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: Aptivus		**EudraCT No.:** 2006-001932-35	
Name of active ingredient: Tipranavir		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 APR 09	**Trial No. / U No.:** 1182.104 / U09-1337-01	**Date of trial:** 23 FEB – 25 MAY 07	**Date of revision** (if applicable)**:**

Title of trial:	An open-label one-sequence cross-over pharmacokinetic interaction study of steady-state tipranavir/ritonavir 500/200 mg with single-dose valaciclovir (500 mg) in healthy volunteers
Principal Investigator:	[redacted]
Trial sites:	[redacted] Germany
Publication (reference):	Sabo JP, Cong XJ, Haas D, Eskoetter H, Kraft M, Mauss S Lack of a pharmacokinetic effect between steady-state tipranavir/ritonavir (TPV/r) and single-dose valacyclovir in healthy volunteers (P08-14827).
Clinical phase:	I
Objectives:	Assessment of the interaction of tipranavir/ritonavir (TPV/RTV) and valaciclovir (VAL), a prodrug of acyclovir (ACV)
Methodology:	Open label, one-sequence, cross over, pharmacokinetic study in healthy male and female HIV-negative adult volunteers
No. of subjects:	
planned:	enrolled: 29; entered: 29; evaluated: 26
actual:	enrolled: 29; entered: 29; analysed: 29 (safety set); 26 (primary endpoint)
Diagnosis and main criteria for inclusion:	Healthy female and male subjects, age > 19 and < 59 years (20 to 58 years inclusive), weight ≥ 60 kg, BMI > 18.5 and < 29.9 kg/m^2; signed written informed consent
Test products:	Tipranavir (TPV), ritonavir (RTV) and valaciclovir (VAL)
dose:	TPV/RTV (500/200 mg, twice daily) VAL (500 mg, single dose)
mode of admin.:	p.o.

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batch no.:	TPV (250 mg soft capsules): B063000257 RTV (100 mg soft capsules): B063000518 VAL (500 mg coated tablets): 8099
Reference therapy:	n.a.
dose:	n.a.
mode of admin.:	n.a.
batch no.:	n.a.
Duration of treatment:	VAL 2 days (on days 1 and 13), TPV/RTV 12 days (on days 2 to 13)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary endpoints: $AUC_{0\text{-}12h}$ and C_{max} for ACV Secondary endpoints: $AUC_{0\text{-}12h}$, C_{max} and C_{12h} (or C_{last}) for TPV and RTV CL/F, V_Z/F and $t_{½}$ for ACV, TPV and RTV
Safety:	Physical examination, vital signs (blood pressure, pulse rate, temperature, respiratory rate), laboratory tests, adverse events (AEs) and tolerability
Statistical methods:	Pharmacokinetics Two-sided 90% confidence intervals (CIs) for the median of intra-subject ratios of $AUC_{0\text{-}12h}$ and C_{max} were calculated to determine whether the CIs are contained in the acceptance range of 80-125%. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios and the associated confidence intervals were provided. The statistical model was ANOVA on log transformed parameters including effects for "subjects" and “treatment”. Descriptive statistics for all other parameters were calculated.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Coadministration of steady-state TPV/r 500/200 mg bid with single-dose VAL 500 mg did not affect acyclovir Cmax or AUC (less than a 10% change relative to VAL alone, with p-values for testing bioequivalence of 0.0002 and <0.0001, respectively), but was associated with an 18.9% increase in the concentration of ACV measured 12 h after VAL dosing (Cp_{12h}) with p-value for testing bioequivalence of 0.1009.
Tipranavir Cmax, Cp_{12h} and AUC_{0-12h} were unaffected by VAL (less than a 10% change relative to TPV/r alone), which is strongly supported by the statistical testing of bioequivalence (p-value < 0.0001).
A single dose of VAL had no effect on RTV Cp_{12h} (less than a 10% decrease relative to TPV/r alone, with p-value for testing bioequivalence of 0.015), but was associated with a 19.4% decrease in Cmax and a 14.0% decrease in AUC_{0-12h}, with p-value for testing bioequivalence of 0.4588 and 0.0814, respectively.

Safety results:

There were 4 serious adverse events (SAEs) in 2 subjects [redacted] and 1 other significant AE in 1 subject [redacted], all of which leading to discontinuation of treatment: two subjects [redacted] were withdrawn due to elevated ALT and one subject [redacted] due to elevated ALT and AST, which were described as toxic hepatitis. Apart from administrations with study medication, these subjects continued the remaining study activities and completed the study.

A total of 24/29 subjects experienced an AE during the trial. By comparing the different treatment periods with VAL tablets on day 1, TPV capsules co-administered with RTV capsules (TPV/r) on days 2 to 12 and co-administration of VAL tablets together with TPV capsules and RTV capsules (TPV/r + VAL) on day 13, most AEs occurred during TPV/r treatment (7/29 subjects under VAL, 23/29 subjects each under TPV/r and 4/26 subjects under TPV/r + VAL). Overall, 70 AEs were recorded during the study period, of which 60 AEs were assessed to be drug-related. While the majority of the documented AEs was of mild intensity (45 AEs), some of the recorded AEs were of moderate (11 AEs) or severe intensity (14 AEs). Among the 14 AEs of severe intensity, for 8 subjects elevated ALT values and for 4 subjects elevated AST values were recorded. There was one case with severe vomiting and one case with severe toxic hepatitis (the DAIDS grade 4 elevations of ALT/AST were described as severe toxic hepatitis). The subjects affected did not require therapy for the AEs

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	and recovered fully. In general, the incidence of mild, moderate, and severe AEs was more prominent during TPV/r treatment in comparison to the treatment periods during which VAL or TPV/r + ACV were administered. The pattern of AEs observed in this study was consistent with that seen in previous phase I healthy volunteer trials with VAL administration or TPV/r. The most common adverse events were (by number of subjects and preferred term): increased ALT (8/29 subjects), headache (7/29 subjects), increased AST (4/29 subjects), diarrhoea, flatulence and nausea (4/29 subjects of each) and renal pain (3/29 subjects). A total of each 2/29 subjects experienced vomiting, rash or fatigue during the study. AEs considered as drug-related were reported by 24/29 subjects and the number of subjects exhibiting drug-related AEs was most prominent during TPV/r treatment (5/29 subjects under VAL, 23/29 subjects under TPV/r and 3/26 subjects under treatment with TPV/r + VAL). The most frequently observed drug-related AEs were increases of ALT and AST as to expect for TPV and RTV co-medication from previous clinical trials. VAL has a well established AE profile, which includes mostly headaches and gastrointestinal tract symptoms which were additional, more frequently observed drug-related AEs. All subjects who experienced an AE during the study recovered fully. Apart from the increase of transaminases described above, clinical laboratory analyses (haematology, clinical chemistry, and urinalysis), physical examinations, measurements of vital signs, and ECGs did not show the presence of any clinically relevant abnormalities and did not show treatment related effects. Administration of the three protease inhibitors VAL, RTV and TPV was safe and in general well tolerated in this study.
Conclusions:	Coadministration of steady-state TPV/r 500/200 mg bid with single-dose VAL

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	500 mg did not affect acyclovir Cmax or AUC (less than a 10% change relative to VAL alone), but was associated with an 18.9% increase in the concentration of ACV measured 12 h after VAL dosing (Cp_{12h}). Tipranavir Cmax, Cp_{12h} and AUC_{0-12h} were unaffected by VAL (less than a 10% change relative to TPV/r alone). A single dose of VAL had no effect on RTV Cp_{12h} (less than a 10% decrease relative to TPV/r alone), but was associated with a 19.4% decrease in Cmax and a 14.0% decrease in AUC_{0-12h}. None of these changes were considered to be of clinical relevance. The three study drugs VAL, TPV and RTV administered in the treatment periods on day 1 with VAL alone, on days 2 to 12 with TPV plus RTV (TPV/r) and on day 13 with all three study drugs co-administered (TPV/r + VAL) were generally safe and mostly well tolerated at daily doses given (500 mg single dose of VAL, 500/200 mg twice daily of TPV/r). The treatment period with TPV/r was most noticeable of all the treatments regarding the number of subjects affected by AEs, the number of AEs and the pattern of AEs. No treatment related effects could be detected concerning vital signs, electrocardiogram (ECG). Clinical laboratory parameters examined, except for the well-known changes in transaminases, were within normal ranges. Co-administration of VAL, TPV, and RTV was not associated with clinically relevant pharmacokinetic effects. Therefore, these agents can be co-administered without dose adjustment.