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:				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 21 May 2004	**Number:** U04-1249-01	**Study period (dates):** May 1 - June 24, 2002		**Revision date:** 08 Jul 2004

Title of study:	A Single Centre, Open-Label, Randomised, Parallel, Multiple Dose, Comparison of the Effects of Tipranavir 500 mg and Ritonavir 100 mg or Tipranavir 750 mg and Ritonavir 200 mg twice a day for 11.5 days on the Pharmacokinetic Characteristics of Tenofovir disoproxil fumarate 300 mg in Healthy Volunteers
Investigator:	[redacted]
Study center(s):	[redacted] UK
Publication (reference):	
Clinical phase:	Phase I
Objectives:	To characterise the effects of two dose combinations of tipranavir/ritonavir (TPV 500 mg/RTV 100 mg and TPV 750 mg/RTV 200 mg) administered BID, on the pharmacokinetics of tenofovir disoproxil fumarate as well as the effects of tenofovir disoproxil fumarate on the pharmacokinetics of tipranavir/ritonavir.
Methodology:	
No. of subjects:	
planned:	Total 48 entered. Each treatment 24 (20 complete per treatment arm):
actual:	49 enrolled. 500/100 group: 24 entered: 24 treated: 24 analysed (for primary endpoint): 750/200 group: 25entered: 25 treated: 23 analysed (for primary endpoint):
Diagnosis and main criteria for inclusion:	Male or female of any race, in good health and between the ages of 18 and 60 years inclusive. Negative HIV or active Hepatitis B and Hepatitis C.
Test product:	Tipranavir, 250 mg, Soft Elastic Capsules, Self Emulsifying Drug Delivery System (SEDDS)
dose:	500 mg or 750 mg, BID
mode of admin.:	Oral
batch no.:	
Test product:	Ritonavir, 100 mg, capsules (Norvir®)
dose:	100 or 200 mg, BID

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 21 May 2004	**Number:** U04-1249-01	**Study period (dates):** May 1 - June 24, 2002		**Revision date:** 08 Jul 2004

mode of admin.:	Oral
batch no.:	
Test product.:	Tenofovir disoproxil fumarate, 300 mg, tablets (Viread□)
dose.:	300 mg, once daily on Days 1 and 13 only
mode of admin.:	Oral
batch no.:	
Duration of treatment:	14 consecutive days Tenofovir: 300 mg once daily on Days 1 and 13 only Tipranavir/ritonavir: Twice daily (BID) Days 2-12, once daily Day 13 (11.5 days total)
Reference therapy:	No reference therapy
Criteria for evaluation:	
Efficacy:	Not applicable - healthy volunteer pharmacokinetics study.
Pharmacokinetics	Primary endpoints: TDF pharmacokinetic parameters (AUC0 24h, Cmax and C6h; with/without TPV and RTV) and TPV/r pharmacokinetic parameters (AUC0 12h, Cmax and C12h; with/without TDF). Secondary endpoints: Cmax ss, Cmin, and MRT for TPV/r; T½,Tmax, CL/F, Vz/F, for TDF, TPV and RTV
Safety:	Primary endpoints: none Secondary endpoints: Treatment related AEs and laboratory abnormalities.
Statistical methods:	The following pharmacokinetic parameters were be derived using non-compartmental analysis: area under the plasma concentration time curve (AUC, trapezoidal rule), maximum observed concentration (Cmax) and concentration at a specified time after dosing (tenofovir disoproxil fumarate, 6 hours; tipranavir and ritonavir, 12 hours). Tenofovir disoproxil fumarate pharmacokinetic parameters (90% Confidence Intervals) for AUC, Cmax, and C6h where no effect = 1.00. Comparison days are Day 1 to Day 13. Primary analysis is the calculation of the geometric mean ratio (with 90% confidence intervals) of the primary TVF PK parameters with versus without TPV/r.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 21 May 2004	**Number:** U04-1249-01	**Study period (dates):** May 1 - June 24, 2002		**Revision date:** 08 Jul 2004

SUMMARY – CONCLUSIONS:

Efficacy results: Not applicable - healthy volunteer pharmacokinetics study.

Pharmacokinetic results: For TDF PK, weight and body surface area-adjusted AUC, Cmax, and, to a lesser extent, C12h, have higher values in females than in males. This difference is small and is not likely to be of clinical relevance.

Safety results: The incidence of subjects with adverse events was similar in the 750/200-dose TPV/r group (95.8%) and the 500/100-dose TPV/r group (96.0%). The majority of events were mild-to-moderate in their intensity. Consistent with other TPV trials in both healthy volunteers and HIV positive adults, GI AEs were predominant. GI events were reported in 88.0% of the 750/200-dose group and 79.2% in the 500/100-dose treatment group. The most frequently reported GI events were diarrhoea, nausea, flatulence, upper abdominal pain and loose stools.

In this short-term, healthy volunteer trial, only one subject, in the TPV/r 750/200-dose group, was discontinued from the study due to an adverse event, a severe erythematous rash that resolved without additional therapy after study drug was stopped. There were no deaths and no serious adverse events reported during the study.

Conclusions: TPV/r decreased the maximum plasma TDF concentrations observed in a dose dependent manner, but had no effect on the extent of TDF absorption. The antiviral activity of Tenofovir is dependant on AUC not peak concentration of the drug. Therefore no dose adjustment of TDF is necessary if it is co-administered with TPV/r.

The data for Tipranavir indicates that TDF has a significant effect on TPV/r at the 500/100 mg dose combination, but only a minor effect at 750/200 mg dose combination. This can be attributed to the effect Tenofovir has on Ritonavir thereby decreasing the magnitude of the Tipranavir systemic boost effect.

Tipranavir, when co-administered with Ritonavir 200mg for systemic boosting, can be used with Tenofovir without dose adjustments.