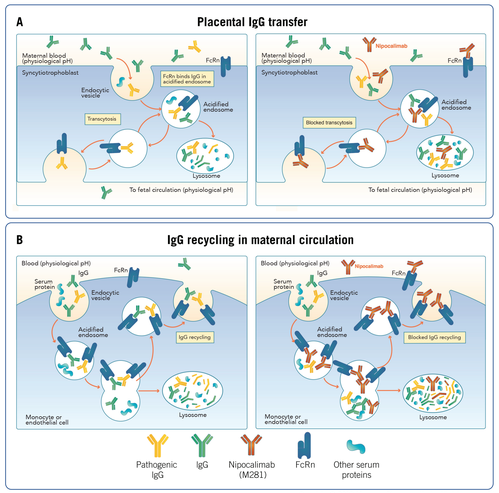
BACKGROUND

- Hemolytic disease of the fetus and newborn (HDFN) is a rare, life-threatening condition of progressive fetal anemia due to maternal-fetal incompatibility in red blood cell (RBC) antigens. Maternal immunoglobulin G (IgG) alloantibodies cross the placenta and cause destruction of fetal RBCs, which can lead to severe morbidity and mortality in the fetus and newborn[1]
  - Surviving neonates may suffer from neonatal anemia and hyperbilirubinemia, potentially leading to kernicterus
- RhD, Kell, and Rhc antigens are most frequently implicated in severe HDFN. The severity of HDFN often increases in subsequent pregnancies where the fetus carries the incompatible paternal RBC antigen due to repeated alloimmunization[1-3]
- Current management of HDFN involves ultrasound monitoring of middle cerebral artery peak systolic velocity (MCA-PSV) by Doppler for fetal anemia and treatment with intrauterine transfusions (IUTs)[4-6]
  - IUT is an invasive rescue intervention that is resource intensive and requires trained personnel (eg, maternal fetal medicine specialist) and a dedicated unit for IUTs
  - IUT is associated with increased maternal alloantibody levels and procedural complications, potentially resulting in premature or preterm birth or fetal demise[5]
- There remains a significant unmet medical need for less invasive intervention to effectively treat or reduce the risk of fetal anemia in pregnant individuals at risk for severe HDFN
- Nipocalimab is a high-affinity, fully human, IgG1 monoclonal antibody that is designed to selectively block neonatal Fc receptor (FcRn) in order to inhibit maternal IgG alloantibody transfer across the placenta to the fetus and to lower circulating maternal IgG alloantibody levels (**Figure 1**)[7,8]

Figure 1. Nipocalimab Mechanism of Action: (A) Inhibiting Placental IgG Transfer and (B) Lowering Maternal IgG Alloantibodies



FcRn, neonatal Fc receptor; IgG, immunoglobulin G.

- The potential safety and efficacy of nipocalimab in the prevention of fetal anemia, IUT, and poor outcomes are supported by results from the ongoing, open-label, single-arm, phase 2 UNITY study (ClinicalTrials.gov Identifier: NCT03842189),[9] which was conducted in alloimmunized pregnant individuals at high risk for early-onset (≤24 weeks gestational age [GA]) severe HDFN

OBJECTIVE

- To present the design of the AZALEA study, a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial, which will evaluate the safety and efficacy of nipocalimab in alloimmunized pregnant individuals at risk for severe HDFN

METHODS

Key Inclusion Criteria

- Pregnant individuals aged 18 to 45 years with singleton pregnancies and estimated GA between 13 and 16 weeks
- History of severe HDFN in a prior pregnancy, defined as 1 of the following:
  - Documented fetal anemia with fetal hemoglobin level <0.84 multiples of the median (MoM) or requiring ≥1 IUT as a result of HDFN
  - Fetal loss or neonatal death as a result of HDFN, with maternal alloantibody titers for RhD, Rhc, RhE, RhC (≥16), or Kell antigens (≥4) and evidence of an antigen-positive fetus
- The presence of alloantibody titers for RhD, Rhc, RhE, RhC (≥16), or Kell antigens (≥4) and an antigen-positive fetus in the current pregnancy

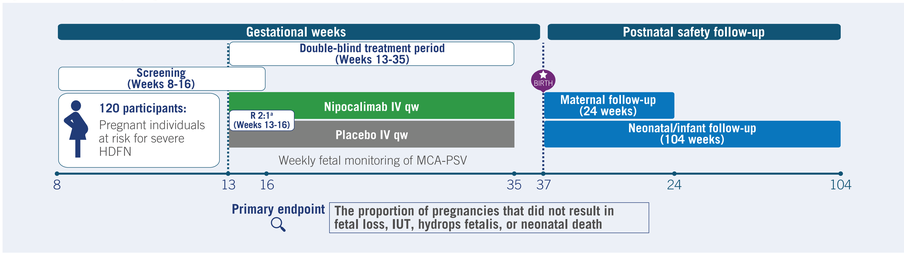
Key Exclusion Criteria

- Evidence of fetal anemia by ultrasound or repeated MCA-PSV for a value ≥1.5 MoM prior to randomization
- History of severe preeclampsia prior to GA Week 34 or severe fetal growth restriction in a previous pregnancy
- Current uncontrolled hypertension; history of myocardial infarction; unstable ischemic heart disease; stroke or severe and/or uncontrolled hepatic, gastrointestinal, renal, pulmonary, cardiovascular, psychiatric, neurologic, or musculoskeletal disorder; hypertension; and/or any other medical or uncontrolled autoimmune disorder(s)
- History of receiving anti-FcRn therapeutics or receiving rituximab or eculizumab in the last 6 months
- Receiving systemic corticosteroids or other immunosuppressants for disorders unrelated to the pregnancy
- Receiving or planning to receive plasmapheresis, immunoadsorption therapy, intravenous IgG (IVIG), or any IgG Fc-related protein therapeutics during the current pregnancy
- Having a severe infection, chronic infection, or requiring chronic treatment with anti-infectives

Study Design

- AZALEA is a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial
- The study aims to enroll 120 alloimmunized pregnant individuals with singleton pregnancies at risk for severe HDFN based on a prior obstetric history of fetal anemia
- The study includes a screening period (8-16 weeks GA), a double-blind treatment period (13-35 weeks GA), planned delivery at approximately 37 weeks GA, and postnatal follow-up periods of 24 weeks for the maternal participants after delivery and 104 weeks for the neonates/infants after birth (**Figure 2**)
- Pregnant participants will be randomized 2:1 to receive weekly intravenous infusions of nipocalimab or placebo
- During the double-blind period, weekly fetal monitoring of MCA-PSV will inform the need for cordocentesis, confirmation of fetal anemia, and the need for IUT
- Subsequent IUTs will be timed empirically by the investigator, giving consideration to the fetal status in total, to mitigate for the less reliable MCA-PSV as a result of the first IUT
  - The assessment parameters for fetal status include trends of alloantibody titers, fetal well-being through ultrasound, and hematologic values obtained at the previous IUT

Figure 2. AZALEA Study Design



GA, gestational age; HDFN, hemolytic disease of the fetus and newborn; IUT, intrauterine transfusion; IV, intravenous; MCA-PSV, middle cerebral artery peak systolic velocity; qw, weekly; R, randomization.
*Randomization Day 1 (first dose of study intervention) occurs at GA Weeks 13 to 16.

Primary Endpoint

- The proportion of pregnancies that do not result in fetal loss, IUT, hydrops fetalis, or neonatal death during the neonatal period (through Week 4 or 41 weeks postmenstrual age [PMA; defined as GA at birth plus chronologic age in weeks], whichever is later)

Key Secondary Endpoints

- The severity of HDFN as measured by a composite HDFN severity index (**Table 1**)
- The earliest time to occurrence of IUT or hydrops fetalis
- The modified neonatal mortality and morbidity index in liveborn neonates through 38 weeks PMA or at discharge (if <38 weeks PMA)
- The number of IUTs received

Table 1. Severity of HDFN Based on a Composite HDFN Severity Index[a]

Category	Description
5 (fatal)	Fetal or neonatal death due to any reason
4 (severe)	Hydrops fetalis or receiving IUT during pregnancy due to HDFN (not classified as fatal)
3 (moderate)	Neonatal exchange transfusions due to HDFN-related hemolysis and jaundice (not classified as severe or fatal)
2 (mild)	Neonatal simple transfusions due to HDFN after birth, with or without phototherapy (not classified as moderate, severe, or fatal)
1 (minimal or none)	Neonatal phototherapy due to HDFN (not classified as mild, moderate, severe, or fatal)

HDFN, hemolytic disease of the fetus and newborn; IUT, intrauterine transfusion; PMA, postmenstrual age.
[a]Measured through Week 4 after birth or 41 weeks PMA, whichever is later, and Week 12 after birth.

Antenatal/Pregnancy Outcomes

- The proportion of pregnancies with fetal loss, IUT, hydrops fetalis, or neonatal death during the neonatal period
- GA at first IUT and delivery
- The proportion of pregnancies with emergency cesarean delivery due to IUT complications; preterm birth less than 28, 32, 34, or 37 weeks GA; fetal growth restriction; or preeclampsia

Neonatal Outcomes

- The proportion of liveborn neonates/infants receiving exchange transfusions, simple transfusions, phototherapy, or IVIG for HDFN

Safety Endpoints

- Maternal death, adverse events (AEs), serious AEs, AEs leading to discontinuation, hypoalbuminemia, bleeding with a corresponding placental finding on ultrasound, infections, serious infections, infusion reactions, hypersensitivity reactions, pregnancy complications, and IUT-related complications
- Neonate/infant death, AEs, serious AEs, hypogammaglobulinemia, infections, and serious infections

Patient-/Caregiver-reported Outcomes

- Change from baseline in the Generalized Anxiety Disorder 7-item (GAD-7) over time during pregnancy and postpartum
- Change from baseline in domain scores and physical component summary and mental component summary scores on the 36-item Short Form Survey version 2 (SF-36 v2), Acute over time during pregnancy and postpartum
- Summary of Infant Health-related Quality of Life Instrument (IQI) scores over time

Exploratory Endpoints

- Pharmacokinetics, pharmacodynamics (eg, FcRn placental receptor occupancy and IgG), and immunogenicity of nipocalimab

CONCLUSION

- **The AZALEA study, the first placebo-controlled, randomized, global, multicenter, prospective clinical trial in severe HDFN, is designed to evaluate the safety and efficacy of nipocalimab, a novel, noninvasive treatment, to reduce the risk of fetal anemia in at-risk HDFN pregnancies**

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Acknowledgments

This study is sponsored by Janssen Research & Development, LLC. The authors would like to acknowledge James B. Streisand, MD, for his contribution to the study design. Medical writing support was provided by Panita Maturavongsadit, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC.

Disclosures

DO and ET received consulting fees for membership on steering committees and advisory boards for clinical studies from Momenta, Inc., and Janssen Pharmaceuticals. KJM Jr received funding from Janssen Pharmaceuticals paid on his behalf to Dell Medical School at The University of Texas at Austin for a clinical trial on a monoclonal antibody for the treatment of HDFN; received royalty funding from UpToDate, Inc., for authorship on various chapters; received consulting fees from Health Management Associates, Inc., for consultation on the formation of fetal centers; received consulting fees from BillionToOne, Inc., paid on his behalf to Dell Medical School at The University of Texas at Austin; received honoraria from GLC Healthcare, Inc., for podcast content on HDFN; and serves as a nonpaid consultant in immunology for Janssen Pharmaceuticals. E Lopriore received consulting fees for membership on steering committees and advisory boards for clinical studies from Momenta, Inc., and Janssen Pharmaceuticals. EV is the principal investigator of the UNITY and CLARITY studies in The Netherlands. PA, RB, AB, YK, E Lam, JHL, LEL, RMN, VO, SS-K, LBS, MLT, JW, XLX, UA, and WS are employees of Janssen Pharmaceutical Companies of Johnson & Johnson and may hold stock/stock options from Johnson & Johnson.

Please scan the QR code to email maternalfetalmedicine@its.jnj.com to request more information on the AZALEA study.

Poster presented at the 20th World Congress in Fetal Medicine; June 25-29, 2023; Valencia, Spain.