Rapid and Complete Clearance of HPA-1a Mismatched Platelets in a Human Model of Fetal and Neonatal Alloimmune Thrombocytopenia by a Hyperimmune Plasma Derived Polyclonal Anti-HPA-1a Antibody

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INTRODUCTION

RLYB211 is an intravenously administered, investigational, plasma-derived polyclonal anti-Human Platelet Antigen (HPA)-1a hyperimmune Immunoglobulin G being developed for the prevention of Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT). FNAIT is a rare condition in which the pregnant woman's immune system attacks the platelets of her fetus, leading to potentially catastrophic fetal and neonatal morbidity and mortality. Fetal-maternal incompatibility in the HPA-1a system is the most common (85-95%) cause of FNAIT. Treatment with RLYB211 is designed to rapidly eliminate fetal HPA-1a positive platelets from a pregnant woman's circulation and prevent maternal alloimmunization, eliminating the risk of FNAIT in the fetus. There are no currently approved treatments for the prevention of FNAIT.

AIM

The primary objective of this study is to determine a dose of RLYB211 that can markedly (10-fold or greater) accelerate the clearance of HPA-1a positive platelets transfused to HPA-1b/b healthy male volunteers. Cohort 1 of this study assessed RLYB211 at a dose of 1000 IU compared to placebo.

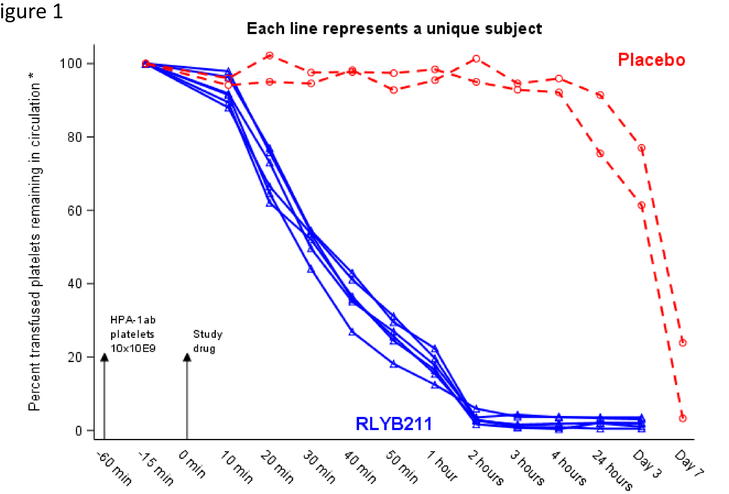
STUDY DESIGN

Cohort 1 Study Design

PRIMARY EFFICACY ENDPOINT

Administration of RLYB211 1000 IU markedly accelerated the clearance of HPA-1a/b positive platelets compared with placebo ($t_{1/2}$ of mismatched platelets 0.32 hrs vs 65.29 hrs. respectively; p value < 0.001) (Figure 1), representing a 200-fold increase in clearance rate.

Figure 1



* Data normalized at 100% for sample collected 15 minutes prior to study drug at 0 mins.

Two placebo treated and one RLYB211 treated subjects were administered more than the 10 X 10^9 intended number of HPA-1a/b platelets

RESULTS

12 healthy male participants consented to the study, of whom 8 were randomized in a single blind manner to receive RLYB211 1000 IU or placebo (sodium chloride solution, 0.9%) in Cohort 1. Of the remaining 4 subjects, 3 were not eligible for the study and 1 withdrew consent. All subjects enrolled were aged 23 to 65 years and with race documented as white.

METHODS

Following approval by the Paul Ehrlich Institut, Germany and the Ethics Committee, University Hospital Frankfurt, informed consent was obtained from 8 healthy male subjects (HPA-1b/b and human leukocyte antigen HLA-A2 negative). Subjects were administered either 1000 IU RLYB211 (n=6) or placebo (n=2) intravenously, 60 minutes after administration of 10 X 10^9 HPA-1a/b and HLA-A2 positive platelets. The proportion of normalized HLA-A2 positive platelets in circulation following administration of RLYB211 or placebo was determined with a qualified flow cytometric method. Identification of the HPA-1b/b subjects for the study, supply of HPA-1a/b positive, HLA-A2 positive platelets for administration to study subjects and flow cytometry testing of platelet rich plasma samples for survival of HLA-A2 positive platelets were carried out by Deutsches Rotes Kreuz (DRK, German Red Cross) Blood Transfusion Service, Frankfurt.

Clearance of platelets was based on the proportion of HLA-A2 positive transfused platelets remaining in the recipient, following administration of RLYB211 or placebo. Platelet clearance was assessed at frequent intervals through the first 4 hours post study drug administration and then at 24 hours, Day 3, and at Day 7 (only if transfused platelets were detected at Day 3).

SUMMARY OF SAFETY

Safety data was reviewed by a Safety Review Team (SRT). There were no serious adverse events (SAEs) reported in the study. The SRT did not find any clinically significant issues in their review of safety data from Cohort 1 and recommended that the study should continue as planned to the next dose Cohort.

CONCLUSION

RLYB211 1000 IU provides proof of concept of the ability of anti-HPA-1a antibodies to rapidly and completely clear mismatched HPA-1a/b positive platelets in HPA-1b/b individuals. RLYB211 1000 IU was safe and well tolerated and no SAEs were reported.