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:**	
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Report date: 30-Aug-04	**Number:** U04-1751	**Study period (dates):** 07-Oct 03 to 18-Dec 03		

Title of study:	Relative bioavailability of 500/200 mg of tipranavir/ritonavir paediatric solution compared to 500/200 mg of tipranavir/ritonavir capsules following oral administration and bioavailability of 500/200 mg tipranavir/ritonavir paediatric solution under the influence of food in healthy female and male subjects. An open-label, randomised, single-dose, three-way crossover trial.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Str. 65 D-88397 Biberach/Riss
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	To determine the relative bioavailability of 500/200 mg of tipranavir/ritonavir (TPV/r) oral solution compared to 500/200 mg of TPV/r capsules following oral administration and to investigate the relative bioavailability of 500/200 mg of TPV/r oral solution with food versus without food.
Methodology:	This study was performed to assess the treatment with 500/200 mg of TPV/r oral solution before and after breakfast and 500/200 mg of TPV/r capsules before breakfast in an open-label, randomised, three-way crossover trial (six sequences).
No. of subjects:	30
planned:	entered: 30 (a maximum of 36 subjects would have been entered into the trial, if less than 24 subjects were evaluable)
actual:	enrolled: 57; entered 30; Treatment 1 (C): TPV/r 500/200 mg oral solution with food entered:30 treated:30 analysed (for primary endpoint): 29 Treatment 2 (B): TPV/r 500/200 mg oral solution entered: 30 treated:30 analysed (for primary endpoint): 30 Treatment 3 (A): TPV/r 500/200 mg capsules entered:30 treated:30 analysed (for primary endpoint): 28
Diagnosis and main criteria for inclusion:	Healthy female and male subjects, age ≥18 and ≤55 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	tipranavir oral solution /ritonavir oral solution
dose:	500 mg TPV/200 mg RTV
mode of admin.:	Oral administration with 240 mL mineral water

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batch no.:	TPV oral solution: EXTE 69 LO 99 1A 1A; Ch.-B.: LG01478 RTV oral solution (Norvir®): EXTE 69 LO 99 1A 2A; Ch.-B.: 07443AW21
Duration of treatment:	One day (single dose per os) for each treatment, total: 3 days
Reference therapy:	TPV/r capsules
dose:	500 mg TPV/200 mg RTV
mode of admin.:	Oral administration with 240 mL mineral water
batch no.:	TPV SEC SEDDS capsules: EXTE 69 KAW 99 1B 1A; Ch.-B.: PD-2196B RTV soft gel capsules (Norvir®): EXTE 69 KAW 99 1A 2A; Ch.-B.: 909212E21
Criteria for evaluation:	
Efficacy:	There are no efficacy endpoints.
Pharmacokinetics	primary endpoints: $AUC_{0-\infty}$, and C_{max} for TPV secondary endpoints: AUC_{0-tz}, t_{max}, $t_{1/2}$, MRT_{po}, CL_{po}/F, V_z/F for TPV
Safety:	Physical examination, vital signs (BP, HR), ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$ and C_{max} and their two-sided 90% CIs were calculated.
SUMMARY – CONCLUSIONS:	
Efficacy results:	There are no efficacy endpoints. PK results: Comparing the results obtained following administration of a fasted oral solution to a fasted TPV SEDDS capsule the relative bioavailability of the fasted oral solution can be estimated as 1.37 (90% confidence interval 1.30 – 1.43) in extent (AUC) of absorption and 1.50 (1.40 – 1.60) in rate and extent (C_{max}) compared to TPV SEDDS capsule under fasting conditions. Urinary excretion data was consistent with these estimates. The oral solution should not be given under fasted conditions. Comparing the results obtained following TPV oral solution administered under fed conditions to a fasted oral solution, food did not affect the extent of bioavailability (AUC point estimate of 0.95, confidence interval 0.90 – 1.00), but had a significant effect on rate of absorption (C_{max} point estimate 0.71, confidence interval 0.67 – 0.76). Again, the urine data was consistent, albeit more variable, with an amount excreted unchanged ratio of 0.92 (confidence interval 0.77 – 1.09). Comparing the results obtained following TPV oral solution administered under fed conditions to a fasted TPV SEDDS capsule, food aided extent of bioavailability (AUC point estimate of 1.30, confidence interval 1.23 – 1.36), but food had a significant effect on rate that was consistent with the capsule profile

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	(C_{max} point estimate 1.07, confidence interval 1.00 – 1.14). The oral solution should be administered with food if drug disposition comparable to capsule is desired.
Safety results:	Both treatments TPV/r capsules fasted as well as TPV/r oral solution fasted were tolerated comparably. Improved tolerability could be seen with the intake of TPV/r oral solution after a high fat meal which can be demonstrated by the decrease of gastrointestinal (GI) related adverse events. Twenty-five of the 30 subjects reported a total of 60 episodes of adverse events. Of these 46 were assessed to be treatment related. No severe intensity of AEs, SAEs or deaths were reported. Most episodes were of mild (53/60) intensity, the remaining were of moderate (7/60) intensity. From all adverse events the following were the most frequent and considered to be related to the trial medication: gastrointestinal disorders (17 subjects with 28 episodes) like abdominal pain upper (10 episodes), diarrhoea (7), nausea (5), dyspepsia (4) and nervous system disorders (9 subjects with 15 episodes) like headache (9) and dizziness (4). Fourteen episodes of adverse events reported by 11 subjects were judged to be not related to the trial medication like influenza like illness, nasopharingitis, cough, throat irritation, headache, tension headache, dizziness, haematoma and hypotension. No relevant safety problems concerning vital signs, ECG, physical examination and clinical laboratory safety test results occurred.
Conclusions:	In conclusion regarding pharmacokinetics, TPV/r oral solution, should be given with food for optimal bioavailability, and to ensure interchangeability with the SEDDS capsule. All drug related adverse events have been reported in some way in previous clinical trials and are listed accordingly in the IB. Most of the episodes of adverse events that were judged to be not related to the trial medication reflect cold season dependent illnesses. In conclusion regarding safety, TPV/r capsules and TPV/r solution have a similar safety profile when administered fasted. The treatment with TPV/r oral solution was tolerated better after intake of a high fat meal.