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Study No: TPL111716			
Title: A Phase I, Open-label, Single Sequence, Crossover Study Evaluating the Safety and the Pharmacokinetics of Lopinavir/Ritonavir and Eltrombopag Given Alone and when Co-administered in Healthy Adult Subjects.			
Rationale: Eltrombopag is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP). In addition to ITP, eltrombopag is being developed for the treatment of thrombocytopenia associated with other diseases that includes infections with Hepatitis C Virus (HCV). Since co-infection with HIV and HCV is relatively common, this study was designed to evaluate the potential drug-drug interaction between eltrombopag and the HIV protease inhibitor lopinavir/ritonavir (LPV/RTV) in order to guide dosing of this combination in HIV infected patients.			
Phase: I			
Study Period: 19 Jan 2009 - 11 Mar 2009			
Study Design: Phase I, open-label, single sequence, incomplete crossover study in healthy subjects evaluating the potential drug interaction between eltrombopag and LPV/RTV.			
TPL111716 Study Design			
PERIOD	DAYS	TREATMENT	ORAL STUDY DRUG
Period 1	Days 1-4	A	Day 1 Only- Single Dose of Eltrombopag 100mg
Period 2	Days 1-14	B	LPV/RTV 400/100mg BID Dosing
Period 3	Days 1-4	C	Day 1 Only- Single Dose of Eltrombopag 100mg in AM and LPV/RTV 400/100mg AM and PM Dose
<p>There was a 3-day washout between eltrombopag dosing on Period 1, Day 1 and initiation of LPV/RTV dosing on Period 2, Day 1 (Period 1, Day 4 and Period 2, Day 1 are the same calendar day).</p> <p>There was no washout between LPV/RTV dosing on Period 2, Day 14 and eltrombopag + LPV/RTV dosing on Period 3, Day 1 (Period 2, Day 14 and Period 3, Day 1 are consecutive calendar days).</p>			
The duration of each subject's participation in the study from screening to follow-up was approximately 8-9 weeks.			
Centres: One site: Buffalo Clinical Research Center, LLC, Buffalo, NY, USA			
Indication: Thrombocytopenia			
Treatment:			
Subjects received eltrombopag and LPV/RTV orally as follows:			
<ul style="list-style-type: none"> • Treatment A: Eltrombopag alone (100 mg single dose on Day 1 of Period 1) • Treatment B: LPV/RTV alone (400/100 mg BID on Days 1 through 14 of Period 2) • Treatment C: Eltrombopag 100 mg single dose + LPV/RTV 400/100 mg AM and PM on Day 1 of Period 3 			
The site obtained the LPV/RTV 400/100 mg tablets from local commercial supplies.			
Objectives:			
Primary Objectives:			
<ul style="list-style-type: none"> • To evaluate the impact of LPV/RTV on plasma eltrombopag PK following administration of LPV/RTV 400/100 mg BID for 14 days with a single dose of eltrombopag 100 mg in healthy adult subjects. • To evaluate the impact of eltrombopag on plasma LPV/RTV following administration of LPV/RTV 400/100 mg BID for 14 days with a single dose of eltrombopag 100 mg in healthy adult subjects. 			
Secondary Objectives:			
<ul style="list-style-type: none"> • To assess the safety of the combination of eltrombopag and LPV/RTV following administration of LPV/RTV 400/100 mg BID for 14 days with a single dose of eltrombopag 100 mg in healthy adult subjects 			
Primary Outcome/Efficacy Variable: The primary outcome variables were to evaluate the AUC(0-∞) and Cmax of plasma eltrombopag and the AUC(0-τ), Cmax, and C _t of plasma LPV and RTV.			
Secondary Outcome/Efficacy Variable(s): The secondary outcome variables were to evaluate the safety parameters including vital signs, clinical safety laboratory assessments, 12-lead ECG evaluations, and AE reporting; and to evaluate the AUC(0-t), %AUC _{ex} , t _{max} , t _{1/2} , and CL/F of plasma eltrombopag and the t _{max} and CL/F of plasma LPV and RTV.			
Statistical Methods:			
Pharmacokinetics (PK): Plasma eltrombopag, LPV, and RTV PK parameters were separately analyzed by analysis of			

variance (ANOVA), fitting terms for treatment and subject. Point estimates and 90% confidence intervals for the differences of Period 3 Day 1 (eltrombopag + LPV/RTV) – Period 1 Day 1 (eltrombopag) and Period 3 Day 1 (eltrombopag + LPV/RTV) – Period 2 Day 14 (LPV/RTV) were constructed using the appropriate error terms. The point estimates and associated 90% confidence intervals were then exponentially back-transformed to provide the point and 90% confidence interval estimates for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment.

The final planned analysis was performed after all subjects completed the study and the database was frozen.

Study Population:

The study population was comprised of healthy adult male and female subjects 18 to 64 years of age, and body mass index of 18.5 to 29.9 kg/m² inclusive.

Number of Subjects: 40	Treatment A	Treatment B	Treatment C
Number of subjects planned, N:	40	40	40
Number of subjects enrolled, N:	40	40	40
Number of subjects dosed, N:	40	40	40
Number of subjects included in All subjects (safety) population, n (%):	40	40	40
Number of subjects included in PK population, n (%):	40	40	40
Number of subjects completed as planned, n (%):	40	40	40
Number of subjects withdrawn (any reason), n (%):	0	0	0
Demographics	Treatment A	Treatment B	Treatment C
Age in Years, Mean (SD)	33 (11.9)	33 (11.9)	33 (11.9)
Sex, n (%)			
Female:	23 (58%)	23 (58%)	23 (58%)
Male:	17 (43%)	17 (43%)	17 (43%)
BMI in kg/m ² , Mean (SD)	25.3 (3.1)	25.3 (3.1)	25.3 (3.1)
Height in cm, Mean (SD)	169 (9.4)	169 (9.4)	169 (9.4)
Weight in kg, Mean (SD)	72.4 (12.9)	72.4 (12.9)	72.4 (12.9)
Ethnicity, n (%)			
Hispanic or Latino:	7 (18%)	7 (18%)	7 (18%)
Not Hispanic or Latino:	33 (83%)	33 (83%)	33 (83%)
Race, n (%)			
African American/African Heritage	9 (23%)	9 (23%)	9 (23%)
Asian – Central/South East Asian Heritage	1 (3%)	1 (3%)	1 (3%)
White – White/Caucasian/European Heritage	30 (75%)	30 (75%)	30 (75%)

Pharmacokinetics (PK), PK Endpoints:

Co-administration of LPV/RTV with eltrombopag resulted in an average 17% reduction in plasma eltrombopag AUC(0-∞) and no change in C_{max}; the t_{1/2} of eltrombopag was decreased by 41% on average as described in the table below.

Summary of Plasma Eltrombopag PK Summary and Treatment Comparison

PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	Treatment A	Treatment C	Treatment C vs Treatment A
AUC(0-∞) (µg.h/mL)	140 [121, 162] (48)	116 [100, 134] (49)	0.828 [0.734, 0.934]
AUC(0-t) (µg.h/mL)	127 [111, 145] (45)	112 [96.2, 129] (49)	0.879 [0.781, 0.990]
C _{max} (µg/mL)	11.1 [9.68, 12.6] (44)	11.5 [10.1, 13.0] (42)	1.04 [0.915, 1.17]
t _{max} ¹ (h)	4.00 (2.00-6.00)	4.00 (2.00-6.02)	ND

t _{1/2} (h)	23.6 [21.4, 26.0] (31)	13.9 [12.4, 15.5] (35.5)	0.588 [0.546, 0.635]
CL/F (mL/h)	716 [619, 829] (48)	865 [746, 1003] (49)	1.21 [1.07, 1.36]

1. median (minimum, maximum)

A= Eltrombopag 100 mg

C= Eltrombopag 100 mg + LPV/RTV 400/100 mg

Co-administration of eltrombopag with LPV/RTV had no impact on plasma LPV PK as described in the table below.

Summary of Plasma Lopinavir PK Summary and Treatment Comparison:

PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	Treatment B	Treatment C	Treatment C vs Treatment B
AUC(0- τ) (μ g.h/mL)	92.6 [84.4, 102] (30)	91.0 [82.9, 99.9] (30)	0.982 [0.945, 1.02]
C _{max} (μ g/mL)	10.7 [9.93, 11.6] (24)	10.5 [9.70, 11.4] (26)	0.980 [0.943, 1.02]
C τ (μ g/mL)	4.08 [3.40, 4.89] (62)	4.11 [3.48, 4.84] (55)	1.01 [0.940, 1.08]
t _{max} ¹ (h)	3.00 (2.00-5.03)	3.00 (1.00-5.00)	ND
CL/F (L/h)	4.32 [3.94, 4.74] (30)	4.40 [4.00, 4.83] (30)	1.02 [0.979, 1.06]

1. median (minimum, maximum)

B= LPV/RTV 400/100 mg

C= Eltrombopag 100 mg + LPV/RTV 400/100 mg

Co-administration of eltrombopag with LPV/RTV had no impact on plasma RTV PK as shown in the table below.

Summary of Plasma Ritonavir PK Treatment Comparison:

PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	Treatment B	Treatment C	Treatment C vs Treatment B
AUC(0- τ) (μ g.h/mL)	4.84 [4.21, 5.56] (46)	4.66 [4.05, 5.35] (46)	0.962 [0.885, 1.05]
C _{max} (μ g/mL)	0.911 (0.788, 1.05) (48)	0.841 [0.718, 0.984] (52)	0.923 [0.835, 1.02]
C τ (μ g/mL)	0.086 [0.072, 0.102] (58)	0.089 [0.076, 0.105] (54)	ND
t _{max} ¹ (h)	3.00 (2.00-5.00)	3.00 (1.00-5.00)	1.04 [0.971, 1.12]
CL/F (L/h)	20.7 [18.0, 23.8] (46)	21.5 [18.7, 24.7] (46)	1.04 [0.956, 1.13]

1. median (minimum, maximum)
 B= LPV/RTV 400/100 mg
 C= Eltrombopag 100 mg + LPV/RTV 400/100 mg

Safety results:

Most Frequent Adverse Events – On-Therapy

Number of Subjects with Adverse Events	A Eltrombopag 100 mg (N=40) ¹	B LPV/RTV 400/100 mg (N=40)	C Eltrombopag 100 mg + LPV/RTV 400/100 mg (N=40)
Ocular hyperaemia	0	0	2 (5%) ²
Diarrhea	3 (8%)	26 (65%)	3 (8%)
Nausea	5 (13%)	17 (43%)	0
Abdominal pain upper	2 (5%)	5 (13%)	0
Flatulence	2 (5%)	5 (13%)	0
Vomiting	1 (3%)	4 (10%)	0
Abdominal pain	0	4 (10%)	0
Stomach discomfort	0	2 (5%)	1 (3%)
Fatigue	1 (3%)	5 (13%)	1 (3%)
Nasopharyngitis	0	3 (8%)	1 (3%)
Decreased appetite	0	3 (8%)	0
Headache	5 (13%)	7 (18%)	2 (5%)
Dysgeusia	1 (3%)	2 (5%)	0

1. N= Number of subjects
2. %= Percentage of subjects

All AEs were mild in intensity, with the exception of one case of a moderate headache and one case of a moderate abdominal pain. No subject experienced a serious adverse event.

No unexpected treatment-related trends were seen in vital signs or clinical laboratory values.

The most frequent AEs were reported during Period 2 when LPV/RTV 400/100 mg BID was taken by the subjects. These AEs corresponded with some of the most common AEs of diarrhea, nausea, abdominal pain, asthenia, vomiting, headache, and dyspepsia that were reported in the product safety information for LPV/RTV.

Conclusion:

Safety Conclusions:

- All AEs were mild in intensity, with the exception of one case of a moderate headache and one case of abdominal pain.
- The most frequent AEs were reported with LPV/RTV in Period 2, and the AEs were consistent with the safety data in the product information for LPV/RTV.
- There were no deaths, SAEs, or treatment-related AEs leading to discontinuation reported and no healthy volunteers withdrew from the study.

Pharmacokinetics Conclusions:

- Co-administration of a single dose of eltrombopag 100 mg with repeat dose LPV/RTV 400/100 mg BID resulted in an average 17% reduction in plasma eltrombopag AUC(0-∞) and no change in Cmax.
- Co-administration of a single dose of eltrombopag 100 mg with repeat dose LPV/RTV 400/100 mg BID resulted in a no change in plasma LPV or RTV PK.

Overall Conclusion:

Eltrombopag and LPV/RTV may be co-administered without dose adjustment.

Publications: None at the time of this report.