Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Aptivus®				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 26 Jul 2006	**Number:** U06-1681-01	**Study period (dates):** 21 Dec 2005 to 30 Mar 2006		**Date of revision:** 30 May 2007

Title of study:	Assessment of electrophysiological effects of tipranavir co-administered with ritonavir given b.i.d. for 2.5 days on the QT interval in healthy female and male subjects. A double-blind, randomised, placebo controlled, two-way crossover study with a positive control (moxifloxacin) and parallel dose groups
Investigator:	[redacted]
Study center:	[redacted] USA
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	To demonstrate that tipranavir co-administered with ritonavir does not affect the QT interval more than placebo co-administered with ritonavir
Methodology:	Double-blind, randomised, placebo controlled, two-way crossover, positive control
No. of subjects:	
planned:	entered: 80
actual:	enrolled: 126 entered: 81 subjects, with 80 subjects receiving at least one dose of study drug Sequences with tipranavir 500 mg/ritonavir 200 mg (TPV/r 500/200 mg): entered: 40 treated: 39 analysed (for primary endpoint): 39 Sequences with tipranavir 750 mg/ritonavir 200 mg (TPV/r 750/200 mg): entered: 41 treated: 41 analysed (for primary endpoint): 41
Diagnosis and main criteria for inclusion:	Healthy female and male subjects; ≥ 18 and ≤ 55 years old; BMI ≥ 18.5 and ≤ 29.9 kg/m^2; signed informed consent
Test product:	Tipranavir 250 mg capsules/ritonavir 100 mg capsules
dose:	Tipranavir 500 mg and ritonavir 200 mg (both b.i.d.) or tipranavir 750 mg and ritonavir 200 mg (both b.i.d.)
mode of admin.:	Oral
batch no.:	Tipranavir: PD-2534 ritonavir: 317082E22

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Duration of treatment:	Moxifloxacin: one single dose tipranavir/ritonavir 500/200 mg or 750/200 mg b.i.d.: 2.5 days placebo/ritonavir 200 mg (placebo/r) b.i.d.: 2.5 days
Reference therapy:	Placebo matching in appearance to tipranavir 250 mg capsules; ritonavir 100 mg capsules; moxifloxacin (Avelox®) 400 mg tablets as positive control
dose:	Placebo: not applicable; moxifloxacin: one single dose of 400 mg
mode of admin.:	Oral
batch no.:	Placebo: PD-2578 moxifloxacin: 5400LPV
Criteria for evaluation:	
Efficacy:	Pharmacokinetics of tipranavir: $AUC_{0 \rightarrow 12}$ (day 1), C_{max} (day 1), t_{max} (day 1) $AUC_{0 \rightarrow 12}$ (day 3), C_{max} (day 3), t_{max} (day 3)
Safety:	Primary endpoint: Mean time-matched QTcI change from baseline derived as the mean of the ECGs obtained between 2:00 and 4:00 h following administration of the study drugs on day 3 minus the time-matched ECGs obtained on the baseline day (i.e. previous visit) Secondary endpoints: Mean QTcI change from baseline on day 1, QTcI change from baseline at each time point, categorical ECG endpoints and, as further safety parameters, vital signs (blood pressure, heart rate), laboratory tests, physical examinations, occurrence and intensity of adverse events (AEs), and global tolerability
Statistical methods:	To assess the mean QTcI change from baseline, an ANCOVA model was used with sequence, period, and treatment as fixed effects, subjects nested within sequence as a random effect, and baseline as a covariate. Descriptive statistics for pharmacokinetic parameters were calculated.

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SUMMARY – CONCLUSIONS:

Efficacy results:

A total of 80 subjects (33 female and 47 male healthy subjects ranging in age from 19 to 52 years) were treated with study medication. There were no major differences in the demographic and baseline data between subjects despite for gender. While in the 750 mg dose groups an approximately balanced number of female and male subjects were entered (22 subjects, 54% vs. 19 subjects, 46%), the 500 mg dose groups comprised less female than male subjects (11 female; 28% vs. 28 male, 72%). A total of 80 subjects completed treatment with moxifloxacin; 77 subjects completed the entire planned observation period and all assessments. None of the subjects discontinued the trial prematurely due to the occurrence of an AE.

Pharmacokinetics

The first-dose pharmacokinetics for the TPV/r 500/200 mg (N = 38) and TPV/r 750/200 mg (N = 41) dose groups were characterised by a mean C_{max} of 70.7 µM and 116.3 µM, by a mean Cp_{12h} of 26.2 µM and 48.7 µM, and by a mean AUC_{0-12h} of 506 h•µM and 864 h•µM, respectively. An increase in mean C_{max} to 155.5 µM and 247.3 µM, in mean Cp_{12h} to 68.5 µM and 126.6 µM, and in mean AUC_{0-12h} to 1271 h•µM and 2160 h•µM was observed following 5 doses of TPV/r 500/200 mg and TPV/r 750/200 mg, which were administered every 12 h.

Compared with the therapeutic steady-state population estimates, tipranavir concentrations and exposure approximately 3 days after the start of b.i.d. dosing with TPV/r was substantially higher in both, the TPV/r 500/200 mg and the TPV/r 750/200 mg dose groups (C_{max}: approximately 1.5-fold and 2.4-fold; AUC_{0-12h}: approximately 1.4-fold and 2.4-fold, respectively).

The TPV plasma concentrations in this trial were within the expected range and were considered adequate for a thorough QT trial.

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Safety results:

The primary objective of this study was to demonstrate that TPV/r at therapeutic and supra-therapeutic doses does not prolong the QT interval more than placebo/r.

The study evaluated the effect of two different doses of TPV co-administered with RTV (TPV/r 500/200 mg and TPV/r 750/200 mg) on the QTc interval in healthy volunteers using moxifloxacin (400 mg) as a positive control.

For the primary endpoint analysis, the adjusted difference to baseline of QTcI between 2:00 and 4:00 h post drug administration on day 3 was about -7.5 ms in both placebo groups, -5.8 ms in the TPV/r 500/200 mg dose groups, and -1.0 ms in the TPV/r 750/200 mg dose groups. The upper bound of the one-sided 95% confidence intervals (95% UCL) of the placebo-adjusted difference from baseline was +3.9 ms for TPV/r 500/200 mg and +8.6 ms for TPV/r 750/200 mg and thus below the predefined margin of 10 ms. For the positive control moxifloxacin, the mean change from baseline was 9.0 ms between 2:00 to 4:00 h with a 95% UCL of 14.1 ms. This was in the expected range of this compound and demonstrated the sensitivity of the study to detect a QTc prolongation.

In the secondary analysis, the adjusted difference to baseline of QTcI between 2:00 and 4:00 h after drug administration on day 1 was about -3.5 ms in both placebo groups, -1.2 ms in the TPV/r 500/200 mg dose groups, and -3.8 ms in the TPV/r 750/200 mg dose groups. The upper bound of the one-sided 95% confidence intervals of the placebo-adjusted difference from baseline was +3.6 ms for TPV/r 500/200 mg and +2.0 ms for TPV/r 750/200 mg and thus well below the predefined margin of 10 ms.

The time course of the adjusted means of the QTcI time-matched change from baseline and the difference from placebo was determined for each dose level on day 1 and on day 3 to identify the largest time matched mean effect.

In the groups with the therapeutic dose of TPV/r 500/200 mg, the 95% UCL for the placebo-adjusted time-matched change from baseline of the QTcI interval did not exceed 10 ms at any measured time point on day 1 and day 3; the 95% UCL ranged from 1.7 to 5.6 ms. In the groups with the supra-therapeutic dose of TPV/r 750/200 mg, the 95% UCL on day 1 varied between -2.0 and 4.4 ms and were thus also well below the margin of 10 ms.

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On day 3 at time point 2:00 h, the time-matched change from baseline of the QTcI interval at the TPV/r 750/200 mg dose was 0.0 ms. At this time point, the change from baseline for the placebo/r treatment was negative with a mean value of -8.1 ms, which resulted in a placebo-adjusted value of 8.1 ms for TPV/r 750/200 mg with a 95% UCL of 10.8 ms slightly exceeding the margin as defined by the ICH E 14 guideline. As the maximum plasma concentrations for the supra-therapeutic dose were substantially higher than the therapeutic steady-state population estimates, the exceedance of the 10 ms margin on day 3 was not considered a clinically relevant QT prolongation.

No notable changes of the QTcI interval defined as a new onset of QTcI > 450 ms, QTcI >500 ms or time-matched QTcI changes from baseline larger than or equal to 30 ms or 60 ms on day 1 or day 3 occurred in any of the subjects. In particular, at the time point when the 95% UCL of the time-matched change from baseline of the QTcI interval crossed 10 ms in the TPV/r 750/200 mg dose groups (at time point 2:00 h on day 3), none of the subjects experienced a new onset of QTcI > 450 ms, QTcI >500 ms or time-matched QTcI changes from baseline larger than or equal to 30 ms or 60 ms. The analysis of other parameters of interest such as additional heart rate corrections QTcN, QTcF, QTcB, the uncorrected QT interval, and the RR interval did not reveal any QT prolonging or arrhythmogenic effects for either of the two doses of TPV/r. No notable findings concerning heart rate, the PR, and the QRS interval were observed in any of the subjects. PR and QRS did not reveal any treatment related changes in central tendency.

All AEs which occurred during the trial were of mild intensity. The AEs with the highest frequency of subjects affected belonged to the system organ classes ‘gastrointestinal disorders’ (39 subjects, 48.8%) and ‘nervous system disorders’ (22 subjects, 27.5%). The most common AEs by number of subjects and preferred term were nausea (30 subjects, 37.5%), headache (10 subjects, 12.5%), dizziness (8 subjects, 10.0%), and vomiting (8 subjects, 10.0%). Drug-related AEs were observed in 38 subjects (47.5%). The frequency of drug-related AEs in the TPV/r 750/200 mg dose groups was considerably higher than in the TPV/r 500/200 mg dose groups (20 subjects, 48.8% vs 10 subjects, 26.3%). The majority of the drug-related AEs were reported on treatment with TPV/r and were mainly nausea, vomiting, and diarrhoea; vomiting only occurred in the supra-therapeutic dose groups. On treatment with placebo/r, 9 subjects (11.7%) experienced drug-related AEs.

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	Three subjects showed clinically significant laboratory abnormalities on treatment with TPV/r or placebo/r, i.e. elevations in eosinophils, creatine kinase, or amylase and lipase of grade 3 or 4. Nine subjects had laboratory values of grade 2 or 3 during the study periods with TPV/r or placebo/r administration. The main finding when assessing the laboratory values was an increase in triglycerides which is a known side effect of TPV/r. No adverse effects were revealed upon evaluation of the vital signs and physical examination. The adverse event profile and the changes in laboratory values observed in some individual subjects were consistent with the results of previous trials on TPV/r in healthy volunteers.
Conclusions:	In summary, the results of this trial indicated that therapeutic and supra-therapeutic doses of tipranavir/r do not prolong the QT interval of the ECG compared to baseline. The upper bound of the one-sided 95% confidence intervals of the primary endpoint, the placebo-adjusted difference from baseline on day 3 between 2:00 and 4:00 h after drug administration, was +3.9 ms for TPV/r 500/200 mg and +8.6 ms for TPV/r 750/200 mg and thus below the predefined margin of 10 ms. At time point 2:00 h post drug administration on day 3, the time-matched change from baseline of the QTcI interval at the TPV/r 750/200 mg dose was 0.0 ms; on treatment with placebo, a decrease in the time-matched change from baseline of 8.1 ms was seen at this time point. This resulted in a difference from placebo of 8.1 ms at the supra-therapeutic dose at this single time point with an upper 95% confidence interval of 10.8 ms, which slightly exceeded the margin of 10 ms of the ICH E14 guideline. As expected, the maximum plasma concentrations for the supra-therapeutic dose were substantially higher than the therapeutic steady-state population estimates. Therefore, exceedance of the 10 ms margin on day 3 is not considered an indication for a clinically relevant QT prolongation for the therapeutic use of TPV/r. No notable changes of the QTcI interval (absolute value > 450 ms or change from baseline>30 ms) occurred in any of the subjects on day 1 and day 3 including the time point when the upper 95% confidence interval of 10.8 ms was noted at the supra-therapeutic dose. The tipranavir plasma concentrations in this trial were considered adequate for a thorough QT trial for both the therapeutic and the supra-therapeutic dosage. The analysis of adverse events, laboratory parameters, and vital signs demonstrated that tipranavir co-administered with ritonavir was safe and well tolerated at the given doses.