A Phase I, Single-sequence, Open-label Study to Evaluate the Drug-Drug Interaction Between Hetrombopag and Cyclosporine in Healthy Chinese Subjects.

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What is already known about this subject

1. Hetrombopag is a novel small-molecule thrombopoietin receptor agonist developed for the treatment of severe aplastic anemia (SAA).

2. Hetrombopag is expected to be co-administered with cyclosporine in treatment-naïve SAA patients.

3. Cyclosporine is a known BCRP inhibitor and previous studies in vitro showed that hetrombopag is a substrate of BCRP.

What this study adds

1. Multiple doses of cyclosporine had minimal effects on hetrombopag exposure. A single dose of hetormbopag had no impact on the exposure of cyclosporine.

2. These results suggest that coadministration of hetrombopag and cyclosporine was well tolerated and no additional dose adjustment is warranted for this combination.

Abstract

Aims: This study aims to evaluate the drug-drug interaction（DDI） between hetrombopag and cyclosporine in healthy Chinese subjects.

Methods: Twenty-six eligible subjects enrolled in this single-center, single-sequence, open-label, DDI study with three treatment periods, receiving 5 mg hetrombopag once on day 1, 100 mg cyclosporine twice daily from day 11 to day 15, and 5 mg hetrombopag + 100 mg cyclosporine on day 16. Serial blood samples were collected for pharmacokinetic evaluation. Adverse events were monitored throughout the study.

Results: The plasma hetrombopag geometric mean ratios (GMRs) (90% CI) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of co-administration of hetrombopag with cyclosporine vs hetrombopag alone are 95.97% (70.08%, 131.43%), 105.75% (75.04%, 149.04%) and 104.19% (74.71%, 145.32%), respectively, indicating multiple doses of cyclosporine had minimal effects on hetrombopag exposure. The GMRs (90% CI) of C_{max} and $AUC_{ss,tau}$ for blood cyclosporine of co-administration vs cyclosporine alone were 100.49% (91.89%, 109.89%) and 100.81% (107.88%, 103.82%), respectively, suggesting a single dose of hetormbopag had no impact on the exposure of cyclosporine. Co-administration of hetormbopag with cyclosporine was generally well tolerated.

Conclusion:

No clinically significant DDI was observed when co-administration of

hetrombopag with cyclosporine. No additional dose adjustment is warranted for this combination.

Introduction

Severe aplastic anemia (SAA) is a hematologic disorder characterized by bone marrow hypoplasia and peripheral pancytopenia[1]. Immunosuppressive therapy (IST) with anti-thymocyte globulin (ATG) and cyclosporine (CsA) is the standard first-line treatment for patients with SAA who are ineligible for hematopoietic stem cell transplantation (HSCT) in China. In 2018,the US Food and Drug Administration (FDA) approved eltrombopag, a thrombopoietin receptor agonist (TPORA), in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients with severe aplastic anemia[2]. However, eltrombopag hasn't been approved for use in patients with SAA in many countries, including China. Hetrombopag is another novel small-molecule, orally bioavailable TPORA developed by Jiangsu Hengrui Pharmaceuticals Co. Ltd. On 16 June 2021, hetrombopag received its first approval in China as a second-line treatment for primary immune thrombocytopenia (ITP) and severe aplastic anemia (SAA) in adults[3]. The drug is also undergoing phase III development in China for treatment-naïve SAA patients as first-line treatment in combination with IST and patients with chemotherapy-induced thrombocytopenia.

Hetrombopag pharmacokinetics have been characterized extensively[3-6]. In

healthy volunteers receiving an oral dose of 2.5 mg, 5 mg, or 7.5 mg, hetrombopag plasma concentrations peaked twice, first after 1–2 h and the second after 7–10 h. It is highly bound to human plasma proteins (> 99%) with an elimination half-life ($t_{1/2}$) of approximately 23.2–39.8 h. Hetrombopag pharmacokinetics displayed high inter-individual variability in both healthy subjects and patients. A high-fat and-calorie meal taken with hetrombopag or within 1–2 h post-dose markedly reduced hetrombopag exposure. With a high-calorie, high-fat meal ingested after administration of hetrombopag olamine for 1 and 2 hours, the maximum plasma concentration decreased by 56% and 74.6% compared to the fast condition, and the AUC decreased by 44% and 61%, respectively. The previous in-vitro study indicated hetrombopag is not a substrate of P-glycoprotein (P-gp), nor organic anion transporting polypeptide (OATP; OATP1B1, OATP1B3), but it is a substrate of breast cancer resistance protein (BCRP), which is an efflux transporter that acts as barriers to tissue permeability, thereby regulating tissue exposure of their substrates. Cyclosporine inhibits of cytochrome P450 3A4 (CYP3A4), P-gp and OATP transporters (OATP1B1, OATP1B3, OATP2B1). Cyclosporine is also an inhibitor but not a substrate of BCRP, thereby could potentially increase the systemic exposure of drugs that are BCRP substrates[7-9].

The combination of hetrombopag and immunosuppressive therapy (such as cyclosporine) is currently being evaluated in patients with treatment-naive SAA.

This study was designed to evaluate the potential drug-drug interaction between hetrombopag and cyclosporine to guide the dosing of this combination.

Materials and Methods

The study was conducted at West China Second University Hospital (Chengdu, Sichuan, P.R. China) in accordance with the Declaration of Helsinki and the Good Clinical Practice of the International Conference on Harmonization (ICH-GCP). The study protocol and informed consent documents were approved by the Clinical Trial Ethics Committee of the West China Second University Hospital, Chengdu, Sichuan, P.R. China (Approval Number: Y2020019). This study was registered at www.clinicaltrials.gov as # NCT05088174. All individuals provided informed consent before any study-related activities.

Study design

This study was a single-center, single-sequence, open-label, drug-drug interaction study conducted in healthy subjects with three treatment periods (Figure1). In period 1 (day 1), twenty-six subjects received a single dose of 5 mg hetrombopag under fasted conditions followed by a 10-day wash-out. Period 2 started with the administration of cyclosporine 100 mg twice daily for consecutive 5 days under fasted conditions, which is sufficiently long to reach steady-state conditions. In period 3 (day 16), 5 mg of hetormbopag were co-administrated with cyclosporin under fasted conditions. Serial pharmacokinetic sampling was performed during day 1 to day 6, and day 14 to day 21. There was no washout

between periods 2 and 3 to allow for the assessment of repeated-dose cyclosporine effects on hetrombopag PK.

To ensure treatment compliance and continuous safety monitoring, subjects received all doses of study drugs at the clinical research center. In periods 1 and 3, subjects were domiciled at a minimum from the evening prior to dosing through at least 72 hours post-dose for pharmacokinetic sample collection, at which time they were discharged from the study center. The next two mornings, subjects returned to the study center under fasting conditions to finish the remaining pharmacokinetic samples collection (i.e., 96-, and 120-hour post-dose samples).

All study drugs were administered orally with ~240 mL of water. Food is prohibited within 4 hours after drug administration on days 1,15 and 16 when intensive PK sampling was performed. On days 11 to 14, dosing was followed by a 2-hour post-dose fast.

Participants

Healthy men and women (postmenopausal or surgically sterile) aged 18 to 55 years with a body mass index between 18 and 26 kg/m^2 were enrolled based on screening results of a medical history, physical examination, vital signs assessments, laboratory profile, and a 12-lead electrocardiogram (ECG). All male participants agreed to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and to refrain from donating sperm. Female subjects of childbearing potential had to use double-barrier local contraception during the

study. Subjects were excluded from the study if they reported a history of deep-vein thrombosis or other thromboembolic event(s). Use of any known inhibitors or inducers of drug-metabolizing enzymes within 28 days before the study start and through the course of the study was prohibited. Smoking and use of any prescription drugs and alcohol use were prohibited during the study.

Pharmacokinetic sampling and bioanalysis

Serial blood samples were collected in K2-EDTA collection tubes to determine plasma concentrations of hetrombopag and blood concentrations of cyclosporine. For hetrombopag, blood samples were collected on day 1 of period 1 and on day 16 of period 3 prior to dosing and at 0.5,1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120 hours after hetrombopag dosing. Plasma was separated by centrifugation at 1500g for 10 minutes at room temperature within 1 hour of sample collection and stored at −20 ˚C or lower until bioanalysis. For cyclosporine, blood samples were collected at the following time points: pre-dose in the morning and evening of day 14; and day 15 of period 2 and day 16 of period 3 at 0h(pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12 hours after dosing. At each collection time point, 4.0 mL blood samples were collected. Samples were collected separately into labeled K2-EDTA tubes for hetrombopag and cyclosporine analysis.

Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were used to measure the plasma concentration of hetrombopag and blood concentration of cyclosporine at Frontage Holdings Corporation (Shanghai,

China). The standard curve concentration range of hetrombopag is 0.2-150ng/ml, and concentration below the lower limits of qualification (LLOQ) was reported as 0.2ng/ml. The standard curve concentration range of cyclosporine is 5-2000ng/ml, and concentration below the LLOQ was reported as 5ng/ml.

Safety and tolerability assessments

Safety assessments included collecting all adverse events (AEs) and serious adverse events (SAEs) with severity and relationship to study drugs. Laboratory evaluations consisted of hematology, biochemistry, urinalyses, and coagulation function. Vital signs, physical condition, standard 12-lead ECG, and pregnancy were also assessed.

Pharmacokinetic parameters and statistical analyses

PK parameters were determined using standard non-compartment analysis: maximum plasma concentration (C_{max}), area under the plasma concentration–time curve from time zero(pre-dose) to infinity ($AUC_{0\text{-}inf}$), AUC from time zero to time of last quantifiable sample (AUC_{0-t}), area under the blood concentration time curve at steady state during a dosing interval($AUC_{ss,tau}$), time to maximum plasma concentration (T_{max}), terminal half-life(t½), apparent clearance (CL/F) and apparent volume of distribution (V_z/F). PK parameters determine hetrombopag included C_{max}, AUC, T_{max}, CL/F and V_z/F; for cyclosporine, included C_{max}, $AUC_{ss,tau}$, and T_{max}. PK computations were performed using Phoenix for WinNonlin (Certara USA,Inc, Princeton, NewJersey).

Sample size calculation was based on within-subject standard deviation (SD_{within}) for log-transformed PK parameters (C_{max}, AUC). Assuming the SD_{within} for PK parameters of hetrombopag were 0.5 to 0.65, a total of 22 subjects would provide 0.291 to 0.378 width for 90% CI of estimated treatment ratio, with 80% assurance. A total of 26 subjects were enrolled to account for dropouts.

All participants who received at least one dose of study treatment (hetrombopag or cyclosporine) were included in the safety analysis. The PK concentration analysis set comprised all treated participants with at least one drug concentration value. All treated subjects with at least one PK parameter of interest made up the PK parameter analysis set.

All pharmacokinetic parameters were summarized using descriptive statistics. The effect of cyclosporine on the pharmacokinetics of hetrombopag was assessed through a repeated measures analysis for the natural logarithms of C_{max} and AUC using data from day 1 of period 1 and day 16 of period 3. Similarly, the effect of hetrombopag on the pharmacokinetics of cyclosporine was evaluated by comparing cyclosporine pharmacokinetic parameters on days 16 of period 3 relative to those on day 15 of period 2. Following log trans-formation, C_{max}, AUC, were analyzed separately by mixed-effect analysis of variance (ANOVA), fitting terms for treatment as a fixed effect and patient as a random effect. The estimated mean and 90% confidence interval (CI) for treatment difference (hetrombopag + cyclosporine vs. hetrombopag or cyclosporine alone)

were back-transformed to obtain a geometric mean ratio and 90% CI of ratio. SAS 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all statistical analysis.

Results

Participants

Twenty-six healthy Chinese subjects were enrolled in this study, of whom 20 were male and 6 were female. Mean ± standard deviation (SD) age was 25.0(4.2) years (range 19–41 years). Mean (SD) BMI was 21.5 (2.2) kg/m^2. Overall, 22 subjects completed the study. Four volunteers discontinued the study due to AE (n = 3) or volunteer decision (n= 1). Overall, 22 volunteers received hetrombopag plus cyclosporine, 26 received hetrombopag alone and 24 received cyclosporine alone. All 26 subjects were included in the PK and safety analysis.

Pharmacokinetic Results

The mean plasma concentration-time profiles for hetrombopag when it was administered alone and with cyclosporine are shown in Figure 2. The pharmacokinetic parameters of hetrombopag in the presence or absence of cyclosporine and the statistical comparison analysis are presented in Table 1. The plasma hetrombopag geometric least squares mean (LSM) ratio (90% CI) of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of co-administration vs hetrombopag alone were 95.97% (70.08%, 131.43%), 105.75% (75.04%, 149.04%) and 104.19% (74.71%, 145.32%), respectively. Although the 90%CI of plasma hetrombopag geometric

LSM ratio did not fall within the traditional bioequivalence limits of 0.8–1.25, the point estimate was close to 1, indicating that administration of multiple doses of cyclosporine had minimal effects on hetrombopag exposure (C_{max} and AUC). In addition, both T_{max} and $t_{1/2}$ for hetrombopag were unaffected by co-administration with cyclosporine.

The mean blood trough concentration–time profiles for cyclosporine are shown in Figure 3. After repeated twice-daily dosing alone, blood cyclosporine concentrations achieved steady state by day 15.

The mean blood concentration-time profiles for cyclosporine when it was administered alone and with hetrombopag are shown in Figure 4. The pharmacokinetic parameters of cyclosporine in the presence or absence of hetrombopag and the statistical comparison analysis are listed in Table2.

No notable differences between cyclosporine blood concentration-time profiles were observed when cyclosporine was administered alone or with hetrombopag. The blood cyclosporine geometric LSM ratio (90% CI) of C_{max} and $AUC_{ss,tau}$ of co-administration vs cyclosporine alone were 100.49% (91.89%, 109.89%) and 100.81% (107.88%, 103.82%), respectively. 90% CIs of the geometric LSM ratios for $AUCss_{,tau}$ and C_{max} were within the no effects limits, demonstrating that a single dose of 5 mg hetrombopag did not affect exposure to cyclosporine.

Safety evaluation

All 26 subjects enrolled were included in the safety evaluation. Overall, 19/26 volunteers (73.1%) reported at least one AE, 1/22 (4.5%) with hetrombopag plus cyclosporine, 2/26(7.7%) with hetrombopag alone and 17/24 (70.8%) with cyclosporine alone. Three subjects discontinued from study treatment due to AEs. Of these three subjects, two subjects discontinued the study treatment due to abnormal alanine aminotransferase (ALT) values following administration of hetrombopag alone, one subject was due to vomiting which was considered mild and resolved spontaneously following administration of cyclosporine alone. No serious adverse events or deaths were reported for the study.

The most frequently reported treatment emergent adverse events (TEAEs) were indigestion, nausea, and diarrhea, fever, abnormal liver function tests. All TEAEs reported during the study were primarily grade 1 events (except for 1 incidence of a grade 2 vomiting post dose in 1 subject). No new safety findings for hetrombopag alone or with the cyclosporine, were identified in this study. The regimens were well tolerated by the healthy subjects in this study (Table 3).

Discussion

Cyclosporine, which is a widely used immune suppressant, is recommended by FDA as BCRP inhibitor for clinical DDI studies[10]. Cyclosporine has inhibitory effects on OATPs and CYP3A enzymes as well as P-gp. Hetrombopag was identified in-vitro as a substrate of BCRP, but not of other transporters (OAPTs,P-

gP). In addition, the human metabolite identification studies suggested that CYP3A4 plays either a minor or no role in the elimination of hetrombopag (unpublished data). Therefore, it was considered that hetromboapg and cyclosporine were potentially mechanistically interacted via BCRP. The primary objective of this study is to evaluate the impact of BCRP inhibitor cyclosporine on the exposure of hetrombopag. Given the potential increase in hetrombopag level when co-administered with cyclosporine, 5 mg was selected for hetrombopag dosage (lower than the approved starting dose for SAA patients), However, the results of this study demonstrated that co-administration of multiple dosing cyclosporine (100mg bid) with hetrombopag had minimal effect on the systemic exposure of hetormbopag. Although the 90%CI of plasma hetrombopag geometric mean ratio did not fall within the no effect limits of 0.8–1.25 due to the high intra-subject variability, the geometric mean ratio was close to 1 for both C_{max} and AUC. The result is not consistent with the hypothesis that cyclosporine was expected to increase hetrombopag exposure due to inhibition of mediated efflux. To interpret this result, we can hypothesize that BCRP inhibition by cyclosporine did not occur below the trigger concentration, as Xie et al. reported, cyclosporine has the potential to cause DDI with BCRP substrate drugs, under a high pharmacological concentration (measured inhibitory constant (Ki) in the Xie' study is ~ 6.7 to 7.8 μM, equivalent to 8.5-9.4 μg/ml)[11], which is nearly 8~10-fold higher than the peak cyclosporine concentration achieved in this study. According

to Chinese expert consensus on diagnosis and treatment of aplastic anemia, the target trough concentration of cyclosporine treatment for aplastic anemia is 100-200 ng/mL[12]. Trough blood concentration of cyclosporine at steady state after 100 mg twice daily dosing is around 100 ng/mL (Figure 3), suggesting that 100 mg is an appropriate starting dose for cyclosporine therapy. The DDI was not estimated for higher dose of cyclosporine in this study. Since platelet should be monitored regularly following any hetrombopag dose adjustment to achieve and maintain the desired target platelet count throughout therapy, clinically significant DDI between cyclosporine and hetrombopag is at low risk.

Platelet was monitored throughout the study mainly for safety purpose since hetrombopag is expected to increase platelets. Only slight increase (~10-20%) from baseline in platelet was observed in this study since hetrombopag in this study is administrated single dose at a low dose level (5 mg). Delayed PD response was observed in previous study, the platelet peaked 10-12 days after a single dose of hetrombopag[4]. Therefore, 10-day washout period is not enough to evaluate the difference in PD response of hetrombopag when administrated alone and co-administrated with cyclosporine.

The effect of hetrombopag on the PK profile of cyclosporine was also evaluated for exploratory purpose. The result indicated that a single dose of hetrombopag had no impact on the PK of cyclosporine. Cyclosporine is primarily metabolized by CYP3A4, and the metabolites are mainly excreted in the bile.

Approximately, 3% of cyclosporine undergoes renal elimination[13]. The in-vitro data suggested that hetrombopag had a weak inhibitory effect on CYP3A4 (IC50 > 10 μM) and did not show any CYP3A4 induction potential at concentrations up to 30 μM (unpublished data). Considering the high protein binding of hetrombopag(> 99%), CYP3A4 induction or inhibition is unlikely to occur at therapeutic hetrombopag concentrations up to 15 mg. Therefore, no dedicated stand-alone clinical DDI study was conducted to evaluate the impact of hetrombopag on CYP3A4 substrate. In this study, hetrombopag was administrated as a single dose of 5 mg, which is lower than the maximal therapeutic dose for SAA patients, to explore the potential effect on cyclosporine exposure. Furthermore, it was ethically difficult to conduct a clinical DDI study with 15 mg multiple dose of hetrombopag in healthy subjects, since the platelet counts remarkably increased in most subjects who received the 7.5 mg multiple dosing, suggesting the multiple dosing of the highest clinical dosage (15 mg) would not be allowable for a DDI study in healthy subjects from safety perspectives[4]. Based on the integrated in-vitro and in-vivo data, it is concluded that hetrombopag is unlikely to affect the PK profile of cyclosporine.

In conclusion, the data from this study suggest that the co-administration of hetrombopag with cyclosporine is safe and well-tolerated. No clinically significant DDI was observed when co-administration of hetrombopag with cyclosporine. Additional dose adjustment is not needed for the therapy.

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F.L and L.Z were involved in study design and data collection and analysis. F.L. and H.L. wrote the manuscript. All authors revised the manuscript and approved the final version for submission.

H. L., S. F., K.S. and Y. W. were the employees of Jiangsu Hengrui Pharmaceuticals Co Ltd. Hengrui contributed to the study design, research, and interpretation of data, and the writing, reviewing, and approving of the publication.

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Data availability statement

The data that support the findings of this study have not been made openly available.

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Table.1 Pharmacokinetic parameters of hetrombopag following administration of a single dose (5 mg) of hetrombopag alone or with cyclosporine (100 mg bid.)

Parameters(unit)	**Hetrombopag N=26**	**Hetrombopag + cyclosporine N=22**	**Geometric LSM ratio (90 % CI)** [a]
C_{max}(ng/ml)	19.0(104.3)	18.1(51.1)	95.97% (70.08%, 131.43%)
AUC_{0-t}(h*ng/ml)	405(139.4)	422(63.6)	105.75% (75.04%, 149.04%)
AUC_{0-inf}(h*ng/ml)	428(134.6)	438(64.5)	104.19% (74.71%, 145.32%)
T_{max}(hr)[b]	8.00(2.00~10.00)	8.00(1.02~10.00)	-
$t_{1/2}$(h)	23.0(52.9)	26.4(38.9)	-
V_z/F(L)	389(67.1)	434(50.8)	-
CL/F(L/hr)	11.7(134.6)	11.4(64.5)	-

Values are expressed as geometric mean (coefficient of variation %) unless specified otherwise

C_{max} maximum plasma concentration, AUC_{0-t} area under the plasma concentration–time curve from time zero to the time of last quantifiable concentration, AUC_{0-inf} area under the plasma concentration–time curve from time zero to infinity, t_{max} time to maximum plasma concentration, $t_{1/2}$ half-life of terminal phase, V_z/F apparent volume of distribution, CL/F apparent clearance

[a] Geometric least square mean (LSM) ratio of hetrombopag + cyclosporine/ hetrombopag

[b] Median(range)

Table.2 Pharmacokinetic parameters of cyclosporine following administration of a multiple doses of cyclosporine (100 mg bid.) alone or with a single dose (5 mg) of hetrombopag

Parameters(unit)	**Cyclosporine N=26**	**Cyclosporine + hetrombopag N=22**	**Geometric LSM ratio (90 % CI)** [a]
$C_{ss,max}$(ng/ml)	818 (16.9)	825 (24.9)	100.49% (91.89%, 109.89%)
$AUC_{ss,tau}$(h*ng/ml)	3020 (16.1)	3060 (18.5)	100.81% (107.88%, 103.82%)
t_{max}(hr)[b]	2.00 (1.00~2.00)	1.00 (1.00~2.00)	-

Values are expressed as geometric mean (coefficient of variation %) unless specified otherwise

$C_{ss\ max}$ maximum blood concentration at steady state, $AUC_{ss,tau}$ area under the blood concentration time curve at steady state during a dosing interval

[a] Geometric least square mean (LSM) ratio of cyclosporine + hetrombopag / cyclosporine

[b] Median(range)

Table.3 Summary of treatment-emergent adverse events (TEAEs) for all treated population.

System Organ Class (SOC) Preferred Term (PT)	Number (%) of subjects			
	Hetrombopag alone N=26	Cyclosporine alone N=24	Hetrombopag + cyclosporine N=22	Overall (N=26)
Number of subjects with TEAEs	2(7.7)	17(70.8)	1(4.5)	19(73.1)
Gastrointestinal disorders	0	11(45.8)	0	11(42.3)
Dyspepsia	0	6(25.0)	0	6(23.1)
Nausea	0	5(20.8)	0	5(19.2)
Diarrhea	0	4(16.7)	0	4(15.4)
Abdominal pain upper	0	2(8.3)	0	2(7.7)
Abdominal distension	0	1(4.2)	0	1(3.8)
Vomiting	0	1(4.2)	0	1(3.8)
Gingival pain	0	0	1(4.5)	1(3.8)0
General disorders and administration site conditions	0	4(16.7)	0	4(15.4)
Feeling hot	0	3(12.5)	0	3(11.5)
Asthenia	0	1(4.2)	0	1(3.8)
Hepatobiliary disorders	2(7.7)	1(4.2)	0	3(11.5)
Hepatic function abnormal	2(7.7)	1(4.2)	0	3(11.5)
Metabolism and nutrition disorders	0	1(4.2)	0	1(3.8)
Gout	0	1(4.2)	0	1(3.8)
Investigations	0	1(4.2)	0	1(3.8)
Neutrophil count decreased	0	1(4.2)	0	1(3.8)
Nervous system disorders	0	1(4.2)	0	1(3.8)
Headache	0	1(4.2)	0	1(3.8)
Cardiac disorders	0	1(4.2)	0	1(3.8)
Palpitations	0	1(4.2)	0	1(3.8)

Legend to Figures

Figure.1 Schematic of study design.

Figure. 2 Mean (standard deviation) hetrombopag plasma concentration–time profiles after administration of single doses of hetrombopag alone or in combination with cyclosporine.

Figure. 3 Mean (standard deviation) cyclosporine blood trough concentration at steady state.

Figure. 4 Mean (standard deviation) cyclosporine blood concentration–time profiles after administration of single doses of cyclosporine. alone or in combination with hetrombopag

Figure.1 Schematic of study design.

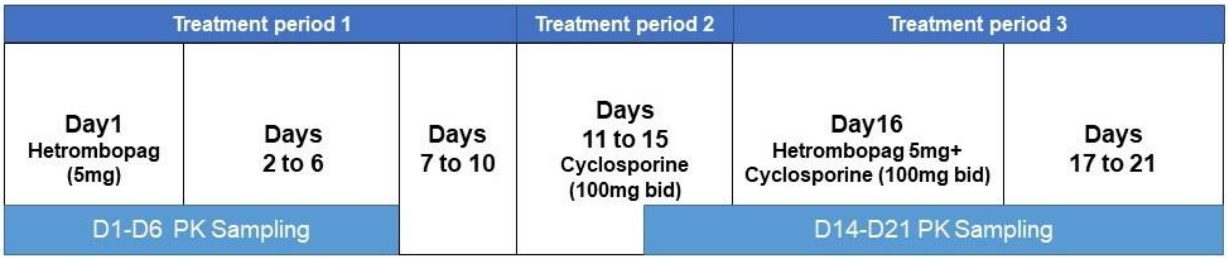

Figure. 2 Mean (standard deviation) hetrombopag plasma concentration–time profiles after administration of single doses of hetrombopag alone or in combination with cyclosporine.

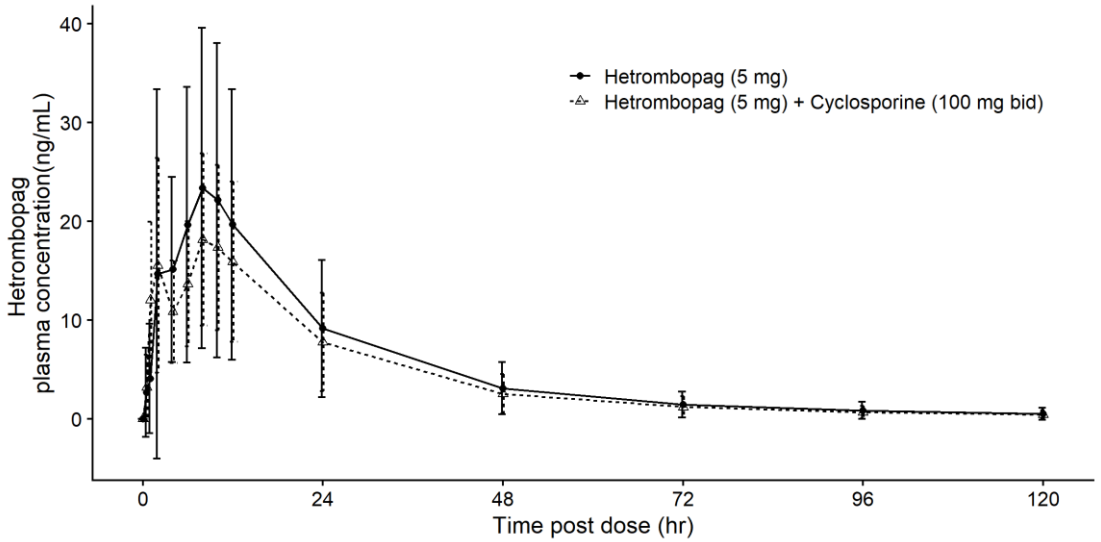

Figure. 3 Mean (standard deviation) cyclosporine blood trough concentration at steady state.

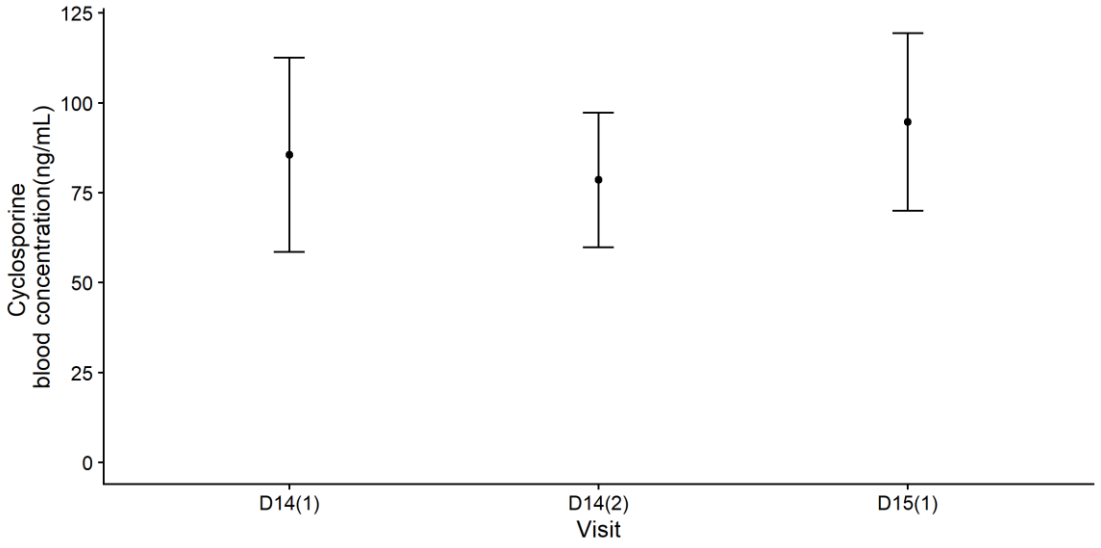

Figure. 4 Mean (standard deviation) cyclosporine blood concentration–time profiles after administration of single doses of cyclosporine. alone or in combination with hetrombopag