Dose-Dependent Elimination of HPA-1a Platelets by Subcutaneous RLYB212, a Monoclonal Antibody to Prevent Fetal and Neonatal Alloimmune Thrombocytopenia

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- Patents for drugs or devices: **Antibody Detection Method and System Patent**
- Other: **Employee of German Red Cross**

Presentation Learning Objectives

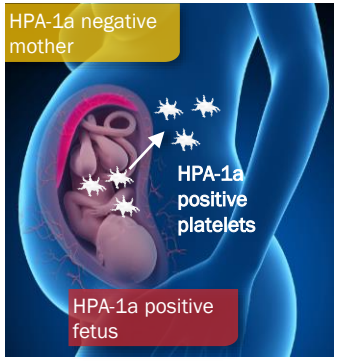
At the conclusion of this presentation, participants will be able to:

- **Describe** FNAIT and recognize that FNAIT is analogous to HDFN, with the distinction that it may occur during the first pregnancy
- **Summarize** data demonstrating that RLYB212 exhibits rapid and dose-dependent elimination of circulating antigen positive cells and **explain** why this is expected to prevent maternal alloimmunization
- **Evaluate** the potential use of RLYB212 as an effective prophylactic approach for pregnancies at risk of FNAIT

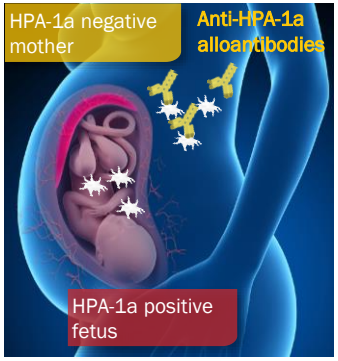
FNAIT, fetal and neonatal alloimmune thrombocytopenia; HDFN, hemolytic disease of the fetus and newborn; HPA, human platelet antigen; MOA, mechanism of action.

FNAIT Is the Platelet Counterpart to HDFN[1]

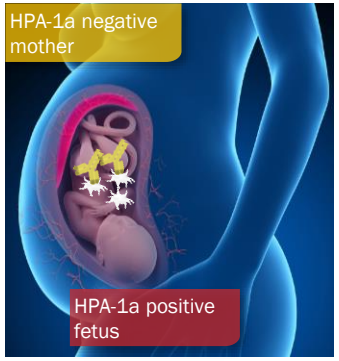
Both are caused by antigen mismatch between maternal and fetal cells[1]



HPA-1a positive platelets from the fetus enter maternal circulation



Immune system of the **mother triggered to produce anti-HPA-1a alloantibodies**



Maternal alloantibodies **cross the placenta** and **destroy HPA-1a positive fetal platelets**

Potential for uncontrolled bleeding in the fetus or newborn

Important Distinguishing Features

- Fetal thrombocytopenia may occur in the **first pregnancy**[2]
- Alloantibodies may be detected early in the **second trimester**[3]
- **No treatments exist to prevent HPA-1a alloimmunization**

FNAIT, fetal and neonatal alloimmune thrombocytopenia; HDFN, hemolytic disease of the fetus and newborn; HPA, human platelet antigen.

1. Bussel JB, et al. *Am J Obstet Gynecol*. 2021;225(2):120-127. 2. Jin JC, et al. *Am J Hematol*. 2019;94(8):213-215. 3. Williamson LM, et al. *Blood*. 1998;92(7):2280-2287.

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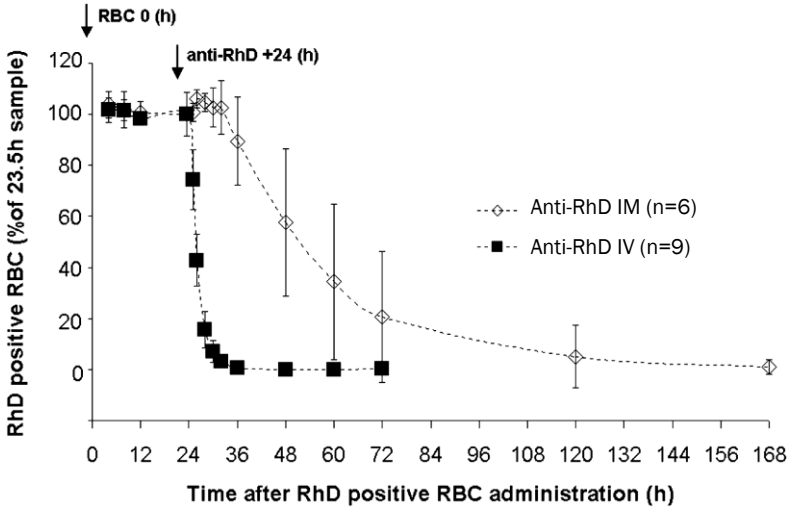
Precedent for Preventing Maternal Alloimmunization Is Well Established by IM and IV Anti-RhD Treatment

Kinetics of concentration of RhD-positive RBCs (mean ± SD) following IV or IM administration of 1500 IU (300 µg) anti-RhD in healthy RhD-negative males



Reprinted from *Blood*, 103, Miescher S, et al, A single recombinant anti-RhD IgG prevents RhD immunization: association of RhD-positive red blood cell clearance rate with polymorphisms in the FcγRIIA and FcγIIIA genes, 4028-4035, Copyright (2004), with permission from Elsevier

- More than 95% of RhD positive RBCs cleared within 8 hours of IV administration of anti-RhD[1]
- After IM administration of anti-RhD, ~10% of the RhD-positive RBCs cleared in 12 hours and 95% cleared in 4 days[1]
- Anti-RhD prophylaxis is highly effective when administered as an IM injection (up to 72 hours postpartum)[2,3]

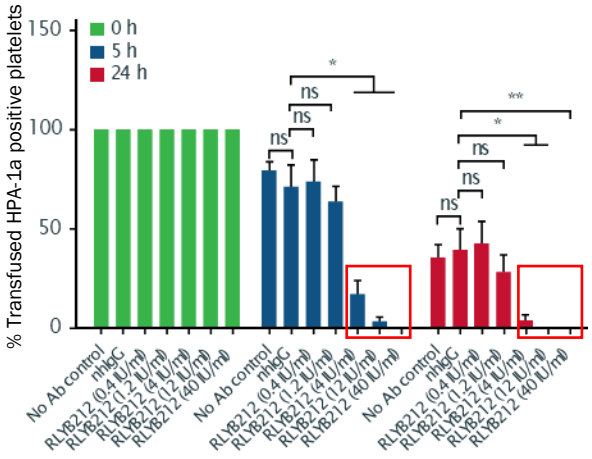
IM, intramuscular; IV, intravenous; RBC, red blood cell.

1. Miescher S, et al. *Blood*. 2004;103(11):4028-4035. 2. Crowther C, et al. Cochrane Database Syst Rev. 1997;(2):Cd000021. 3. RhoGAM. Prescribing information. Kedrion Biopharma. Inc.; March 2019.

In a Preclinical FNAIT Model, RLYB212 Eliminated Platelets at Doses That Prevent Alloimmunization

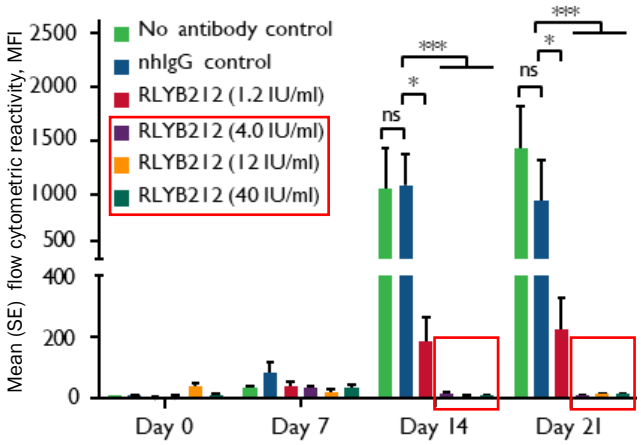
RLYB212 is a novel, recombinant human anti-HPA-1a monoclonal antibody developed to prevent HPA-1a alloimmunization and FNAIT[1]

Elimination of transfused HPA-1a positive platelets



- In a **murine model** of FNAIT, **concentrations of RLYB212 ≥4 IU/mL drove complete elimination** of transfused HPA-1a positive platelets **within 24 h** and **prevented alloimmunization**[1]
- ~4 IU/mL of RLYB212 binds to <10% of the HPA-1a antigen,[1] consistent with the clinical prophylactic treatment paradigm for anti-RhD[2]

Prevention of alloimmunization



Murine model of FNAIT + RLYB212 → Platelet clearance ✓ Prevention of alloimmunization ✓

Figures originally published in [1]. © the American Society of Hematology.
FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; IgG, immunoglobulin G; nhIgG; normal human immunoglobulin G.
1. Zhi H, et al. *Blood.* 2022;140(20):2146-2153. 2. Brinc D, Lazarus AH. *Hematology Am Soc Hematol Educ Program.*2009;2009(1):185–191.

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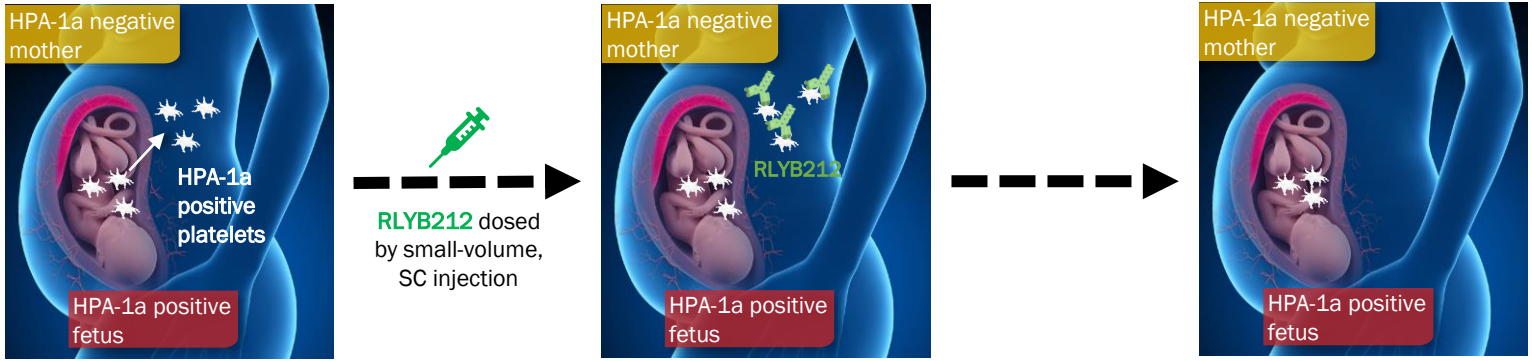
RLYB212, a Novel Candidate for Prevention of HPA-1a Alloimmunization and FNAIT



Prophylactic low-dose SC **RLYB212** is **intended** to drive **rapid elimination** of **fetal**-derived HPA-1a positive **platelets** in maternal circulation

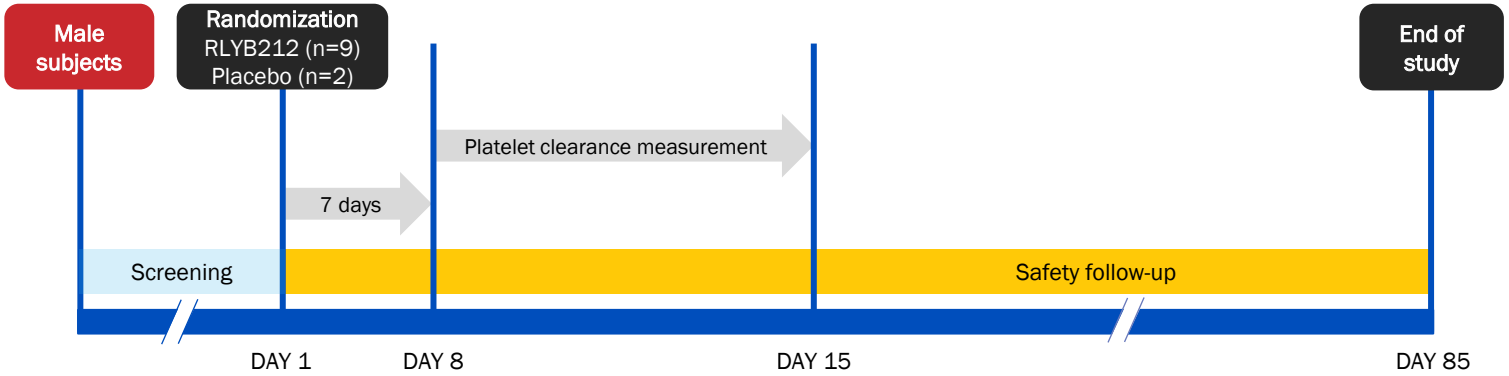
Potentially prevent maternal anti-HPA-1a alloantibody formation and the catastrophic consequences of FNAIT

Here we report results from a **clinical proof-of-concept study** investigating the **capacity of SC RLYB212** to **eliminate HPA-1a positive platelets** transfused to **HPA-1a negative subjects**

FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; SC, subcutaneous.

Proof-of-Concept Study Design and Objectives

Phase 1b, randomized, single-blind, placebo-controlled study



Platelet challenge mimics a worst-case 30 mL fetal-maternal hemorrhage, as precedented in anti-RhD clinical trials[1,2]

Eligibility criteria

- Males aged 18 to 65 years
- HPA-1a negative and HLA-A2 negative
- BMI <35 kg/m^2

Primary Objective

- Assess the ability of SC RLYB212 to rapidly eliminate transfused HPA-1a positive platelets (PoC defined as ≥90% mean reduction in platelet elimination half-life vs placebo)

Secondary Objectives

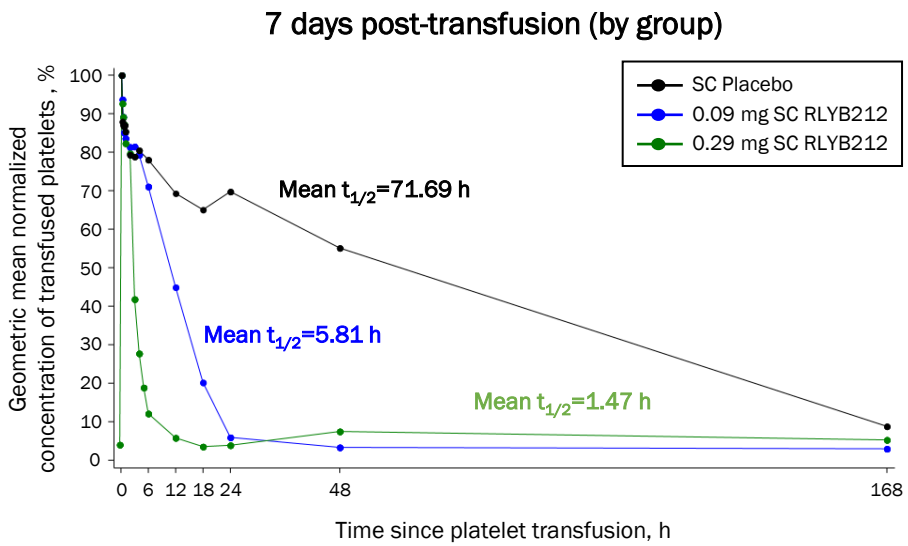
- Characterize the RLYB212 concentration-effect relationship
- Evaluate the safety of SC RLYB212

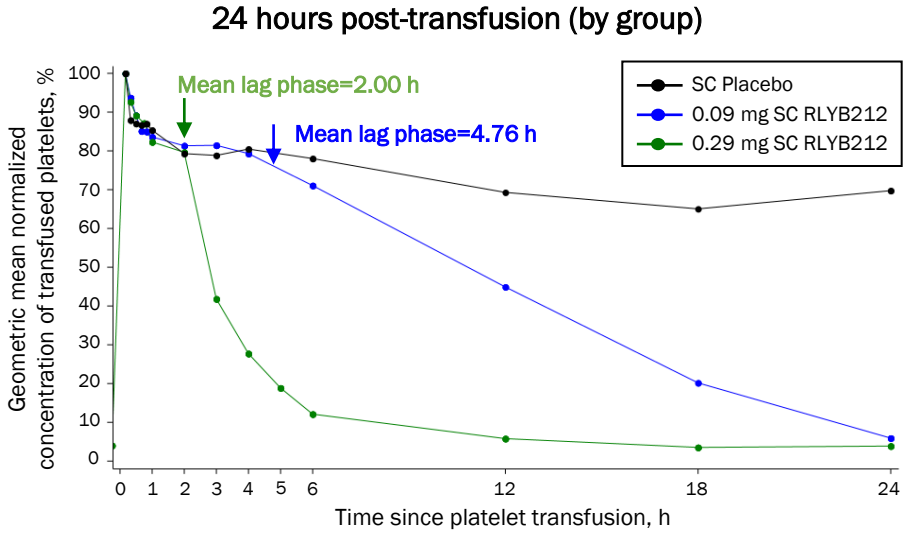
BMI, body mass index; HLA, human leukocyte antigen; HPA, human platelet; SC, subcutaneous.

1. Sebring ES, Polesky HF. *Transfusion*. 1990;30:344-357. 2. Visser GHA, et al. *Int J Gynaecol Obstet*. 2021;152(2):144-147.

Platelet Elimination Kinetics Were Dose Dependent and Biphasic

Time course of transfused platelet elimination

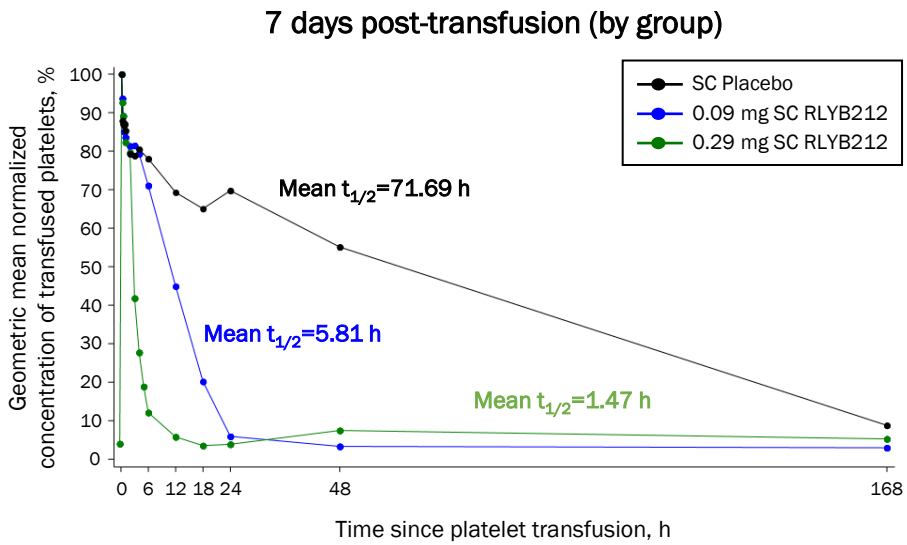


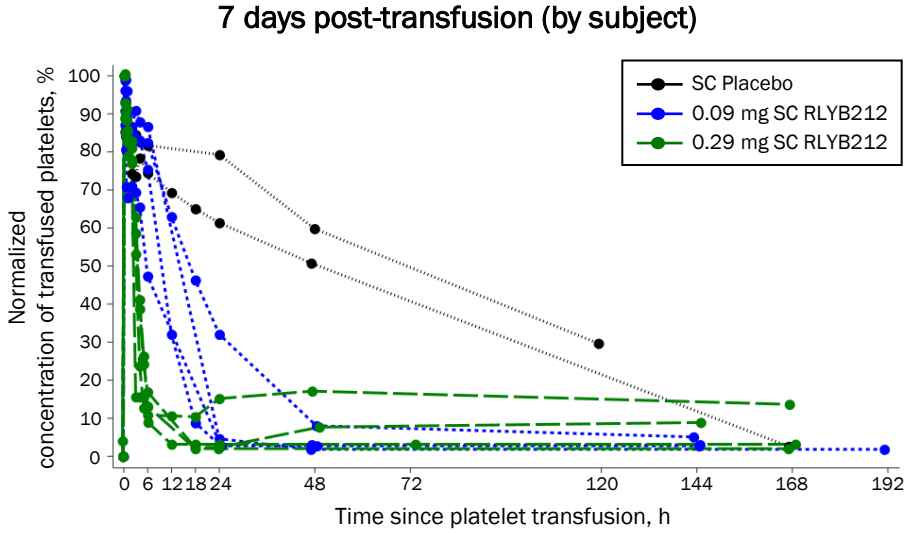


Platelet concentration was normalized at 100% for sample collected 10 minutes after platelet transfusion.
SC, subcutaneous; $t_{1/2}$, half-life.

Platelet Elimination Kinetics Were Dose Dependent and Biphasic

Time course of transfused platelet elimination

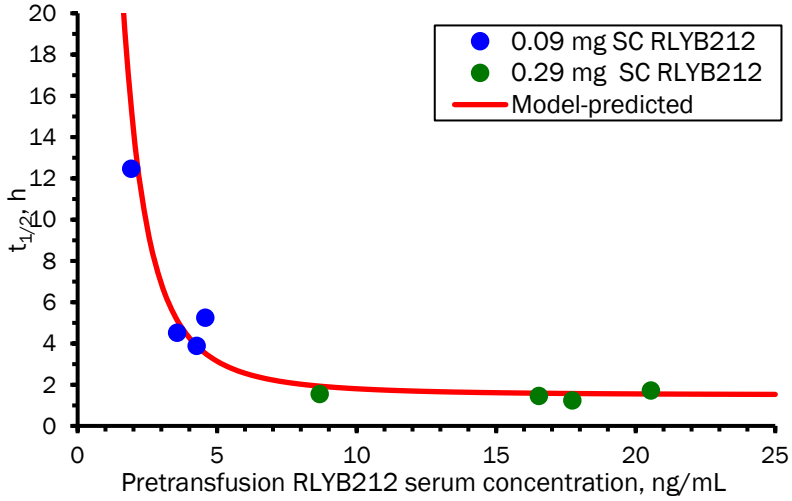




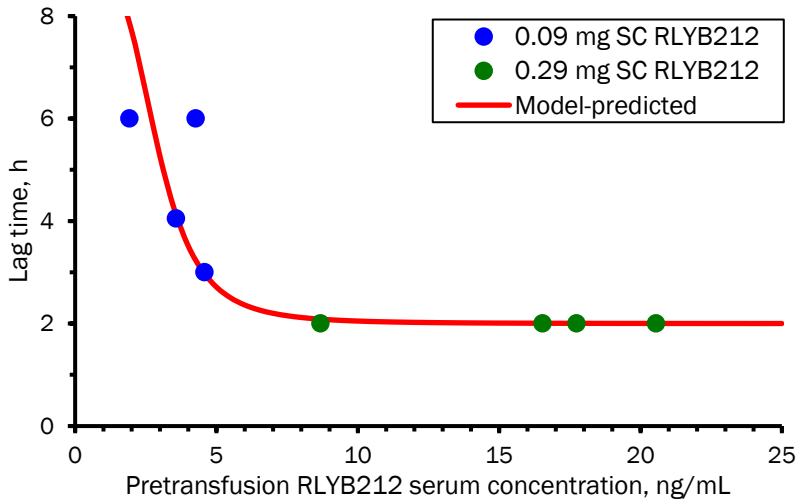
Platelet concentration was normalized at 100% for sample collected 10 minutes after platelet transfusion.
SC, subcutaneous; $t_{1/2}$, half-life.

Parameters of Platelet Elimination Kinetics Were SC RLYB212 Concentration Dependent

Platelet elimination half-life vs RLYB212 concentration before transfusion



Lag time vs RLYB212 concentration before transfusion



Timing the platelet challenge during the RLYB212 absorption phase and including 2 SC dose levels expanded the range of RLYB212 concentrations before transfusion, resulting in a clear picture of the concentration-effect relationship.

SC, subcutaneous; $t_{1/2}$, half-life.

SC RLYB212 Was Well Tolerated

No reports of:

- Related or possibly related AEs
- Severe or serious AEs

AE, adverse event; SC, subcutaneous.

Conclusions

- SC RLYB212 treatment **rapidly and completely eliminated HPA-1a positive platelets** in HPA-1a negative subjects in a concentration-dependent manner
- Both doses of SC **RLYB212 met the prespecified proof-of-concept criteria** of ≥90% mean reduction in platelet elimination half-life

- Platelet elimination kinetics after a single SC dose of RLYB212 were consistent with elimination kinetics of RhD positive erythrocytes after IM administration of anti-RhD agents[1]
- SC RLYB212 was well tolerated
- Collectively, our data support the potential use of SC RLYB212 as a prophylactic for FNAIT

FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; IM, intramuscular; SC, subcutaneous.

1. Miescher S, et al. *Blood*. 2004;103(11):4028-4035.

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- This study was funded by Rallybio IPA, LLC