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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Tipranavir (APTIVUS®)				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 28 November 2005	**Number:** U05-2261	**Study period (dates):** 17 January 2005 to 2 February 2005		

Title of study:	A single-centre, open-label study of multiple doses of tipranavir 500 mg and ritonavir 200 mg (twice daily) on the pharmacokinetic characteristics of methadone administered as a single dose in healthy volunteers.
Investigator:	[redacted]
Study centers:	[redacted] UK
Publication (reference):	None
Clinical phase:	I
Objectives:	The primary objective of this study is to characterise the effects of tipranavir 500 mg and ritonavir 200 mg (TPV/r; given twice daily) at steady-state on the pharmacokinetics of methadone administered as a single dose in healthy adult volunteers.
Methodology:	Open label study in adult healthy volunteers. The effects of a single dose strength of TPV/r at steady-state on the pharmacokinetics of a single dose of methadone will be determined by comparing the pharmacokinetic profile of methadone on study day 9 (+TPV/r) to the baseline pharmacokinetic profile of methadone on study day 1 (-TPV/r). The effects of a single dose of methadone on the steady-state pharmacokinetics of TPV/r will be determined by comparing the pharmacokinetic profile of TPV/r on study day 9 (+ methadone) to the pharmacokinetic profile of TPV/r on study day 8 (- methadone).
No. of subjects:	
planned:	entered: 15
actual:	enrolled: 15
	entered: 15 treated: 15 analysed (for primary endpoint): 14
Diagnosis and main criteria for inclusion:	Adult, male and female, healthy volunteers between the ages of 18 and 60 inclusive. Negative for HIV-1 or hepatitis A, B or C.
Test product:	Tipranavir (TPV) 250 mg soft elastic capsules, self emulsifying drug delivery system.
dose:	500 mg twice daily on study days 2 to 9
mode of admin.:	oral
batch no.:	PD-2456A

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Duration of treatment:	Eight days
Test product:	Ritonavir (RTV; Norvir®) 100 mg soft gelatine capsules
dose:	200 mg twice daily on study days 2 to 9
mode of admin.:	oral
batch no.:	132962E21
Duration of treatment:	Eight days
Test product:	Methadone hydrochloride 1mg/mL liquid (Physeptone®), sugar-free
dose:	5 mg once daily on study day 1 and study day 9 only
mode of admin.:	oral
batch no.:	538168
Duration of treatment:	One dose on study day 1 and one dose on study day 9
Criteria for evaluation:	
Efficacy:	Efficacy was not evaluated in this study. The following pharmacokinetics endpoints were evaluated: Primary endpoints: methadone pharmacokinetic parameters ($AUC_{0\ 24h}$, Cmax and C_{6h}; with/without TPV/r). Tipranavir and ritonavir pharmacokinetic parameters ($AUC_{0\text{-}12h}$, Cmax and C_{12h}) with/without methadone. Secondary endpoints: Mean Residence Time for tipranavir and ritonavir, $t_{½}$, Tmax, CL/F, V_z/F, for methadone and tipranavir and ritonavir.
Safety:	Spontaneous adverse events and laboratory assessments.

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Statistical methods:	The following pharmacokinetic parameters were derived using non-compartmental analysis: area under the plasma concentration time curve (AUC, trapezoidal rule; 0 to 24 hours for methadone and 0 to 12 hours for tipranavir and ritonavir), maximum observed concentration (C_{max}) and concentration at a specified time after dosing (methadone: 6 hours; tipranavir and ritonavir: 12 hours). Geometric mean ratios and 90% confidence intervals for methadone pharmacokinetic parameters for AUC_{0-24h}, C_{max}, and C_{6h} were calculated, where no effect = 1.00. Comparison days were Day 9 (with TPV/r) versus Day 1 (without TPV/r). Geometric mean ratios and 90% confidence intervals for tipranavir and ritonavir pharmacokinetic parameters for AUC_{0-12h}, C_{max}, and C_{12h} were calculated, where no effect = 1.00. Comparison days were Day 9 (with methadone) versus Day 8 (without methadone).
SUMMARY – CONCLUSIONS:	
Efficacy results:	No efficacy analyses were performed.

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Pharmacokinetic results:

Co-administration of single-dose methadone with steady-state TPV/r resulted in a decrease of methadone AUC of 52.8% and C_{max} of 55.1% in fasted subjects. The pharmacokinetics data in the current study suggest that patients treated with methadone may require monitoring for clinical symptoms of opiate withdrawal when TPV/r is co-administered. The reduction in methadone exposure observed in this study was comparable to that observed with Kaletra®, Norvir®, and ritonavir/saquinavir.

Co-administration of methadone with TPV/r resulted in a decrease in TPV AUC and C_{12h} by approximately 22.7% and 44.2%, respectively. C_{max} remained unchanged (geometric mean ratio 0.94; 90% CI 0.82, 1.07). The effect of this interaction on RTV pharmacokinetics was greater and resulted in a 61.7% decrease in AUC, 59.5% decrease in C_{max}, and 62.8% decrease in C_{12h}. Although subjects were to be fasted on Days 1 (methadone alone), 8 (TPV/r alone) and 9 (TPV/r + methadone), due to a protocol deviation subjects were fasted only on Days 1 and 9 and fed on Day 8. Therefore, the effect of methadone on steady-state pharmacokinetics of TPV/r is difficult to interpret.

In a previous study (BI Protocol 1182.11), the effect of a high-fat meal on steady-state TPV/r pharmacokinetics was investigated following twice-daily dosing of TPV/r 500/200 mg with co-administration of clarithromycin. In this study, plasma concentrations of TPV increased after simultaneous ingestion of TPV/r 500/200 mg with a high-fat meal. TPV AUC_{0-12h}, C_{max}, and C_{12h} increased by approximately 31%, 16%, and 75%, respectively (TPV/r + high-fat meal compared to TPV/r + light snack).

In the present study, TPV AUC_{0-12h}, C_{max}, and C_{12h} were greater on Day 8 (TPV/r alone) when compared to Day 9 (TPV/r + methadone) by approximately 31%, 9% and 85%, respectively. These data suggest that the higher TPV exposure on Day 8 compared to Day 9 could be attributed to a food effect. While the absolute values of TPV AUC_{0-12h}, C_{max}, and C_{12h} were greater in the 1182.11 study when compared to the present study as a result of the interaction with clarithromycin (AUC_{0-12h}, C_{max}, and C_{12h} increased 66%, 40% and 100% when compared to historical TPV results, the relative effect of food on the pharmacokinetics of TPV is consistent between the studies.

Safety results:

Nausea occurred in seven subjects (46.7%). Thirteen subjects (86.7%) had transient increases in ALT and/or AST, seven subjects (46.7%) had transient increases in triglycerides and three subjects (20.0%) had transient elevations in gamma glutamyl transferase to above the normal range. there were no deaths or serious adverse events.

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Conclusions:

Co-administration of single-dose methadone with TPV/r resulted in a decrease in methadone exposure (decreases of 52.8% in the AUC and 55.1% in the C_{max}) in fasted subjects. The pharmacokinetics data in the current study suggest that patients treated with methadone co-administered with TPV/r require monitoring for clinical symptoms of withdrawal and may require an increased dose of methadone.

The steady-state TPV exposure decreased (decreases of 22.7% in AUC and 44.2% in C_{12h}; C_{max} remained unchanged) when methadone was co-administered with steady-state TPV/r. However, the reason for the decrease in TPV exposure when co-administered with methadone is unclear as the subjects were fed on Day 8 (TPV/r alone) and fasted on Day 9 (methadone + TPV/r).

In conclusion, methadone systemic exposure decreased when co-administered with TPV/r. The decrease in methadone plasma concentrations observed in this study were comparable to those observed with Kaletra®, Norvir®, and ritonavir/saquinavir. Clinical monitoring for symptoms of opiate withdrawal in patients receiving TPV/r and methadone is recommended and patients may require an increased dose of methadone.