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M281, an anti-FcRn antibody, inhibits IgG transfer in a human ex vivo placental perfusion model

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Disclosures

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Research

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are current or former employees of Momenta Pharmaceuticals and may own Momenta Pharmaceuticals stock

Maternal Pathogenic IgG-mediated Alloimmune and Autoimmune Diseases of the Fetus and Newborn

Indication	Pathogenic IgG	Adverse Outcomes
Hemolytic Disease of the Fetus and Newborn (HDFN)	Anti-Red Cell IgG1,3	•Fetal anemia, hydrops, thrombocytopenia, asphyxia, fetal demise •Neonatal anemia, hyperbilirubinemia, kernicterus, coagulopathy, cholestasis, cardiopulmonary and neurodevelopmental morbidity, mortality
Fetal-neonatal Alloimmune Thrombocytopenia (FNAIT)	Anti-Platelet IgG1,3	•Patechiae •Intracranial bleed •Fetal demise •Postnatal disability
Autoimmune Congenital Heart Block (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, Behcet's disease, neonatal polymyositis and dermatomyositis, neonatal scleroderma and neonatal type I diabetes mellitus

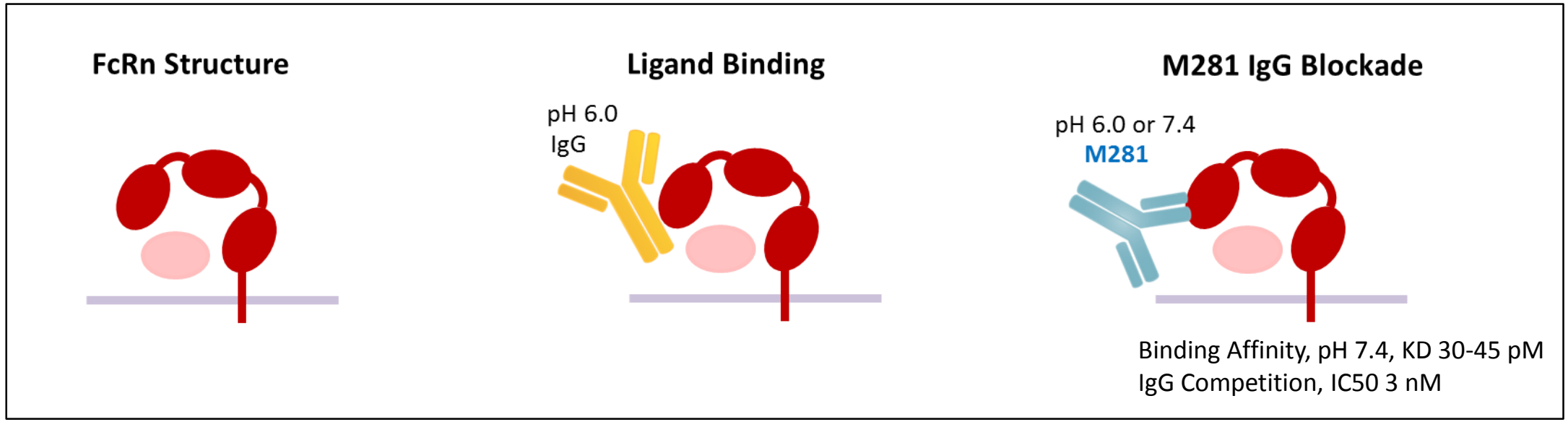
M281, An Investigational anti-FcRn Monoclonal Antibody for Maternal Antibody-induced Diseases of the Fetus and Newborn

Anti-FcRn Mechanism suggests that M281 will:

- Block pathogenic IgG transfer from mother to fetus
- Lower maternal pathogenic IgG titer

Hypothesis: Maternal administration of M281 starting in the early second trimester when IgG transfer begins may inhibit fetal exposure to pathogenic maternal antibodies.

M281 Target Engagement and Hypothesized Pharmacodynamics



FcRn is the sole IgG transporter responsible for the placental IgG transfer

M281 binds with high affinity to FcRn's IgG binding site which is expected to prevent placental IgG transport[1] including that of pathogenic alloantibodies

M281 is also expected to lower maternal pathogenic titers by inhibiting FcRn-mediated IgG recycling and lowering IgG halflife[2]

[1] Supported by results of nonhuman primate reproductive toxicology study
[2] Supported by results of phase I healthy volunteer study and nonclinical toxicology

Human Term Placenta Dual Perfused Single Cotyledon Model

Confirm M281 inhibition of placental IgG transfer and investigate the transport of M281 itself

Background

- An human ex vivo tissue-based model of placental function
- Demonstrates both active transfer mechanisms (IgG) and diffusion/exchange (nutrients, small molecules, gases)
- Demonstrates active transfer of IgG which requires FcRn-binding site.
- Insignificant transfer of IgM, IgA, IgE reflects lack of FcRn-binding site in these Ig isotypes and in vivo observations.

Test Articles

M281, Representative IgG (monoclonal IgG1-adalimumab)

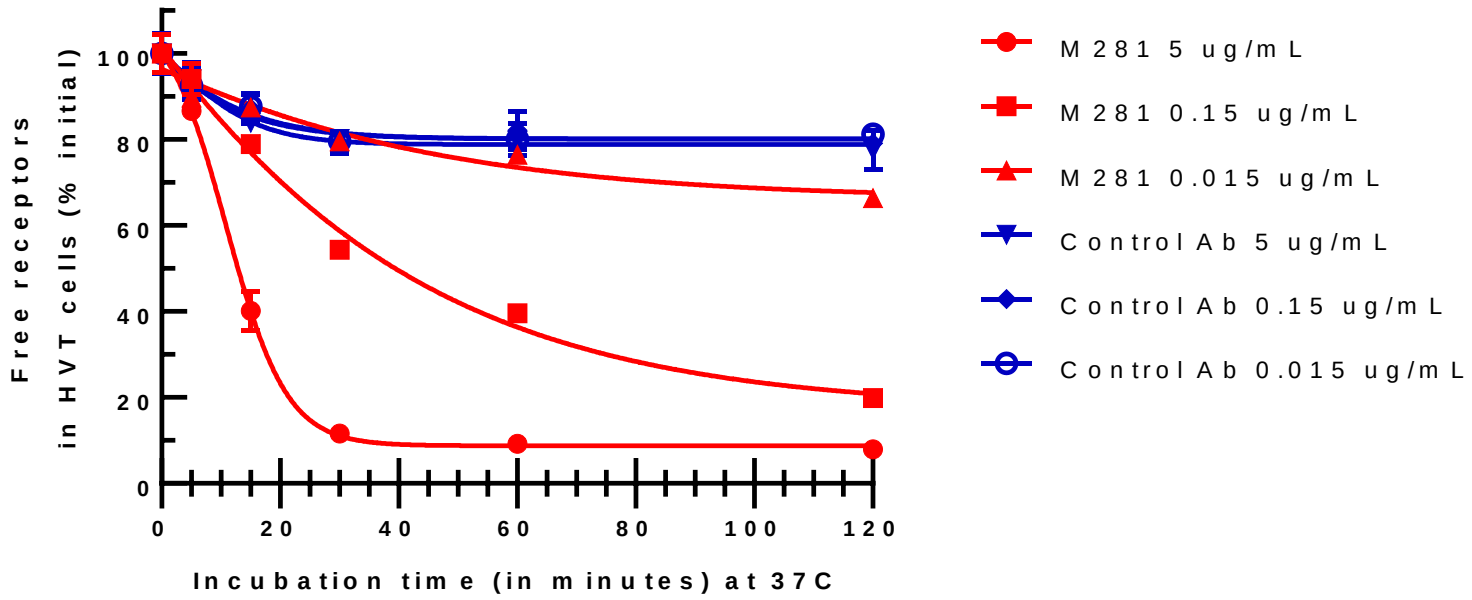
Method, Controls, Model Integrity Assessments

- Healthy human term placentas obtained under UTMB protocol #02-106 (38-40 wks GA)
- Cotyledon perfusion established rapidly, 12 mL/min maternal and 3 mL/min fetal flow rates
- 1 hour open circuit control period (monitor O_2, reservoir volume)
- 4 to 6 hour closed circuit experimental period (t=0 add test compounds and control antipyrine; monitor O_2, reservoir volume)
- Fetal Transfer Rate = 100 x (fetal conc of test agent/maternal conc of test agent) at end of the expt'l period

Concentration-Time Dependence of FcRn Saturation by M281 in Cultured Human Villuous Trophoblasts

FcRn Saturation (Receptor Occupancy) by M281

vs control antibody in primary human villous trophoblasts



Rapid M281 uptake and saturation of FcRn within 30 minutes of exposure at drug concentrations ~ 5 μg/mL

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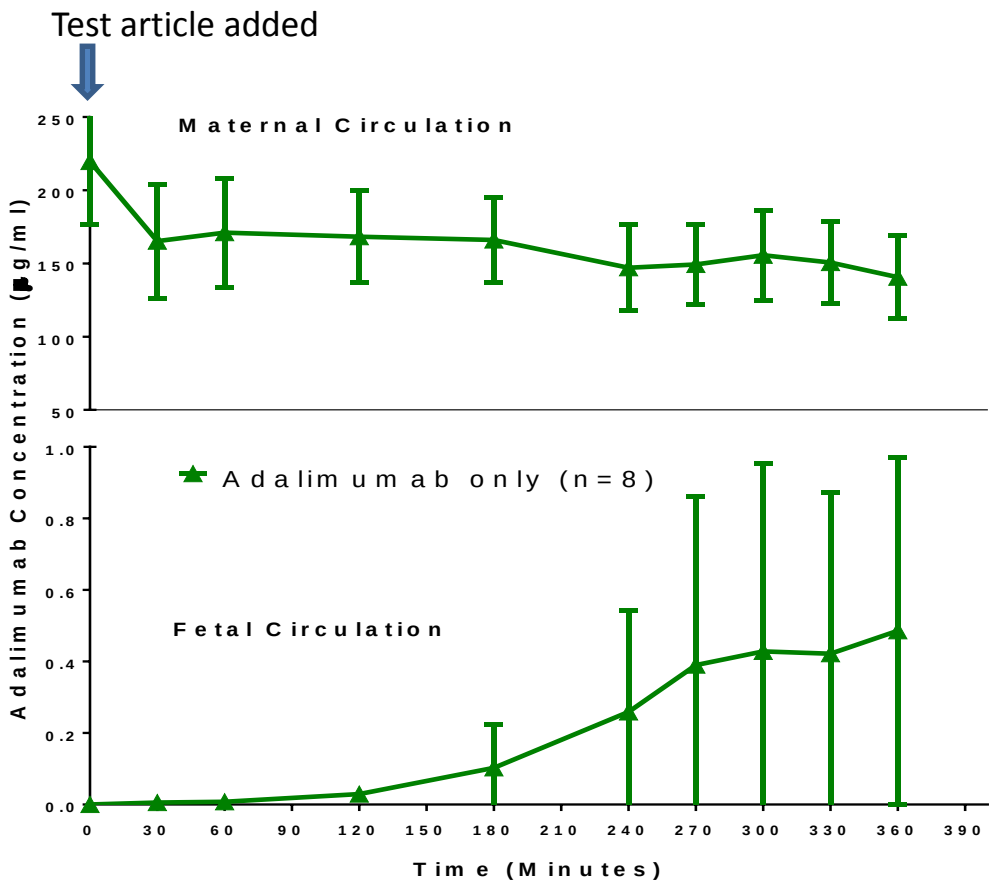
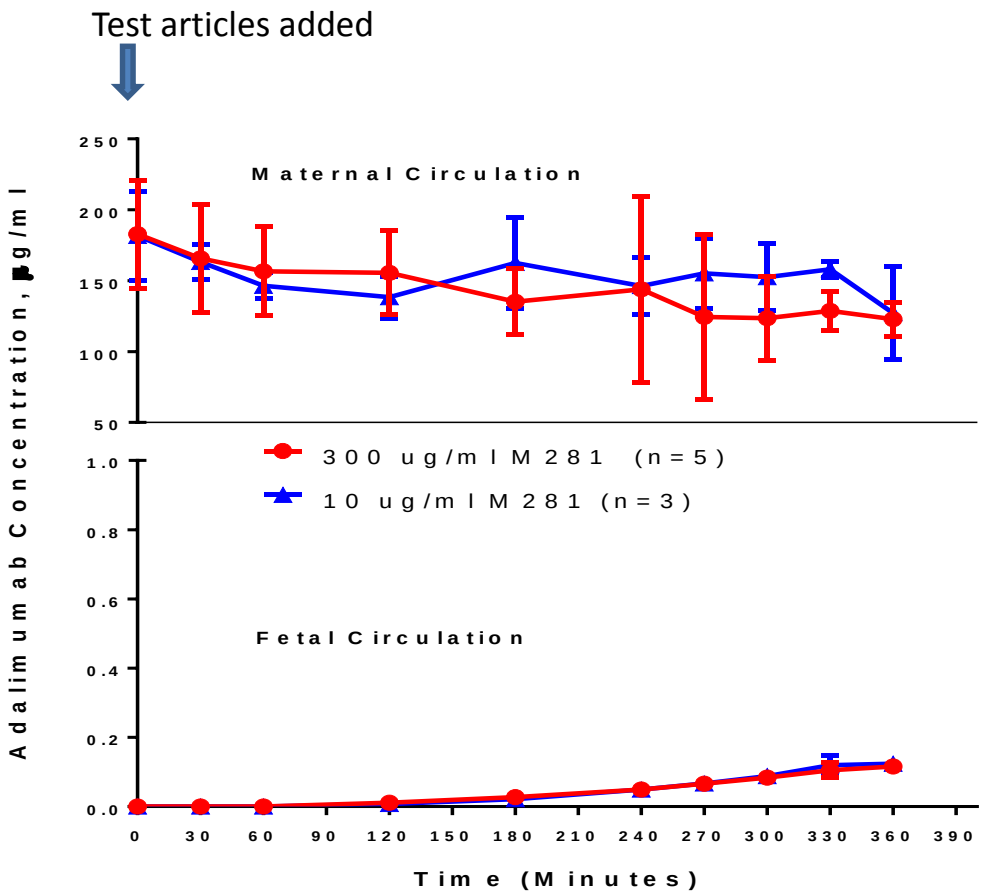
Maternal to Fetal Transfer of IgG and Inhibition by M281 in the Placental Perfusion Model

IgG (adalimumab) Transfer



IgG (adalimumab) Transfer + M281



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M281 Inhibition of IgG Placental Transfer

Effect of M281 on Placental Transfer of IgG (adalimumab)

Maternal circuit M281[a] (µg/mL)	Maternal circuit adalimumab[a] (µg/mL)	Adalimumab FTR Mean (SD) (%)	*P* value[b] (vs 0 µg/mL M281)	No. of studies (n)	Test period (hours)
0	270	0.23 (0.21)	NA	8	6
10	270	0.07 (0.01)	<0.001	3	6
300	270	0.06 (0.01)	<0.001	5	6

All placentas were obtained on delivery at 38–40 weeks' gestation.

Mean antipyrine FTR for these studies was 41.7 (2.7) for adalimumab alone and 43.8 (4.2) for all adalimumab + M281 studies.

FTR, fetal transfer rate; *NA*, not applicable; *SD*, standard deviation.

[a]Concentration of test articles at initiation of the test period; [b]*P* values were calculated using a linear mixed-effects model with random slope and intercept.

M281 inhibits placental IgG (adalimumab) transfer at concentrations consistent with saturation of FcRn by M281 at conc's ≥ 5 ug/mL

Placental Transfer of M281

Maternal to Fetal Transfer Rates of M281 in the Placental Perfusion Model

Study type	Maternal circuit adalimumab[a] (µg/mL)	Maternal circuit M281[a] (µg/mL)	M281 Fetal Transfer Rate Mean (SD) (%)	Test period (hours)	No. of studies (n)
M281 alone	—	300	0.005 (0.003)	4	3
M281 alone	—	3000	0.002 (0.001)	4[b]	6
M281 alone	—	3000	0.002 (0.001)	6	3
M281 alone	—	20,000	0.003 (0.001)	4	5
M281 + adalimumab	270	10	ND	6	3
M281 + adalimumab	270	300	0.006 (0.008)	6	5

Abbreviations: SD standard deviation; ND not determined due to below limit of quantitation. [a]Concentration of test articles at beginning of test period; [b]One experiment was terminated early at 3 hours. Mean antipyrine fetal transfer rates ranged from 40.6 – 41.9%

M281 placental transfer is extremely low

Summary

- M281 rapidly saturates FcRn in human villous trophoblasts
- M281 inhibits IgG transfer in the human term placental dual perfused single cotyledon model
- M281 transfer from maternal to fetal circulation is insignificant in this model

M281 has completed a first-in-human study and a full set of nonclinical chronic, reproductive and immunological toxicology studies. And has initiated a phase 2 study in myasthenia gravis.

Momenta is initiating a phase 2 study in patients with high risk of early onset antenatal HDFN

(Obstetric history of HDFN ≤24 wks; antigen positive fetus; above critical titers: ≥32 D or ≥4 K alloantibody)

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