Rozrolimupab, A Mixture of 25 Recombinant Human Monoclonal RhD Antibodies, in the treatment of Primary Immune Thrombocytopenia


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Short title: Rozrolimupab in Primary Immune Thrombocytopenia Preliminary results of this study were presented at the 52nd Annual Meeting of the American Society of Hematology, San Diego, California, December 9-12, 2011.

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ABSTRACT
Rozrolimupab, a recombinant mixture of 25 fully human RhD-specific monoclonal antibodies, represents a new class of recombinant human antibody mixtures. In a phase 1/2 dose escalation study, RhD+ patients (61 subjects) with primary immune thrombocytopenia (ITP) received a single intravenous dose of rozrolimupab ranging from 75 to 300µg/kg. The primary outcome was the occurrence of adverse events (AEs). The principal secondary outcome was the effect on platelet levels 7 days after the treatment. The most common AEs were headache and pyrexia, mostly mild and reported in 20% and 13% of the patients, respectively, without dose relationship. Rozrolimupab caused an expected transient reduction of hemoglobin concentration in the majority of the patients. At the dose of 300µg/kg platelet responses, defined as platelet count $\geq 30 \times 10^9$/L and an increase in platelet count by $> 20 \times 10^9$/L from baseline, were observed after 72 hours and persisted for at least 7 days in 8 of 13 patients (62%). Platelet responses were observed within 24 hours in 23% of patients and lasted for a median of 14 days. Rozrolimupab was well tolerated and elicited rapid platelet responses in patients with ITP and may be a useful alternative to plasma-derived products. This trial is registered at www.clinicaltrials.gov as NCT00718692).
INTRODUCTION

Primary immune thrombocytopenia (ITP) is an autoimmune disease mediated by anti-platelet antibodies that cause opsonization of platelets and elimination through binding to FcγR-bearing phagocytic cells and subsequent phagocytosis. In addition, the same autoantibodies bind to megakaryocytes and impair platelet production.

The annual incidence of ITP in the United States is estimated to be approximately 16,000 cases. Although the thrombocytopenia in ITP can be severe, most patients have only minor signs of bleeding. Persistently low platelet counts (<20×10^9/L), however, are associated with an increased risk of serious bleeding, such as intracranial hemorrhage. Treatment is indicated for ITP associated with significant mucous membrane bleeding and is also indicated for patients with risk factors for bleeding (e.g., hypertension, peptic ulcer disease, anti-platelet drug ingestion), in adult patients with a platelet count < 30×10^9/L, and in patients prior to surgical procedures.

The initial treatment for ITP comprises corticosteroids, intravenous high dose immunoglobulin (IVIg), or intravenous RhD immune globulin (anti-D). These compounds act primarily by interfering with platelet destruction and cytokine modulation. Immunomodulatory agents suppress the production of antiplatelet antibodies, but the use of immunosuppressive agents, corticosteroids and later splenectomy may be associated with complications.

The platelet response to plasma-derived anti-D, including early onset and duration of response, seems to be dose dependent and at a dose of 75µg/kg anti-D has an effect similar to IVIg. However, these data were derived from studies in which human plasma was the source of anti-D.

Rozrolimupab, a mixture of 25 recombinant, fully human, RhD-specific monoclonal antibodies, represents the first in class of recombinant human monoclonal antibody mixtures that can be produced independently of human plasma supply. We here report safety and efficacy data from a trial of a single dose of rozrolimupab in non-splenectomized adults with ITP.
METHODS

TRIAL MEDICATION

Rozrolimupab comprises 25 genetically unique IgG1 antibodies, all specific for the RhD erythrocyte antigen, derived from B-lymphocytes of eight RhD-negative female donors with high serum antibody titers against RhD. The drug substance was produced by single batch manufacturing of a working cell bank composed of an equal mixture of 25 CHO cell lines each expressing one particular human monoclonal antibody specific for RhD. Twenty antibodies have a κ light chain and 5 antibodies a λ light chain. The hypervariable regions of the heavy chains are homologous with published human anti-RhD sequences. Rozrolimupab comprises antibodies specifically selected to recognize the complete D antigen expressed in > 99% of the human population, including rare D variants DIII, DIV, DVI and DVII expressed in < 1% of the overall RhD-positive population. The rozrolimupab drug product exhibits stable composition in consecutive batches.

Validated flow cytometry studies according to the European pharmacopoeia demonstrated that rozrolimupab binds to RhD variants with a potency comparable to that of two marketed plasma-derived anti-D products, Rhophylac® and WinRho®. Explorative in vitro studies showed that rozrolimupab mediated specific phagocytosis and antibody-dependent cell-mediated cytotoxicity of RhD-expressing erythrocytes using either normal human mononuclear cells or THP-1 monocytic leukemia cells (ATCC, Manassas, VA, USA) as effector cells. In the latter case, the potency of rozrolimupab appeared 5-fold reduced compared to plasma-derived anti-D products. (data not shown).
ELIGIBILITY

Adult patients with ITP were enrolled at 27 investigational sites in Europe, Israel and India. Eligibility criteria included the diagnosis of primary ITP documented response following initial therapy with corticosteroids, anti-D or IVIG defined as an increase in platelet count >30×10⁹/L, and a pretreatment platelet count of less than 30×10⁹/L. Key exclusion criteria included prior splenectomy, secondary thrombocytopenia, clinical splenomegaly, a history of abnormal bone marrow examination (except for megakaryocytosis), hemoglobin concentration lower than 2g/dL below the lower limit of the normal range, and positive results of direct Coombs’ test.

DESIGN

The trial was approved by independent ethics committees and the governmental authorities in each participating country, as required, and was carried out in accordance with the Declaration of Helsinki (October 1996). All patients provided oral and written informed consent prior to trial start.

This was an open-label, international, multi-center, exploratory dose finding, phase 1/2 trial. The trial was designed to include cohorts receiving a single dose of rozrolimupab 75, 100, 125, 150, 200, 250, 300 and 350µg/kg, that each consisted of 5-11 patients. An Independent Data Monitoring Committee evaluated safety and efficacy between each dose escalation. Once the final dose level was achieved following this evaluation, the final dose cohort was repeated.

All patients received a single intravenous dose of rozrolimupab. For doses up to 150µg/kg, rozrolimupab was given as a slow bolus IV injection of 3-5 minutes duration. For doses ≥ 150 µg/kg, rozrolimupab was added to a 100 mL sterile infusion bag containing 0.9% NaCl and infused over 15-20 min using a sterile inline filter (0.2µm).

Patients were followed for 6 weeks.
The primary endpoint of the trial was the incidence and severity of adverse events (AEs), including serious adverse events (SAEs), during the 6-week trial period. Secondary safety endpoints included laboratory parameters (including maximum reduction of hemoglobin concentration), and presence of human anti-human antibodies (HAHA).

Efficacy endpoints included measures of platelet response and use of rescue medication. Responders were defined as patients with platelet count $\geq 30 \times 10^9$/L and an increase in platelet count by $> 20 \times 10^9$/L from baseline at 7 days after rozrolimupab treatment.

Analysis of hematology, clinical chemistry, coagulation and hemolysis parameters were performed prior to treatment and at predefined intervals post treatment. The concentrations of interleukin 6 (IL-6), IL-10, monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor $\alpha$ (TNF$\alpha$) were measured by Luminex Technology kit (Merck Millipore, Billerica, MA, USA).

Rozrolimupab serum concentrations were measured by flow cytometry as previously described. The lower limit of quantification was validated to 4ng/mL in whole serum.

A double-antigen enzyme linked immunosorbent assay with detection limit of 6.3ng/mL was used to detect HAHA. Analysis for the Fc$\gamma$RIIA-131 H/R and Fc$\gamma$RIIIA-158 V/F genotypes was performed on DNA extracted from blood samples.

No formal sample size calculations were performed. Linear regression was used to analyze possible relations between predictor and dependent variables.
RESULTS

CHARACTERISTICS OF PATIENTS

Patients had a median age of 51 years and were predominantly female (64%) (Table 1). The vast majority of patients (89%) were Caucasian.

The median baseline platelet counts varied between the cohorts with the numerically highest baseline median counts in the 100µg/kg cohort, and the lowest in the 75µg/kg cohort. Across all cohorts, 12 patients had a baseline platelet count < 10×10⁹/L. The 100µg/kg cohort had a numerically younger group of patients compared with the other cohorts.

The median time from ITP diagnosis until screening for all patients was 21 months, spanning from a median of 5 months (125µg/kg cohort) to a median of 68 months (75µg/kg cohort).

The most frequently used ITP related medications prior to enrolment were steroids (87%). IVIg had been used by 30% of the patients and 13% had used other immunosuppressants like azathioprine. None of the patients had been treated with anti-D.

SAFETY

The dose escalation was suspended after reaching the 300µg/kg level following evaluation of safety and efficacy data by an Independent Data Monitoring Committee.

Forty-five patients reported a total of 198 AEs during the trial (Table 2). Approximately 75% of the events (149/198) were assessed to be mild in intensity. Eighty events were assessed as related to rozrolimupab treatment. No AEs led to withdrawal from trial and no deaths were recorded.
Headache was the most frequently reported event with 12 patients reporting 16 events; 10 events were mild, 5 were moderate and 1 was severe in intensity (Table 2). The majority of the events resolved on the day of onset and was not treated. The single case of severe headache was treated with paracetamol and had a duration of 2½ hours. The longest duration of headache was 20 days for an event of moderate severity which was treated with paracetamol. Eleven of the 16 events of headache, including 3 of the moderate events and the severe event, were reported in the 75 or 100 µg/kg cohorts.

A reduction in hemoglobin concentration was observed in the majority of patients (Fig. 1B) with a trend towards larger reductions with increasing doses. All patients were direct Coombs positive when tested 24 hours after treatment with rozrolimupab and remained positive at 6 weeks, except for 1 patient in each of the 250 and 300µg/kg cohorts, respectively, who returned to negativity at 4 weeks and 6 weeks after treatment, respectively. A fall in hemoglobin concentration >2.5g/dL was observed at 72 hours and 7 days after treatment in 11 (18%) and 15 (25%) of the patients, respectively. No patient had a fall in hemoglobin concentration >5g/dl. In the dose group of 300µg/kg, the hemoglobin concentration returned to baseline in 8 of the 13 patients in a median of 28 days (range 1-43); none of the 13 patients received blood transfusions. In the remaining dose cohorts, one patient received a blood transfusion on the day of treatment and 3 other patients received one or more blood transfusions after treatment.

Increases in reticulocyte counts were observed in 1 of 6 patients in the 200µg/kg, 3 of 6 patients in the 250µg/kg and in 5 of 13 patients in the 300µg/kg cohort, all of whom also had lowering of their haptoglobin levels. Reduction in haptoglobin without concomitant increase in reticulocytes was also seen in 3 patients in the 100µg/kg cohort and in additional patients in the 200, 250 and 300µg/kg cohorts. On the day of treatment 11 patients reported 19 events of fever and/or 6 events of chills. For a twelfth patient an infusion reaction consisting of chills and rigors was reported. Elevation of
concentrations of IL-6, IL-10, MCP-1 and TNFα following infusion with rozrolimupab was observed across all dose cohorts, and median levels peaked 2-24 hours after treatment with return to baseline levels by 2-7 days after treatment (data not shown).

In the 200 – 300µg/kg cohorts, the FcγIIA-131HH, -HR and –RR genotypes were found in 9, 14, and 4 patients, respectively. The FcγIIA-158FF, -VF and -VV genotypes were demonstrated in 6, 17, and 4 patients, respectively. Patients with the FcγIIA-131HH genotype had the highest peak levels of all 4 cytokines while patients with FcγIIA-131RR genotype had the lowest peak levels. Patients with the FcγIIA-158VV genotype had the highest peak levels of IL-6, IL-10 and MCP-1, while patients with the FcγIIA-158FF genotype had the lowest peak values of these 3 cytokines. There was no change in the hemolytic activity as measured by CH50 at the sampled time points (screening, 5-8 hours and day 7) for the 150, 200, 250 or 300µg/kg cohorts. Pretreatment values of D-dimer were within normal limits across all dose groups (data not shown). Transient rise in the concentration of D-dimer was seen in all cohorts in a dose-dependent manner. The increase peaked at 24 hours after treatment and returned towards baseline level by day 7 after treatment. The largest increase was seen in a patient from the 300µg/kg cohort (baseline: 0.166µg/mL; 24 hours: 9.41µg/mL). In the 300µg/kg cohort the D-dimer values returned to baseline levels after 7 days in 5 of 13 patients. The rise in D-dimer levels was not associated with clinical symptoms or changes in the other coagulation parameters (prothrombin time, INR, fibrinogen and activated partial thromboplastin time) or the hemolysis parameters (concentrations of hemoglobin, reticulocytes, haptoglobin, bilirubin, lactate dehydrogenase, and free hemoglobin).

SAEs were recorded in 9 patients during the trial. No SAEs were recorded in the 125 or 300µg/kg cohorts. Four of these events were assessed as related to rozrolimupab treatment:
1. A decrease in hemoglobin concentration from 14.1 to 11.0g/dL (mild intensity) on day 8 was considered possibly related to rozrolimupab treatment, lasted for 22 days and recovered without treatment (100µg/kg cohort); 2. Extravascular hemolysis with reduction of hemoglobin from 14.1 to 9.6g/dL (severe intensity) with onset on day 7 was reported in one patient in the 200µg/kg cohort who received 2 blood transfusion; 3. Increase in D-dimer (mild in severity) with onset on the day of treatment and duration of 8 days was reported in one patient in the 250µg/kg cohort. The patient had no clinical symptoms; 4. Another case of increase in D-dimer, reported as disseminated intravascular coagulation (DIC) of moderate severity, with onset on the infusion day was observed in the 250µg/kg cohort. The D-dimer levels returned towards baseline at day 7 and the event was reported as probably related to trial drug. The event was an isolated increase in D-dimer with no clinical symptoms indicative of DIC.

PLATELET RESPONSES

Overall, there was a trend towards a dose response with the 100µg/kg cohort as an outlier (Fig. 1A). An analysis of platelet response data by treatment groups is shown in Table 3. Across all cohorts 21 of 61 patients (34%) met the response criterion on day 7. The highest percentages of responders were seen in the 100 and 300µg/kg cohorts (70 and 62%, respectively). No patients from the 75µg/kg cohort responded to the treatment. The highest median platelet counts were recorded 7 days after treatment for all patients (34×10^9/L), with the highest median values in the 300µg/kg cohort (130×10^9/L, range 15-634×10^9/L). Six weeks after treatment the median platelet count for all patients was 25×10^9/L. Again, the highest median platelet count after 6 weeks was recorded in the 300µg/kg cohort (35×10^9/L). Unlike the other dose cohorts, the 300µg/kg dose was able to induce platelet responses in both of 2 patients with baseline platelets <10×10^9/L.
The onset of platelet responses for the 300µg/kg cohort is shown in Table 4. Already 5-8 hours after treatment, 23% of patients had platelet responses. The number of patients with platelet responses increased with time and peaked at 72 hours and at day 7, where 8 of 13 patients had platelet responses (62%). The median time to platelet response was 59 hours. The median duration of the platelet response in the 300µg/kg cohort was 14 days.

No relationship between baseline hemoglobin concentrations and platelet responses was found. For patients in the 300µg/kg cohort, the relationship between platelet count at day 7 and maximal decrease in hemoglobin concentration is shown in Figure 2. Linear regression with platelet count as dependent variable and maximal decrease in hemoglobin concentration as predictor showed a significant correlation (p=0.021; R²=0.40) between the absolute platelet count at day 7 and the maximal fall in hemoglobin concentration. There was also a similar relationship between the change in platelet count from baseline to day 7 and the maximal decrease in hemoglobin concentration for this cohort (p=0.023; R²=0.39; data not shown). No apparent relationships between platelet response and FcγRIIA or FcγRIIIA genotype were found.

The majority of patients had a bleeding score of 0 or 1 during the trial. Two patients with a WHO bleeding score of 2 at entry recorded bleeding scores of 0 or 1 following treatment. Two other patients with low platelet counts at baseline recorded scores >2 during the trial and both received rescue medication.

Twenty-one of the 61 patients (34%) used rescue medication during the trial, with IVIg and steroids (prednisolone or methylprednisolone) being the most commonly used. In the 300 µg/kg dose cohort only 1 of 13 patients (8%) received rescue medication.
PHARMACOKINETICS AND IMMUNOGENICITY

At 30 minutes post infusion, the maximal concentration of rozrolimupab was <1% of the expected values as calculated by the dose and plasma volume, arbitrarily set to 2.5 L, indicating that rozrolimupab was already bound to RhD+ positive erythrocytes.

HAHA response of borderline magnitude was observed in a single patient.
DISCUSSION

This dose escalation trial showed that rozrolimupab is active in previously treated patients with ITP. The 300µg/kg was identified as the optimal dose where 62% of patients achieved platelet responses and only 1 of 13 patients needed rescue treatment. Although a selection bias cannot be excluded as all patients in this trial had responded to previous first line treatment, this result seems comparable to platelet responses after treatment with plasma-derived anti-D7, 8, 20, 22 and IVIg6, 23, 24.

Rozrolimupab demonstrated a rapid onset of effect, as 24% of patients treated with 300µg/kg had platelet responses within 24 hours, comparable with observations following treatment with IVIg6 and anti-D at 75µg/kg.7 This rapid increase of platelets was associated with a reduced the need for rescue medication and in the 300µg/kg cohort, where only 1 patient (8%) received rescue medication during the trial. The rapid increase of platelets in combination with a very short infusion time of 15-20 minutes is an advantage for acute treatment of ITP in non-splenectomized patients with ITP.

The platelet responses to plasma-derived anti-D is dose-dependent in terms of onset, magnitude and duration6, 7, but not all non-splenectomized patients with ITP respond to the treatment.6, 19, 20, 21, 22 Response rates are generally high in children and in young adults20 and generally lower in patients with pretreatment platelet levels <10×10⁹/L6, 21. The final dose of rozrolimupab (300µg/kg) was established after dose escalation showing both a trend towards dose-dependent platelet response (except for the 100µg/kg cohort), and a trend towards trend towards larger reductions of hemoglobin with increasing doses. In the 100 µg/kg cohort the baseline platelet counts were numerically higher and patients were younger compared to other cohorts. Both factors may have contributed to the observed response rate of 70% at day 7. It is of note that the dose of 300µg/kg had a higher median platelet count on day 7 than the other doses, and elicited platelet responses in patients with pretreatment platelet counts <10×10⁹/L.
In this study baseline hemoglobin levels did not correlate with platelet responses, contrary to the findings of Scaradavou et al.\textsuperscript{21} In this study, a significant correlation between the maximal fall in hemoglobin concentration and the absolute platelet count at day 7 was found for patients in the 300µg/kg cohort. A similar correlation was observed comparing the maximal reduction in hemoglobin concentration and the change of platelets from baseline to day 7. If this correlation would be confirmed in a larger trial, it may be possible to use the magnitude of the fall in hemoglobin concentration as a predictor of response. During treatment with plasma-derived anti-D, treatment doses of even 100µg/kg may be beneficial in selected patients with absence of platelet responses at lower doses.\textsuperscript{25} Further studies are needed to determine the therapeutic value of repeated rozrolimupab treatments for patients with ITP with small reductions of hemoglobin concentration and lack of platelet responses following treatment. In this study we were not able to confirm the predictive value of the FcγIII genotypes for platelet responses as reported by Cooper et al.\textsuperscript{5}, most likely due to an insufficient number of patients for this type of analysis.

The clinical value of any treatment for ITP lies in the rapidity and duration of platelet concentration rise. Early onset and duration of platelet response are important benchmarks for therapy with anti-D. In this study, the median duration of response following treatment with rozrolimupab was 2 weeks for the 300µg/kg cohort. This observation is comparable to results obtained in trials with IVIg.\textsuperscript{6, 23, 24} Most studies with anti-D reported an average response duration of 3 weeks, although with large variations.\textsuperscript{7, 20, 21, 22} However, a randomized study is needed to evaluate the duration of response after treatment with rozrolimupab in comparison with IVIg or anti-D.

The safety profile of rozrolimupab was favorable. Approximately 75% of patients reported one or more AEs during the trial, but 75% of these 198 events were mild in intensity. It is of note that only 20% of patients reported headaches following rozrolimupab treatment. Most of the 16 events of headache in were reported in the 75 or 100µg/kg cohorts, including 3 events of moderate intensity
and 1 of severe intensity. The majority of the headaches resolved on the day of onset with little or no treatment. However, 1 patient had a persistent headache for 20 days (treated with paracetamol) and another had intermittent headaches over an 8 day period (not treated). The prevalence (20%) and short duration of these headaches need confirmation in a randomized trial that include patients with ITP treated with IVIg or anti-D.

Infusion reactions may occur during treatment with anti-D. In this study, medications to alleviate possible infusion-related events prior to the infusion of rozrolimupab were not planned per protocol. Two events of pyrexia were reported in the same patient from the 75µg/kg cohort. All other treatment-related events of fever or chills were reported in the 200, 250 or 300µg/kg cohorts. All events were resolved on the day of onset, with the exception of one event of pyrexia which resolved after 33 hours. Fever and chills coincided with the cytokine release that peaked 2 -24 hours after the infusion. The observation of maximal levels of IL-6, IL-10, MCP-1 among patients with the FcγIIIA-158VV genotypes is in accordance with previous findings.

Based on the mechanism of action, some degree of extravascular hemolysis is an expected outcome of treatment with rozrolimupab. Approximately one fourth of the patients had a fall in hemoglobin concentration >2.5g/dL, but dramatic changes > 5.0g/dL were not observed during the dose escalation. In the highest dose group, 300µg/kg, the hemoglobin concentration returned to baseline in most patients within 28 days, and in this dose cohort no blood transfusions were given. These observations are in line with the reduction in hemoglobin concentration seen in other trials of anti-D for ITP at 50 -75µg/kg.

Acute intravascular hemolysis and DIC have been described as serious complications of anti-D treatment. It has been hypothesized that antibodies among anti-D preparations binding to blood groups other RhD may play a pathogenetic role for these events. With rozrolimupab, containing
only recombinant monoclonal antibodies specific to RhD, binding to antigens other than RhD on the erythrocytes can be ruled out. Careful analysis of such cases of intravascular hemolysis and DIC has, however, also pointed to co-morbidities among patients with ITP as risk factors for the development of severe hemolysis and DIC.26, 27, 28 In this study, frequent monitoring of coagulation parameters was carried out, and a transient increase in D-dimer was observed across all dose cohorts. This increase in D-dimer was not accompanied by clinical symptoms or changes in other measured coagulation factors. A recent randomized study in patients with ITP did not show changes in D-dimer levels following treatment with IVIg and methylprednisolone, where patients in the methylprednisolone treatment arm had low levels of protein S, protein C and antithrombin III that normalized after therapy.29 Similar changes of low levels of protein S and protein C following treatment with methylprednisolone for ITP were demonstrated in another recent report.30 The demonstrated changes in D-dimer levels observed in the present study may represent compensatory mechanisms to maintain hemostasis which merit further exploration in future trials.

In conclusion, rozrolimupab is effective in the treatment of ITP at a dose of 300µg/kg and exhibits a favorable safety profile at all tested dose levels. Rozrolimupab has a rapid effect on platelet levels which is sustained for a median of 14 days. Further randomized studies are needed to compare the safety and efficacy of rozrolimupab with current treatment modalities for ITP like plasma-derived anti-D and IVIg.
Acknowledgments

The following collaborators contributed to this work:

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The investigators received payments to cover trial-related expenses. Henrik Næsted, Niels J. Ø.
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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>75µg/kg</th>
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<td>1 (20.0%)</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>6 (46.2%)</td>
<td>22 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median</td>
<td>51.0</td>
<td>40.0</td>
<td>41.0</td>
<td>52.0</td>
<td>60.5</td>
<td>42.5</td>
<td>55.0</td>
<td>51.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>40.0;65.0</td>
<td>19.0;75.0</td>
<td>26.0;74.0</td>
<td>32.0;62.0</td>
<td>25.0;81.0</td>
<td>21.0;74.0</td>
<td>25.0;77.0</td>
<td>19.0;81.0</td>
</tr>
<tr>
<td>Age Category</td>
<td>&lt; 40 y</td>
<td>0</td>
<td>4 (40.0%)</td>
<td>5 (50.0%)</td>
<td>2 (40.0%)</td>
<td>2 (33.3%)</td>
<td>3 (50.0%)</td>
<td>4 (30.8%)</td>
<td>20 (32.8%)</td>
</tr>
<tr>
<td></td>
<td>40-60 y</td>
<td>10 (90.9%)</td>
<td>4 (40.0%)</td>
<td>3 (30.0%)</td>
<td>2 (40.0%)</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>7 (53.8%)</td>
<td>28 (45.9%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 60 y</td>
<td>1 (9.1%)</td>
<td>2 (20.0%)</td>
<td>2 (20.0%)</td>
<td>1 (20.0%)</td>
<td>3 (50.0%)</td>
<td>2 (33.3%)</td>
<td>2 (15.4%)</td>
<td>13 (21.3%)</td>
</tr>
<tr>
<td>Race</td>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (16.7%)</td>
<td>5 (38.5%)</td>
<td>6 (9.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>11 (100%)</td>
<td>10 (100%)</td>
<td>9 (90.0%)</td>
<td>5 (100%)</td>
<td>6 (100%)</td>
<td>5 (83.3%)</td>
<td>8 (61.5%)</td>
<td>54 (88.5%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>1 (10.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>Median</td>
<td>26.0</td>
<td>23.6</td>
<td>25.9</td>
<td>28.9</td>
<td>27.2</td>
<td>27.3</td>
<td>26.7</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>18.5;36.8</td>
<td>18.0;30.8</td>
<td>21.0;38.1</td>
<td>22.7;30.5</td>
<td>18.7;31.3</td>
<td>20.1;38.7</td>
<td>21.1;40.7</td>
<td>18.0;40.7</td>
</tr>
<tr>
<td>Time from First ITP Diagnosis to Screening (months)</td>
<td>Median</td>
<td>68</td>
<td>20</td>
<td>5</td>
<td>8</td>
<td>27</td>
<td>28</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1;166</td>
<td>4;354</td>
<td>2;187</td>
<td>4;141</td>
<td>1;117</td>
<td>3;223</td>
<td>1;273</td>
<td>1;354</td>
</tr>
<tr>
<td>Baseline Platelet Count (10⁹/L)</td>
<td>Median</td>
<td>11.5</td>
<td>22.3</td>
<td>13.3</td>
<td>20.5</td>
<td>19.3</td>
<td>16.0</td>
<td>18.5</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5.0;24.5</td>
<td>10.5;26.5</td>
<td>3.0;26.5</td>
<td>4.5;21.5</td>
<td>3.0;26.0</td>
<td>6.0;26.0</td>
<td>7.3;27.0</td>
<td>3.0;27.0</td>
</tr>
</tbody>
</table>
Table 2. Adverse Events Reported in >5% of Patients Treated with a Single Dose of Rozrolimupab

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Adverse event grading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Headache</td>
<td>13.1%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9.8%</td>
</tr>
<tr>
<td>Petechiae</td>
<td>8.2%</td>
</tr>
<tr>
<td>Hematoma</td>
<td>9.8%</td>
</tr>
<tr>
<td>Low platelet counts</td>
<td>1.6%</td>
</tr>
<tr>
<td>Chills</td>
<td>9.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.6%</td>
</tr>
<tr>
<td>Increased D-dimer</td>
<td>4.9%</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>3.3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4.9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.9%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.6%</td>
</tr>
</tbody>
</table>
Table 3. Number of patients with platelet responses on day 7 following a single dose of rozrolimupab

<table>
<thead>
<tr>
<th>Dose of rozrolimupab</th>
<th>75µg/kg</th>
<th>100µg/kg</th>
<th>125µg/kg</th>
<th>150µg/kg</th>
<th>200µg/kg</th>
<th>250µg/kg</th>
<th>300µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Responders&lt;sup&gt;1&lt;/sup&gt; (%)</td>
<td>0 (0.0%)</td>
<td>7 (70.0%)</td>
<td>2 (20.0%)</td>
<td>2 (40.0%)</td>
<td>2 (33.3%)</td>
<td>3 (50.0%)</td>
<td>8 (61.5%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Only patients that did not receive rescue medication before day 8 are counted as responders.

Table 4. Platelet responses over time for the 300µg/kg cohort

<table>
<thead>
<tr>
<th>Time points</th>
<th>2 hours</th>
<th>5-8 hours</th>
<th>24 hours</th>
<th>48 hours</th>
<th>72 hours</th>
<th>7 days</th>
<th>14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders&lt;sup&gt;1&lt;/sup&gt; (%)</td>
<td>0 (0.0%)</td>
<td>3 (23.1%)</td>
<td>4 (30.8%)</td>
<td>6 (46.2%)</td>
<td>8 (61.5%)</td>
<td>8 (61.5%)</td>
<td>7 (53.8%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Only patients that did not receive rescue medication before the specific time points are counted as responders.
**Figure Legends**

Fig. 1. Platelet responses (A) and corresponding values of hemoglobin in individual patients (B). Continuous lines: patients treated without rescue medication. Dashed lines: patients that received rescue medication.

Fig. 2. The difference between baseline and day 7 hemoglobin concentration (X-axis) and the corresponding values of platelet counts on day 7 (Y axis). The graph represents the fitted linear regression line with 95% confidence limits.
Rozrolimupab, a mixture of 25 recombinant human monoclonal RhD antibodies, in the treatment of primary immune thrombocytopenia

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