# Design of a Phase 3, Multicenter, Randomized, Open-label Study of Nipocalimab or IVIG in Pregnancies at Risk for Fetal and Neonatal Alloimmune Thrombocytopenia (FREESIA-3)

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## Key Takeaway

**The open-label FREESIA-3 trial will assess the efficacy and safety of nipocalimab in at-risk FNAIT pregnancies**

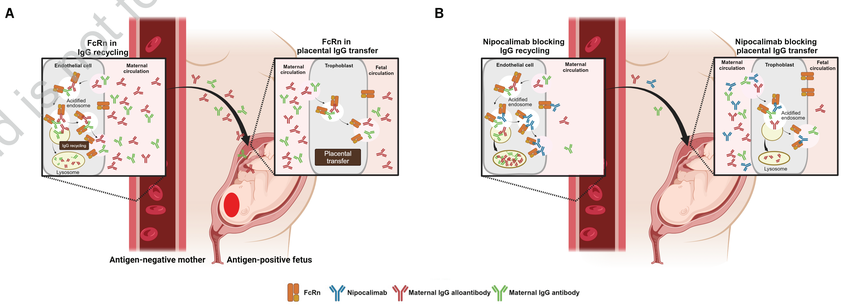
## Background

- Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare, life-threatening condition that leads to intracranial hemorrhage (ICH) in the most severe cases[1]
  - FNAIT is caused when maternal immunoglobulin G (IgG) alloantibodies against fetal human platelet antigens (HPAs) cross the placenta, most likely through neonatal Fc receptors (FcRns), during pregnancy[2] and bind to fetal platelets and megakaryocytes, leading to platelet destruction and thrombocytopenia (**Figure 1A**)
- HPA-1a and HPA-5b are the most common HPA subtypes, occurring in 80% to 85% and 7% to 16% of FNAIT cases, respectively[1,3,4]
- Currently, there is no routine prenatal screening for HPA alloimmunization
- Intravenous immunoglobulin (IVIG) with or without prednisone is the standard-of-care treatment for FNAIT in most countries and has been described in literature for use in at-risk pregnancies[1,5-8]
- Nipocalimab is a fully human, IgG1, high-affinity, aglycosylated, FcRn-blocking monoclonal antibody that inhibits transplacental IgG transfer and lowers circulating maternal IgG levels available for transfer (**Figure 1B**)[9]
- Nipocalimab showed proof-of-concept efficacy in preventing or delaying fetal anemia with an acceptable safety profile in an open-label, phase 2 study of an analogous condition, early-onset severe hemolytic disease of the fetus and newborn (ClinicalTrials.gov Identifier: NCT03842189)[9]
  - These findings have supported the potential of nipocalimab for the treatment of other IgG alloantibody–mediated perinatal diseases, including the ongoing, pivotal, phase 3 clinical development program of nipocalimab in FNAIT (FREESIA-1 [ClinicalTrials.gov Identifier: NCT06449651] and FREESIA-3 [ClinicalTrials.gov Identifier: NCT06533098])
- As nipocalimab reduces the transfer of both pathogenic IgG and beneficial IgG antibodies from mother to fetus, potential risks of nipocalimab may include hypogammaglobulinemia and infection in mothers and their neonates, and further investigation is warranted to understand its safety profile in neonates at risk of FNAIT

## Objective

**To present the design of the open-label FREESIA-3 study, which aims to evaluate the efficacy and safety of nipocalimab with a contemporaneous reference arm of IVIG with/without prednisone in pregnancies at risk for FNAIT**

**FIGURE 1: Development of FNAIT (A) and anticipated prevention of FNAIT by nipocalimab (B)**



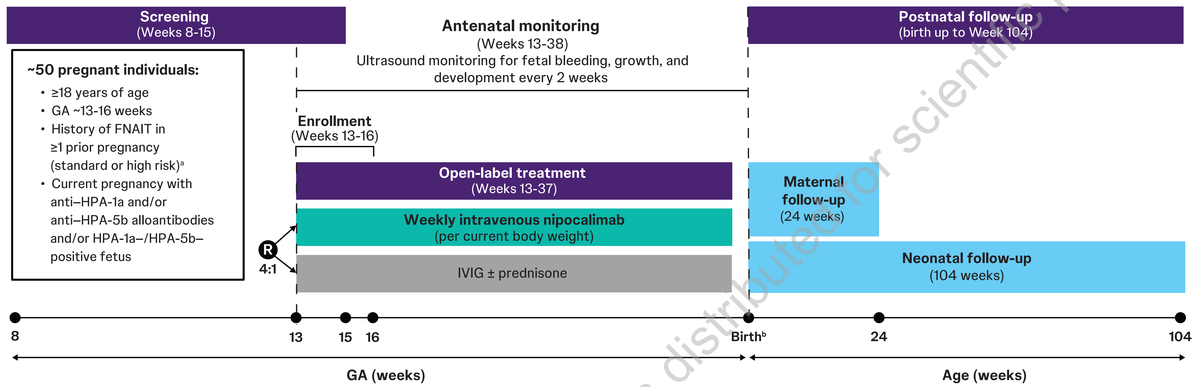

**FcRn**=neonatal Fc receptor, **FNAIT**=fetal and neonatal alloimmune thrombocytopenia, **IgG**=immunoglobulin G.

## Methods

### Study Design

- FREESIA-3 is an open-label, multicenter, randomized, phase 3 study enrolling HPA-1a– and/or HPA-5b–alloimmunized pregnant individuals with an HPA-1a– and/or HPA-5b–positive fetus and a prior FNAIT-affected pregnancy without fetal/neonatal ICH or severe bleeding (standard risk) or with fetal/neonatal ICH or severe bleeding (high risk; **Figure 2**)
- HPA incompatibility subtypes will be considered as the 2 cohorts in this study
  - Cohort 1: participants with anti–HPA-1a antibodies
  - Cohort 2: participants with anti–HPA-5b antibodies
- Participants from each cohort will be randomized (4:1) to weekly intravenous nipocalimab or IVIG with/without prednisone at 13 to 16 weeks of gestation
  - The IVIG reference arm will provide contemporaneous information on outcomes associated with the current standard of care for pregnancies at risk for FNAIT[10]
- Maternal participants will receive ultrasound monitoring for fetal bleeding and fetal growth and development every 2 weeks during the treatment period
- At birth and prior to hospital discharge, neonates will undergo cranial ultrasound to scan for perinatal/neonatal ICH, assess platelet count, and, if necessary, receive platelet transfusion as per protocol
- Postnatal follow-up periods are 24 weeks for maternal participants and 104 weeks for neonates/infants

**FIGURE 2: FREESIA-3 study design**




[a]Standard risk: neonatal platelet count <150 × $10^9$/L with no fetal/neonatal ICH or severe hemorrhage. High risk: fetus/neonate with a history of ICH or severe hemorrhage in a previous child.
[b]Delivery is planned at 38 weeks but may occur earlier at the discretion of the investigator and the study participant.
**FNAIT**=fetal and neonatal alloimmune thrombocytopenia, **GA**=gestational age, **HPA**=human platelet antigen, **ICH**=intracranial hemorrhage, **IVIG**=intravenous immunoglobulin, **R**=randomization.

### Key Inclusion Criteria

- Individuals ≥18 years of age who are pregnant at an estimated gestational age of 13 to 16 weeks
- History of FNAIT in ≥1 prior pregnancy
- Current pregnancy with the presence of alloantibody titers for anti–HPA-1a and/or –HPA-5b and an HPA-1a– and/or HPA-5b–positive fetus diagnosed by cell-free fetal DNA

### Primary composite endpoint

Fetal/neonatal death or adjudicated severe bleeding (including ICH) in utero up to the first week post birth, or a neonatal platelet count at birth <30 × $10^9$/L

### Secondary endpoints

- Neonatal platelet count at birth
- Adverse outcome of death of a fetus/neonate
- Neonatal platelet count at birth <10 × $10^9$/L
- Neonatal platelet count at birth <30 × $10^9$/L
- Neonatal platelet count at birth <50 × $10^9$/L
- Neonatal platelet count at birth <150 × $10^9$/L
- Nadir neonatal platelet count over the first week post birth
- Neonate requiring platelet transfusion(s), including the number of platelet transfusions and number of donor exposures for platelet transfusions
- Adjudicated fetal and neonatal bleeding up to the first week post birth
- Neonate requiring IVIG or platelet transfusions for the treatment of thrombocytopenia
- A neonate with a treatment-emergent adverse event of infection

### Selected exploratory endpoints

- Patient- and caregiver-reported outcomes over time
  - 36-Item Short Form Health Survey version 2 Acute scores
  - EuroQol 5-dimension 5-level questionnaire scores
  - Infant health-related Quality of Life Instrument scores
- Pharmacokinetics
  - Nipocalimab concentration in maternal blood over time during pregnancy and postpartum
  - Nipocalimab concentration in colostrum/breast milk at birth up to 4 weeks postpartum
  - Nipocalimab concentration in the neonate over time
- Pharmacodynamics (eg, IgG reduction, alloantibody levels)
- Immunogenicity

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