Immunomodulation for Red Cell Alloimmunization: Now and the Future

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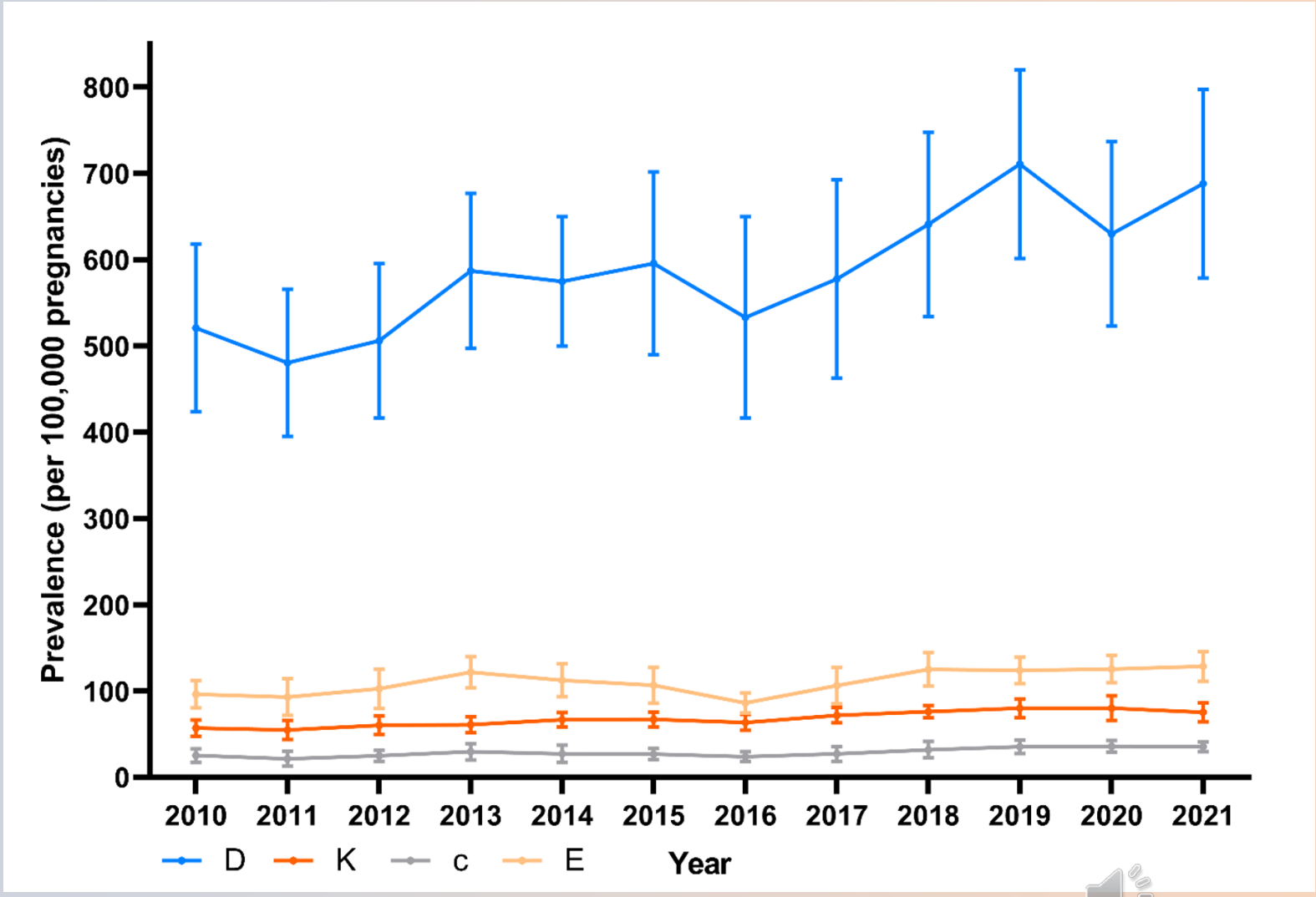
Conflicts of Interest

NAME	TASK	FUNDING
Johnson and Johnson, Inc	Research	Fees paid to UT-Austin on behalf of Moise
Johnson and Johnson, Inc	Advisory board phase 2 & 3 clinical trials on Nipocalimab for HDFN	No fees paid
Johnson and Johnson, Inc	Immunologic advisory Board regarding Nipocalimab uses in pregnancy	No fees paid
BillionToOne, Inc.	Consultant	Fees paid directly to Moise
UpToDate, Inc.	Royalties for authored chapters	Fees paid directly to Moise
Health Management Associates, Inc.	Consulting for formation of fetal care centers	Fees paid to UT-Austin on behalf of Moise
Global Learning Collaborative, Inc	Podcasts on HDFN disease	Fees paid directly to Moise

Incidence of Antibodies in a US Population

- Commercial lab
- Prenatal panels
- 2010 - 2021
- 9.9 million pregnancies
- 1.5% w/ pos antibody
  - ✓ D: 586/100,000 D: 21
  - ✓ E: 110/100,000 E: 8
  - ✓ K: 68/100,000 K: 46
  - ✓ c: 29/100,000 c: 1.9

Sugrue et al. Blood Adv 2024;8:4311-9



Early Onset HDFN

- Gestational age of 20 – 22 weeks at onset of fetal disease
- Fetal death
- Hydrops
- Fetal anemia requiring intrauterine transfusions

Definition of Early Onset HDFN

IUT < 20 weeks associated with higher rate of procedure-related loss and overall perinatal loss

- ✓ 5% vs 1% (RR: ↑4.6X)
- ✓ 24% vs 8% after 20 weeks (RR: ↑3.9X)

Lindenberg et al. 2013;120:847-52

So what is the current treatment available for these pregnancies?

Intravenous immune globulin

Mechanism of action:

- Suppress maternal antibody production
- Decrease transplacental transfer of anti-D
- RE blockade in the fetus

Intravenous Immune Globulin
PETIT Study

- 52 patients treated from 12 fetal centers worldwide
  - ✓ (24 treated w/IVIG in subsequent pregnancy; 28 w/o IVIG)
- Outcomes compared to previous pregnancy

Outcome	IVIG	No IVIG	p
Change in gest age at first IUT (days)	+15	- 9	0.11
IUT < 20 weeks EGA	38%	21%	0.20
Hydrops at IUT	4%	24%	0.09
Survival	92%	85%	0.48
Neonatal exchange transfusions	9%	37%	0.045

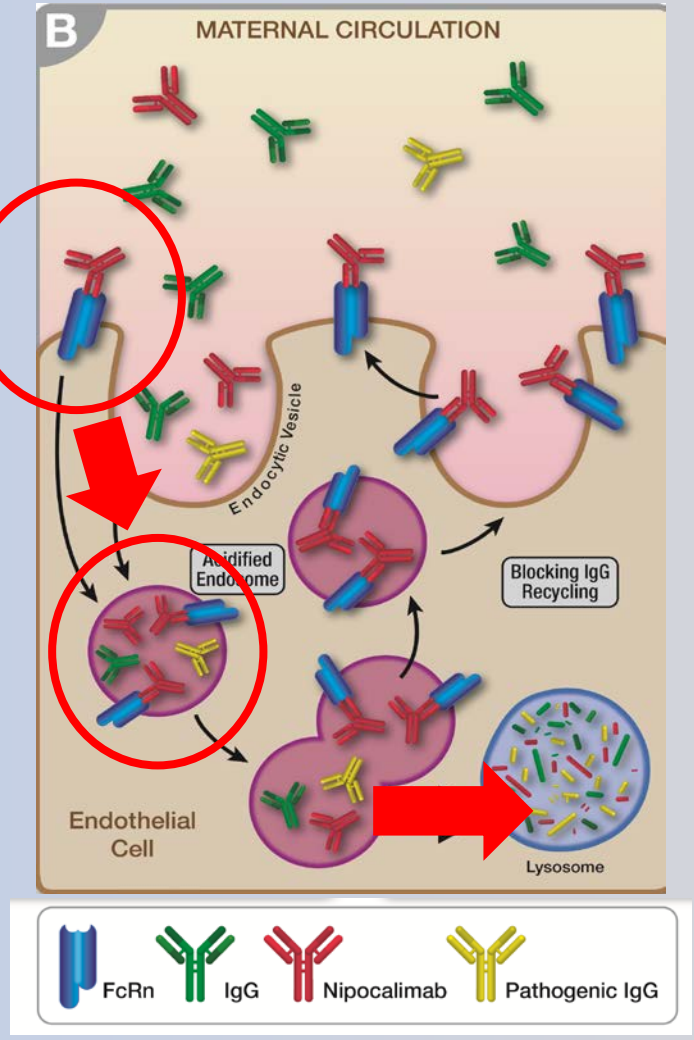
If IVIG started at < 13 weeks EGA = gain of 25 days and > 30% reduction in IUT's < 20 weeks EGA

Zwiers et al. Am J Obstet Gynecol 2018;219:.e1-9

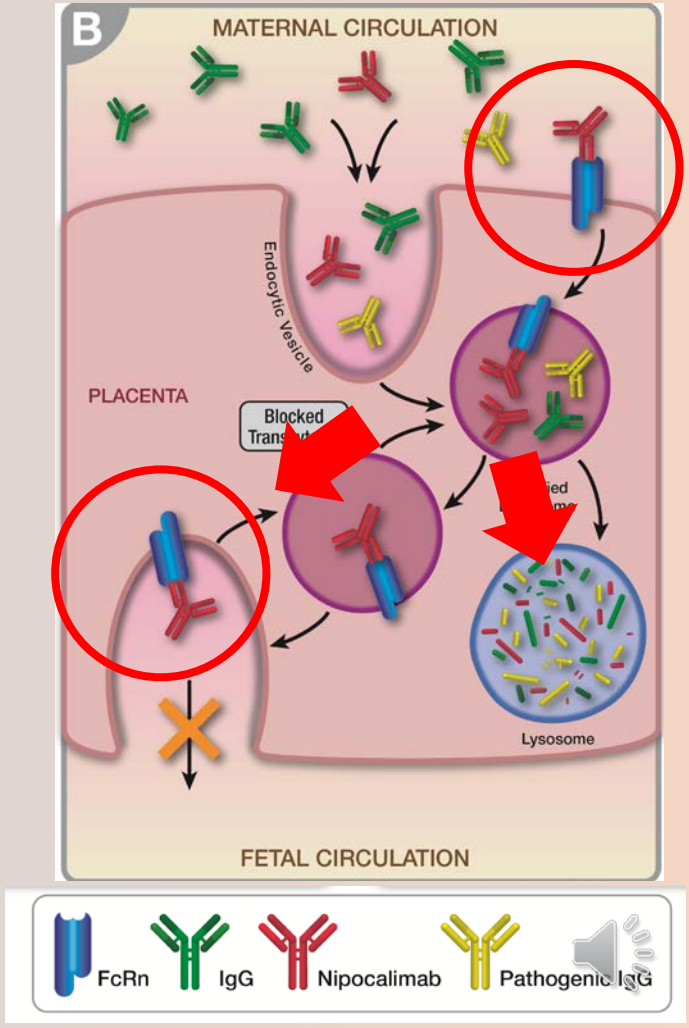
What’s on the Horizon for Treatment?

Mechanism of FcRn blockade

FcRN Peripheral Blockage



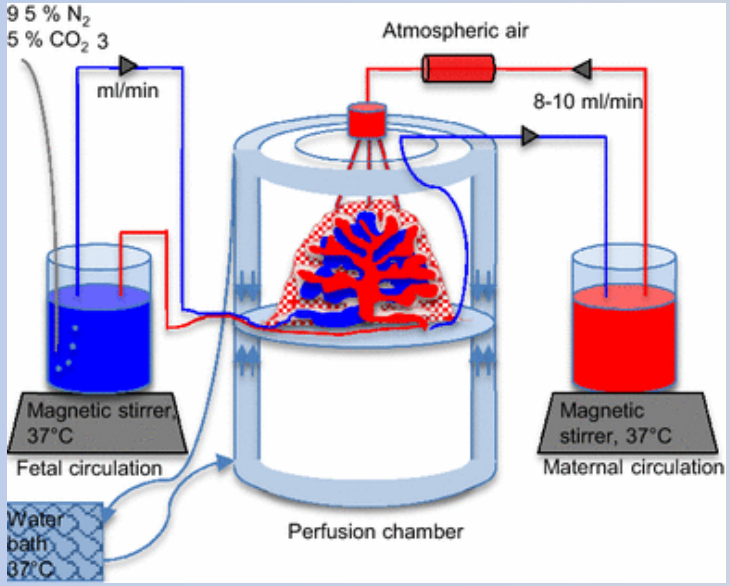
FcRN Placental Blockade

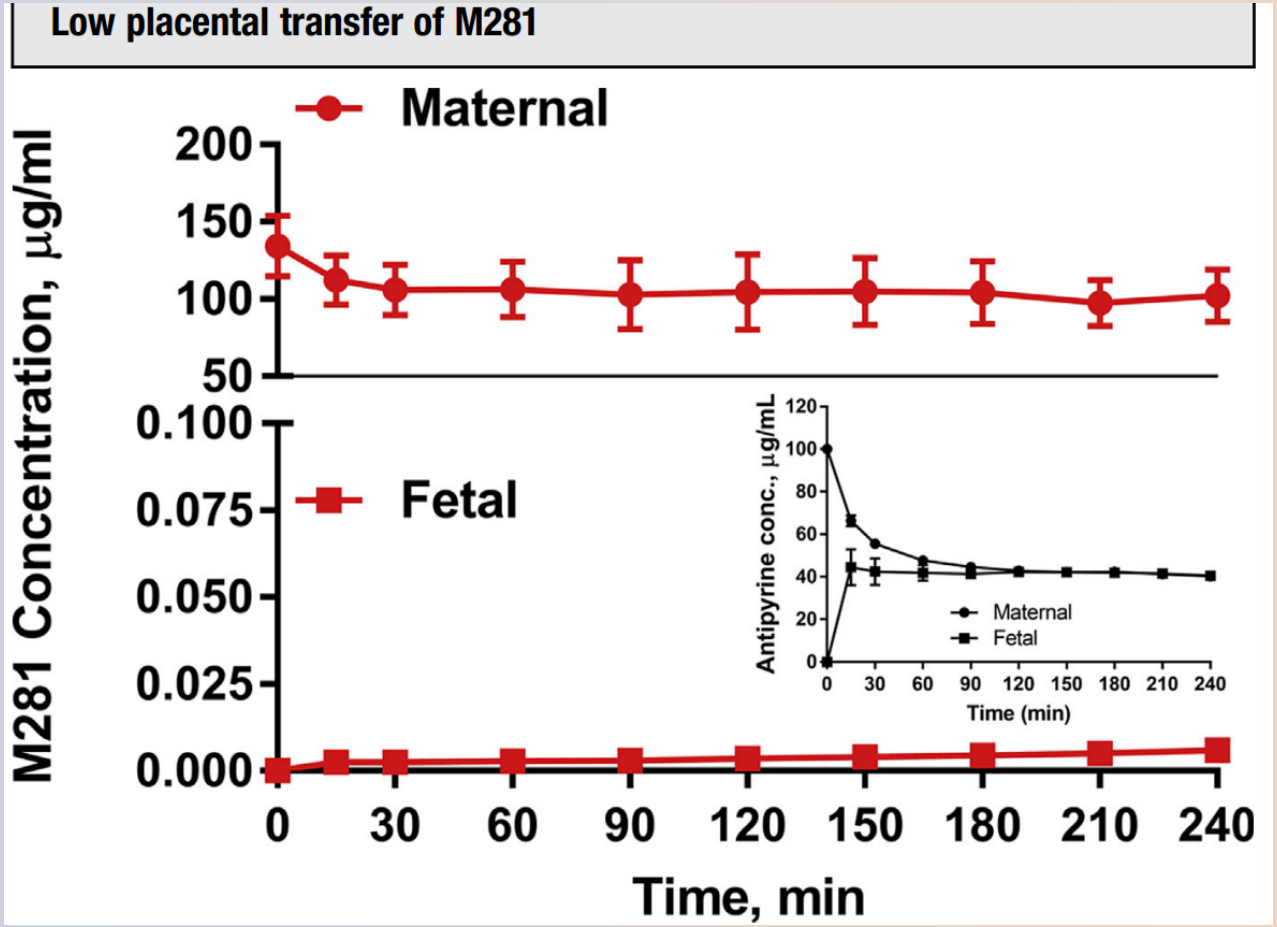


Pre-Clinical Studies of M281 (Nipocalimab)

- Performed in cynomolgus monkeys
- No safety issues noted in pregnancy or in neonates

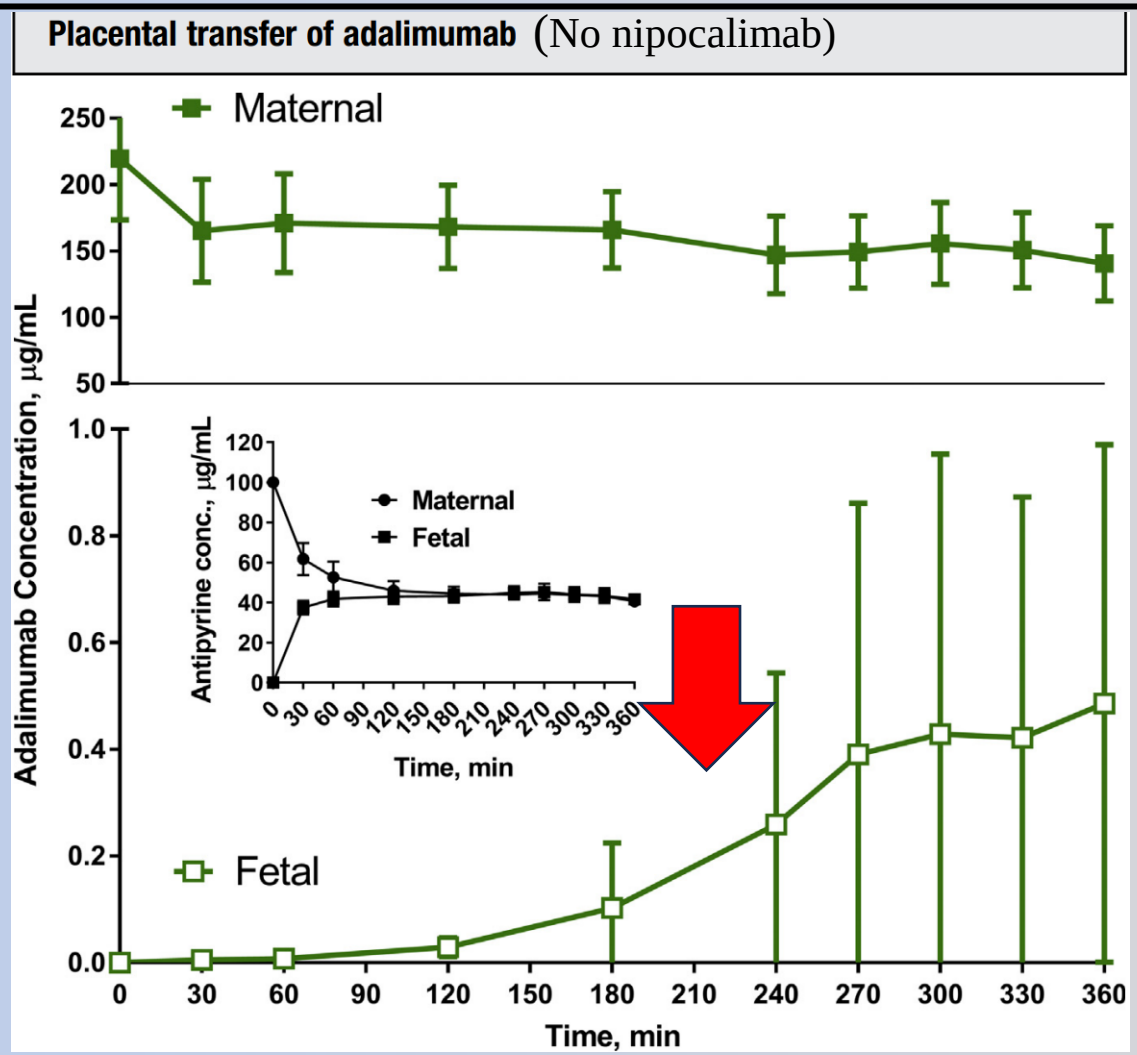
M281 (Nipocalimab) In Vitro Placental Studies

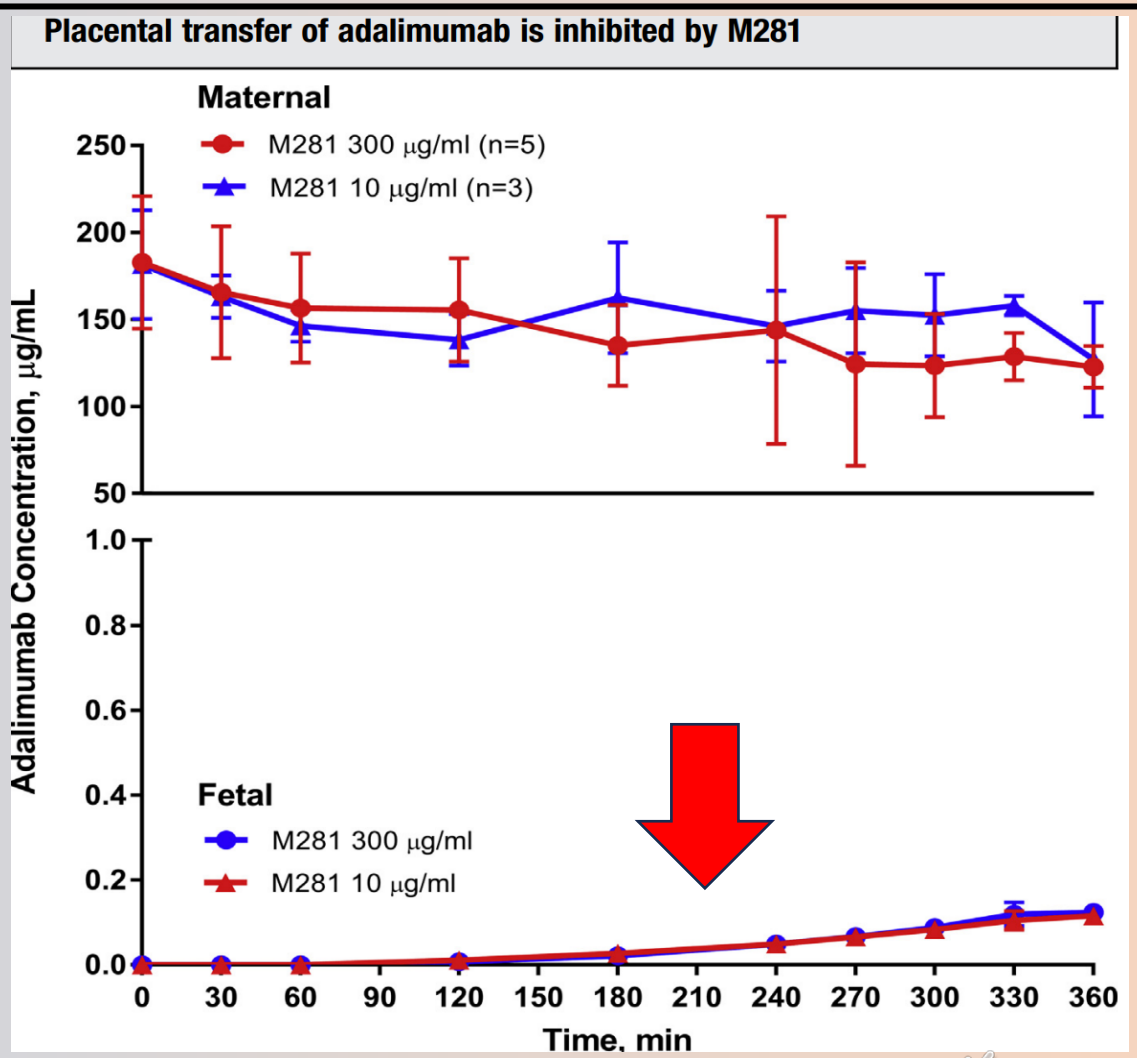




Roy et al. Am J Obstet Gynecol 2019;220:498 e1-9

Nipocalimab Placental Studies





Roy et al. Am J Obstet Gynecol 2019;220:498 e1-9

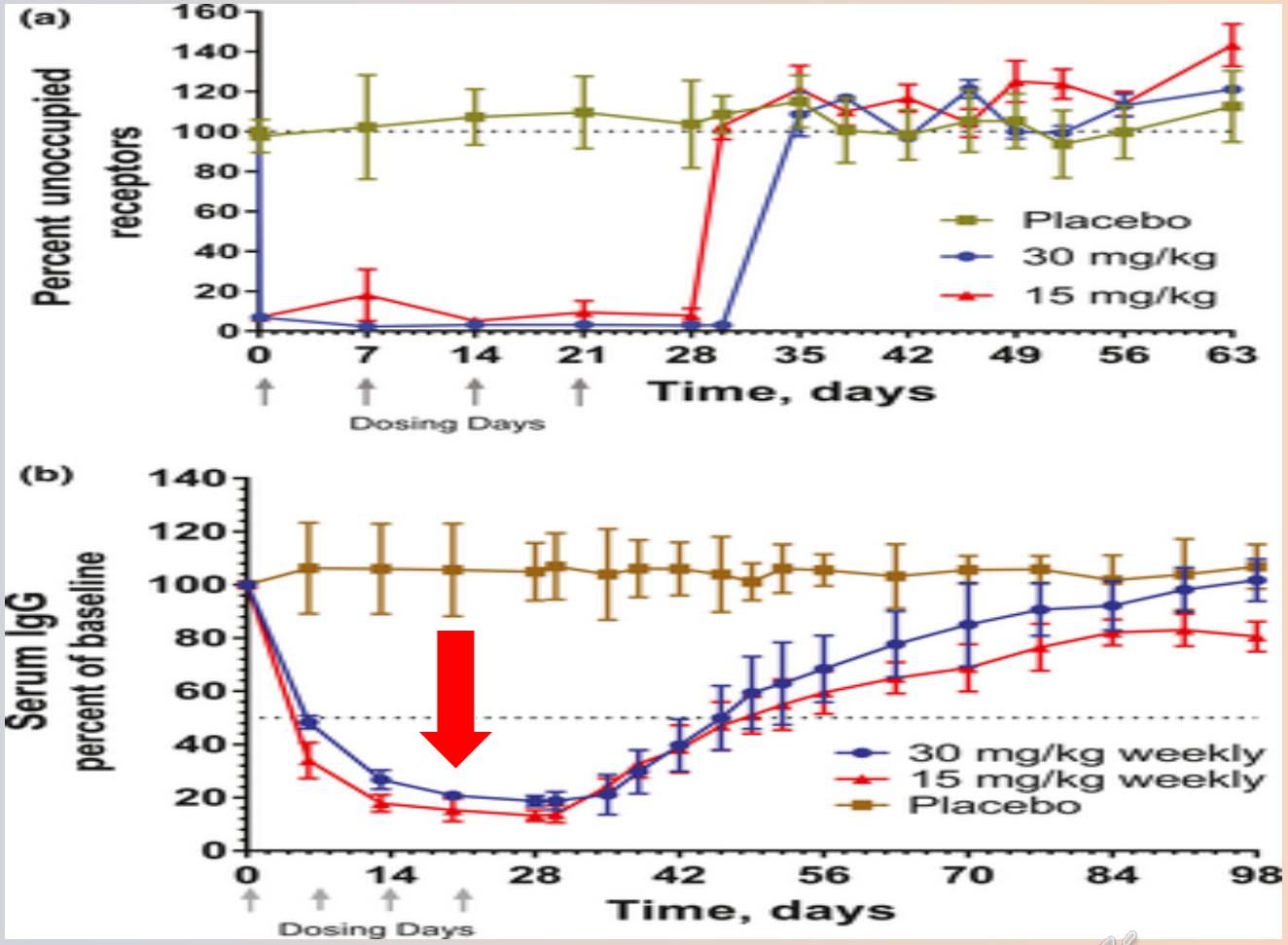
Risks of FcRN Blockade

- Maternal infection
  - ✓ CD8 T-cell and NK killer cell function preserved
  - ✓ No effect on IgA, IgE, or IgM
  - ✓ Able to respond with IgG production
- Neonatal infection
  - ✓ Neonate gets IgG from transplacental passage
- Low maternal serum albumin
  - ✓ Albumin recycling associated with FcRN receptor
  - ✓ Albumin levels decline in pregnancy

Moise et al. Ultrasound Obstet Gynecol 2022;60:167-75

Nipocalimab First in Human Studies

Phase I data



Nipocalimab Phase II Trial
Entry Criteria

UNITY® trial (NCT # 03842189)

- Phase II, open labeled
- History of previous loss or need for IUT's < 24 weeks gestation
- Patients alloimmunized to RhD (titer ≥ 16) or Kell (≥ 4)
- Fetus antigen positive by free fetal DNA in current pregnancy

Moise et al. N Eng J Med 2024;391: 526-37

The NEW ENGLAND JOURNAL of MEDICINE

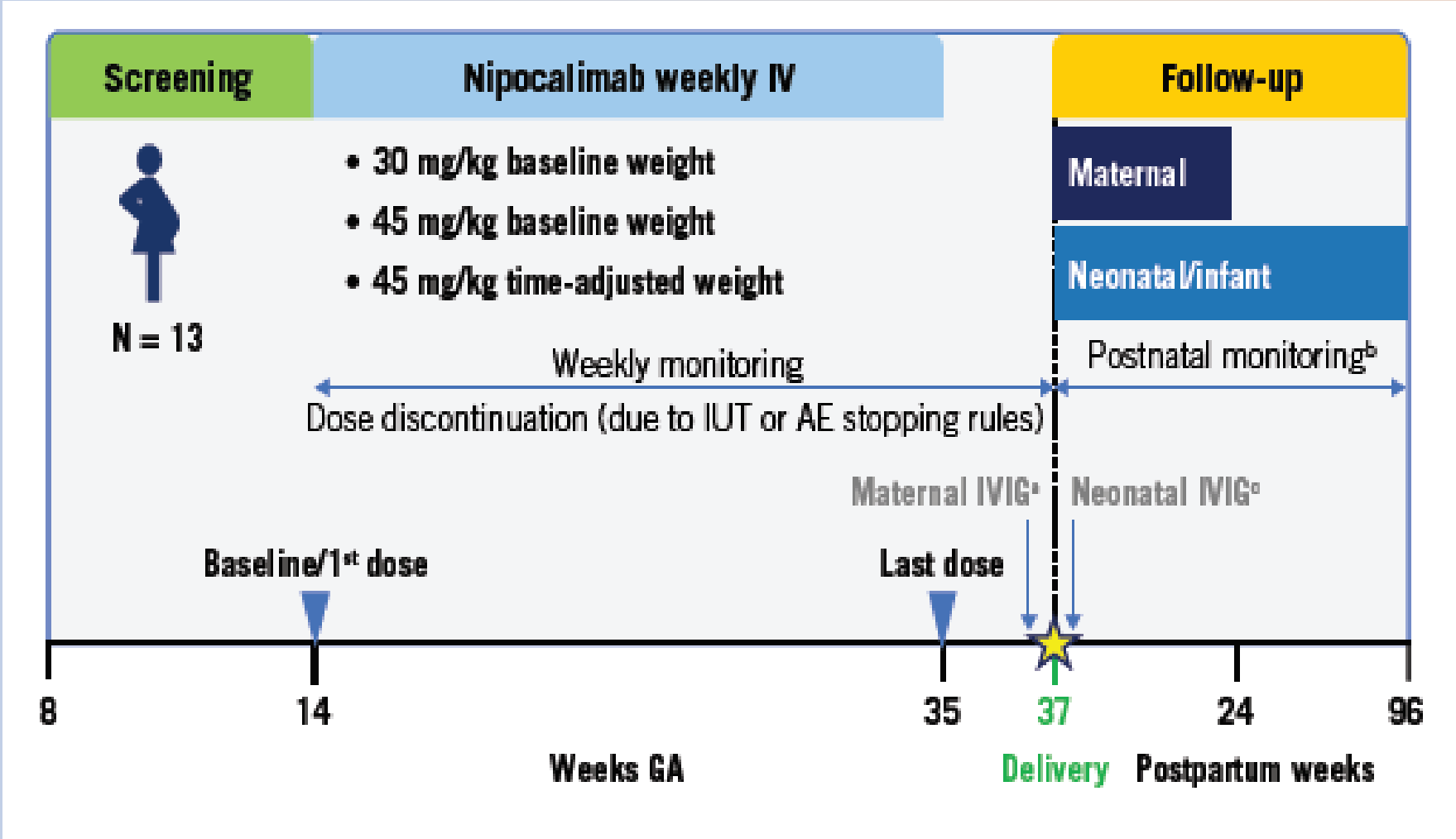
ORIGINAL ARTICLE

Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn

K.J. Moise, Jr., L.E. Ling, D. Oepkes, E. Tiblad, E.J.T.J. Verweij, E. Lopriore, J. Smoleniec, U.J. Sachs, G. Bein, M.D. Kilby, R.S. Miller, R. Devlieger, F. Audibert, S.P. Emery, K. Markham, M.E. Norton, O. Ocón-Hernández, P. Pandya, L. Pereira, R.M. Silver, R. Windrim, J.B. Streisand, J.H. Leu, A. Mirza, V. Smith, L.B. Schwartz, M.L. Tjoa, S. Saeed-Khawaja, Y. Komatsu, and J.B. Bussel, for the UNITY Study Group*

Moise et al. N Engl J Med 2024;391:526-37

Nipocalimab Phase II trial (Study Design)



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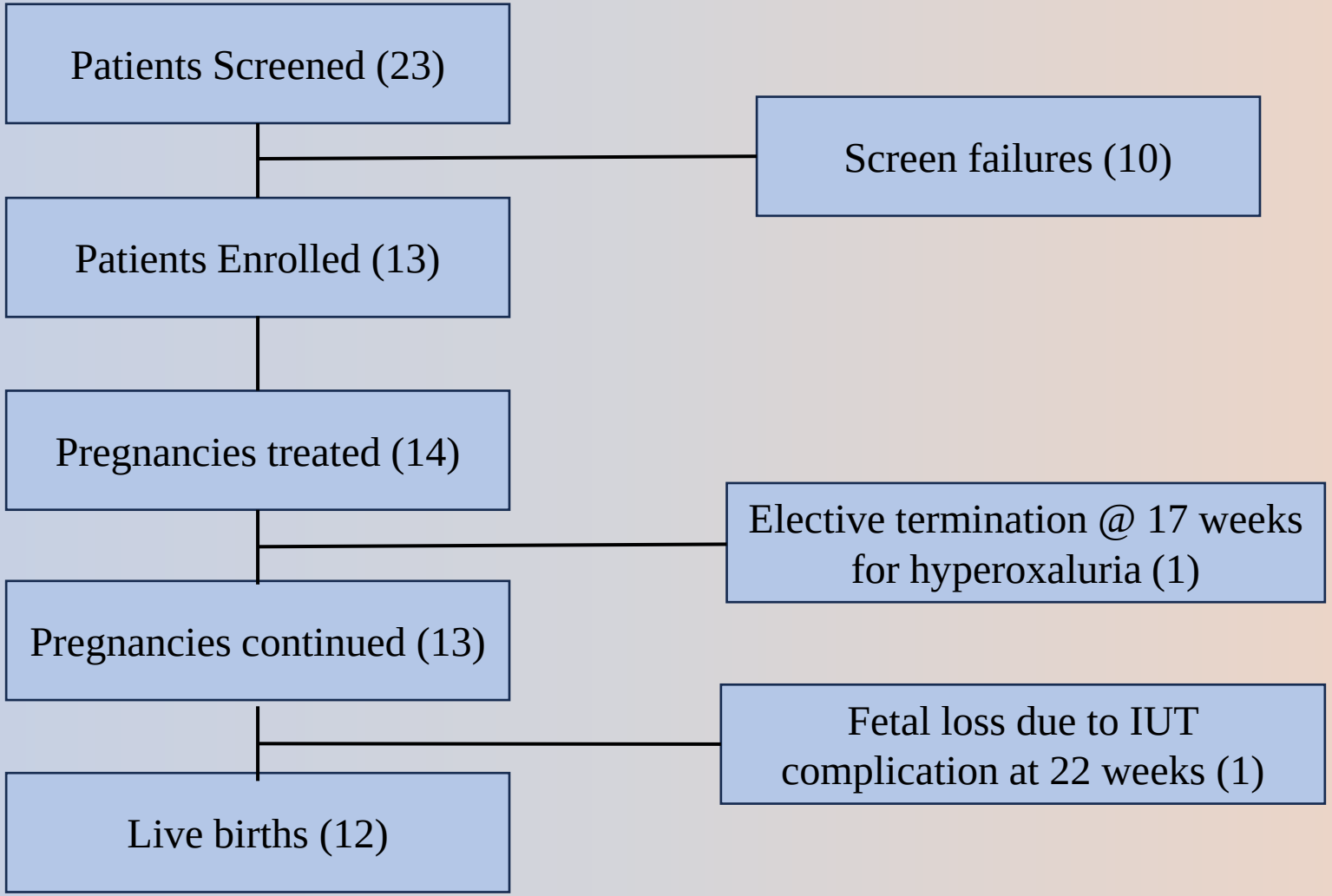
Nipocalimab Phase II Trial
Patient Population



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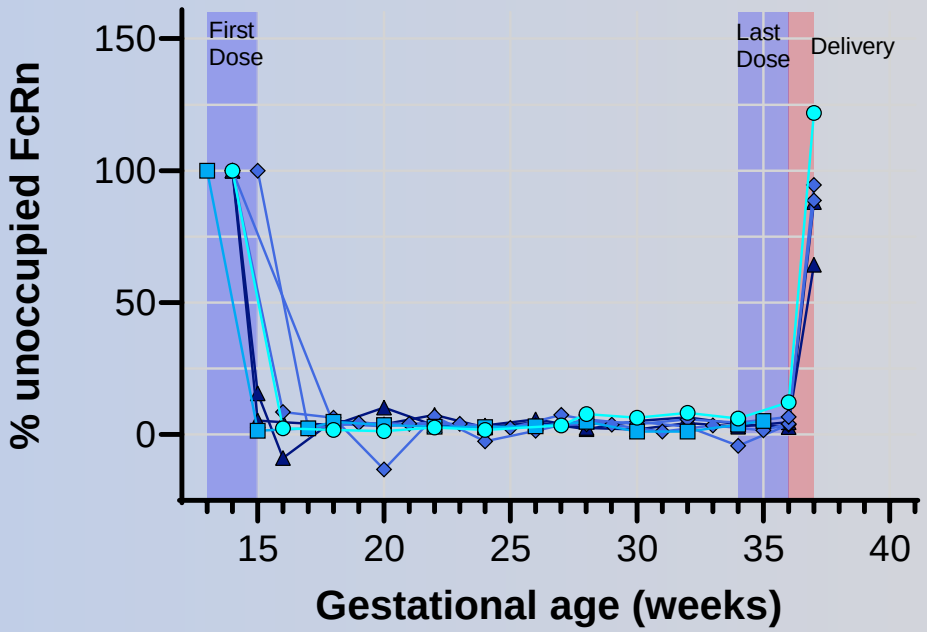
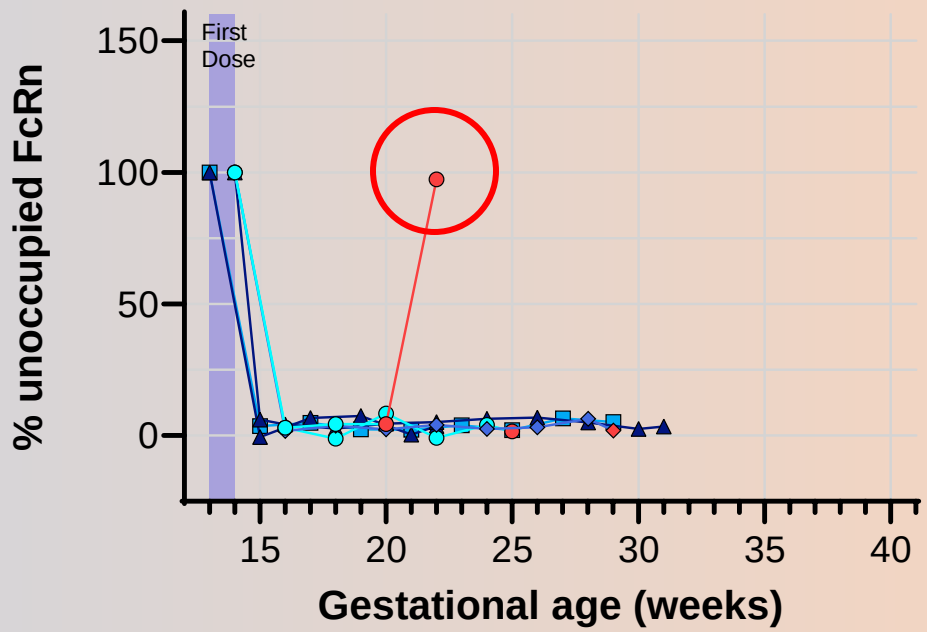
Receptor Occupancy in UNITY Trial

Participants without IUT:
Free FcRn up to delivery



Participants with IUT:
Free FcRn up to the first IUT



Dose: 30 mg/kg BLW | 30 to 45 mg/kg BLW | 45 mg/kg BLW | 45 mg/kg TAW | Post-last dose

Nipocalimab Phase II Trial
Results

Parameter	Qualifying (previous) pregnancy	On-study pregnancy
Enrolled participants (11 RhD, 2 Kell)	13	13
Number with IUT	11 (84.6%)	6 (46.2%)
Live birth at ≥32 weeks GA without an IUT	0	7 (53.8%)*
GA at first IUT (median, range; weeks)	20 $^{4/7}$ ($17\ ^{1/7}$-$23\ ^{5/7}$)	27 $^{1/7}$ ($22\ ^{5/7}$-$31\ ^{5/7}$)
Hydrops	7 (53.8%)	0
Live births	5 (38.5%)	12 (92.3%)†
GA at delivery (median, range; weeks)	23 $^{6/7}$ ($18\ ^{3/7}$-$36\ ^{6/7}$)	36 $^{4/7}$ ($23\ ^{6/7}$-$37\ ^{3/7}$)
Neonates with exchange transfusion	0	1 (8.3%)
Neonates with simple transfusion	4 (80%)	6 (50%)

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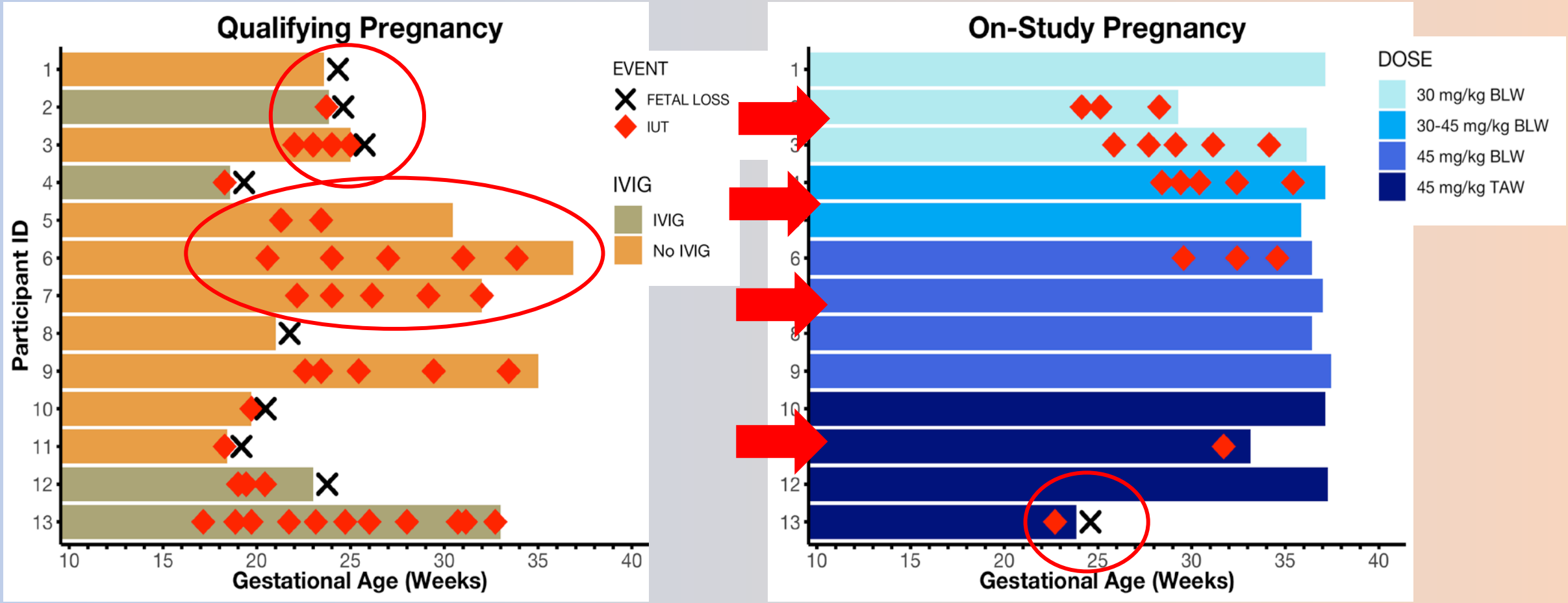
Nipocalimab Phase II Trial
Results



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Nipocalimab Phase II Trial
Maternal Adverse Events

8/13 participants had infections (grade 1 or 2); none required hospitalization
- Oral antibiotics required for 5 participants for UTI, bacteriuria, or mastitis
- 2 participants with COVID-19 infection

3 infusion reactions during a total of 234 infusions (1.3%)
- 1 required temporary interruption of the infusion due to peripheral arm swelling and paresthesia

Overall, albumin decreases did not fall below 2 g/dL, were asymptomatic, did not require intervention, and recovered postpartum

Asymptomatic and variable increases in total cholesterol, which decreased after delivery, were observed in
- 8/13 (62%) participants with elevations above reference range at ≥1 time point
- All returned to baseline levels postpartum

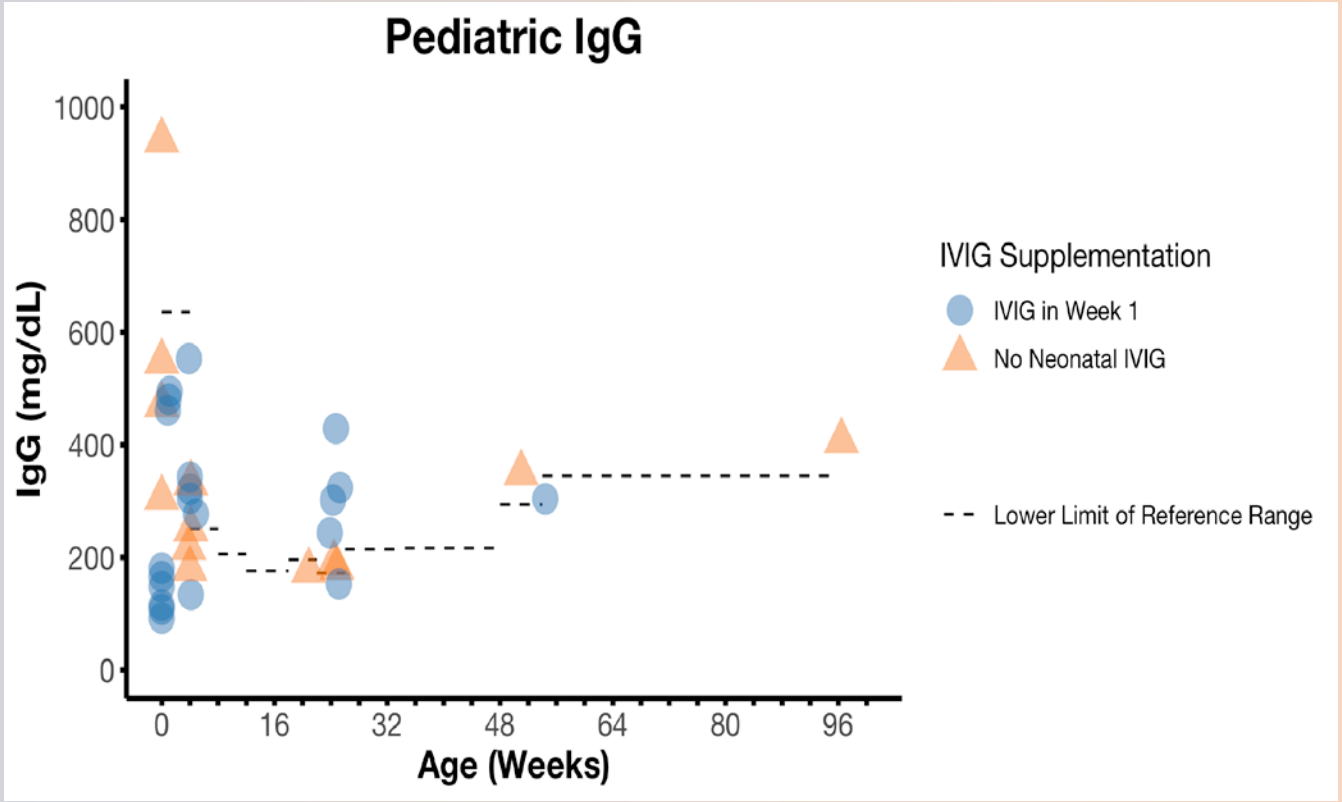
Moise et al. N Eng J Med 2024;391: 526-37

Nipocalimab Phase II Trial
Neonatal Adverse Events

- IgG below the lower limit of normal seen at delivery in 9/10 neonates with available values. 5/6 neonates with IgG <200 mg/dL received 500 mg/kg IVIG

- Evaluable total IgG levels in neonates/infants remained near or just below the lower limit of normal at 4 and 24 weeks of age

- Overall, there were a total of 12 infections in 7 of the 12 neonates/infants (1 with thrush, 1 with thrush and common cold, 1 with common cold, 1 with pyrexia and upper respiratory infection, 1 with pyrexia, 1 with conjunctivitis, and 1 with 3 ear infections and COVID-19)



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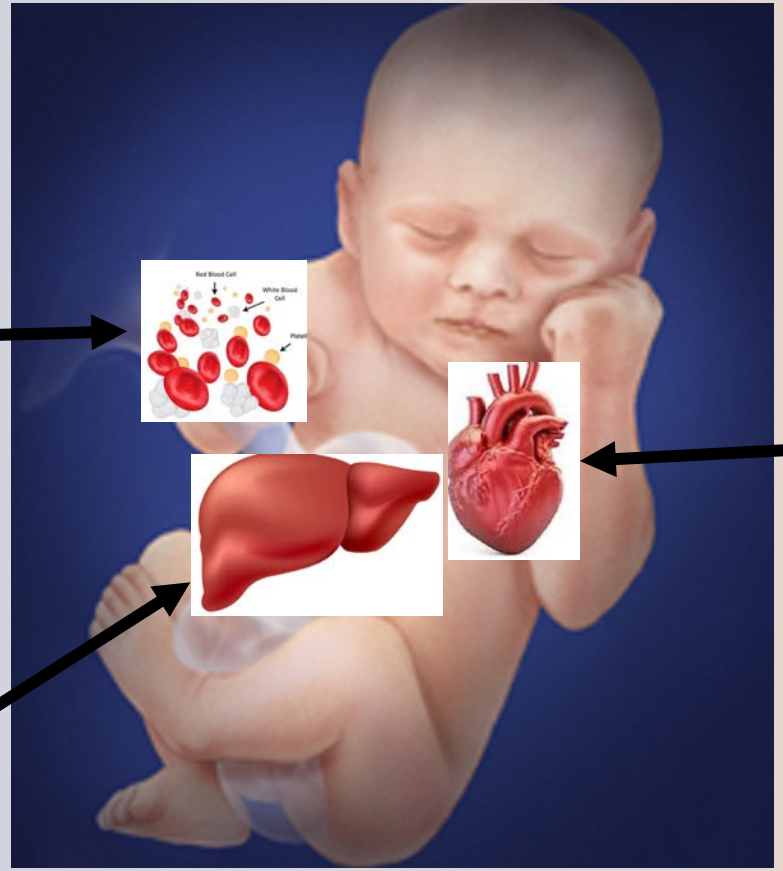
Nipocalimab Phase III trial

- Plan for a phase 3 randomized clinical trial (AZALEA) in pregnant individuals at risk for severe HDFN
- Key inclusion criteria
  - Alloimmunization of anti-D, C, E, c, or Kell
  - Antecedent pregnancy with documented HDFN-associated fetal anemia, ≥1 IUT, or fetal/neonatal death
  - Currently pregnant with an antigen-positive fetus by free fetal DNA
- Participants will be randomized 2:1 to nipocalimab vs placebo infusions

Fetal/Maternal Alloimmune Diseases

- Hemolytic Disease of the fetus/newborn
- Fetal/Neonatal Alloimmune Thrombocytopenia
- Neonatal Alloimmune Neutropenia



Antibody-mediated congenital heart block

Gestational Alloimmune Liver Disease

Last of the Mohicans

Thank you