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: Tipranavir				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 30 December 2003	**Number:** U03-3605-01	**Study period (dates):** 1 July 2003 to 25 July 2003		**Date of Revision:** 10 May 2004

Title of study:	A Phase I multiple oral dose trial of Tipranavir 500 mg/Ritonavir 200 mg dosed to steady state followed by single-dose ^{14}C-radiolabeled tipranavir co-administered with Tipranavir 500 mg/Ritonavir 200 mg to characterize the excretion balance and metabolite profile of ^{14}C-radiolabeled Tipranavir in healthy male subjects
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	None
Clinical phase:	I
Objectives:	To characterize the pharmacokinetics of tipranavir and its metabolites including excretion and mass balance of parent compound and radioactivity at steady-state; to isolate, identify and quantify major metabolites of tipranavir in plasma, urine and feces.
Methodology:	This was an open label, single arm study. A single dose of 549 mg of unlabeled tipranavir and approximately 90 µCi of ^{14}C-tipranavir (2 mg) were coadministered with ritonavir (200 mg) to nine healthy male subjects who had already received 13 doses of tipranavir (500 mg) and ritonavir (200 mg) (TPV/r) to achieve steady state. After ^{14}C TPV/r was administered on Day 7, blood, urine and stool samples were collected while subjects continued receiving unlabeled TPV/r. Subjects stayed in the unit for at least 14 days and until the total radioactivity in a 24-hour collection period was <1% of the dose administered. Maximum length of stay was 21 days.
No. of subjects:	
planned:	12 subjects were planned to be enrolled and entered; nine were planned to receive radiolabeled TPV/r.
actual:	enrolled: 27 entered: 12; selected to receive ^{14}C-tipranavir: 9; treated with radiolabeled TPV: 9; analysed (for primary endpoint): 9

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Diagnosis and main criteria for inclusion:	Healthy, HIV-1 negative males, who were between 18 and 60 years old, who were within 20% of the normal height:weight range, who were able to swallow numerous large pills, and who were willing to abstain from alcohol, smoking, St. John's Wort, milk thistle, garlic supplements, Seville oranges, grapefruit or grapefruit juice and methylxanthine containing beverages or food for the duration of the study were eligible to participate.
Test product:	Tipranavir and ^{14}C- tipranavir
dose:	549 mg and 2 mg containing 90 µCi
mode of admin.:	Oral
batch no.:	PD-21249
Duration of treatment:	One dose (Day 7)
Test product:	Ritonavir (NORVIR-SEC®) Soft Gel Capsules (100 mg)
dose:	200 mg BID
mode of admin.:	Oral
batch no.:	Product Acquired Commercially Lot #932942E21
Duration of treatment:	Maximum of 21 days
Test product:	Tipranavir
dose:	500 mg BID
mode of admin.:	Oral
batch no.:	PD-21249
Duration of treatment:	Maximum of 21 days
Criteria for evaluation:	
PD and PK:	There are no efficacy endpoints. The primary endpoints were the concentration-time profiles of ^{14}C-radioactivity and tipranavir, C_{max}, AUC, $Cp_{12}h$, t_{max}, $t_{1/2}$ in plasma and blood, cumulative % dose excreted in feces and urine, isolation, identification and quantification of metabolites in urine, feces and plasma.
Safety:	The primary safety endpoints were the incidence of adverse events and laboratory evaluation abnormalities including ECG.
Statistical methods:	Descriptive statistics and graphical summaries were used.

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SUMMARY – CONCLUSIONS:

PD and PK results: When ^{14}C-tipranavir was coadministered with ritonavir to steady state, most tipranavir was excreted in the feces (total radioactivity recovery: 87.1% of administered dose, stool recovery was 82.3%, urine recovery was 4.4%). TPV steady state was achieved after 7 days of TPV/r coadministration. Day 7 TPV PK showed results similar to the TPV PK results seen in other trials using the same TPV/r doses: median t_{max} was 3 hours, median $t_{1/2}$ was 4 hours, and median normalized C_{max} and C_{p12} were 83.6 and 20.4 μM, respectively.

Safety results: Nausea and loose stools were the most common adverse events associated with TPV/r administration. There were no serious adverse events and only two subjects prematurely discontinued study drug due to adverse events. The most common laboratory abnormalities were increases in transaminases (≥ DAIDS Grade 3: 2 subjects, 17%) and mild increases in cholesterol and triglycerides. There were no treatment induced electrocardiographic abnormalities. None of the study subjects developed QT or QTc prolongation (QT or QTc >500 msecs or QT or QTc prolongation >30 msecs).

Conclusions: When ^{14}C-TPV was coadministered with ritonavir, most radioactivity was excreted in feces. The time to achieve TPV steady state when using TPV/r 500 mg/200 mg BID was 7 days.