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ORIGINAL ARTICLE

# A randomized, double-blind, comparative study of the pharmacodynamics and pharmacokinetics of GP40141 (romiplostim biosimilar) and reference romiplostim in healthy male volunteers

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## Abstract

**Aims:** The pharmacodynamic (PD) similarity between GP40141, a proposed romiplostim biosimilar, and reference romiplostim was evaluated. Pharmacokinetics and safety were also assessed.

**Methods:** In this phase 1, randomized, double-blind, single-dose, crossover comparative study with an adaptive design, 56 healthy male volunteers were randomized 1:1 to receive a 3 $ug \times kg^{-1}$ subcutaneous dose of GP40141 and reference romiplostim. The PD similarity between GP40141 and the reference romiplostim was determined using the standard equivalence criteria (80%–125%) for the area under the platelet count-time curve from time 0 to the time of the last sampling for PD ($AUC_{plt}$) and the maximum observed platelet count ($P_{max}$).

**Results:** GP40141 and the reference romiplostim exhibited similar PD profiles. 90% CI for the geometric mean ratios for the primary PD parameters ($AUC_{plt}$, $P_{max}$) for GP40141 (T) and the reference romiplostim (R) were fully contained within the predefined equivalence limits of 80%–125%: 98.13%–102.42% for $AUC_{plt}$ and 97.56%–105.80% for $P_{max}$. The pharmacokinetic profiles of GP40141 and the reference romiplostim were well described. No adverse events were observed during the clinical trial after the administration of GP40141 and the reference romiplostim.

**Abbreviations:** AE, Adverse event; $AUC_{0-\infty}$, Area under the curve from time 0 extrapolated to infinity; $AUC_{0-t}$, Area under the curve from time 0 to the time of the last observable concentration; $AUC_{plt}$, Area under the platelet count curve from time 0 to the time of the last sampling for PD; CI, Confidence interval; $C_{max}$, Maximum observed serum concentration; CV, Coefficient of variation; ECG, Electrocardiogram; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-linked Immunosorbent Assay; Fc, Fragment crystallizable; GMR, Geometric means ratios; GPIb-IX-V, Glycoprotein Ib-IX-V; GPIIb/IIIa, Glycoprotein IIb/IIIa; IgG, Immunoglobulin G; ITP, Idiopathic thrombocytopenic purpura; JAK2, Janus Kinase 2; LLOQ, Lower limit of quantitation; MedDRA, Medical Dictionary of Regulatory Activities; PD, Pharmacodynamics; PK, Pharmacokinetics; $P_{max}$, Maximum observed platelet count; $P_{max}/P_0$, Maximum number of platelets count to the basal level of platelets; R, Reference drug; SAE, Serious adverse event; SAF, Safety analysis set; SD, Standard deviation; T, Test drug; $t_{max}$, Time of maximum observed serum concentration; TMDD, Target mediated drug disposition; $t_{Pmax}$, Time to reach the maximum number of platelets count; TPO-R, Thrombopoietin receptor; TPO-RA, Thrombopoietin receptor agonist.

**Conclusion:** This study demonstrates the PD similarity of GP40141 to the reference romiplostim. Both treatments had comparable safety profiles (NCT05652595)

**KEYWORDS**
biosimilarity, GP40141, pharmacodynamics, pharmacokinetics, romiplostim

## 1 | INTRODUCTION

Idiopathic (immune) thrombocytopenic purpura (ITP) is an autoimmune condition characterized by isolated thrombocytopenia ($<100\times10^9$/L) that is not associated with other known causes.[1] The incidence of ITP in the population is 1.9–6.4 cases per 100 000 children and 3.3 per 100 000 adults.[2,3]

The etiology of this condition is still uncertain, but there are some trigger factors that enhance the probability of contracting ITP. Trigger factors include infections (predominantly viral) – 59% of patients, pregnancy – 19%, stress – 15%, surgical intervention – 4%, physical activity – 4%, and vaccination – 1% of patients. The main contribution to the pathophysiology of ITP is autoimmune damage to intact platelets. This relates to identifying increased antiplatelet antibodies (IgG) against surface glycoproteins GPIIb/IIIa and GPIb-IX-V complex[4] in the serum of patients with ITP. The cause of this platelet-specific autoimmunity is complex and poorly understood, but recent evidence suggests that B- and T-cell dysregulation may play a central role.[5]

Romiplostim, as a second-generation thrombopoietin receptor agonist (TPO-RA), is a part of a second-line therapy for persistent ITP, as well as for chronic, relapsing, and refractory forms of the disease. It is effective and safe for short-term and long-term (more than 5 years) therapy to treat ITP and can be prescribed for continuous use in order to maintain the patient's platelet count at a safe level (at least $50.0\times10^9$/L). After discontinuation of treatment, the platelet count often decreases to baseline concentrations or lower, but in rare cases, there is a prolonged remission, and treatment may be discontinued[6].

Romiplostim is a peptibody comprising four TPO-R binding domains with high affinity for the TPO-R and one carrier Fc domain.[7] Romiplostim stimulates growth and platelet production of megakaryocytes in blood marrow by binding to the extracellular domain of the TPO-R. The romiplostim molecule consists of two single-chain subunits, each consisting of 269 amino acid residues. Each subunit includes an IgG1 Fc domain and a specific domain consisting of two identical peptides (14 amino acid residues each) capable of interacting with the TPO-R.

A biosimilar is a biological medicine that is highly similar to a reference medicine in terms of structure, biological activity, PK/PD properties, efficacy, safety and immunogenicity profile. The romiplostim biosimilar GP40141 is now under development by pharmaceutical company GEROPHARM. In accordance with current regulatory requirements for conducting analytical comparability studies, several orthogonal complementary methods have been used for each type of quality parameter, such as primary structure, higher-order structures, impurities, and biological activity. The full range of analytical methods included 23 quality parameters. Preclinical in vivo studies were also conducted on the comparative pharmacodynamics of the romiplostim drugs in rats after single administration, as well as studies on the comparative pharmacodynamics, pharmacokinetics and safety in primates after single and multiple administrations.[8] The results served as evidence of non-clinical comparability between GP40141 and Nplate®. The aim of developing the romiplostim biosimilar GP40141 is to reduce the cost of the drug and therefore make the treatment more affordable among patients with ITP.

The aim of the study was to assess the PD comparability, as well as PK and safety parameters of GP40141 and Nplate® in healthy male volunteers.

## 2 | METHODS

### 2.1 | Study population

Eligible participants were healthy Caucasian male subjects aged between 18 and 45 years, with a total body weight between 60 and 100 kg and a body mass index between 18.5 and 30. The subjects were in good general health, determined by no clinically significant findings from their medical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements and clinical laboratory evaluations (complete blood count, coagulation tests, biochemistry profile and urinalysis). The subjects had to have a platelet count in the range of $150.0–306.0\times10^9$/L; this criterion allowed us to use variability data from previous studies,[9] considering the potential for target mediated drug disposition (TMDD), which is well described for romiplostim. Key exclusion criteria included a known history of clinically significant autoimmune diseases, any surgical intervention related to the spleen (including splenectomy), cardiac failure or history of thromboembolic events, certain blood conditions such as leukemia and lymphoma, and especially conditions involving immune mechanisms, such as autoimmune hemolytic anemias, as well as significant hypersensitivity, intolerance or allergy to any drug compound.

### 2.2 | Study treatments

Test drug (T) – GP40141, lyophilized powder for injection, 250 mcg (GEROPHARM). Reference drug (R) – Nplate®, lyophilized powder

for injection, 250 mcg (Amgen Europe B.V.). Each volunteer was randomly assigned to one of the drug sequences: RT or TR. The investigated drugs were administered to volunteers subcutaneously in the shoulder area at a dose of 3 mcg/kg as a single injection. The dose was chosen based on the information for medical use of the reference drug, as well as published data on the PK/PD properties of romiplostim and its safety.[9,10]

## 2.3 | Study design

This was a Phase 1, randomized, double-blind, single-dose, crossover comparative adaptive study performed in one research center located in Yaroslavl between July 2022 and December 2022 (NCT05652595). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice Guideline (E6), and local regulatory requirements. All subjects provided written informed consent before any screening procedures were carried out in accordance with local ethical committee regulations. The trial protocol was reviewed and approved by the Ministry of Health of the Russian Federation (Clinical trial authorization No. 365 and Date 03.06.2022) and by the independent ethics committee at the research center.

The trial was initially planned using an adaptive design with possible sample size recalculation. After obtaining PD data from the first 56 subjects, the interim analysis in terms of intraindividual variability of primary PD parameters was planned in order to estimate power and adjust the number of participants included (in case of failure to achieve the target power). The interim analysis was planned to be performed without unblinding.

The clinical part of the study consisted of a screening period and two treatment periods. After the screening period, which lasted for 14 days, the subjects enrolled in the study were randomly assigned to one of two groups. The first group received T in the first period and R in the second period. The second group received R in the first period and T in the second period. Each of the two treatment periods lasted for 33 days (4 days of inpatient administration of the treatment and evaluation of PK/PD and safety parameters, 29 days of outpatient evaluation of PK/PD and safety parameters). Between the administration of T or R on the first day of each treatment period, there was a 33-day washout period, during which no treatment is given to allow the effects to wear off.

## 2.4 | Study objectives and endpoints

The primary objective of this study was to establish equivalence between GP40141 and the reference romiplostim by comparing primary PD endpoints: the area under the platelet count curve from time 0 to the time of the last sampling for PD ($AUC_{plt}$) and the maximum observed platelet count ($P_{max}$). It is important to mention that time 0 (or the basal platelet level) for $AUC_{plt}$ was calculated as an arithmetic mean of the platelet counts obtained at 45, 30 and 15 min before the treatment. The secondary endpoints include the following: the maximum number of platelets count to the basal level of platelets ($P_{max}/P_0$) and the time to reach the maximum number of platelets count ($t_{Pmax}$). All pharmacokinetics endpoints were secondary in this study: the time of maximum observed serum concentration ($t_{max}$); the AUC from time 0 to the time of the last observable concentration ($AUC_{0\text{-}t}$); the maximum observed serum concentration ($C_{max}$); the serum terminal elimination half-life ($t_{1/2}$); the AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$). The zero time point for the assessment of PK parameters corresponds to 15 min before the treatment. The safety profile for GP40141 and the reference romiplostim was also evaluated.

## 2.5 | Sample size estimation

Variability of the main parameters ($AUC_{plt}$, $P_{max}$) needed to calculate the sample size was estimated based on review of the relevant literature.[9] An intrasubject variability of 29% was assumed for the most variable parameter ($P_{max}$). Considering the variability and possible dropouts, 56 subjects (28 per sequence) were randomized to provide at least 90% power to show the 90% confidence interval (CI) of the ratio of means for $AUC_{plt}$ and $P_{max}$ between two drugs to be within the 80% and 125% equivalence limits.

## 2.6 | PK/PD evaluation

During each period, 21 samples (containing 6 mL of venous blood) were collected from all participants at regular time intervals to assess the serum concentration of romiplostim (PK evaluation). In the inpatient setting, 13 blood samples were collected for the PK evaluation: before drug administration (−15 min) and 1, 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, and 72 h later. As part of outpatient visits, another 7 samples for PK evaluation were collected at 4, 5, 6, 8, 10, 12, 16, and 20 days after drug administration.

During each period, 20 samples (containing 2 mL of venous blood) were collected from all participants at regular time intervals to assess the PD parameters: −45, −30, −15 min predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, and 32 days postdose. Most of the PD samples were collected at the same time as PK samples, except for points at −45 and − 30 min, as well as points on the following days after T or R injection: 14, 18, 22, 24, 28, and 32.

To obtain serum samples for the bioanalytical part, the blood samples (collected in test tubes with clotting activator) were stored for 30 min at room temperature before being centrifuged at 3000 rpm for 15 min. The supernatant was transferred into clean tubes. Romiplostim determination in serum was performed by a validated quantitative enzyme immunoassay (ELISA) method using a Multiscan GO (Thermo Scientific) analyzer. The assay measured free romiplostim concentrations in human serum. The lower limit of quantification

for the method was 1.00 pg/mL, and the upper level of quantification was 120 pg/mL. The performance of the method during the validation was acceptable: intraassay precision (CV) and accuracy (% of nominal) ≤ 15%. Incurred sample reanalysis demonstrated the reproducibility of drug concentrations in the study samples.

An analysis of the blood samples (collected in EDTA tubes) to assess the platelet count was performed using a standard automated hematology analyzer (MEK 7300 K, Nihon Kohden) in the local laboratory at the research center. Based on platelet count at the time intervals listed above, primary and secondary PD endpoints were calculated: $AUC_{plt,}$ $P_{max,}$ $P_{max}/P_0$, and $t_{Pmax}$.

## 2.7 | Safety evaluation

The safety and tolerability of both studied drugs were also assessed. Safety and tolerability were analyzed in all subjects who received at least one administration of the investigated drug (T or R). Throughout the trial, adverse events (AEs) were monitored and all participants underwent physical examination, assessment of vital signs, ECG recording, and laboratory blood and urine testing. AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) – the version used was the current version as of when the last participant finished the study. The safety endpoints were summarized descriptively, as were the baseline demographic characteristics.

## 2.8 | Statistical analysis

The biosimilarity of the compared drugs was concluded using an approach based on the estimation of 90% CI for the ratios of geometric mean values of the primary pharmacodynamic parameters ($AUC_{plt}$, $P_{max}$). The drugs were considered biosimilar if the boundaries of the estimated confidence intervals were within the following limits: 80%–125%.

The geometric means ratios (GMR) of GP40141 to the reference product, with corresponding 2-sided 90% adjusted and repeated confidence intervals (CIs), were calculated for each primary endpoint. Equivalence for each primary endpoint was declared if the 2-sided 90% repeated CI for the GMR of GP40141 to the reference product was entirely contained within the equivalence margins of 80.00% and 125.00%. Biosimilarity between GP40141 and the reference product was declared if equivalence was demonstrated for all primary endpoints. For all PK/PD parameters, descriptive statistics were presented.

The data analysis for this article was generated using software package R V3.6.3.

## 2.9 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY[11] and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22[12].

# 3 | RESULTS

## 3.1 | Study subjects or participants

A total of 56 healthy male volunteers were enrolled and randomly assigned to 1 of 2 treatment arms: T/R (28 subjects), and R/T (28 subjects). The per protocol population included all 56 randomized subjects. The baseline characteristics of the subjects are given in Table 1.

## 3.2 | Pharmacodynamics

The per protocol population was used to analyze PD data. The mean observed absolute platelet count-time profile values are summarized in Table 2. The PD curves of GP40141 and the reference romiplostim are shown in Figure 1. The mean $AUC_{plt}$ was 253366.65 ($10^9$/L × h) for GP40141 and 252053.01 ($10^9$/L × h) for the reference formulation, and the mean $P_{max}$ was 559.78 ($10^9$/L) for GP40141 and 546.27 ($10^9$/L) for the reference romiplostim. The mean time to $T_{Pmax}$ was approximately 283.71–292.29 h across the treatments. The 90% CI for the geometric mean ratios (T/R) for the primary PD parameters ($AUC_{plt,}$ $P_{max}$) were fully contained within the predefined equivalence limits of 80%–125%. Intraindividual variability coefficient was

**TABLE 1** Baseline characteristics of subjected volunteers.

| Characteristics | Subjects (*N* = 56), mean ± SD/% of *N* |
|---|---|
| Age, years | 29.54 ± 4.56 |
| Gender (males) | 56 (100.0%) |
| Ethnicity (Caucasian) | 56 (100.0%) |
| Body weight, kg | 78.5 ± 11.0 |
| Height, cm | 178.1 ± 7.5 |
| BMI, kg/m$^2$ | 24.7 ± 2.7 |
| Smokers | |
| • Yes | • 0 (0.0) |
| • No | • 56 (100.0) |
| • Previously | • 0 (0.0) |
| Alcohol | |
| • Yes | • 3 (5.4%)* |
| • No | • 53 (94.6%) |
| • Previously | • 0 (0.0) |
| Platelet count | 217.91 ± 32.85 |

BMI, body mass index; SD, standard deviation; *N*, number of randomized subjects.

*According to eligibility criteria alcohol consumption less than 10 units in a week considered acceptable.

**TABLE 2** Primary and secondary pharmacodynamic (PD) and pharmacokinetic (PK) endpoints (healthy volunteers, $N = 56$).

| PK/PD | Endpoint | GP40141 (*T*) mean (SD) | Nplate® (*R*) mean (SD) | T/R Gmean ratio (90% CI) |
|---|---|---|---|---|
| Primary endpoints | | | | |
| PD | $AUC_{plt}$, $10^9$/L×h | 253366.65 (60389.64) | 252053.01 (56857.98) | 1.00 (98.13%; 102.2%) |
| PD | $P_{max}$, $10^9$/L | 559.78 (170.63) | 546.27 (150.30) | 1.02 (97.56%; 105.80%) |
| Secondary endpoints | | | | |
| PD | $P_{max}/P_0$ | 2.67 (0.73) | 2.60 (0.65) | – |
| PD | $t_{Pmax}$, h | 292.29 (47.80) | 283.71 (35.78) | – |
| PK | $AUC_{0-t}$, pg/mL×h | 3181.84 (2251.56) | 2763.17 (1743.81) | – |
| PK | $AUC_{0-\infty}$, pg/mL×h | 3813.64 (2421.20) | 3445.15 (1830.33) | – |
| PK | $C_{max}$, pg/mL | 43.75 (27.87) | 40.06 (21.90) | – |
| PK | $t_{1/2}$, h | 78.50 (98.68) | 85.22(78.96) | – |
| PK | $t_{max}$, h | 42.93 (17.30) | 37.79 (17.46) | – |

Abbreviations: $AUC_{plt}$, area under the serum concentration-time curve from time 0 to the time of the last sampling for PD; $P_{max}$, maximum observed platelets serum concentration; $P_0$, baseline platelets serum concentration; $C_{max}$, maximum plasma concentration of romiplostim; $t_{Pmax}$, time to reach $P_{max}$; $t_{1/2}$, serum terminal elimination half-life; mean, arithmetic mean; $AUC_{0-\infty}$, the AUC from time 0 extrapolated to infinity; $AUC_{0-t}$, the AUC time from time 0 to the time of the last observable concentration; Gmean, geometric mean; SD, standard deviation; CI, confidence interval.

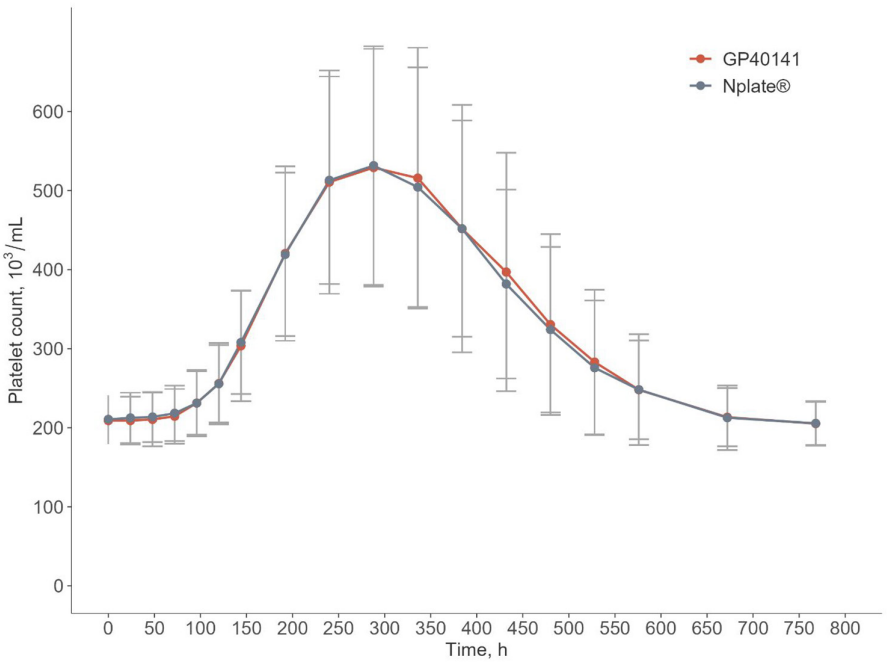


**FIGURE 1** Absolute blood platelet count during both periods after administration of GP40141 and reference romiplostim (mean ± SD, $N = 56$).

6.77% for $AUC_{plt}$ and 12.87% for $P_{max}$. Descriptive statistics for all PD data are given in Table 2.

## 3.3 | Pharmacokinetics

The per protocol population was used to analyze PK data. The PK endpoints after a single dose of GP40141 or the reference romiplostim are summarized in Table 2. The PK curves of GP40141 and reference romiplostim are shown in Figures 2 and 3. The mean PK parameters for $AUC_{0-t}$ were 3181.84 (pg/mL×h) and 2763.17 (pg/mL×h); the $C_{max}$ was 43.75 (pg/mL) and 40.06 (pg/mL) for GP40141 and the reference romiplostim, respectively. Descriptive statistics for all PK data are given in Table 2.

## 3.4 | Safety and tolerability

The safety analysis set (SAF) included all the randomized subjects who received at least one dose of T or R drug. In our study, the SAF population was equal to the PP population. During the course of the clinical trial, no adverse events were observed in relation to GP40141 or the reference romiplostim. According to the results of complete blood count test and biochemical profile,

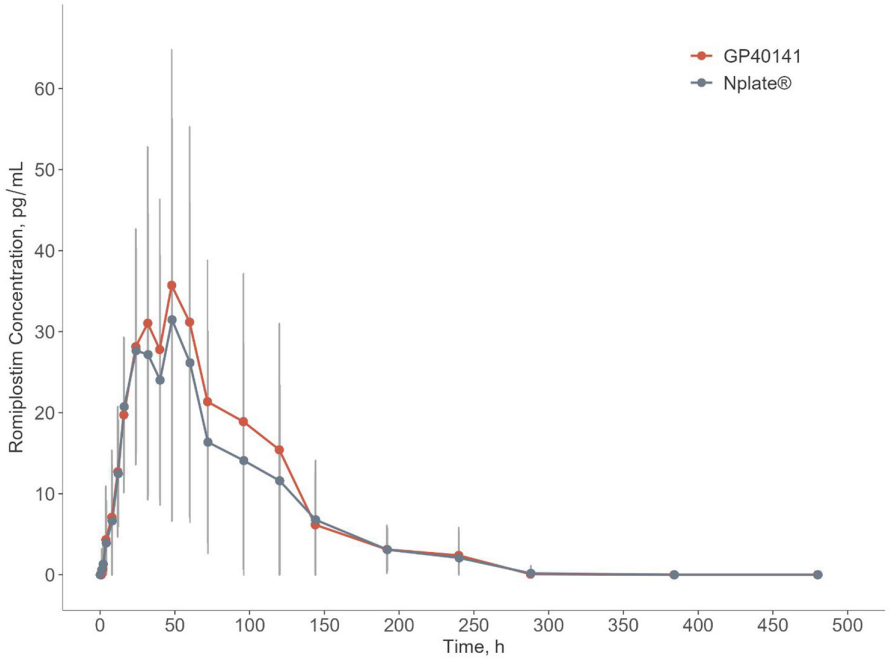


**FIGURE 2** Romiplostim serum concentrations during both periods after administration of GP40141 and reference romiplostim (mean ± SD, $N = 56$).

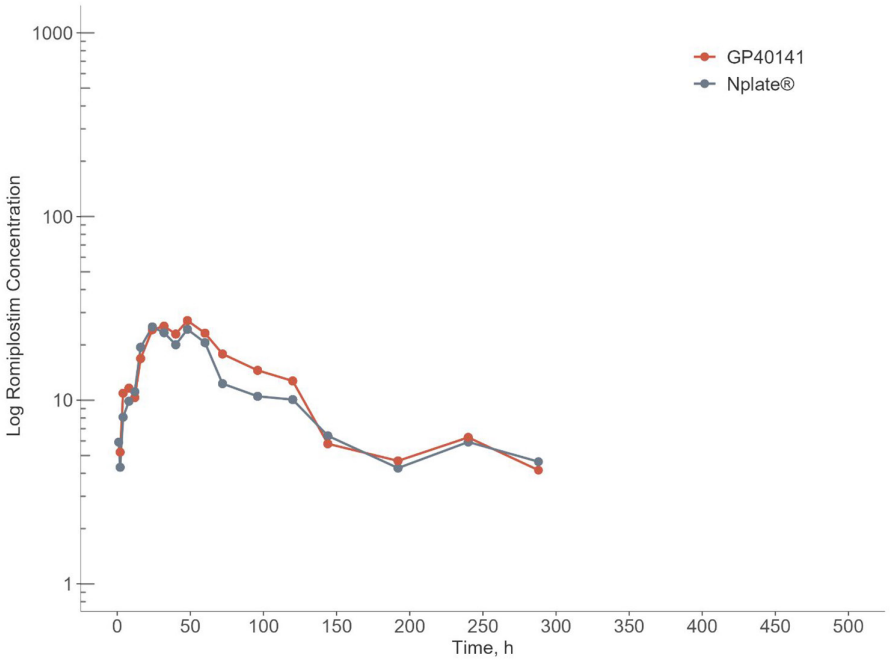


**FIGURE 3** Arithmetic mean pharmacokinetic profile on semilogarithmic scale of GP40141 and reference romiplostim.

there were no deviations from normal values or clinically relevant deviations. Urinalysis, assessment of the vital signs, physical examination and evaluation of injection site tolerability also showed no deviations.

## 4 | DISCUSSION

GP40141 is a biosimilar candidate to the reference product romiplostim. Its high similarity to the reference product has been demonstrated through an extensive exercise of physicochemical and functional characterization. Valid comparison of the in vitro pharmacodynamic properties of GP40141 and the reference product was conducted as part of the comparability program: functional similarity in terms of thrombopoietin-induced proliferation and phosphorylation of TPO-R and JAK2, and a similar binding profile to the TPO-R and neonatal Fc-receptor.[8] This study was part of the clinical development program and was conducted to provide evidence of similarity from the point of view of clinical pharmacology. In this study, the clinical pharmacology of GP40141 and the reference romiplostim

formulation was investigated. The goal of this phase 1 study was to demonstrate PD similarity and assess PK properties and safety parameters of the investigated formulations.

This clinical trial was performed in normal-weight healthy subjects without concomitant drug usage as a homogenous and sensitive population to investigate PK/PD. The eligibility criteria were designed to decrease TMDD-related PK/PD variability; for this reason, the range of baseline absolute platelet count in all subjects was standardized from 150.0 to 306.0 $\times 10^9$/L. These values correspond to the interval of $P_0$ values in healthy subjects involved in a previous study of romiplostim after subcutaneous administration.[9] To avoid a carryover effect, a known weakness of a crossover study, each treatment injection was separated by a 33-day washout, which is more than five half-lives (the mean half-live was in the range 78.5–85.22 h). This allowed for effective systemic elimination of the drug before initiation of subsequent treatment.

Due to the fact that there are no reliable data on PK/PD variability of romiplostim in healthy volunteers, to reduce the risks of an underpowered study, we planned an unblinded interim analysis after receiving PK/PD data for the first 56 subjects to evaluate the variability of primary PD endpoints. According to the analysis, recalculation of the sample size was not necessary.

Results from the present study showed a comparable PD profile of GP40141 to that of the reference romiplostim. The investigated romiplostim formulations were considered equivalent in terms of the primary parameters ($AUC_{plt}$, $P_{max}$) because the 90% CI for the geometric means ratios for both parameters fell within the predefined equivalence limits of 80%–125%, complying with international guidelines on biosimilarity.[13] The use of PD endpoints as evidence of biosimilarity is reasonable for romiplostim and is consistent with current scientific and regulatory requirements. Platelet count is a reliable surrogate pharmacodynamic marker that is used as a substitute for a clinically meaningful endpoint correlating to a decreased bleeding risk in ITP patients.[14,15]

It is important to note that the current clinical trial was the first of its kind to fully describe the pharmacokinetic profile of romiplostim in healthy male volunteers at a clinically relevant and safe dose (3 $\mu g \times kg^{-1}$ subcutaneously) after subcutaneous administration. This was possible due to sufficient sensitivity of the validated bioanalytical method (LLOQ was 1 pg/mL).

Both investigated formulations were well tolerated by healthy volunteers. AE, SAE, discontinuations for safety or tolerability reasons were not observed in this study.

## 5 | CONCLUSIONS

Thus, the results from the present study provide evidence to support the similarity between GP40141 and the reference romiplostim and contribute to obtaining complete evidence for biosimilarity in a phase III confirmatory trial as required by international guidelines.

## AUTHOR CONTRIBUTIONS

IM and AD designed the current clinical trial, and RD, IM and EZ directed the project. AK supported the project in the role of independent clinical pharmacology expert. SN managed the clinical part as principal investigator. AN was responsible for pharmacokinetics testing. BZ and MG supported data management and analyzed the data. All authors discussed the results and contributed to the final manuscript. AD, VS and VB wrote the manuscript.

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## CONFLICT OF INTEREST STATEMENT

This study was funded by GEROPHARM, Russia. The team of authors includes GEROPHARM employees.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

The trial protocol was reviewed and approved by the Ministry of Health of the Russian Federation (Clinical trial authorization No. 365 and Date 03.06.2022) and by independent ethics committee at the research center. All subjects provided written informed consent before any screening procedures were carried out in accordance with local ethical committee regulations.

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