Nipocalimab (M281) HDFN Program Overview

June 29, 2020

Presentation V 8.0

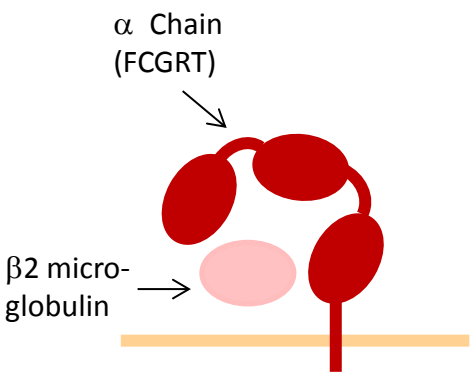
M281(Nipocalimab): A Novel Antibody-based Drug under investigation for Pathogenic IgG-driven Diseases of the Fetus and Newborn

Study Outline

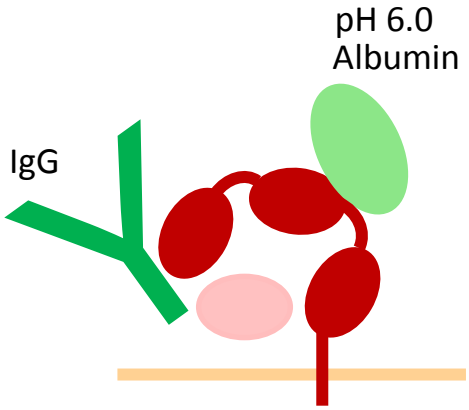
PROTOCOL	MOM-281-003 (Clinicaltrials.gov) NCT03842189
PHASE	2
PATIENT POPULATION	Patients will be screened for inclusion between GA Week 8 to GA Week 14. To be eligible for the study, patients must have an obstetrical history of severe fetal anemia, hydrops, or stillbirth related to HDFN at ≤24 weeks gestation, have anti-D or anti-Kell IgG alloantibody titers consistent with disease, and be pregnant with an antigen-positive fetus. The study will include approximately 15 eligible patients and their offspring.
METHOD OF ADMINISTRATION	Intravenous
PRIMARY OBJECTIVES	• To evaluate the safety in mother and neonate/infant of nipocalimab administered to pregnant women at high risk for early onset severe HDFN (EOS-HDFN). • To evaluate the efficacy of nipocalimab as measured by the proportion of patients with live birth at or after gestational age (GA) Week 32 and without an intrauterine transfusion (IUT) throughout their entire pregnancy.
LENGTH OF STUDY PARTICIPATION	Total time on study will be approximately 50 weeks for each pregnant woman entering the study and 96 weeks for each child born during the study. This study includes a maternal screening period of up to 6 weeks, a treatment period of approximately 20 weeks, a 24-week postnatal follow-up period for mothers, and a 96-week follow-up period for all neonates/infants.

M281 (nipocalimab)
A Fully Human, Effectorless IgG1 Monoclonal Antibody

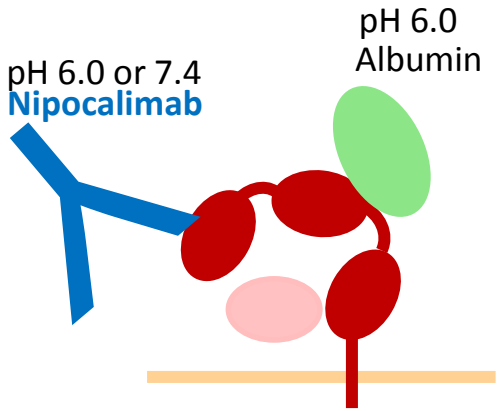
FcRn Structure



Ligand Binding



Nipocalimab IgG Blockade



- Blocks IgG binding site on FcRn, binding at high affinity at both pH 7.4 and 6.0
- Binds to IgG binding site on FcRn (distant from albumin binding site)
- Blocks IgG recycling and facilitates IgG catabolism (by endothelial or myeloid cells)
  - Full circulating volume of blood undergoes this process in 5-7 days
- No effect on IgM, IgA, IgE or cellular response to immunization or nonIgG titers

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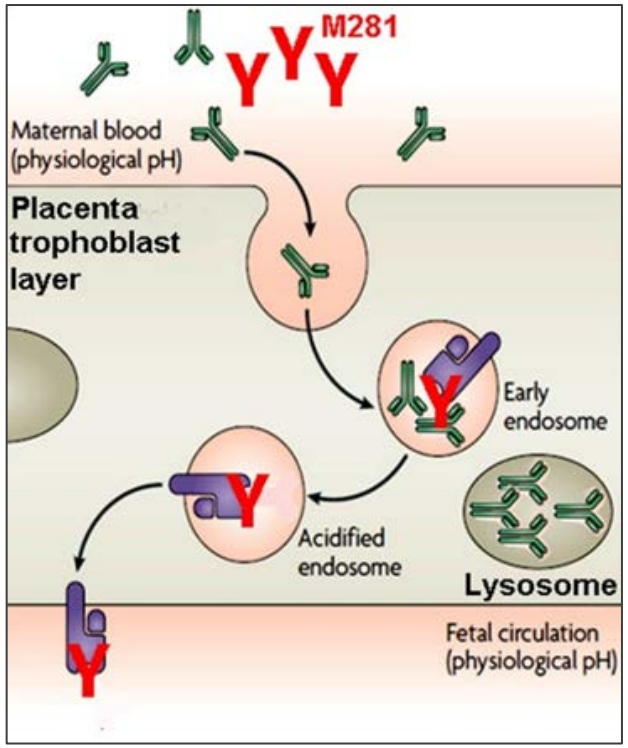
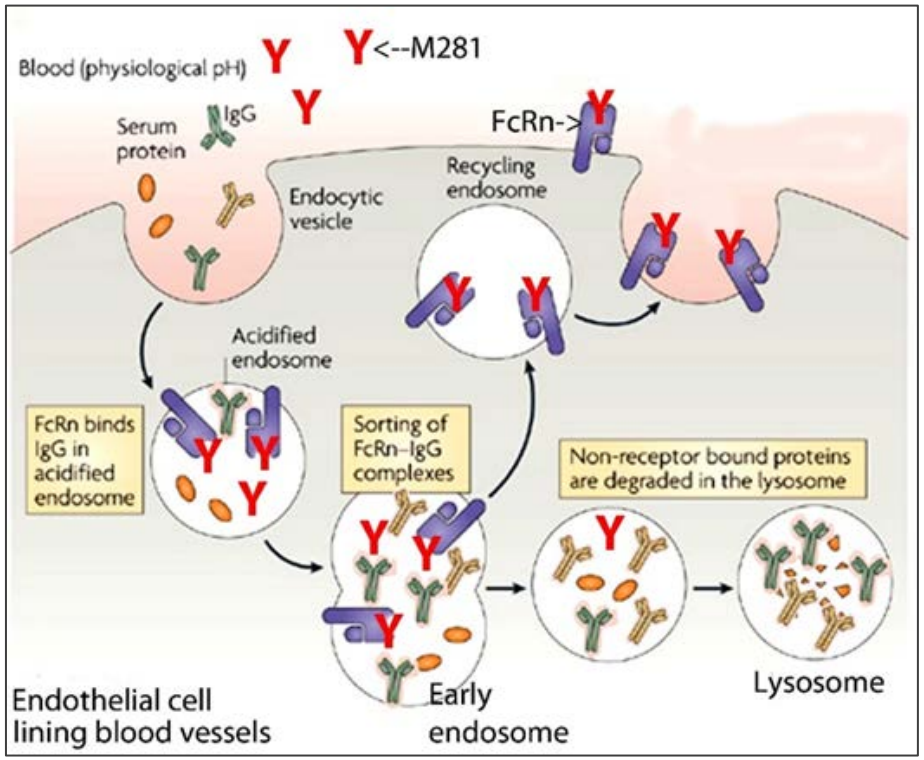
FcRn Function and M281 (nipocalimab) Blockade

Blocking Maternal to fetal IgG transport across the placenta



Anticipated 1º mechanism for efficacy in pathogenic IgG-induced diseases of the fetus and newborn

Decreased Systemic IgG by blocking Maternal FcRn-dependent IgG Recycling



Seen in First-in-Human study
and
Expected in Maternal Circulation

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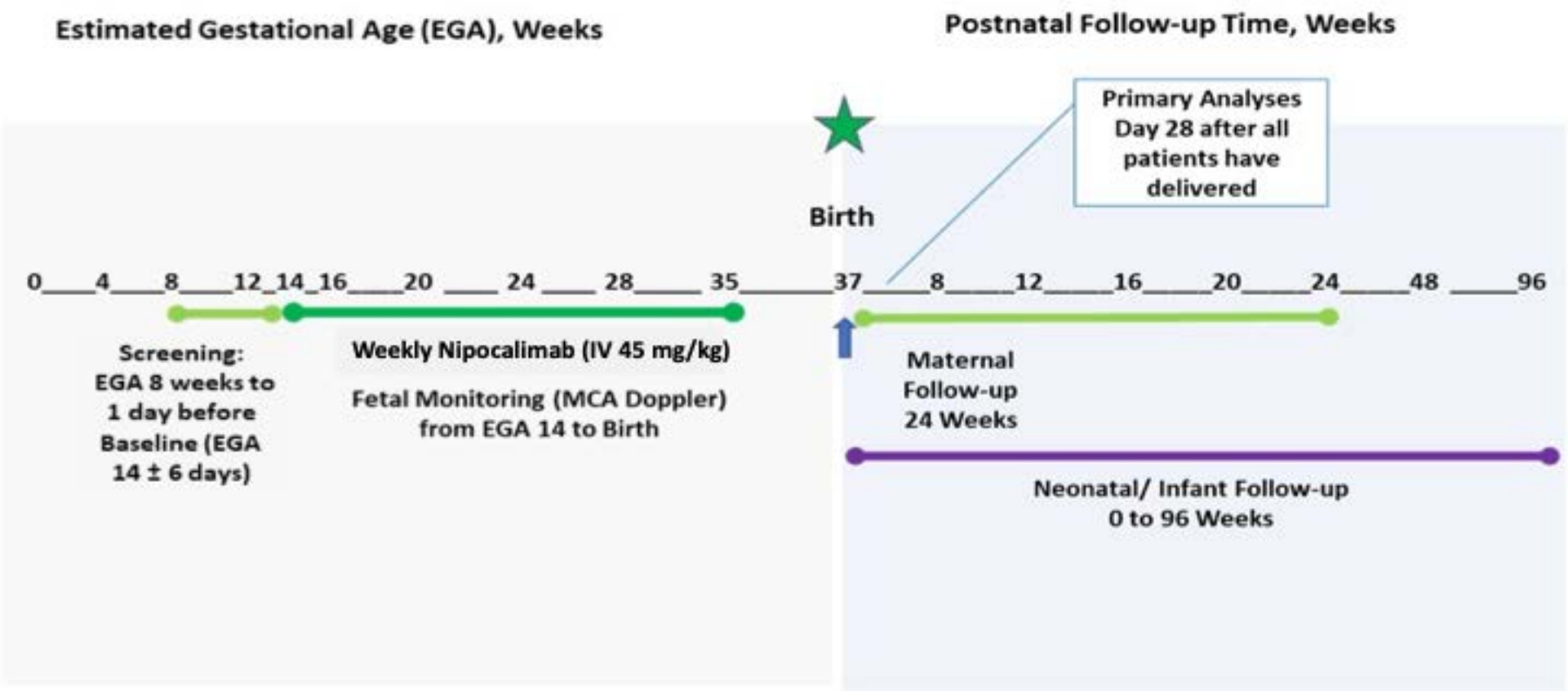
Key Inclusion Criteria for M281-003 Study

- Approximately 15 eligible patients and their offspring will be enrolled.
- Each patient must meet all of the following criteria to be enrolled in the study:
- Female and ≥18 years of age.
- Pregnant to an estimated gestational age of between 8 up to 14 weeks.
- A previous pregnancy with a gestation that included at least one of the following prior to week 24 gestation:
  - Severe fetal anemia, defined as hemoglobin ≤0.55 multiples of the median (MOM) for gestational age (see table in synopsis, from Mari et al, NEJM 2000)
  - Fetal hydrops with PSV MoM ≥1.5
  - Stillbirth with fetal or placental pathology indicative of HDFN
- Maternal alloantibody titers for anti-D of ≥32, or anti-Kell titers ≥4.
- Free fetal deoxyribonucleic acid (DNA) consistent with an antigen positive fetus (blood sample taken from mother).
- Maternal evidence for immunity to measles mumps, rubella, and varicella, as documented by serologies performed during Screening.
- Screening IgG and albumin levels within the laboratory normal range for gestational age of pregnancy.
- Willing to receive standard of care with IUT if clinically indicated.
- Agree to receive recommended vaccinations per local standard of care for both mother and child throughout the course of the study.

Key Exclusion Criteria for M281-103 Trial

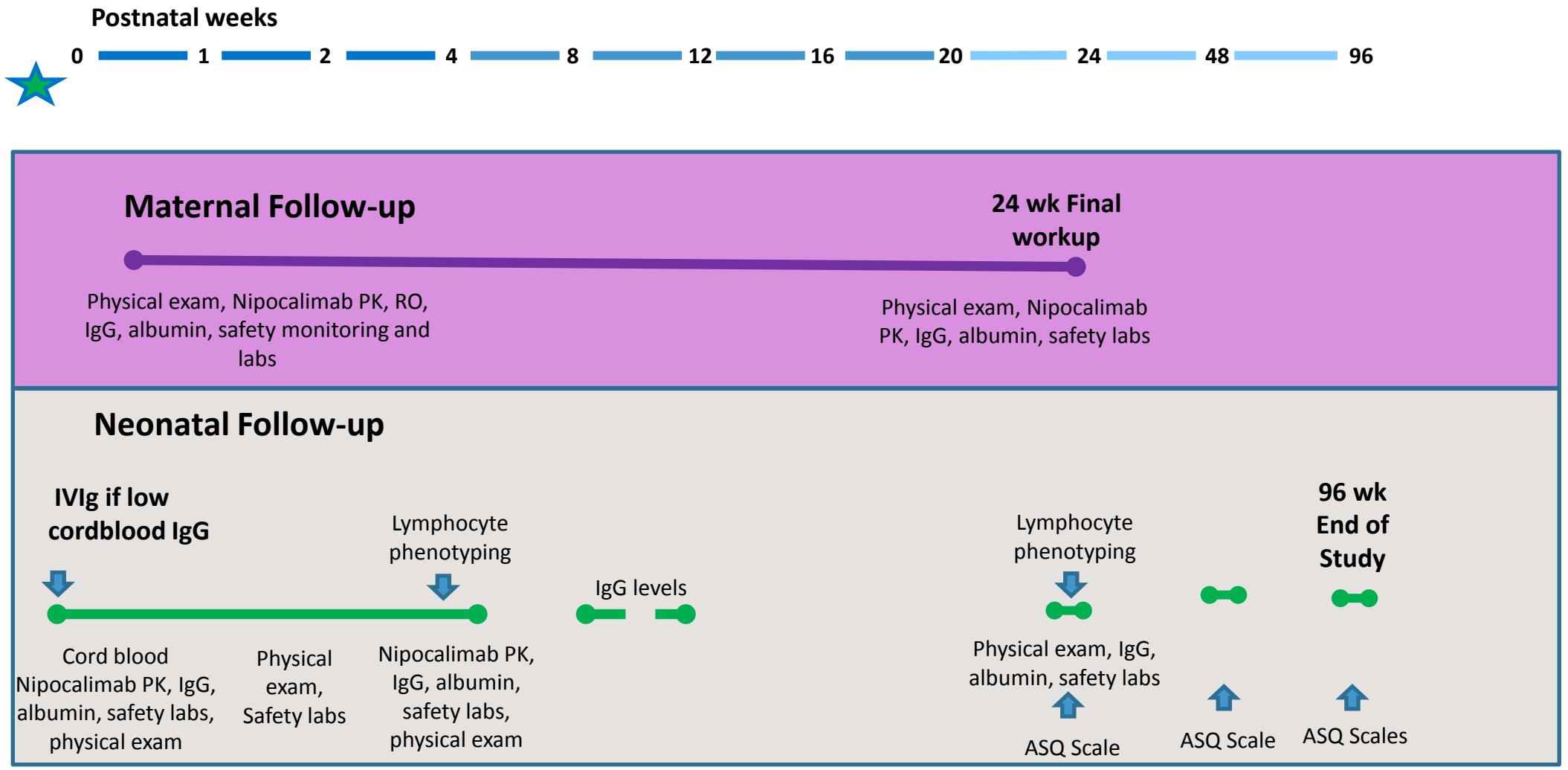
- Currently pregnant with multiples (twins or more).
- Pre-eclampsia in current pregnancy or history of pre-eclampsia in a previous pregnancy.
- Gestational hypertension in the current pregnancy
- Current unstable hypertension.
- History of severe or recurrent pyelonephritis, 4 or more lower urinary tract infections in the past year or in a previous pregnancy.
- History of genital herpes infection.
- Active infection at Screening or Baseline with Coxsackie, syphilis, cytomegalovirus, toxoplasmosis or herpes simplex 1 or 2, as evidenced by clinical signs and symptoms (evidence for prior infection or exposure, but without clinical signs and symptoms of active infection is acceptable).
- Active infection with tuberculosis as evidenced by positive QuantiFERON-TB testing.
- Requires treatment with corticosteroids or immunosuppression for disorders unrelated to the pregnancy (use of low-potency topical corticosteroids or intra-articular corticosteroids is permitted).
- Received live vaccine within 3 months prior to first IV infusion of nipocalimab.
- Currently receiving an antibody-based drug or an Fc-fusion protein drug.
- Received plasmapheresis and/or IVIG during the current pregnancy for treatment of HDFN.

Study Design: Overview and Antenatal and Postnatal Period



Nipocalimab will be administered by IV infusion at a dose based on body weight at Baseline.

Study Design: Postnatal Period



Analysis: The main analyses (efficacy, safety, PK/PD) will be conducted 28 days after the last maternal patient's delivery. Supplemental safety analysis will be conducted for mothers at 6 months after the last patient's delivery, and for neonates, at 24 months after delivery of the last neonate.

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Rationale for Open Label Trial

Reasonable understanding of natural history of EOS- HDFN

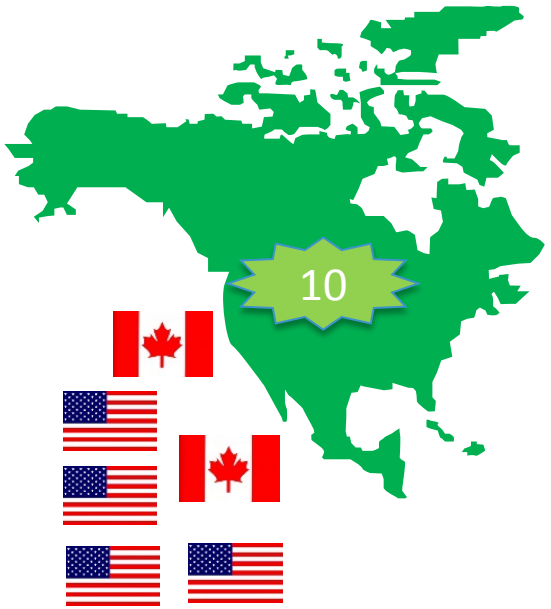
- Risk of fetal demise up to 24%
- Nearly all patients will require IUT at < 24 weeks GA and all will require IUT at some time during pregnancy

Potential for large treatment effect

Disease is acute-

- Cannot postpone treatment in a placebo/std care arm and then treat- it will be too late

14 of 18 sites Activated for Enrollment into the M281-003 Study



- Ken Moise- UT Houston
- Bob Silver- University of Utah
- Kara Markham- University of Cincinnati
- Marie-France Delisle - University of British Columbia, Vancouver, Canada
- Russ Miller–Columbia University
- Windrim – Toronto Mount Sinai Hospital

- Dick Oepkes- Leiden University Medical Center, Netherlands
- Eleonor Tiblad – Karolinska University Hospital, Sweden
- Roland Devlieger – University Hospitals Leuven, Belgium
- Mark Kilby – University of Birmingham, UK
- Pranav Pandya – University College London Hospitals, UK
- Olga Ocon- University of Grenada, Spain
- Dr. Bettina Kemkees-Matthes / Gregor Bein - Justus-Liebig-Universitat Gieben-Institut fur Klinische Immunologie und Transfusionsmedizin (Germany)

- John Smoleniec – Liverpool Hospital, Australia

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Additional Backup Slides

Diseases of the Fetus and Newborn due to Increased Production and Placental Transfer of Maternal Pathogenic IgG

Indication	Pathogenic IgG	Adverse Outcomes
HDFN	Anti-Red Cell IgG1,3	•Fetal anemia, hydrops, thrombocytopenia, pulmonary hypertension, asphyxia, fetal demise •Neonatal anemia, icterus, kernicterus, coagulopathy, cholestasis, cardiopulmonary, neurodevelopmental morbidity, mortality
FNAIT	Anti-Platelet IgG1,3	•Patechiae •Intracranial bleed •Fetal demise •Postnatal disability
aCHB	Anti-Ro(SSA) or Anti-La(SSB) IgG1,3	•AV node damage •Need for cardiac pacing •Fetal, neonatal demise •Chronic disability

Other similar diseases include gestational alloimmune liver disease, neonatal autoimmune thyroid disease, neonatal anti-phospholipid syndrome, Behcet's disease, neonatal polymyositis and dermatomyositis, neonatal scleroderma and neonatal type I diabetes mellitus

Human Volunteer Study Design

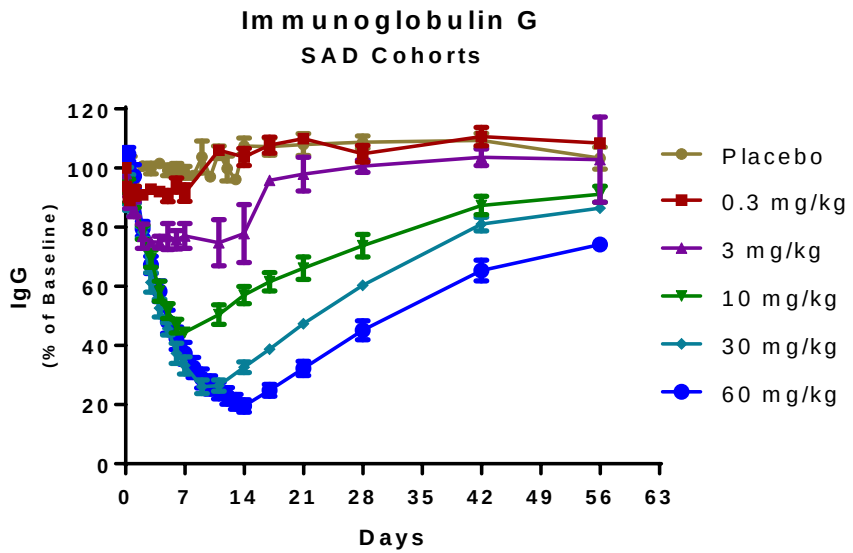
Single Ascending Dose (IV)

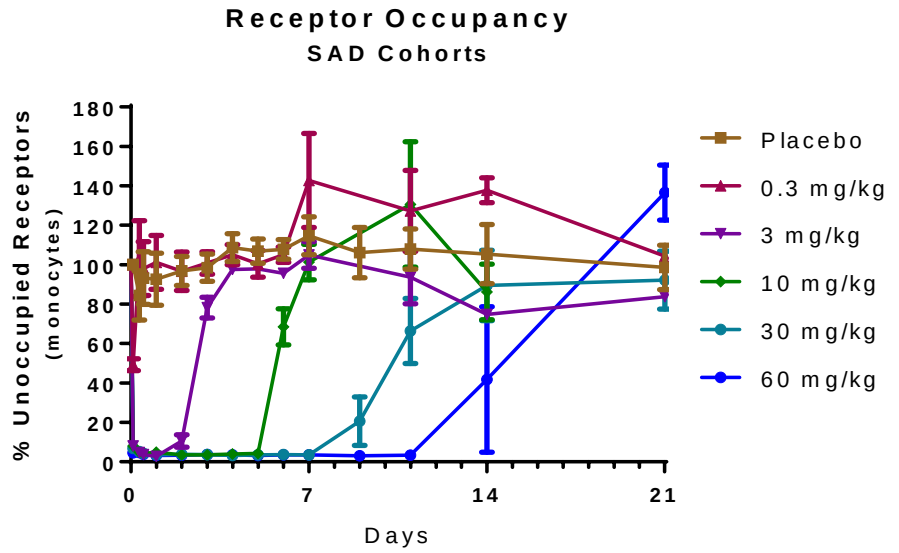
- 0.3mg/kg
- 3 mg/kg
- 10 mg/kg
- 30 mg/kg
- 60 mg/kg

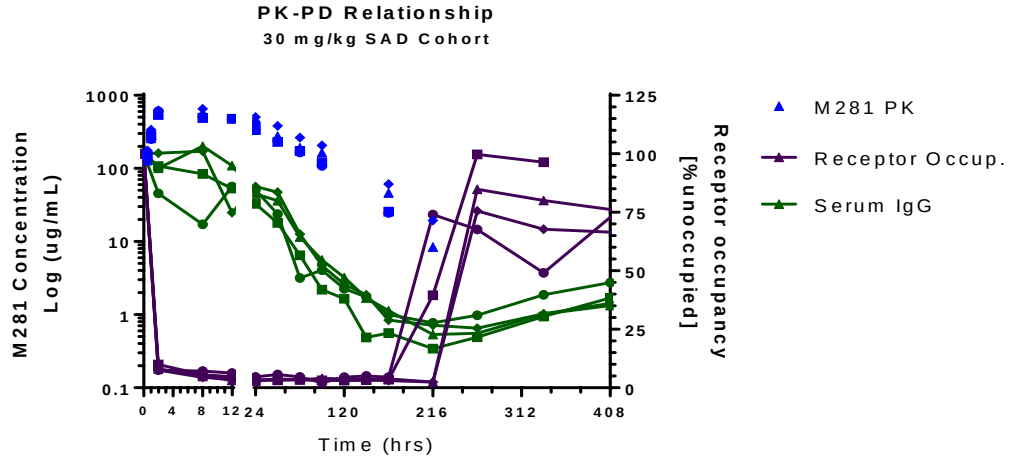
Multiple Dose (4 doses administered weekly)

- 30 mg/kg
- 15 mg/kg

Single Dose Cohorts: IgG Suppression, Receptor Occupancy, PK







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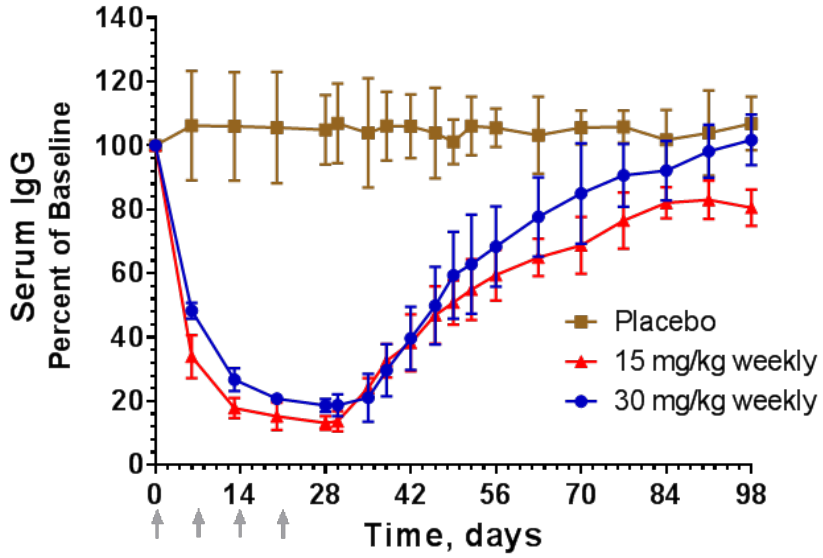
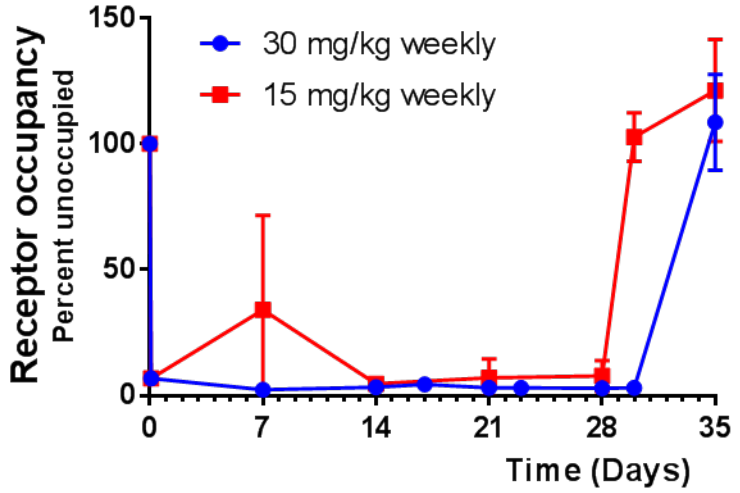
Multiple Dose Cohorts

15 and 30 mg/kg weekly dosing show similar reductions in IgG



But FcRn Saturation (receptor occupancy) is not maintained at 15 mg/kg



Loss of receptor occupancy suggests inhibition of placental transfer would be incomplete at 15 mg/kg

Phase II Dose: 30 mg/kg maintains continuous FcRn saturation and the placental blockade over the entire dosing period

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Natural History Prospective study M281-103

- A Multicenter, Prospective Observational Study to Characterize the Clinical Course of Pregnant Women and Children at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn
- This study is designed to collect health information to gain further understanding on the clinical course and management of pregnant women and their offspring at high risk for EOS-HDFN.
- No investigational drug will be administered as part of this study.
- The M281-003 Proof of concept trial is a single arm study. Statistical comparisons in efficacy analysis will be performed in the context of prospective external concurrent control, historical benchmark, or historical control.

M281-103 Observational Study

- Gather data in robust way to support evaluation of efficacy from open label trial
- Two additional studies

  Each will have separate protocol, case record form, and data analysis plan
- Prospective, observational (MOM M281-103)
  - Characterize the current standard of care, clinical course, and outcomes of pregnant women and their offspring at high risk for early onset severe hemolytic disease of the fetus and newborn (EOS-HDFN).
- Retrospective
  - Focus on similar patient population (early severe) but consider expanded patient population
  - Key aspects will consider how far back in time, availability of patient records, what specific data to collect

Independent Oversight for both M281-103 and M281-003 Studies

Independent Data Safety Monitoring Board (DSMB)

- MFM with experience in HDFN
- Infectious Disease Specialist
- Neonatologist

Objectives of the DSMB

- The primary objectives of the DSMB are as follows:
- Safeguard study trial participant interests
- Monitor overall study conduct
- Provide an ongoing assessment of safety during the course of the trial
- Provide recommendations to the Sponsor based on their review