



A Phase 1b PK/PD Study to Demonstrate Antigen Elimination with RLYB212, a Monoclonal Anti-HPA-1a Antibody for FNAIT Prevention

Christof Geisen¹ Erika Fleck¹ Stephan Martin Gastón Schäfer² Carmen Walter²
Susanne Braeuninger¹ Jens Søndergaard Jensen³ Douglas Sheridan⁴ Kiran Patki⁴
Róisín Armstrong⁴ Bjørn Skogen⁵ Frank Behrens^{2,6,7} Erhard Seifried¹ Jens Kjeldsen-Kragh^{5,8}
Mette Kjær^{9,10,*} Michaela Köhm^{2,6,7,*}

¹Institute of Transfusion Medicine and Immunohaematology, German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen GmbH, Frankfurt am Main, Germany

²Division Clinical Research, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Frankfurt am Main, Germany

³Aixial Danmark A/S, Herlev, Denmark

⁴Rallybio, New Haven, Connecticut, United States

⁵Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway

⁶Division of Rheumatology, University Hospital Goethe-University Frankfurt am Main, Germany

Address for correspondence Jens Kjeldsen-Kragh, MD, PhD, Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, 221 85 Lund, Sweden (e-mail: jkk@jkkmedical.com).

⁷Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD, Frankfurt am Main, Germany

⁸Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Lund, Sweden

⁹Faculty of Health Sciences, UiT—The Arctic University of Norway, Hammerfest, Norway

¹⁰Finnmark Hospital Trust, Hammerfest, Norway

Thromb Haemost

Abstract

Background Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare bleeding disorder of the fetus/newborn caused by development of maternal alloantibodies against fetal human platelet antigens (HPAs), predominantly HPA-1a. Currently there are no treatments available to prevent maternal alloimmunization to HPAs or FNAIT.

Methods This proof-of-concept study (EudraCT Number: 2021-005380-49) was designed to assess the ability of subcutaneous (SC) RLYB212, a monoclonal anti-HPA-1a antibody, to eliminate HPA-1a-positive platelets in an antigen challenge model of a 30 mL fetal–maternal hemorrhage. Subjects were randomized to receive a single SC dose of RLYB212 or placebo on day 1 in a single-blinded manner, followed by transfusion of 10×10^9 HPA-1a-positive platelets on day 8.

Results Four subjects received 0.09 mg SC RLYB212, five received 0.29 mg SC RLYB212, and two received placebo. RLYB212 achieved rapid elimination of HPA-1a-positive platelets in a concentration-dependent manner, with concentrations as low as 3.57 ng/mL meeting the prespecified proof-of-concept criterion of $\geq 90\%$ reduction in platelet elimination half-life versus placebo. Following HPA-1a-positive platelet transfusion, a rapid decline was observed in the concentration of RLYB212 over a period of 2

Keywords

- ▶ alloimmunization
- ▶ HPA-1a
- ▶ fetal and neonatal alloimmune thrombocytopenia
- ▶ prophylaxis
- ▶ RLYB212

* These authors share senior authorship.

received

June 14, 2024

accepted after revision

August 17, 2024

accepted manuscript online

August 21, 2024

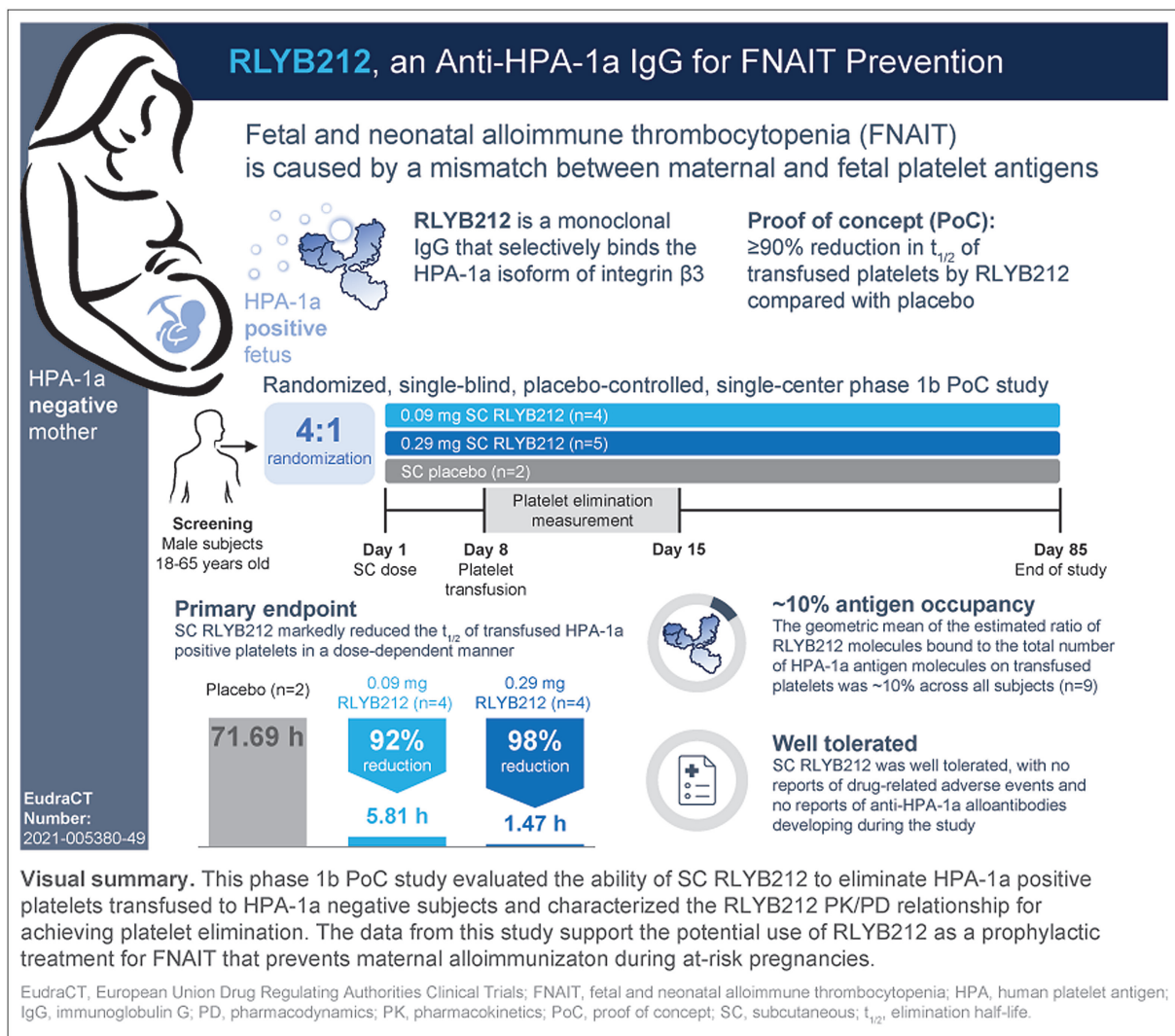
DOI <https://doi.org/10.1055/a-2398-9344>.

ISSN 0340-6245.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



to 24 hours, corresponding to the time needed for RLYB212 to bind to ~10% of HPA-1a on cell surfaces. RLYB212 was well tolerated with no reports of drug-related adverse events.

Conclusion The data from this study are consistent with preclinical efficacy data and support the potential use of RLYB212 as a prophylactic treatment for FNAIT that prevents maternal HPA-1a alloimmunization during at-risk pregnancies.

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare and potentially serious condition that develops during pregnancy and is characterized by destruction of fetal platelets by maternal alloantibodies.¹⁻³ It has been estimated that maternal alloantibodies to human platelet antigen (HPA) 1a are present in approximately 2 in 1,000 pregnancies,⁴ potentially leading to FNAIT, with clinical consequences spanning a continuum from no symptoms to a range of bleeding sequelae including petechiae, hematomas, and intracranial hemorrhage (ICH), which may lead to fetal or neonatal death or severe neurological deficits.^{3,5,6} Estimates of the frequency of maternal HPA-1a antibodies leading to

ICH in newborns have been reported to range from 26 in 1,000,000 in a recent prospective study in the Netherlands⁷ to as many as 11 in 100,000 in a retrospective literature review of a nonselected newborn population.⁸

Antibodies against HPA-1a account for approximately 75 to 80% of FNAIT cases.⁹⁻¹¹ Maternal-fetal HPA-1 mismatch arises from a single-nucleotide polymorphism that results in either a leucine (HPA-1a) or a proline (HPA-1b) at residue 33 of integrin $\beta 3$.¹² In pregnant women negative for HPA-1a (HPA-1bb homozygous), fetal HPA-1a-positive cells or cell fragments that enter the maternal circulation can trigger production of maternal anti-HPA-1a alloantibodies.^{1,2} Anti-HPA-1a alloantibodies can cross the placenta and destroy fetal platelets, resulting in fetal thrombocytopenia.^{1,2}

Pregnant women who are HPA-1a-negative and also carry the *HLA-DRB3*01:01* allele are 25 times more likely to become alloimmunized to HPA-1a than those who are *HLA-DRB3*01:01* negative.¹³

There are no current treatments to prevent HPA-1a alloimmunization in HPA-1a-negative mothers, nor is prenatal screening routinely done for FNAIT.^{3,14} The current recommended treatment strategy for FNAIT relies solely on off-label administration of intravenous (IV) immunoglobulin, with or without corticosteroids, in pregnant women already alloimmunized after a previous pregnancy affected by FNAIT.^{15–18} RLYB212 is a recombinant human monoclonal anti-HPA-1a immunoglobulin G (IgG) that selectively binds the HPA-1a isoform of integrin $\beta 3$ ^{19,20} and is being investigated as a prophylactic therapeutic to prevent maternal alloimmunization to HPA-1a. The parental antibody sequence for RLYB212 was developed from a single B cell from a woman who had become HPA-1a alloimmunized as a result of pregnancy and was originally developed as monoclonal antibody 26.4 at the University of Tromsø—the Arctic University of Norway.^{19,20} Although it is established that the passive transfer of IgGs can effectively suppress maternal alloimmunization to RhD antigen, the mechanism of antibody-mediated immune suppression is unknown.^{21–24} Therefore, a canonical IgG1 Fc isotype was selected for RLYB212 to ensure that it retained full effector function capabilities as would be expected for a native human IgG1, including binding complement component c1q, Fc γ receptors (Fc γ Rs), and the neonatal Fc receptor (FcRn).^{25,26} The ability of RLYB212 to accelerate elimination of HPA-1a-positive platelets and simultaneously prevent HPA-1a alloimmunization was previously demonstrated in a murine platelet alloimmunization model.^{20,27} This preclinical evidence supports the hypothesis that prophylactic treatment with low doses of RLYB212 in pregnant women at risk of HPA-1a alloimmunization can rapidly eliminate fetal HPA-1a-positive cells and cell fragments that enter the maternal circulation and that this corresponds to prevention of alloimmunization in a manner analogous to anti-RhD alloimmunization prevention in RhD-negative pregnant women.

Here we report results from a clinical proof-of-concept (PoC) study assessing the ability of subcutaneous (SC) RLYB212 to eliminate HPA-1a-positive platelets transfused to HPA-1a-negative subjects and characterizing the RLYB212 pharmacokinetic (PK)/pharmacodynamic (PD) relationship for achieving platelet elimination.

Methods

Trial Design and Oversight

This randomized, single-blind, placebo-controlled, single-center, phase 1b PoC study (EudraCT Number: 2021-005380-49) investigated the capacity of a single dose of RLYB212 to eliminate HPA-1a-positive platelets transfused to HPA-1a-negative male subjects. Following protocol approval by the Ethics Committee at Frankfurt University Hospital and the Paul-Ehrlich-Institut, Germany, written informed consent was obtained from all subjects. The study was initiated in April 2022 and conducted at the Fraunhofer Institute for

Translational Medicine and Pharmacology in Frankfurt am Main, Germany, in accordance with the ethical principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, and applicable laws and regulations.

Subjects

Male subjects aged 18 to 65 years with body mass index (BMI) <35 kg/m² were eligible. Subjects had to be negative for both HPA-1a (HPA-1bb genotype) and human leukocyte antigen A2 (HLA-A2) to ensure HLA discrepancy between donor and recipient platelets, which was used to monitor transfused platelet survival.^{28,29} Women were excluded from this study to avoid any potential risk of alloimmunization from transfused HPA-1a-positive platelets, which could potentially cause FNAIT in a subsequent pregnancy. Additional exclusion criteria used in this study are provided in the **►Supplementary Appendix** (available in the online version).

Study Intervention, Randomization, and Blinding

Subjects were randomized 4:1 to receive a single SC dose of RLYB212 (0.09 or 0.29 mg) or placebo on day 1 in a single-blinded manner, followed by transfusion of 10×10^9 platelets from an HPA-1ab/HLA-A2-positive donor on day 8 (**►Fig. 1**), simulating prophylactic administration of RLYB212 before a fetal–maternal hemorrhage (FMH). Details on the randomization and selection of RLYB212 doses used in this study are provided in the **►Supplementary Appendix** (available in the online version). The dose of transfused platelets was based on the established paradigm for testing RhD prophylaxis, where 30 mL of fetal blood represents a large FMH.^{30,31} Safety was evaluated over a 12-week period from the day of SC dosing.

Objectives and Endpoints

The primary objective of the study was to determine whether RLYB212 could markedly accelerate the elimination of HPA-1a-positive platelets transfused to HPA-1a-negative subjects. The primary endpoint was the terminal elimination half-life ($t_{1/2}$) of transfused platelets. PoC was defined as $\geq 90\%$ reduction in $t_{1/2}$ of transfused platelets by RLYB212, compared with placebo.

Secondary objectives of the study included the characterization of additional elimination kinetics of transfused HPA-1a-positive platelets and the PK and PD of RLYB212, as well as the evaluation of the safety and immunogenicity of RLYB212. Secondary endpoints evaluated in the study are provided in the **►Supplementary Appendix** (available in the online version).

Assessments and Procedures

Platelet Preparation

Transfused platelets were obtained by single-donor platelet apheresis from three different ABO-compatible repeat

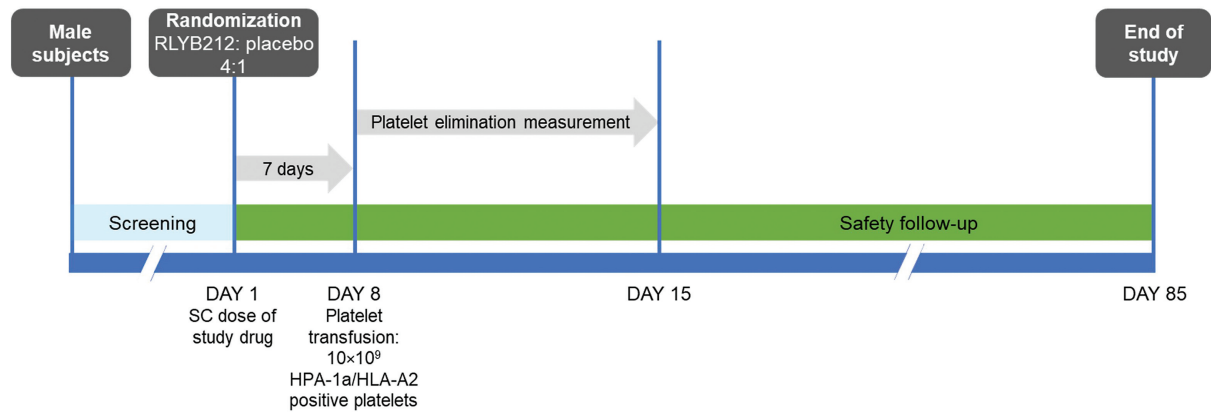


Fig. 1 Study design. HLA, human leukocyte antigen; HPA, human platelet antigen; SC, subcutaneous.

platelet donors from the local platelet donor registry and prepared by the German Red Cross Blood Donor Service Baden-Württemberg-Hessen in compliance with German Transfusion Law. The platelet donors were heterozygous for HPA-1a (HPA-1ab) and homozygous for HLA-A2 and did not have HLA antibodies. Platelet apheresis was completed 17 to 24 hours before transfusion.

RLYB212 PK Analysis

The PK analysis of RLYB212 was validated and performed by Charles River Laboratories (Senneville, Quebec, Canada) using anti-idiotypic monoclonal antibodies as capture and detection reagents on a ligand-binding assay platform. Serum samples for PK analysis of RLYB212 were obtained 1 hour before study drug administration; 1, 4, 8, 12, and 24 hours after study drug administration on day 1; 1 hour before platelet transfusion on day 8; and 30 minutes and 1, 2, 4, and 24 hours after platelet transfusion on day 8. Serum samples were also collected on days 4, 15, 29, 57, and 85. PK samples taken after platelet transfusion were used to inform the magnitude of antigen-mediated clearance of RLYB212.

HPA-1a-Positive Platelet Elimination Kinetics Analysis

A flow cytometry-based method, developed by Vetlesen et al in 2012,²⁹ was used to monitor the survival of transfused platelets by detecting the proportion of HLA-A2-positive platelets in recipient samples.^{28,29} Blood samples for this analysis were collected 15 minutes before transfusion; 10, 20, 30, and 45 minutes and 1, 2, 3, 4, 5, 6, 12, 18, and 24 hours after platelet transfusion; on day 10; and on day 15 if transfused platelets were detected on day 10. Before a protocol amendment, blood samples from some subjects were collected at 40 and 50 minutes after platelet transfusion instead of at 45 minutes, and no collection was performed at 5 hours after platelet transfusion.

RLYB212 Clearance and Platelet Elimination

The amount of RLYB212 consumed during platelet elimination was calculated as:

$$\text{RLYB212 consumed} = (\text{pretransfusion RLYB212 concentration} - \text{RLYB212 } C_{\min} \text{ within 24 h of transfusion}) \times \text{estimated blood volume},$$

where C_{\min} is minimum concentration and the Lemmens-Bernstein-Brodsky equation was used to estimate blood volume.³²

Antigen occupancy (i.e., the ratio of RLYB212 molecules consumed to the total number of HPA-1a-expressing glycoprotein IIb/IIIa receptors present on the platelets transfused) was calculated by assuming 40,000 copies of HPA-1a antigen per HPA-1ab heterozygous platelet.^{33,34}

Safety Assessments

Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0). Treatment-emergent AEs (TEAEs) were defined as AEs that occurred after study drug was first administered through the end of the 12-week follow-up period. The incidence of TEAEs was reported by system organ class and preferred term, and in terms of seriousness, severity, and study drug relatedness.

HPA-1a alloantibody detection was validated and performed by Versiti (Milwaukee, Wisconsin, United States) using a modified platelet antibody bead array assay described in the **►Supplementary Appendix** (available in the online version).³⁵

RLYB212 Immunogenicity Assessments

Antidrug antibody (ADA) detection was performed by Charles River using a tiered approach as described in the **►Supplementary Appendix** (available in the online version).

Statistical Analysis

This was a descriptive study, with no confirmatory hypothesis testing and no formal sample size calculation. Data were descriptively summarized and analyzed by treatment groups; thus, any comparisons between groups are of an informal and nonconfirmative nature. For primary endpoint analysis, four participants at each dose level of RLYB212 and two for placebo were deemed appropriate to determine the ability of RLYB212 to rapidly eliminate transfused HPA-1a-positive platelets and to characterize the RLYB212 concentration-effect relationship for platelet elimination.

Platelet elimination kinetics were analyzed for all subjects with an evaluable profile and for whom sufficient data

existed to characterize platelet elimination $t_{1/2}$ endpoints. Definition of an evaluable profile is described in the ► **Supplementary Appendix** (available in the online version). The Safety Review Team (SRT) reviewed the cumulative data to assess the evaluability of the subjects once all subjects had completed 14 days of follow-up after study drug administration. Up to two additional subjects could be enrolled in the study to replace any existing subjects deemed nonevaluable by the SRT.

The primary endpoint, $t_{1/2}$ of transfused platelets, was calculated using noncompartmental analysis (NCA). Each subjects' platelet elimination $t_{1/2}$ was derived as $\ln(2)$ divided by the slope of the terminal elimination curve (λ_z), where the slope is determined by linear regression of log concentration versus time curve.

PK analysis of RLYB212 was performed on subjects for whom at least one concentration above the lower limit of quantification was available. Serum PK parameters were calculated for RLYB212 using NCA. NCA was performed with Phoenix version 8.3 or higher (Certara, Princeton, New Jersey, United States) and third-party reporting tools, including Microsoft Office Word and Excel 2016 (Microsoft Corporation, Redmond, Washington, United States). Only PK samples taken before platelet transfusion were used in the NCA.

The safety population, which included all subjects who received platelets and/or study drug, was used when reporting safety evaluations, AEs, endogenous anti-HPA-1a alloantibodies, RLYB212 immunogenicity data, and demographics and baseline characteristics.

Results

Subject Demographics

Sixteen subjects were screened beginning in April 2022: 5 were excluded and 11 were randomized. Four subjects were

assigned to 0.09 mg SC RLYB212, 5 to 0.29 mg SC RLYB212, and 2 to SC placebo. For one subject who received 0.29 mg SC RLYB212, two samples collected for platelet analyses were hemolyzed and lipidemic at critical time points; therefore, the subject was deemed nonevaluable per protocol-specified criteria by the SRT and excluded from the assessment for platelet elimination kinetics but retained for all safety and PK analyses. All 11 subjects completed the study, which ended in March 2023 (► **Fig. 2**). All subjects were white men negative for HLA class I antibodies and *HLA-DRB3*01:01*, aged 28 to 55 years, with a BMI ranging from 20.8 to 27.8 kg/m² (► **Table 1**).

Platelet Elimination Kinetics

SC RLYB212 markedly accelerated the elimination of transfused HPA-1a-positive platelets in a dose-dependent manner (► **Fig. 3**), with a geometric mean (CV%) $t_{1/2}$ of 5.81 (61.3) hours in the 0.09 mg SC RLYB212 group and 1.47 (13.3) hours in the 0.29 mg SC RLYB212 group, compared with 71.69 (7.6) hours for placebo. Individual values for terminal platelet elimination $t_{1/2}$ are shown in ► **Table 1**. Both dose groups met the PoC criterion, with a reduction in the geometric mean $t_{1/2}$ of platelet terminal elimination of 92% in the 0.09 mg SC RLYB212 group and 98% in the 0.29 mg SC RLYB212 group, compared with placebo. Platelet elimination kinetics were biphasic for the RLYB212 treatment groups, with an initial lag phase of 2 to 6 hours (wherein the platelet elimination rate was similar to that observed in subjects given placebo), followed by a markedly accelerated terminal elimination phase (► **Fig. 3**). The duration of the initial lag phase, defined as the time from platelet transfusion to the beginning of the terminal elimination phase of the transfused platelets, was dose-dependent, with mean durations of 4.8 and 2.0 hours for the 0.09 and 0.29 mg SC RLYB212 groups, respectively. Individual platelet elimination curves in the 0.29 mg dose group showed less variability than

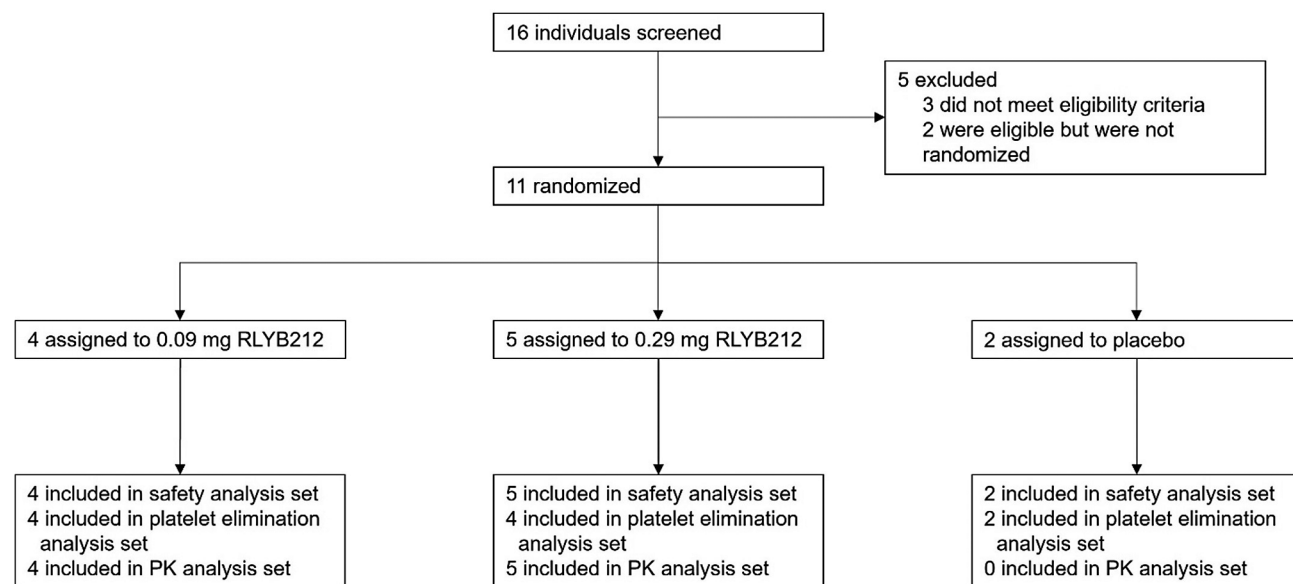


Fig. 2 Subject disposition. PK, pharmacokinetics.

Table 1 Summary of individual subject characteristics

Subject ^a	Treatment	Age, y	Weight, kg	BMI, kg/m ²	Blood group	Platelet elimination half-life, h
1	0.09 mg SC RLYB212	29	85.1	23.3	A+	4.51
2		46	94.0	25.8	O+	5.24
3		28	94.3	26.1	B+	3.87
4		33	82.0	27.1	A+	12.46
5	0.29 mg SC RLYB212	55	75.0	20.8	A+	1.71
6		33	91.0	27.8	O+	1.45
7		41	85.5	27.0	A+	NA ^b
8		46	93.0	27.2	O+	1.23
9		50	99.7	27.3	B+	1.54
10	Placebo	53	66.5	23.3	B+	67.96
11		50	99.7	27.3	B+	75.62

Abbreviations: BMI, body mass index; NA, not applicable; SC, subcutaneous.

^aAll subjects were white and none had human leukocyte antigen class I antibodies.

^bSubject 7 was excluded from the platelet elimination analysis due to lipemic and hemolyzed samples at critical time points.

those in the 0.09 mg dose group, as judged by eye. The apparent persistent residual platelet counts observed several days after the initial elimination phase in subjects receiving RLYB212 are likely an artifact of the flow cytometry methods used to monitor platelet survival, rather than an indicator of incomplete elimination or increase in the

number of transfused platelets (**-Supplementary Fig. S1**, available in the online version).

PK Profile of RLYB212

Both dose groups of SC RLYB212 displayed a slow absorption profile, typical of a subcutaneously administered monoclonal

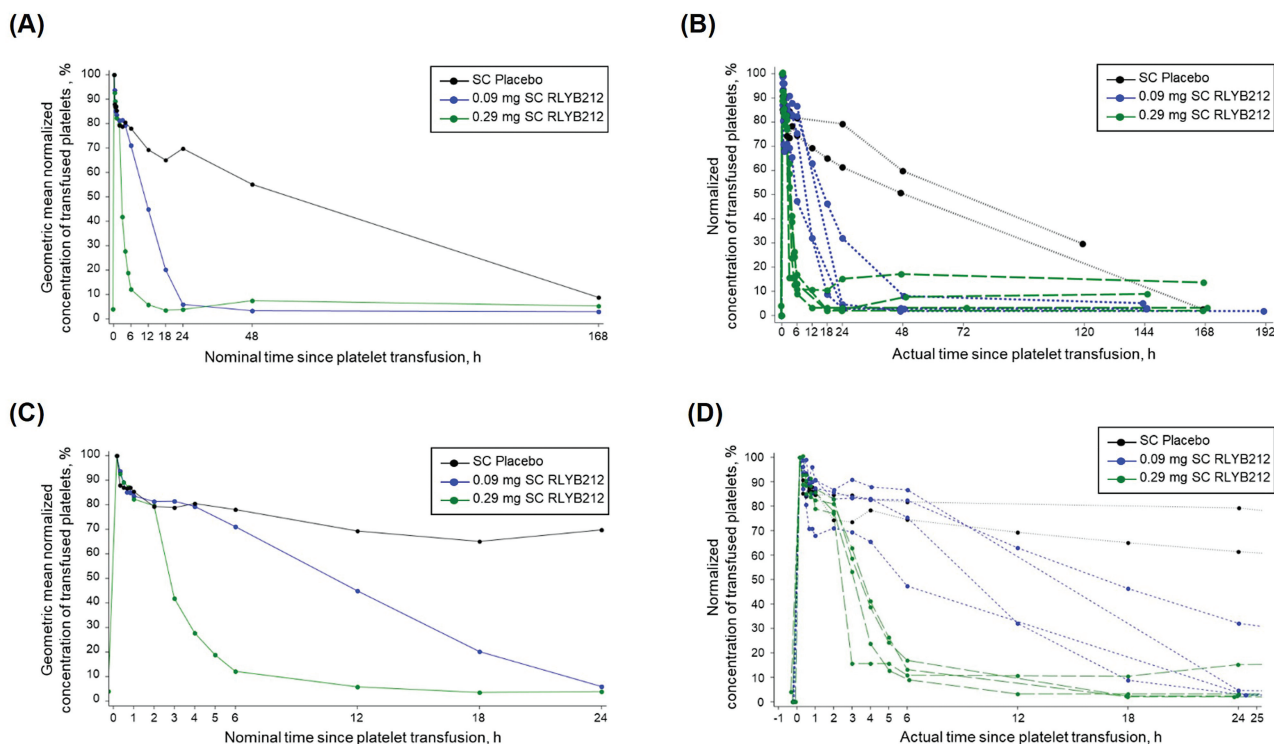


Fig. 3 Transfused platelets remaining in circulation versus time. Proportion of transfused platelets remaining through 7 days after transfusion by group (A) and by subject (B). Proportion of transfused platelets remaining through 24 hours after transfusion by group (C) and by subject (D). Platelet concentration was normalized at 100% for the sample collected 10 minutes after platelet transfusion. It is noted that the non-zero values for the platelets remaining at the tail end of the elimination curves reflect an assay artifact associated with the use of flow cytometry to detect transfused HLA-A2-positive platelets. SC, subcutaneous.

antibody.³⁶ The geometric mean time to maximum concentration (t_{\max}) across all subjects was 12.25 days (► **Table 2**). PK parameters of absorption before the platelet challenge on day 8 (area under the curve over the 7 days after dosing [AUC_{0-7}] and concentration at day 7 [C_7]) were dose-dependent and displayed greater intersubject variability than parameters of the terminal elimination phase (apparent clearance [CL/F] and $t_{1/2}$), which were similar across both the doses (► **Table 2**). The RLYB212 concentration 1 hour before platelet challenge ranged from 1.9 to 4.6 ng/mL in the 0.09 mg group and 8.7 to 20.6 ng/mL in the 0.29 mg group (► **Table 2**). The PK profile of RLYB212 was transiently impacted following HPA-1a-positive platelet transfusion, with a rapid decline in RLYB212 concentrations over the next 2 to 24 hours before resuming accumulation (► **Fig. 4**).

RLYB212 Concentration–Effect Relationship for Platelet Elimination

All parameters of platelet elimination kinetics, including the proportion of platelets remaining at 6, 12, 18, and 24 hours posttransfusion; area under the elimination curve over 24 hours; duration of the lag phase; and platelet elimination terminal $t_{1/2}$, were found to be dependent on the concentration of RLYB212 just before transfusion (► **Fig. 5** and ► **Supplementary Fig. S2**, available in the online version). Given both the small number of data points and steep slope in the dynamic part of the curve (at the 4 to 5 lowest

concentrations of RLYB212), we have estimated only a rough approximation of the concentration required to saturate the platelet elimination kinetics. In this platelet challenge model, the effect of RLYB212 concentration on platelet elimination kinetics appears to be dynamic at concentrations below ~5 ng/mL and reaches saturation of maximal effect at concentrations above ~5 ng/mL (► **Fig. 5** and ► **Supplementary Fig. S2**, available in the online version), with RLYB212 concentration as low as 3.57 ng/mL meeting PoC criteria of $\geq 90\%$ reduction in the $t_{1/2}$ of platelet elimination.

PK–PD Relationship of RLYB212 Clearance and Platelet Elimination

After the platelet challenge, the rapid decline in RLYB212 concentration approximated a first-order clearance rate coinciding with the lag phase and preceding accelerated platelet elimination (► **Fig. 6**). The estimated amount of RLYB212 consumed during platelet elimination ranged from 7.60 to 20.38 μg across nine subjects, with a geometric mean of 8.60 μg for the 0.09 mg group and 14.00 μg for the 0.29 mg group (► **Table 3**). In addition, the geometric mean of the ratio of the number of RLYB212 molecules consumed to the total number of HPA-1a antigens present on platelets expressed as a percentage was 8.7 and 14.2% for the 0.09 mg dose group and the 0.29 mg dose group, respectively, and 10.5% across all subjects (► **Table 3**).

Table 2 PK Parameters of a single SC dose of RLYB212 with an HPA-1a-positive platelet challenge 7 days later

		0.09 mg SC RLYB212	0.29 mg SC RLYB212
RLYB212 concentration up to 1 hour before platelet transfusion, ng/mL	<i>n</i>	4	5
	Geometric mean (CV%)	3.4 (33.1)	14.2 (33.0)
	Min;max	1.9;4.6	8.7;20.6
t_{\max} , h	<i>n</i>	4	5
	Geometric mean (CV%)	285.6 (67.2)	300.7 (59.0)
	Min;max	168.1;647.3	168.5;672.7
C_7 , ng/mL	<i>n</i>	4	5
	Geometric mean (CV%)	3.4 (33.4)	14.2 (33.1)
	Min;max	1.9;4.6	8.6;20.5
AUC_{0-7} , h*ng/mL	<i>n</i>	4	5
	Geometric mean (CV%)	344 (36)	1538 (38)
	Min;max	181.0;465.3	731.6;2,255.4
CL/F, mL/h	<i>n</i>	2 ^a	4
	Geometric mean (CV%)	16.5 (25.0)	15.4 (28.1)
	Min;max	13.8;19.8	11.6;20.0
$t_{1/2}$, h	<i>n</i>	2 ^a	4
	Geometric mean (CV%)	749.1 (39.5)	596.0 (17.8)
	Min;max	562.4;997.8	467.0;700.1

Abbreviations: AUC_{0-7} , area under the curve over the 7 days after dosing; C_7 , concentration at day 7; CL/F, apparent clearance; PK, pharmacokinetic; SC, subcutaneous; $t_{1/2}$, half-life; t_{\max} , time to when maximum concentration is reached.

^aThe first two individuals did not have adequate sampling at time points that would allow reasonable extrapolation of terminal elimination kinetic parameters.

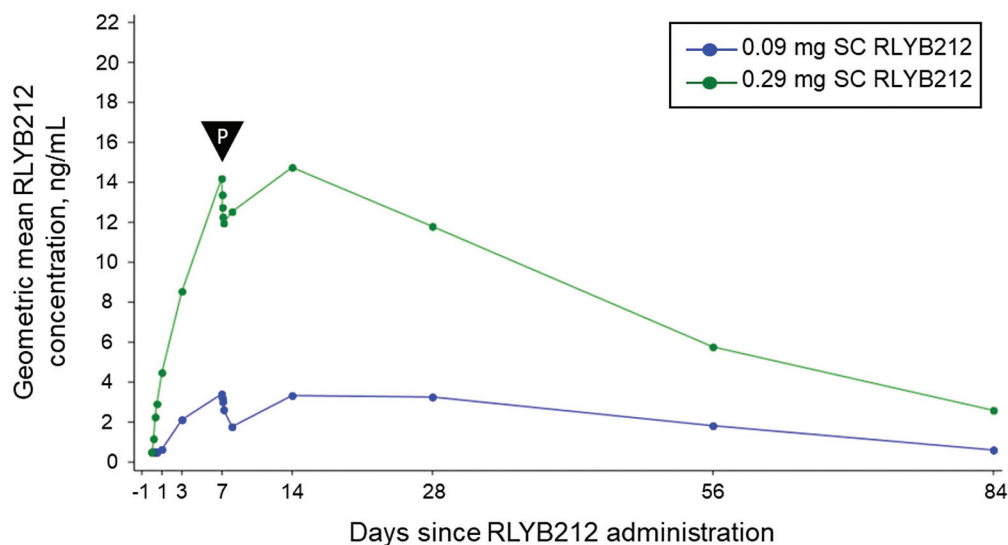


Fig. 4 PK profile of a single SC dose of RLYB212 with an HPA-1a-positive platelet challenge 7 days later. Only PK samples taken before the platelet transfusion were used in the noncompartmental analysis. P denotes the platelet challenge 7 days after the SC RLYB212 administration. HPA, human platelet antigen; PK, pharmacokinetic; SC, subcutaneous.

Safety

No clinically meaningful findings related to vital signs, physical examinations, electrocardiogram, and laboratory assessments were observed during the study. TEAEs reported were comparable between subjects who received RLYB212 and those who received placebo (**–Supplementary Table S1**, available in the online version). No serious or severe TEAEs were observed, and none of the TEAEs reported were related to the study drug or led to withdrawal from the study. No participants developed anti-HPA-1a alloantibodies.

Immunogenicity of RLYB212

For one subject in the 0.29 mg SC RLYB212 group, the ADA assay was positive for the pre-dose sample, and low-titer ADA was detected in samples from days 15, 29, and 85; however, the ADA assay for the sample on day 57 was negative, and the RLYB212 PK values in this subject did not notably differ from the PK values of other subjects receiving 0.29 mg SC RLYB212. Given the positive pre-dose sample and low-titer intermittent ADA samples post-dose, it is unlikely that the positive ADA values are indicative of an immune response elicited by RLYB212.

Discussion

A single, SC dose of either 0.09 mg or 0.29 mg RLYB212 rapidly eliminated HPA-1a-positive platelets in HPA-1a-negative subjects in a concentration-dependent manner, meeting the PoC criterion of $\geq 90\%$ reduction in $t_{1/2}$ of platelet elimination for both dose groups. The capacity of RLYB212 to accelerate the elimination of a large bolus challenge of HPA-1a-positive platelets in this study is proposed as a surrogate for prevention of maternal alloimmunization and consequently FNAIT based on nonclinical and clinical evidence. First, the ability of RLYB212 to accelerate the elimination of HPA-1a-positive platelets was previously demonstrated to correlate with the

prevention of alloimmunization in a mouse model of FNAIT.^{20,27} Second, in RhD-negative women pregnant with an RhD-positive fetus, the successful prevention of alloimmunization with anti-RhD IgG therapeutics correlates with the opsonization and rapid elimination of RhD-positive erythrocytes after a FMH.^{22,23,37,38}

The PK profile of both doses of RLYB212 was generally consistent with that of subcutaneously administered IgG.³⁶ Both doses of RLYB212 had a slow dose-dependent absorption phase followed by a prolonged elimination phase, which is favorable for minimizing fluctuations in peak-to-trough concentrations in a prophylactic dose regimen with extended dosing intervals. Because the intersubject PK variability of RLYB212 was greater during the absorption phase after a SC injection, administering the platelet challenge 7 days after a single dose provided a broad range of RLYB212 concentrations at the time of the platelet transfusion. Thus, with just 2 dose levels (0.09 and 0.29 mg), it was possible to assess the concentration–effect relationship over a 10-fold range with a minimum number of subjects.

Visual inspection of the individual platelet elimination curves in the 0.29 mg dose group showed less variability compared with those in the 0.09 mg dose group, consistent with a saturation of RLYB212 PD effects at the higher dose. Platelet elimination kinetics were biphasic, with an initial lag phase followed by an accelerated terminal elimination phase. The initial lag phase preceding platelet elimination corresponded with a transient depletion of RLYB212 as it accumulated on the HPA-1a-positive platelets, indicating that there is a minimum threshold of antigen opsonization required to trigger accelerated terminal platelet elimination. It was estimated that a threshold of approximately 10% antigen occupancy is both necessary and sufficient to drive platelet elimination. The estimate of a 10% antigen-binding threshold to achieve rapid platelet elimination with RLYB212 is consistent with both the clinical prophylactic treatment paradigm

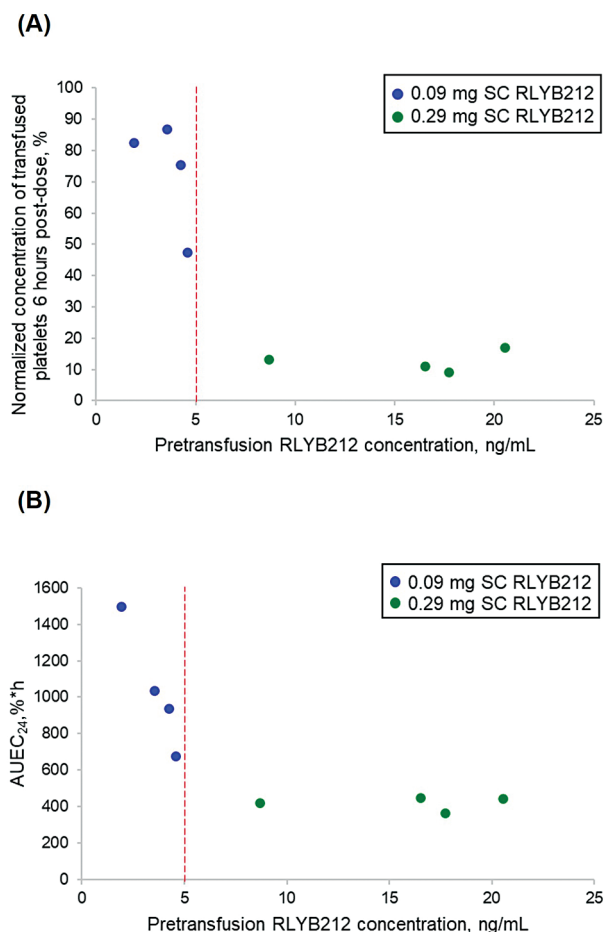


Fig. 5 Pharmacodynamic parameters of HPA-1a-positive platelet elimination as a function of RLYB212 concentration. Percentage of transfused HPA-1a-positive platelets remaining in circulation at 6 hours after the transfusion (A) and AUEC₂₄ for HPA-1a-positive platelets for individual subjects administered 0.09 mg SC RLYB212 or 0.29 mg SC RLYB212 (B) plotted against RLYB212 concentration before platelet transfusion. AUEC₂₄, area under the elimination curve over 24 hours; HPA, human platelet antigen; SC, subcutaneous.

for anti-RhD and previously reported preclinical efficacy studies with RLYB212.^{20,39,40}

Previously, we reported the results of a clinical PoC study demonstrating the ability of a polyclonal anti-HPA-1a antibody preparation (RLYB211) to drive rapid and complete elimination of transfused HPA-1a-positive platelets (with a $t_{1/2}$ of platelet elimination ranging from 0.28 to 2.60 hours) after IV administration.²⁸ Both the slower rate of platelet elimination and the biphasic pattern of platelet elimination kinetics for SC RLYB212 compared with IV RLYB211²⁸ could potentially be attributed to any number of factors, including a higher density of opsonization with the polyclonal IgG (i.e., multiple antibodies binding to the same antigen) or more efficient engagement of macrophage with a mixture of polyclonal Fc isotypes. It is noteworthy that differences in both the rate of elimination and the duration of the lag phase have also been demonstrated when comparing IV and intramuscular administration of anti-RhD therapeutics.³⁷ Despite the differences in elimination rate and duration of lag phase, both IV and

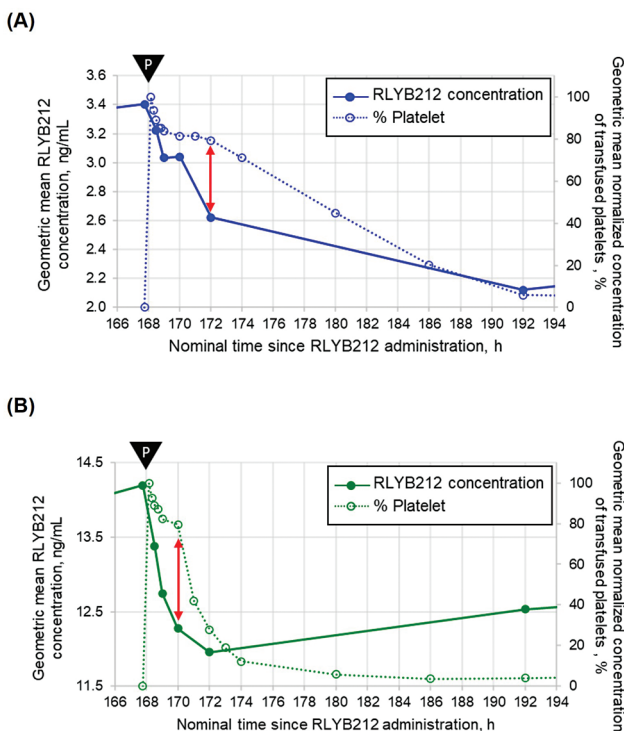


Fig. 6 Duration of HPA-1a-positive platelet elimination lag phase and RLYB212 depletion. HPA-1a platelet concentration and mean RLYB212 concentration in the (A) 0.09 mg group and (B) 0.29 mg group over time. P denotes the platelet challenge 7 days after the SC RLYB212 administration. The upper portion of the red double arrow points to the end of the platelet lag phase, and the lower portion highlights that the majority of RLYB212 is not in circulation at the end of this phase. Thus, this indicates a threshold requirement for RLYB212 opsonization to initiate platelet elimination. Graphs display an overlay of data from ► Figs. 3A and 4 zoomed in on the time 2 hours before to 26 hours after platelet transfusion. HPA, human platelet antigen; PK, pharmacokinetics; SC, subcutaneous.

intramuscular doses of anti-RhD are highly effective in preventing alloimmunization.^{22,38,41}

All parameters of platelet elimination kinetics displayed a similar concentration–effect relationship, wherein they were dynamic at concentrations below ~ 5 ng/mL and saturated at higher concentrations. The minimum required concentration to achieve maximal effect is governed by the magnitude of the antigen challenge given in this study, which is comparable in size to a rare and potentially catastrophic FMH of 30 mL.³¹ Thus, serum concentrations of RLYB212 greater than ~ 5 ng/mL should be sufficient to clear any volume of FMH that might occur, including at parturition. However, although RLYB212 concentrations below 5 ng/mL did not reach the maximal achievable effect in this paradigm, concentrations as low as 3.57 ng/mL were still sufficient to meet the PoC criteria of $\geq 90\%$ reduction in $t_{1/2}$ of platelet elimination.

A single SC-administered dose of RLYB212 was well tolerated. No serious TEAEs, severe TEAEs, or TEAEs considered related or possibly related to administration of RLYB212 or placebo were reported. Given the study design, which involved the transfusion of incompatible platelets, monitoring for an alloimmune response occurred throughout the trial, but no anti-HPA-1a antibodies were ever detected.

Table 3 Estimated ratio of RLYB212 to antigen required to drive elimination of HPA-1a-positive platelets

Subject	Estimated RLYB212 volume of distribution, L	Estimated RLYB212 “consumed,” µg	Estimated ratio of RLYB212 molecules consumed to number of copies of HPA-1a antigen present, % ^a
1	5.785	8.16	8.2
2	6.080	7.60	7.7
3	6.058	8.84	8.9
4	5.173	9.93 ^b	10.0 ^b
Geometric mean of 0.09 mg SC RLYB212 group		8.60	8.7
5	5.402	19.18	19.4
6	5.669	12.70	12.8
7	5.404	12.86	13.0
8	5.858	20.38	20.6
9	6.262	8.45	8.5
Geometric mean of 0.29 mg SC RLYB212 group		14.00	14.2
Geometric mean of all subjects		10.50	10.5

Abbreviations: C_{min}, minimum concentration; HPA, human platelet antigen; LLOQ, lower limit of quantification; PK, pharmacokinetics.

^aThe number of HPA-1a antigens was assumed to be 40,000 copies per platelet.

^bThe posttransfusion C_{min} for subject 4 fell below the PK assay LLOQ (1 ng/mL). For the purposes of this calculation, a RLYB212 concentration of 0 ng/mL was assumed for the posttransfusion C_{min} for subject 4, representing the maximum amount of RLYB212 that could have been consumed during the elimination of HPA-1a-positive platelets.

Limitations of this study derive primarily from the fact that the antigen challenge model is not fully representative of the unique physiological aspects of pregnant women at risk of FNAIT. In addition to the dynamic variables of gestation that might impact the PK of RLYB212 (e.g., changes in blood volume and vascularization), HPA-1a antigen is also expressed on fetal-derived endothelial cells, including syncytiotrophoblasts in the placenta,^{42,43} which may contribute to antigen-mediated clearance of RLYB212. A future phase 2 study is planned to evaluate the PK and safety of RLYB212 in pregnant HPA-1a-negative women bearing an HPA-1a-positive fetus, to assess these questions before a planned phase 3 safety and efficacy study.

In conclusion, these results demonstrate the relationship between RLYB212 concentration and the kinetics of opsonization and elimination of HPA-1a-positive platelets. Although FNAIT is defined by maternal alloantibodies directed against fetal platelet antigens, it is unknown whether placental fetal antigen present in placental tissue may also contribute to maternal alloimmunization. Given that RLYB212 is equally capable of binding HPA-1a antigen on platelets and endothelial cells,^{19,20} this concentration–effect relationship should apply to fetal-derived antigen-positive cells or cell fragments circulating in maternal vasculature generally, regardless of the source. Thus, these results enable a reasonable prediction of the range of target concentrations required for RLYB212 to effect rapid and complete elimination of circulating fetal antigen in the maternal vasculature, which will help inform dose selection for a future registration study. This lays the foundation for continued clinical development of SC RLYB212 as a potential treatment to

prevent maternal HPA-1a alloimmunization, thereby eliminating the risk of FNAIT.

What is known about this topic?

- Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare and potentially serious condition that develops during pregnancy and is characterized by destruction of fetal platelets by maternal alloantibodies.
- Alloantibodies against human platelet antigen (HPA) 1a account for approximately 75 to 80% of FNAIT cases; no treatments to prevent HPA-1a alloimmunization in HPA-1a-negative mothers are currently available.
- RLYB212 is a recombinant human monoclonal anti-HPA-1a immunoglobulin G (IgG) that selectively binds the HPA-1a isoform of integrin β3 and is being investigated as a prophylactic therapeutic to prevent maternal alloimmunization to HPA-1a.

What does this paper add?

- This proof-of-concept (PoC) study established the effect of RLYB212 on the elimination of HPA-1a-positive platelets in an antigen challenge model of a 30 mL hemorrhage in HPA-1a-negative subjects.
- RLYB212 concentrations as low as 3.57 ng/mL met the PoC criterion of ≥90% reduction in the half-life of platelet elimination versus placebo.
- An estimated antigen occupancy of approximately 10% was necessary and sufficient to accelerate platelet elimination.

Data Availability Statement

Proposals for access to deidentified individual subject data should be sent to jkk@jkkmedical.com.

Authors' Contribution

D.S., K.P., and R.A. conceptualized the study and wrote the first draft of the study protocol. The protocol was finalized by Rallybio after being reviewed by C.G., S.M.G.S., C.W., J.S.J., F.B., J.K.-K., M.Kj., and M.Ko., and before submission to the Ethics Committee at Frankfurt University Hospital and the Paul-Ehrlich-Institut. C.G., E.F., J.K.-K., and M.Kj. validated the method for determining transfused platelets; E.F. performed the flow cytometry analyses; and C.G., E.F., J.K.-K., and M.Kj. approved all the flow cytometry plots before entry into the study database. M.Ko. was the principal investigator of the study. C.G. and E.F. performed the selection of platelet concentrates. C.G., E.F., S.M.G.S., C.W., S.B., F.B., and M.Ko. recruited and/or screened study participants. S.M.G.S., F.B., and M.Ko. performed administration of study drug, administration of platelets, and surveillance of study participants. Data were interpreted by C.G., S.M.G.S., C.W., J.S.J., D.S., K.P., R.A., B.S., F.B., E.S., J.K.-K., M.Kj., and M.Ko. Statistical analyses were performed by J.S.J. The manuscript was prepared by C.G., J.S.J., D.S., K.P., R.A., and J.K.-K., with medical writing support provided by Chameleon Communications International, Ltd (funded by Rallybio IPA, LLC). E.F., S.M.G.S., C.W., S.B., B.S., F.B., E.S., M.Kj., and M.Ko. reviewed and revised the manuscript. All authors approved the final manuscript.

Conflict of Interest

B.S., J.K.-K., and M.Kj. are stockholders of Prophylix AS, a Norwegian biotech company, that obtained the license of the monoclonal antibody 26.4 from UiT—the Arctic University of Norway, Tromsø, Norway, which was later purchased by Rallybio. J.K.-K. consults for Rallybio and Janssen Pharmaceuticals, and receives honoraria from these two companies. M.Kj. consults for Rallybio and receives support for attending meetings and/or travel and honoraria from Rallybio. F.B. receives grants or contracts from Janssen Pharmaceuticals, Chugai Pharmaceuticals, and Roche; consults for Janssen Pharmaceuticals, Cilag, Novartis, Amgen, Lilly, UCB, Pfizer, AbbVie, Acelyrin, GSK, Chugai Pharmaceuticals, and Roche; receives honoraria from Janssen Pharmaceuticals, Cilag, Novartis, Amgen, Lilly, UCB, Pfizer, AbbVie, Acelyrin, Sandoz, AstraZeneca, and Chugai Pharmaceuticals; and receives support for attending meetings and/or travel from AbbVie and UCB. R.A., D.S., and K.P. are employees of Rallybio and are stockholders of Rallybio. German Red Cross Blood Donor Service Baden-Württemberg-Hessen gGmbH has a contract with Rallybio for the presented study. The remaining authors declare no competing financial interests.

Acknowledgment

We thank the subjects, study coordinators, and support staff who contributed to this study. This study was funded

by Rallybio IPA, LLC. Medical writing assistance was provided by Iyshwarya Balasubramanian, PhD (Chameleon Communications International, Ltd) and funded by Rallybio IPA, LLC.

References

- 1 Brojer E, Husebekk A, Dębska M, et al. Fetal/neonatal alloimmune thrombocytopenia: pathogenesis, diagnostics and prevention. *Arch Immunol Ther Exp (Warsz)* 2016;64(04):279–290
- 2 Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. *Am J Obstet Gynecol* 2021;225(02):120–127
- 3 Tiller H, Husebekk A, Ahlen MT, Stuge TB, Skogen B. Current perspectives on fetal and neonatal alloimmune thrombocytopenia - increasing clinical concerns and new treatment opportunities. *Int J Womens Health* 2017;9:223–234
- 4 Kamphuis MM, Paridaans N, Porcelijn L, et al. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. *BJOG* 2010;117(11):1335–1343
- 5 Tiller H, Kamphuis MM, Flodmark O, et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. *BMJ Open* 2013;3(03):e002490
- 6 Kjeldsen-Kragh J, Skogen B. Mechanisms and prevention of alloimmunization in pregnancy. *Obstet Gynecol Surv* 2013;68(07):526–532
- 7 de Vos TW, Winkelhorst D, Porcelijn L, et al. Natural history of human platelet antigen 1a-alloimmunised pregnancies: a prospective observational cohort study. *Lancet Haematol* 2023;10(12):e985–e993
- 8 Kamphuis MM, Paridaans NP, Porcelijn L, Lopriore E, Oepkes D. Incidence and consequences of neonatal alloimmune thrombocytopenia: a systematic review. *Pediatrics* 2014;133(04):715–721
- 9 Davoren A, Curtis BR, Aster RH, McFarland JG. Human platelet antigen-specific alloantibodies implicated in 1162 cases of neonatal alloimmune thrombocytopenia. *Transfusion* 2004;44(08):1220–1225
- 10 Mueller-Eckhardt C, Kiefel V, Grubert A, et al. 348 cases of suspected neonatal alloimmune thrombocytopenia. *Lancet* 1989;1(8634):363–366
- 11 Ghevaert C, Campbell K, Walton J, et al. Management and outcome of 200 cases of fetomaternal alloimmune thrombocytopenia. *Transfusion* 2007;47(05):901–910
- 12 Newman PJ, Derbes RS, Aster RH. The human platelet alloantigens, PIA1 and PIA2, are associated with a leucine33/proline33 amino acid polymorphism in membrane glycoprotein IIIa, and are distinguishable by DNA typing. *J Clin Invest* 1989;83(05):1778–1781
- 13 Kjeldsen-Kragh J, Olsen KJ. Risk of HPA-1a-immunization in HPA-1a-negative women after giving birth to an HPA-1a-positive child. *Transfusion* 2019;59(04):1344–1352
- 14 European Commission. Development of a Prophylactic Treatment for the Prevention of Fetal/Neonatal Alloimmune Thrombocytopenia (FNAIT): PROFNAIT. Final Report. Brussels, Belgium: Publication Office of the European Union; 2021
- 15 Lieberman L, Greinacher A, Murphy MF, et al; International Collaboration for Transfusion Medicine Guidelines (ICTMG) Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. *Br J Haematol* 2019;185(03):549–562
- 16 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 166: thrombocytopenia in pregnancy. *Obstet Gynecol* 2016;128(03):e43–e53

- 17 Williams D, Argaez C. Off-Label Use of Intravenous Immunoglobulin for Hematological Conditions: A Review of Clinical Effectiveness. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2018
- 18 Kjeldsen-Kragh J, Bengtsson J. Fetal and neonatal alloimmune thrombocytopenia—new prospects for fetal risk assessment of HPA-1a-negative pregnant women. *Transfus Med Rev* 2020;34(04):270–276
- 19 Eksteen M, Tiller H, Averina M, et al. Characterization of a human platelet antigen-1a-specific monoclonal antibody derived from a B cell from a woman alloimmunized in pregnancy. *J Immunol* 2015;194(12):5751–5760
- 20 Zhi H, Sheridan D, Newman DK, Newman PJ. Prophylactic administration of HPA-1a-specific antibodies prevents fetal/neonatal alloimmune thrombocytopenia in mice. *Blood* 2022;140(20):2146–2153
- 21 Brinc D, Lazarus AH. Mechanisms of anti-D action in the prevention of hemolytic disease of the fetus and newborn. *Hematology (Am Soc Hematol Educ Program)* 2009;185–191
- 22 Crowther C, Middleton P. Anti-D administration after childbirth for preventing Rhesus alloimmunisation. *Cochrane Database Syst Rev* 2000;1997(02):CD000021
- 23 Crowther CA, Middleton P, McBain RD. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation. *Cochrane Database Syst Rev* 2013;(02):CD000020
- 24 Kumpel BM, Elson CJ. Mechanism of anti-D-mediated immune suppression—a paradox awaiting resolution? *Trends Immunol* 2001;22(01):26–31
- 25 de Taeye SW, Rispens T, Vidarsson G. The ligands for human IgG and their effector functions. *Antibodies (Basel)* 2019;8(02):30
- 26 Tang Y, Cain P, Anguiano V, Shih JJ, Chai Q, Feng Y. Impact of IgG subclass on molecular properties of monoclonal antibodies. *MAbs* 2021;13(01):1993768
- 27 Zhi H, Ahlen MT, Skogen B, Newman DK, Newman PJ. Preclinical evaluation of immunotherapeutic regimens for fetal/neonatal alloimmune thrombocytopenia. *Blood Adv* 2021;5(18):3552–3562
- 28 Geisen C, Kjaer M, Fleck E, et al. An HPA-1a-positive platelet-depleting agent for prevention of fetal and neonatal alloimmune thrombocytopenia: a randomized, single-blind, placebo-controlled, single-center, phase 1/2 proof-of-concept study. *J Thromb Haemost* 2023;21(04):838–849
- 29 Vetlesen A, Holme PA, Lyberg T, Kjeldsen-Kragh J. Recovery, survival, and function of transfused platelets and detection of platelet engraftment after allogeneic stem cell transplantation. *Transfusion* 2012;52(06):1321–1332
- 30 Visser GHA, Thommesen T, Di Renzo GC, Nassar AH, Spitalnik SLFIGO Committee for Safe Motherhood, Newborn Health. FIGO/ICM guidelines for preventing Rhesus disease: a call to action. *Int J Gynaecol Obstet* 2021;152(02):144–147
- 31 Sebring ES, Polesky HF. Fetomaternal hemorrhage: incidence, risk factors, time of occurrence, and clinical effects. *Transfusion* 1990;30(04):344–357
- 32 Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. *Obes Surg* 2006;16(06):773–776
- 33 Hadley A, Soothill P. *Alloimmune Disorders of Pregnancy: Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn*. Cambridge, UK: Cambridge University Press; 2002
- 34 Wagner CL, Mascelli MA, Neblock DS, Weisman HF, Collier BS, Jordan RE. Analysis of GPIIb/IIIa receptor number by quantification of 7E3 binding to human platelets. *Blood* 1996;88(03):907–914
- 35 Metzner K, Bauer J, Ponzi H, Ujcich A, Curtis BR. Detection and identification of platelet antibodies using a sensitive multiplex assay system—platelet antibody bead array. *Transfusion* 2017;57(07):1724–1733
- 36 Bittner B, Richter W, Schmidt J. Subcutaneous administration of biotherapeutics: an overview of current challenges and opportunities. *BioDrugs* 2018;32(05):425–440
- 37 Miescher S, Spycher MO, Amstutz H, 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 FcγRIIIA genes. *Blood* 2004;103(11):4028–4035
- 38 RhoGAM. Prescribing information. Kendrion Biopharma Inc; December 2022. Accessed February 1, 2024 at: <https://www.rhogam.com/pdfs/RhoGAM%20Prescribing%20Information.pdf>
- 39 Kumpel BM, Goodrick MJ, Pamphilon DH, et al. Human Rh D monoclonal antibodies (BRAD-3 and BRAD-5) cause accelerated clearance of Rh D+ red blood cells and suppression of Rh D immunization in Rh D- volunteers. *Blood* 1995;86(05):1701–1709
- 40 Kumpel BM, Judson PA. Quantification of IgG anti-D bound to D-positive red cells infused into D-negative subjects after intramuscular injection of monoclonal anti-D. *Transfus Med* 1995;5(02):105–112
- 41 Rhophylac. Prescribing information. CSL Behring; December 2020. Accessed February 1, 2024 at: <https://labeling.cslbehring.com/PI/US/Rhophylac/EN/Rhophylac-Prescribing-Information.pdf>
- 42 Kumpel BM, Sibley K, Jackson DJ, White G, Soothill PW. Ultrastructural localization of glycoprotein IIIa (GPIIIa, β 3 integrin) on placental syncytiotrophoblast microvilli: implications for platelet alloimmunization during pregnancy. *Transfusion* 2008;48(10):2077–2086
- 43 Giltay JC, Leeksa OC, von dem Borne AE, van Mourik JA. Alloantigenic composition of the endothelial vitronectin receptor. *Blood* 1988;72(01):230–233