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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-007627-40	
Name of active ingredient: Tipranavir		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 9 FEB 2009	**Trial No. / U No.:** 1182.124 / U09-1087-01	**Date of trial:** 15 APR 2008 – 29 MAY 2008	**Date of revision:** Not applicable

Title of trial:	Bioequivalence of two different oral solutions of 500 mg of tipranavir (new formulation vs. current formulation) administered in combination with 200 mg of ritonavir (oral solution) to healthy volunteers (an open-label, randomised, single-dose, two-way crossover study)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objective was to establish the bioequivalence of the new tipranavir oral solution formulation with the current tipranavir oral solution formulation following single-dose administration. In each case, 500 mg tipranavir was co-administered with 200 mg ritonavir.
Methodology:	The study was conducted according to a randomised, open-label, single-dose, two-way, two-sequence crossover design.
No. of subjects:	
planned:	entered: 32
actual:	entered: 32 (16 for each treatment sequence) New tipranavir oral solution (500 mg co-administered with ritonavir 200 mg) treated: 32 analysed (for primary endpoint): 32 Current tipranavir oral solution (500 mg co-administered with ritonavir 200 mg) treated: 32 analysed (for primary endpoint): 32
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥18 to ≤55 years, body weight >55 kg, body mass index (BMI) ≥18.5 to ≤29.9 kg/m^2.
Test product:	New tipranavir oral solution and ritonavir oral solution (new TPV/r)
dose:	500 mg tipranavir and 200 mg ritonavir (Norvir®), single dose
mode of admin.:	Oral administration with 240 mL water after a standard continental breakfast

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batch no.:	B071003580 (tipranavir), B081001440 (ritonavir)
Reference therapy:	Current tipranavir oral solution and ritonavir oral solution (current TPV/r)
dose:	500 mg tipranavir and 200 mg ritonavir (Norvir®), single dose
mode of admin.:	Oral administration with 240 mL water after a standard continental breakfast
batch no.:	B073000154 (tipranavir), B081001440 (ritonavir)
Duration of treatment:	In each study period, the treatments were administered as a single dose followed by pharmacokinetic (PK) blood sampling for 72 h. The treatments were separated by a wash-out phase of at least 7 days.
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of tipranavir Secondary endpoints: AUC_{0-tz}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL_{po}/F, V_z/F of tipranavir $AUC_{0-\infty}$, C_{max}, AUC_{0-tz}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL_{po}/F, V_z/F of ritonavir
Safety:	Incidence of adverse events (AEs), physical examinations, vital signs (blood pressure and pulse rate), 12-lead electrocardiograms, clinical laboratory tests (haematology, clinical chemistry, urinalysis), global tolerability assessment.
Statistical methods:	Two-sided 90% confidence intervals (CIs) for the intra-subject ratios (as estimated by the geometric mean of the ratio) of $AUC_{0-\infty}$ and C_{max} were calculated for tipranavir to determine whether the CIs were contained in the acceptance range of 80 to 125% for bioequivalence. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios were calculated. The statistical model was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period' and 'treatment'. CIs were based on the residual error from the ANOVA. For all other parameters, descriptive statistics were calculated.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Thirty-two healthy subjects, 16 of each sex, were entered in the trial and received the new TPV/r oral solution (Test) and the current TPV/r oral solution (Reference) as single doses in randomised order. All subjects were included in the statistical evaluation of bioequivalence.

Geometric mean (gMean) C_{max} and $AUC_{0-\infty}$ of tipranavir were not different between the new and the current TPV/r oral solution (C_{max} 96.8 µmol/L vs. 96.3 µmol/L, $AUC_{0-\infty}$ 950 µmol·h/L vs. 934 µmol·h/L). Median t_{max} of tipranavir was approximately 3.0 h for either solution formulation.

Similarly, gMean C_{max} and $AUC_{0-\infty}$ of ritonavir were not different between the new and the current TPV/r oral solution (C_{max} 2.2 µg/mL vs. 2.2 µg/mL, $AUC_{0-\infty}$ 11.8 µg·h/mL vs. 11.9 µg·h/mL). Median t_{max} of ritonavir was approximately 4.0 h for either solution formulation.

The following table summarises the adjusted gMean Test/Reference ratios and 90% CIs as well as the geometric coefficients of variation (gCV) for the primary endpoints C_{max} and $AUC_{0-\infty}$ of tipranavir.

PK parameter	N	Adjusted by-treatment gMean ratio Test/Reference	Two-sided 90% confidence interval of gMean ratio		Intraindividual gCV
		[%]	Lower limit [%]	Upper limit [%]	[%]
C_{max}	32	100.5	97.4	103.6	7.2
$AUC_{0-\infty}$	32	101.7	100.2	103.3	3.6

The adjusted gMean ratios were close to 100%, the intraindividual variability was very low, and the 90% CIs were fully included in the acceptance range for bioequivalence of 80 to 125%. Also, the 90% CIs for the secondary endpoints AUC_{0-tz} of tipranavir, C_{max}, $AUC_{0-\infty}$, and AUC_{0-tz} of ritonavir were fully contained within the acceptance range of 80 to 125%. Thus, bioequivalence of the new TPV/r oral solution with the current TPV/r oral solution was established.

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Safety results:

All 32 subjects received a total dose of 1000 mg tipranavir (500 mg of each tested formulation, administered as 2 single doses) and a total dose of 400 mg ritonavir during the trial as planned.

A total of 6 subjects (18.8%) experienced an AE during the trial: 1 subject during the screening period (syncope), 3 subjects during treatment with the new tipranavir formulation (diarrhoea in 2 subjects and headache in 1 subject), 1 subject during treatment with the current tipranavir formulation (headache), and 1 subject during the post-treatment period (back pain). All AEs were of either mild or moderate intensity. Both cases of diarrhoea, as well as headache during treatment with the new formulation, were considered drug-related. Only 1 AE (back pain) required therapy and all subjects recovered from their AEs. No serious AEs, no AEs of severe intensity, and no AEs leading to discontinuation were reported.

The overall tolerability assessment was 'good' for all subjects in both treatment periods. There were no clinically relevant findings with respect to the evaluation of laboratory parameters, vital signs, and ECG recordings, and no differences were noted between both treatments.

Conclusions:

The study demonstrated bioequivalence of the new tipranavir oral solution formulation to the current tipranavir oral solution formulation when co-administered with ritonavir oral solution after single TPV/r doses of 500/200 mg. Both treatments were safe and well tolerated.