Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: APTIVUS®				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 22 DEC 06	**Number:** U06-2302	**Study period (dates):** 16 DEC 05 – 20 MAR 06		

Title of study:	Assessment of single-dose oral tadalafil pharmacokinetic characteristics when simultaneously co-administered with single-dose and steady-state tipranavir/ritonavir 500 mg/200 mg to healthy male volunteers
Investigator:	[redacted]
Study center(s):	[redacted]. France
Publication (reference):	Data of this study has not been published at present
Clinical phase:	I
Objectives:	To assess the effects of single-dose and steady-state tipranavir/ritonavir 500 mg/200 mg on the single-dose pharmacokinetics of tadalafil 10 mg
Methodology:	Open-label, transverse, mono-centre, two way crossover study
No. of subjects: **planned:** **actual:**	 entered:16 enrolled: 18 entered: 17 treated: 17 analysed (for primary endpoint): 17
Diagnosis and main criteria for inclusion:	Healthy males, age >18 years to < 55 years and weighing at least 40 kg; acceptable medical history
Test product: **dose:** **mode of admin.:** **batch no.:**	Tadalafil in combination with tipranavir/ritonavir Tadalafil (10 mg single dose) administered alone (Day 1) and in combination with tipranavir/ritonavir (500/200 mg twice daily) on Day 8 (with single-dose TPV/r) and on Day 16 (with steady-state TPV/r) p.o. Tadalafil (A117815) ; Tipranavir (PD-2652) ; Ritonavir (29366VA)
Duration of treatment:	Tadalafil, 3 days (on days 1, 8 and 16); tipranavir/ritonavir, 11 days (from day 8 to day 18)
Reference therapy: **dose:** **mode of admin.:** **batch no.:**	Tadalafil (10 mg) administered alone on day 1 10 mg p.o. Tadalafil (A117815)

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Criteria for evaluation:

Efficacy: Not applicable, there were no efficacy endpoints

Pharmacokinetics: Primary endpoints:

- Tadalafil pharmacokinetic parameters: AUC0-72h, AUC0-∞, Cmax and Cp12h

Secondary endpoints:

- Tipranavir pharmacokinetic parameters: AUC0-12h, Cmax and Cp12h
- Ritonavir pharmacokinetic parameters: AUC0-12h, Cmax and Cp12h
- Tadalafil, tipranavir and ritonavir pharmacokinetic parameters: clearance, volume of distribution, Tmax and t1/2

Safety: Physical examination, vital signs (BP, PR, temperature, respiratory rate), laboratory tests, adverse events, tolerability

Statistical methods: Safety and tolerability:

Adverse events were coded using MedDRA.

Pharmacokinetics:

The following pharmacokinetic parameters for tadalafil, tipranavir and ritonavir were derived using noncompartmental analysis: area under the plasma concentration time curve (AUC, trapezoidal rule), maximum observed concentration (Cmax) and concentration 12 hours after dosing (Cp12h).

In order to reach the primary goal of the study paired t-test (two sided, α=0.10) were performed. Moreover, calculation of two sided 90% confidence interval as a measure of uncertainty of the study results was provided. The 90% confidence intervals (CI) were constructed for the ratio of geometric means.

The following ratios of specified PK parameters with 90% confidence intervals was calculated: tadalafil with/without single-dose and steady-state TPV/r: AUC0-72h, AUC0-∞, Cmax and Cp12h; steady-state tipranavir and ritonavir with/without tadalafil: AUC0-12h, Cmax and Cp12h

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SUMMARY – CONCLUSIONS:

Pharmacokinetics results: Coadministration of tadalafil 10 mg with first-dose TPV/r 500/200 mg resulted in a 133% (2.3-fold) increase in tadalafil exposure (AUC0-∞), however no change in exposure occurred when tadalafil was coadministered with steady-state TPV/r.

The effect of tadalafil on first-dose tipranavir and ritonavir pharmacokinetics resulted in a 33% decrease in tipranavir Cp12h with less effect on Cmax and AUC0-12h (14% and 15% decreases, respectively); first-dose ritonavir pharmacokinetics were similarly affected with a 64% decrease in Cp12h and smaller decreases in Cmax and AUC0-12h (44% and 40%, respectively). When tadalafil was administered with TPV/r at steady-state, tipranavir geometric mean Cp12h decreased 19% (27.0 μM to 22.0 μM) with similar decreases in Cmax and AUC0-12h (10.1% and 15.0%, respectively). Corresponding decreases in ritonavir Cp12h (14.2%), Cmax (3.0%) and AUC0-12h (12.5%) also occurred. It is likely that the effect of tadalafil on tipranavir pharmacokinetics was indirect and the result of lower ritonavir exposure.

Safety results: Sixteen of the 17 subjects treated with TPV/r + TAD (94.1%) reported at least one AE during the study and consistent with the results of previous TPV/r trials the most frequently observed AEs were GI, general disorder and nervous system events (82.4%, 41.2% and 23,5%, respectively).

Almost all AEs were considered as related to Trial Drugs by the investigator but there were no premature discontinuations in this study and all subjects recovered from their AEs.

The vast majority of events occurred during the first 7 days of TPV/r initiation period (Day 8 to Day 14) and were observed in 15 subjects. No AE was reported more than 7 days after last dose of study drug was administred.

Among 7 subjects showing a Transaminase increase, 3 had grade 3 elevation. No grade 4 was observed. All subjects recovered prior to the end of study except one subject who still had elevated Transaminase at the follow-up visit. This subject had already elevated SGOT at screening.

The majority of the Transaminase increases occurred during the first 7 days of TPV/r + TAD initiation period (Day 8 to day 14).

There were no death or serious adverse event (SAE) reported during this trial.

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Conclusions:	The effect of a single dose of tadalafil on the pharmacokinetics of tipranavir and ritonavir resulted in small decreases in exposure after first-dose and steady-state TPV/r, however these decreases are not expected to have clinical importance. Coadministration of tadalafil with TPV/r 500/200 mg resulted in a 2.3-fold increase in tadalafil exposure with first-dose TPV/r and no change in tadalafil exposure with steady-state TPV/r. The clinical implications of these results indicate that if tadalafil is used within the first days of TPV/r treatment when ritonavir exposure is highest, then the lowest dose should be administered. However, after 7-10 days of TPV/r dosing, steady-state for tipranavir and ritonavir is achieved, ritonavir exposure is lower, and the prescribed dose of tadalafil may be used again. Tipranavir/r administered in combination with Tadalafil was safe and showed safety profile consistent with the known safety of Tipranavir/r administration.