Identifying Pregnancies at Higher Risk for HPA-1a Alloimmunization and Fetal/Neonatal Alloimmune Thrombocytopenia (FNAIT): an International, Prospective, Natural History Study

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Background and Significance

- Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare disease that can cause uncontrolled bleeding in a fetus or newborn, especially intracranial hemorrhage (ICH).[1]
- FNAIT is caused by maternal alloimmunization against fetal platelets due to a mismatch between parental HPA-1a antigens resulting in destruction of fetal platelets.[2]
- FNAIT clinical presentation spans from no symptoms to ICH which occurs in up to 10%-20% of cases with severe thrombocytopenia, often resulting in fetal/neonatal loss or lifelong neurological disability.[3,4]
- FNAIT is the platelet counterpart of Rhesus disease (RhD); however, FNAIT is approximately one tenth as common as RhD and, unlike RhD, clinically relevant disease can occur in first-affected pregnancies with alloimmunization detected as early as the second trimester.[5,6]
- Current management of women with existing alloimmunization involves weekly intravenous immunoglobulin administration, with or without steroids.[7,8]
- Unlike screening for RhD, screening for FNAIT in pregnancy is not routinely performed so at-risk pregnancies are not identified prior to birth.[9]
- Previous studies in Caucasian populations suggest 2.1% of expectant women are HPA-1a negative and, therefore, at risk for FNAIT;[10] however, the incidence and risk of FNAIT are likely underestimated because most studies have been limited to Caucasians and have not included pregnancies that fail to reach term or result in live birth.[2,11]
- Among HPA-1a-negative women, ~27% carry the HLA-DRB3*01:01 gene variant, increasing sensitization risk ~25 fold and thus leading to much higher FNAIT risk in approximately 1/200 women.[12,13]

Current Status

- Enrollment for clinical-trial NCT05345561 is ongoing and expected to continue for ~3 years. For further information on the trial, please contact: clinicaltrials@rallybio.com.

Study Objectives

Primary objective

- To inform frequency of higher FNAIT risk among pregnant women of diverse racial and ethnic characteristics.

Secondary objectives

- Frequency of HPA-1a maternal alloimmunization at Week 10 postpartum in women at higher FNAIT risk (HPA-1b/b and HLA-DRB3*0101), and pregnancy outcomes such as:
  - Sensitization of women at higher risk at 10 weeks postpartum
  - Spontaneous abortion: non-deliberate fetal death prior to 19 weeks of gestation.
  - Elective abortion: deliberate termination of pregnancy at any time in gestation.
  - Stillbirth: non-deliberate fetal death after 19 weeks of gestation.
  - Premature birth: live birth prior to 37 completed weeks of gestation.
  - Live births: ≥37 completed weeks of gestation.
- Occurrence of neonatal thrombocytopenia and severe neonatal thrombocytopenia, where data are available: platelet count <150 × 109/L and <50 × 109/L, respectively, within 72 hours of birth.

Study Design and Study Population

- This is a prospective, non-interventional, natural history study that will assess HPA-1a alloimmunization in up to 30,000 pregnant women, conducted in the USA and across multiple European centers in Norway, Netherlands, UK, Germany and Sweden:
  - Inclusion criteria: pregnant women aged ≥18 years.
  - Exclusion criteria: prior history of FNAIT.
- Expectant mothers will be screened at gestational weeks 10–14 (**Figure. 1**), enabling early identification and follow-up of women at high risk of alloimmunization. With this knowledge, in the future, prophylaxis can be initiated in these women at higher risk.
- Informed consent will be requested for blood-sample collection at the 10–14-week visit (see **Figure. 2** for laboratory testing) for evaluation of FNAIT risk.

Figure 1. Study design

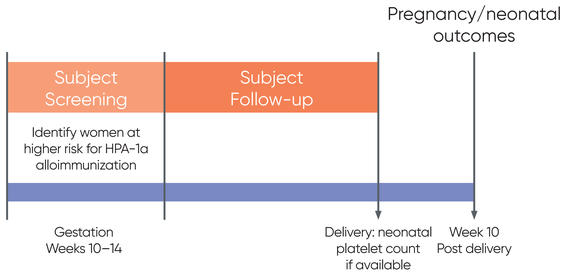
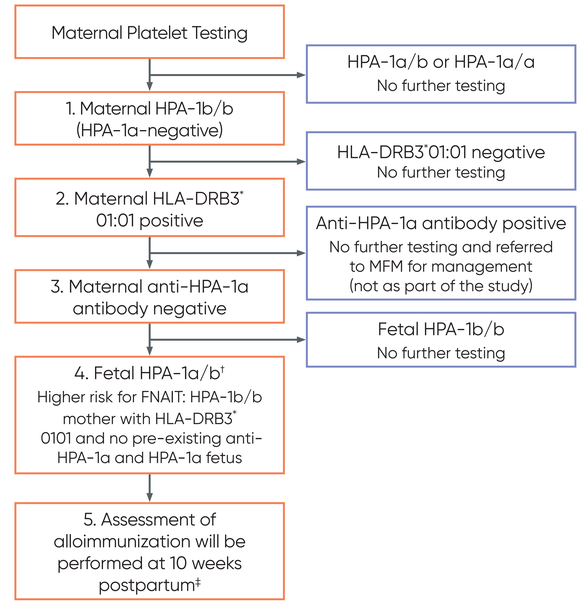


Figure 2. Prenatal FNAIT laboratory testing at gestation weeks 10–14



†Cell-free fetal DNA test to inform on the presence of the antigenic stimulus for maternal alloimmunization.
‡For pregnancies that do not result in a live birth, the assessment will be 10 weeks from the pregnancy-terminating event.
MFM, maternal-fetal medicine.

Study Rationale

- This natural history study is designed to identify HPA-1a-based FNAIT risk and occurrence of alloimmunization in a racially and ethnically diverse international population of pregnant women.
- These data will provide a contemporary control population and are intended to support a future single-arm study of a novel human anti-HPA-1a monoclonal antibody, RLYB212, for FNAIT prophylaxis.

Summary

- **The virtual elimination of RhD by screening of all pregnancies and administration of prophylaxis in at-risk cases remains one of the most significant medical advances ever achieved and provides a roadmap for FNAIT.**
- **This is the first epidemiological study that seeks to identify HPA-1a-based FNAIT risk, and occurrence of alloimmunization in a racially and ethnically diverse international population of pregnant women.**
- **This study will prospectively screen up to 30,000 women and provide a contemporary control population for a future single-arm study of a novel anti-HPA-1a antibody for FNAIT prophylaxis.**
- **There is a need to establish prompt testing and provide a well-tolerated, effective treatment for women at higher risk of FNAIT, with ~22,000 pregnancies at higher risk per year in the US and Europe.[10,13–17]**
- **The study is currently ongoing across the USA and Europe, and more than 6,000 women have been screened as of November 2023.[18]**

References

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