Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

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Title of trial:	Effects of steady state Tipranavir/ritonavir or Darunavir/ritonavir or Ritonavir on platelet function, coagulation and fibrinolysis biomarkers in healthy subjects
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted] USA
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	To determine the effect of steady-state plasma concentration of Tipranavir/ritonavir (TPV/r) on platelet aggregation in healthy subjects and investigate the effect of TPV/r at steady state plasma concentrations on other platelet functions and biomarkers of coagulation and fibrinolysis.
Methodology:	Randomized, open-label, single center, controlled study of TPV/r or Darunavir/ritonavir (DRV/r) or Ritonavir (RTV) in healthy volunteers
No. of subjects:	
planned:	Enrolled: 300/ Entered: 60
actual:	Enrolled: 280/
	Treatment with Aspirin: entered: 52
	Treatment Tipranavir/ritonavir: entered: 23 (analysed for primary endpoint: 16)
	Treatment Darunavir/ritonavir: entered: 12 (analysed for primary endpoint: 12)
	Treatment Ritonavir: entered: 12 (analysed for primary endpoint: 12)
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers; ≥18 years and ≤50 years old; negative Human Immunodeficiency Virus (HIV) type 1 serology by Enzyme-Linked Immunosorbent Assay (ELISA) testing; non-smoker; no use of aspirin or any non-steroidal anti-inflammatory agent (including cyclooxygenase-2 [COX-2] inhibitors), dipyridamole, clopidogrel, ticlopidine or other anti-platelet drugs during 14 days prior to Visit 2 or during the study.

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Test product:	Tipranavir/ritonavir		
dose:	500 mg/200 mg BID		
mode of admin.:	Oral		
batch no.:	317983A		
Reference therapy:	Darunavir/ritonavir	Ritonavir	Aspirin
dose:	600 mg/100 mg BID	100 mg BID	325 mg
mode of admin.:	Oral	Oral	Oral
batch no.:	7AG647-X	441552E21 (for all arms)	225496E
Duration of treatment:	Single dose for Aspirin; 10 days for TPV/r, DRV/r and RTV		
Criteria for evaluation: **Efficacy**	No parameters for efficacy were evaluated		

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Clinical pharmacology:	**Pharmacodynamic Endpoint:** Primary pharmacodynamic (PD) endpoint – Inhibition of platelet aggregation in response to arachidonic acid (AA) at steady state TPV plasma concentrations (Visit 15) compared to baseline (Visit 6). **Key secondary pharmacodynamic endpoint:** Changes in platelet aggregation (in response to AA, collagen, and adenosine diphosphate [ADP]) from baseline to time points during treatment (after 1 day, and after 10 days of treatment), and after discontinuation of treatment (1 and 2 days after last dose of treatment). Comparisons were made between TPV/r and each of the DRV/r and RTV treatment groups. Additional analyses were performed on TPV/r subjects who showed at least 50% inhibition of platelet aggregation. For the biomarkers listed below, the changes from baseline to each time point during treatment period (i.e., 1 and 10 days after treatment initiation) and follow-up period i.e., (1 and 2 days after last dose of treatment) were compared and summarized descriptively with tests for an effect made within each treatment group and comparisons made between TPV/r and DRV/r, and TPV/r and RTV.

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Clinical pharmacology:

Pharmacodynamic (PD) Biomarkers:

Category 1: Platelet Function Biomarkers

- Platelet aggregation in response to
- Platelet aggregation in response to collagen
- Platelet aggregation in response to ADP
- Platelet Function Analyzer (PFA)-100 test with collagen-epinephrine (CEPI) and collagen-ADP (CADP) reported as Closure Time (CT)
- Urinary thromboxane B_2 (TxB_2) metabolites
- Bleeding time

Category 2: Coagulation Biomarkers

- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT)
- Fibrinogen
- Von Willebrand antigen (VWA)
- Anti-thrombin III (ATIII) antigen / activity
- Factors II, VII, IX, X

Category 3: Fibrinolytic Biomarkers

- Plasminogen activity
- Alpha 2-antiplasmin
- D-dimer
- Plasminogen Activator Inhibitor (PAI-1)

Secondary Pharmacokinetic (PK) endpoints:

C_{max}, Cp_{12h} or C_{last}, AUC_{0-12h}, T_{max}, CL/F, V/F, $T_{1/2}$ of TPV, DRV, and RTV.

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Clinical pharmacology:	**Pharmacokinetic – Pharmcodynamic relationships**: All analyzed PD parameters (as percent change from baseline) were matched with corresponding trough levels obtained during treatment and after treatment and additional PK parameters AUC and C_{max} obtained on day 10 (steady-state) of dosing. Additional relationships between the above PK parameters and all analyzed PD parameters were assessed in TPV/r subjects with and without a 50% change in platelet aggregation in response to AA and CEPI CT. Post-hoc within subject comparisons were performed between the effect of single dose aspirin (visit 3/visit 2) and the effect of each of the three treatment groups (TPV/r, DRV/r, and RTV) on platelet functions. These comparisons were made for AA-, collagen-, and ADP-stimulated platelet aggregation, CEPI CT, CADP CT, urine TxB_2 metabolites, and bleeding time.
Safety:	Primary Safety Endpoints: None Secondary Safety Endpoints: Treatment-emergent adverse events (AEs) and laboratory test abnormalities.

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Statistical methods:

1. Primary analysis determined the mean (95% CI) percent reduction in platelet aggregation in response to AA.
2. Secondary analyses consisted of 2-sided t-tests that compared the changes from baseline (Visit 6) to each following on treatment (7, 15) and post treatment (16, 17) visits between TPV/r arm and DRV/r and RTV arm. Due to the small numbers of subjects and numerous number of statistical tests on correlated PD biomarker tests, these comparisons should be considered strictly exploratory.
3. Proportions of subjects with at least 50% reduction in platelet aggregation in response to AA, ADP and collagen from baseline (Visit 6) to all subsequent platelet aggregation assessments were obtained and compared between the treatment groups by Fisher's exact test.
4. Linear regression analyses were performed to explore PK-PD relationships.
5. PK-PD relationships were further examined by Wilcoxon-Mann Whitney (WMW) tests between subsets of subjects within each treatment group that had or did not have a 50% inhibition in platelet function assays. Additional WMW tests compared within same subjects the effect of single dose aspirin on platelet functions with that of the different treatment groups.

SUMMARY – CONCLUSIONS:

EFFICACY:
Efficacy results: N/A

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Clinical pharmacology results:

Primary PD endpoint:

Tipranavir significantly reduced arachidonic acid (AA)-induced platelet aggregation by 43.2 % (AUC). Eight of 21 and 7/16 TPV/r treated subjects showed complete (100%) inhibition of AA-induced platelet aggregation 1 day after first dose and on day 10 (steady state) of dosing.. Two of 16) TPV/r subjects that completed 10 days of dosing did not show any inhibition of AA-stimulated platelet aggregation. This lack of an effect was observed despite adequate TPV trough concentrations in these subjects. In the subset of TPV/r treated subjects with reduced or completely inhibited AA-stimulated platelet aggregation the effect was consistently and rapidly reversed in all subjects within two days after last TPV/r administration. There was no correlation between TPV trough concentrations throughout the dosing interval, additional pharmacokinetic (PK) parameters (AUC and C_{max}) at TPV steady-state and the effect on platelet aggregation in response to AA.

Secondary PD endpoints:

DRV/r treatment had no effect on AA-induced platelet aggregation. RTV treatment resulted in a mean decrease of 25% (95%CI, 49.8% to 0.3% reduction) in AA-induced platelet aggregation from baseline to day 10 of dosing.

Other platelet function biomarkers:

The PFA-100® closure time (CT) with collagen-epinephrine cartridge (CEPI) was increased ≥50% in 15/21 TPV/r treated subjects 1 day after dosing and in 8/16 subjects at TPV steady state (Table 15.7.1.2:23). Prolongation of the CEPI CT was reversed in 13/15 and 14/15 subjects respectively 1 day and 2 days after last TPV/r dose. There was no significant TPV dose-response relationship for the increase in CEPI closure time. Three (30%) of the ten TPV/r subjects that had complete inhibition of AA-induced platelet aggregation (AUC) either one day after the first dose or at steady state, did not show prolongation of greater 50% in CEPI CT at the same time points. This suggests that there was only partial overlap of subjects in whom both AA-dependent platelet aggregation and CEPI closure time was inhibited by TPV/r.

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Clinical pharmacology results (continued):

Comparison between aspirin and TPV effect on platelet aggregation:

A single 325 mg dose of aspirin reduced AA-AUC in all 45 subjects and increased CEPI CT in 38/45 subjects by ≥50%, including subjects in the TPV/r group in whom platelet aggregation and/or CEPI closure time did not change, or changed less than 50%. When the absolute reduction of platelet aggregation in response to AA was compared in individual subjects between aspirin and TPV, inhibition of AA-dependent platelet aggregation by aspirin was more complete ($p = 0.0147$). Most of all subjects had complete inhibition of AA-stimulated platelet aggregation, and overall reduction from baseline AA-AUC (before aspirin mean ±SD, 459±106) was almost complete for the group of 45 subjects following a single dose of aspirin (after aspirin 7.1±14.6). Increase in CEPI CT after a single dose of aspirin was significantly higher when compared to the increases in CEPI CT at steady-state TPV ($p = 0.0135$). Aspirin also reduced collagen-stimulated platelet aggregation (mean reduction of 102±55.8) and TPV had no such effect within the same subjects (mean increase± SD from baseline to 1 day/10 days of TPV/r administration 117±77/ 98±136).

TPV/r, DRV/r and RTV had no effect on bleeding time, and no consistent effect on platelet aggregation in response to collagen or ADP at any observed time points during the study. Urinary TxB_2 metabolite levels were highly variable, and were increased significantly at steady state, and 2 days after the last dose in the TPV/r group.

Coagulation Biomarkers: All included coagulation biomarkers Fibrinogen, VWA, ATIII, Factors II, VII, IX, and X increased moderately from baseline to steady state TPV/r, and remained elevated two days after the last dose of TPV/r. Absolute activity levels of factors II, VII, and IX, and VWA however remained within the normal reference range. Prothrombin time and activated partial thromboplastin times remained well within the normal limits in all treatment groups TPV/r, DRV/r, and RTV.

Fibrinolytic biomarkers: Small to moderate increases in plasminogen and PAI-1 levels/activities were observed in all groups TPV/r, DRV/r and RTV, and levels of alpha-2 antiplasmin and d-dimer did not change.

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Clinical pharmacology results (continued):	**Pharmacokinetic endpoints**: Overall, TPV plasma trough levels were similarly variable between subjects and slightly lower when compared to previous healthy volunteer studies. However, TPV exposure was adequate. TPV trough levels (geometric Mean [µM]/CV% gMean) were highest after 2 days of dosing (51.7/105.7), and approximately 50% lower at TPV steady state (24.1/80.5), due to the net effect of CYP3A4 enzyme induction by TPV/r treatment. TPV trough levels rapidly declined after the last dose (Visit 16: 1.8/77.9, Visit 17: 0.25/95.6). Steady state trough levels (gMean, [ng/mL]/CV% gMean) for the comparators DRV(5358/31) and RTV(15:516/44.9) were similar as has been previously observed, and confirmed adequate subject exposure. **Relationship between pharmacokinetic parameters and PD biomarkers:** There was no consistent association between studied drug PK parameters and changes in platelet function tests, and biomarkers of coagulation and fibrinolysis in any of the treatment groups TPV/r, DRV/r and RTV.
Safety results:	There was no serious adverse event (SAE) in this trial. Proportion of subjects with at least one adverse event (AE) was higher in the TPV/r arm (69%) when compared to DRV/r (50%) and RTV (58%) arms, but not any higher than reported in previous studies with TPV/r in healthy subjects. All AEs reported in this study were consistent with the previously described AE profiles of each of the treatments. There were no early discontinuations in DRV/ r and RTV arms. Seven of the 23 subjects randomized to TPV/r arm prematurely discontinued from the study. Five of the 7 subjects discontinued due to increases in liver function test (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]), one subject due to skin rash and pruritus, and one subject due to non-compliance with the protocol (e.g., use of aspirin or other anti-platelet drug). Study subjects who were discontinued with ALT/AST elevations were clinically without symptoms but discontinued as per protocol when ALT or AST were >2.5 x upper limit of normal (ULN). All 6 subjects with early discontinuation completely recovered from these AEs during follow-up.

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Conclusions:	Taken together, TPV/r effect on platelet aggregation in response to AA stimulation and CEPI closure time is smaller, and less consistently observed in subjects exposed to TPV/r, when compared to the effect of a single dose of aspirin. TPV/r did not reduce coagulation factors, nor did TPV/r or any of the comparator treatments (DRV/r, RTV) prolonged bleeding time, PT, or aPTT. The overall clinical relevance of TPV/r effect on platelet aggregation is unknown at the current time. Despite the overlap in the effects of aspirin and TPV/r to inhibit AA-stimulated platelet aggregation and prolong CEPI closure time, the mechanism of inhibition is different between the two treatments. Aspirin irreversibly inhibits COX-1 and TPV/r has no such effect on COX-1 activity. Pre-clinical data show that TPV functions as a TxA_2 receptor antagonist and weak inhibitor of TXS. Based on the results of this study, a single dose of aspirin has a more profound effect on two pathways of platelet aggregation when compared to TPV/r. In contrast to TPV/r, aspirin also reduced collagen-stimulated platelet aggregation. Therefore, the well-established, and clinically relevant effects of aspirin on platelet aggregation and aspirin-associated risk of bleeding can not be simply ascribed to TPV.