Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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Title of study:	A single-centre open-label study in healthy adult volunteers to assess the pharmacokinetic interactions between steady-state TPV (500 mg) and single-dose and steady-state atazanavir (300 mg QD) in the presence of ritonavir (100 mg)
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	
Clinical phase:	I
Objectives:	To investigate the effects of steady-state TPV/r (500 mg/100 mg BID) on the single-dose and steady-state pharmacokinetics of Atazanavir (300 mg QD) co-administered with Ritonavir (100 mg). To investigate the effects of single-dose and steady-state Atazanavir (300 mg) on the steady-state pharmacokinetics of Tipranavir and Ritonavir.
Methodology:	Open-label, sequential dosing study in healthy male and female volunteers administered TAZ/r (300 mg/100 mg QD) alone, TPV/r (500 mg/100 mg) alone, and TPV/r (500 mg/100 mg BID) in combination with TAZ (300 mg QD). Due to the CYP3A inhibitory effect of TAZ, co-administration of TAZ with TPV/r 500 mg/200 mg could have resulted in increased plasma concentrations of TPV. This could occur as the result of inhibition of CYP3A directly by TAZ and/or indirectly by increasing concentrations of the CYP3A substrate RTV. The higher dose of RTV could also affect TAZ pharmacokinetics leading to an increase in plasma TAZ concentrations. Given that CYP3A is involved in the metabolism of all three drugs (TPV: inducer and substrate; RTV: inhibitor and substrate; TAZ: inhibitor and substrate), TPV/r 500 mg/ 100 mg BID co-administered with TAZ 300 mg QD was compared to TAZ/r 300mg/ 100mg QD to reduce risks of higher drug concentration-related adverse events in the healthy subjects participating in this study."

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No. of subjects:	
planned:	entered: 30
actual:	enrolled: 26
	Treatment A: TAZ/r entered: 21 treated: 21 analysed (for primary endpoint): 21 Treatment B: TPV/r entered: 14 treated: 14 analysed (for primary endpoint): 14
	Treatment C: TPV/r + TAZ entered: 14 treated: 14 analysed (for primary endpoint): 14
Diagnosis and main criteria for inclusion:	Males and females of any race, in good health and between the ages of 18 and 60 years, inclusive. Negative HIV, Hepatitis B and Hepatitis C serology.
Test product:	Tipranavir capsules
dose:	500 mg BID
mode of admin.:	oral
batch no.:	PD-2448
Duration of treatment:	17 Days
Test product:	Ritonavir capsules
dose:	100 mg QD Days 1-9; 100 mg BID Days 16-32
mode of admin.:	oral
Lot no.:	PD-2556
Duration of treatment:	26 Days
Test product:	Atazanavir capsules
dose:	300 mg QD
mode of admin.:	oral
Lot no.:	PD-2557
Duration of treatment:	18 Days
Reference therapy:	Not applicable

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Criteria for evaluation:

Efficacy: Not applicable, there were no efficacy endpoints.

Pharmacokinetics: Primary endpoints:

- To determine the effects of steady-state TPV on the single-dose and steady-state pharmacokinetics of TAZ co-administered with RTV.
- To determine the effects of single-dose and steady-state TAZ on the steady-state pharmacokinetics of TPV and RTV.

Pharmacokinetics (continued): Secondary endpoints:

- Determination of additional pharmacokinetic parameters including T_{max}, CL/F, V, and $t_{1/2}$.

Safety: Subject safety was monitored by assessment of AEs at each visit. In addition evaluation of laboratory safety parameters including haematology, chemistry, and standard urinalysis were carried out during the screening visit and on Study Days 0, 5, 10, 15, 23, 27 and 33. Serum pregnancy tests profiles were carried out during the screening visit and on Study Day 33. All tests were conducted for subjects that prematurely discontinued the study.

Statistical methods: The following pharmacokinetic parameters were derived for TAZ, RTV and TPV using non-compartmental analysis:

- area under the plasma concentration time curve (AUC, trapezoidal rule) from 0 to 24 hr for TAZ (AUC0-24) and from 0 to 12 hr for TPV and RTV (AUC0-12h),
- maximum observed plasma concentration (Cmax)
- plasma concentration at a specified time after dosing (Cp24h for TAZ, Cp12h for TPV and RTV).

The geometric mean ratios and the associated confidence intervals (where a ratio of 1= no effect) were derived and evaluated for the primary pharmacokinetic parameters

To determine the effect of steady-state TPV/r on single-dose and steady-state Atazanavir the geometric means from the following days were used to calculate the geometric mean ratios:

- Day 1-2 (single-dose TAZ [300 mg-QD] co-administered with RTV [100 mgs-QD]) to Day 24-25 (single-dose TAZ [300 mg-QD] + steady-state TPV/r [500/100 mg-BID])

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- Day 9-10 (steady-state TAZ [300 mgs-QD] co-administered with RTV [100 mgs-QD]) to Day 32-33 (steady-state TAZ [300 mgs] + steady-state TPV/r [500/100 mg-BID])

To determine the effect of single-dose and steady-state Atazanavir on steady-state TPV/r the geometric mean from the following days were used to calculate the geometric mean ratios:

- Day 23 (steady-state TPV/r [500/100 mg-BID]) to Day 24 (steady-state TPV/r [500/100 mg-BID]) + single-dose TAZ (300 mgs)
- Day 23 (steady-state TPV/r [500/100 mg-BID]) to Day 32 (steady-state TPV/r [500/100 mg-BID]) + steady-state TAZ (300 mgs)

SUMMARY – CONCLUSIONS:

Pharmacokinetics results:

The pharmacokinetics of atazanavir 300 mg qd coadministered with RTV 100 mg qd (TAZ/r 300/100 qd) were compared to the pharmacokinetics of atazanavir 300 mg qd when it was coadministered with TPV/r 500/100 mg bid.

Coadminsitration of steady-state TPV/r 500/100 mg bid with TAZ 300 mg qd resulted in decreases in TAZ AUC, Cmax and Cp_{24h}. The decrease in AUC was 39.4% (geometric mean ratio 0.61, 90% CI 0.51-0.72) after the first dose of TAZ was coadministered with TPV/r and decreased further to 67.8% (geometric mean ratio 0.32, CI 0.29-0.36) when TAZ was at steady-state. The decrease in Cp_{24h} was 68.8% (geometric mean ratio 0.31, 90% CI 0.23 – 0.42) after the first dose of TAZ was coadministered with TPV/r and decreased further to 81.2% (geometric mean ratio 0.19, 90% CI 0.15 – 0.24) when TAZ was at steady-state.

Coadministration of TAZ 300 mg with steady-state TPV/r 500/100 mg bid resulted in minor increases in TPV AUC (11.4% and 20.0% with first-dose and steady-state TAZ, respectively) and Cmax (6.6% and 8.4% with first-dose and steady-state TAZ, respectively). Larger changes occurred in TPV Cp_{12h} which increased 59.0% (geometric mean ratio 1.59, 90% CI 1.38 – 1.83) after the first dose of TAZ was coadministered with TPV/r and increased to 74.8% (geometric mean ratio 1.75, 90% CI 1.39 – 2.20) when TAZ was at steady-state (compared to steady-state TPV/r 500/100 mg bid administered alone).

Coadministration of TAZ 300 mg with steady-state TPV/r 500/100 mg bid resulted in minor changes in RTV concentrations near the end of the 12-h dosing interval (-2.1% and 15.3% with first-dose and steady-state TAZ, respectively) but caused large increases in RTV AUC (56.8% and 50.9% with first-dose and steady-state TAZ, respectively) and Cmax (49.2% and 37.5% with first-dose and steady-state TAZ, respectively).

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Safety results:

Consistent with previous TPV trials [U03-3217, U04-3216, U03-3236, U04-1257, U04-3198], the most frequently observed AEs during this study were GI-related. The data presented in this report show that TPV/r administered alone or in combination with TAZ was well-tolerated with the majority of AEs occurring during TPV/r treatment being mild, self-limiting, and rarely required treatment intervention. No deaths or serious adverse events were reported in this study. No new TPV/r safety issues arose during this study.

Twelve of the 14 subjects (85.7%) treated with TPV/r (total, days 16-32) reported at least one AE during the study. Nine subjects (64.3%) reported GI-associated AEs and 6 subjects (42.9%) reported nervous system-associated AEs. The most common GI events were diarrhoea and nausea (64.3% and 21.4%, respectively) and the most common nervous system event was headache (42.9%).

Twenty-one subjects (100.0%) reported at least one AE during the TAZ/r treatment phase of the study. During the TAZ/r treatment period: 12 (57.1%) of subjects reported GI events with the most common being flatulence (33.3%) and diarrhoea (19.0%); 9 (42.9%) reported nervous system disorders with the most common being headache (33.3%); 10 (47.6%) of subjects reported eye ocular icterus; 7 (33.3%) reported hepatobiliary disorders; 6 (28.6%) of subjects reported fatigue; 6 (28.6%) of subjects reported laboratory investigation events with the most common being blood bilirubin increases (23.8%); and 5 (23.8%) of subjects reported skin/subcutaneous tissue disorders with the most common being morbilliform rash (9.5%).

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Safety results:

Seventeen subjects developed grades 3 and 4 hyperbilirubinemia during the TAZ/r treatment phase of this study. These elevations in bilirubin were not accompanied by increases in the levels of aminotransferases indicating that most likely cause for these abnormalities is atazanavir's well documented ability to inhibit UGT1A1 [P04-08626, R04-2837, R05-0302, R05-1558]. Five of these elevations were symptomatic (jaundice, ocular icterus and abdominal pain) leading to the premature discontinuations. Two additional subjects were discontinued during the TAZ/r period due to rash. One subject developed a none-confirmed grade 3 and 4 elevations PT and PTT, respectively, while on TPV/r. Both PT and PTT levels returned to normal within one day and remained normal for the remainder of the study. There were no other clinically relevant laboratory abnormalities, nor were there any AEs leading to discontinuations during the TPV/r treatment period. There were no clinically relevant changes in vital sign measurements (blood pressure and pulse rate).

The safety data presented in this report show that AEs occurred with the same or lower frequency (except for diarrhoea and nausea) and intensity during the TPV/r/TAZ treatment than TAZ/r alone treatment phase. This observation may have been due to the fact that TAZ concentration was drastically reduced when coadministered with TPV/r. Moreover, there were no new AEs reported during TPV/r treatment phases. No deaths or serious adverse events were reported and no TPV/r safety issues arose during this study.

Conclusions:

Although, the combination of TPV/r (500 mg/ 100 mg BID) with TAZ (300 mg QD) appeared to be at least as tolerable as TAZ/r alone in this healthy subject population, coadministration of TPV/r (500 mg/ 100 mg BID) with TAZ (300 mg QD) is not recommended due to the PK interaction of the combination leading to dramatic reduction in TAZ levels. This study will not repeat using the currently approved dose of TPV/r (500 mg/ 200 mg BID) due to significant decline in TAZ levels which is not likely to be overcome by increasing the RTV dose to 200 mg.