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.

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Aptivus®				
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Title of study:	A single centre, open-label study with healthy adult volunteers to determine the effects of single-dose and steady-state TPV/r 500/200 mg on the steady-state pharmacokinetics of carbamazepine (200 mg twice daily)
Investigator:	[redacted]
Study center:	[redacted], UK
Publication (reference):	None
Clinical phase:	I
Objectives:	To assess the steady-state pharmacokinetics of carbamazepine (CBZ) at 200 mg or 100 mg twice daily, depending on tolerability, and administered alone and in combination with tipranavir/ritonavir (TPV/r) after a single dose (500/200 mg) and at steady-state (500/200 mg twice-daily)
Methodology:	Open-label, single group pair TPV/r pharmacokinetic study
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 36 entered: 28 Prematurely discontinued: 4 Treatment CBZ100: entered / treated: 1; analysed: 1 Treatment TPV/r+CBZ100: entered / treated: 7; analysed: 7 Treatment CBZ200: entered / treated: 1; analysed: 1 Treatment TPV/r+CBZ200: entered / treated: 19; analysed: 17
Diagnosis and main criteria for inclusion:	Healthy male and female subjects, aged 18 - 59, weight ≥60 kg, BMI >18.5 to <35 kg/m^2
Test product:	CBZ in combination with TPV/r
dose:	CBZ 100 mg for the first cohort of 8 subjects and if tolerated well, subsequent cohorts were treated with CBZ 200 mg administered in combination with TPV/r (500/200 mg twice daily) on days 15-22
mode of admin.:	p.o.

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batch no.:	Tipranavir soft capsule: PD-2555; Ritonavir soft capsule: 28246VA
Duration of treatment:	CBZ for 22 days (on days 1-22), TPV/r for 8 days (on days 15 to 22)
Reference therapy:	CBZ (200 mg or 100 mg depending on tolerability twice daily) administered alone on days 1 - 14 (total administration 22 days)
dose:	200 mg or 100 mg depending on tolerability twice daily
mode of admin.:	p.o.
batch no.:	CBZ 100 mg tablets: U0244
Criteria for evaluation:	
Efficacy:	Primary endpoints: CBZ and carbamazepine-10,11-epoxide (CBZ-E) pharmacokinetic parameters $AUC_{0\text{-}12h}$, C_{max} and Cp_{12h} Secondary endpoints: Tipranavir and ritonavir pharmacokinetic parameters $AUC_{0\text{-}12h}$, C_{max} and Cp_{12h}, CBZ, CBZ-E, tipranavir and ritonavir pharmacokinetic parameters clearance, volume of distribution, t_{max} and $t_{1/2}$
Safety:	Physical examination, vital signs (BP, PR, temperature, respiratory rate), laboratory tests, adverse events, tolerability
Statistical methods:	Safety and tolerability: Summary of adverse events coded using MedDRA. Pharmacokinetics: Pharmacokinetic parameters for CBZ, CBZ-E, tipranavir and ritonavir were derived using non-compartmental analysis: area under the plasma concentration time curve ($AUC_{0\text{-}12h}$, trapezoidal rule), maximum observed concentration (C_{max}) and concentration 12 h after dosing (Cp_{12h}). The following ratios of specified PK parameters with 90% confidence intervals were calculated: CBZ and CBZ-E with/without single-dose and steady-state TPV/r: $AUC_{0\text{-}12h}$, C_{max} and Cp_{12h}. A ratio of 1.00 indicated no effect; comparison days were Day 14 to Day 15 for the effect of single-dose TPV/r on CBZ PK, and Day 14 to 22 for the effect of steady-state TPV/r on CBZ PK.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Approximately twice as many men (67.9%) compared with women participated in this study. The mean (SD) age of the subjects was 29.7 (8.9) years, ranging from 18 to 53 years.

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Efficacy results (continued):

Pharmacokinetic results

First-dose and steady-state TPV/r increased CBZ concentrations in both the CBZ 100 mg bid and 200 mg bid dose groups, but these increases resulted in trough concentrations of CBZ that were within the therapeutic range for adults. The results of the comparison of pharmacokinetic parameters of 100 mg and 200 mg CBZ at steady state after co-administration with TPV/r after first dose and steady state is summarised in Table 1 below.

Table 1: Comparison of pharmacokinetic parameters of CBZ by treatment

PK parameter	Treatment	N	Geometric mean	gCV (%)
CBZ100				
$AUC_{0\text{-}tz,ss}$	CBZ100 (ss)	7	44.0	14.2
[µg•h/mL]	CBZ+TPV/r (fd)	7	46.3	14.7
	CBZ+TPV/r (ss)	7	47.4	29.2
C_{max}	CBZ100 (ss)	7	4.11	13.7
[µg/mL]	CBZ+TPV/r (fd)	7	4.25	15.1
	CBZ+TPV/r (ss)	7	4.51	39.5
CBZ200				
$AUC_{0\text{-}tz,ss}$	CBZ200 (ss)	17	64.7	20.0
[µg•h/mL]	CBZ+TPV/r (fd)	17	67.3	16.4
	CBZ+TPV/r (ss)	17	81.5	26.3
C_{max}	CBZ200 (ss)	17	6.34	20.3
[µg/mL]	CBZ+TPV/r (fd)	17	6.33	14.5
	CBZ+TPV/r (ss)	17	7.74	24.7

Note: fd = first-dose, ss = steady-state
Source: Table

The increase in CBZ concentrations could be attributed to inhibition of CYP3A4 by ritonavir, which also resulted in substantially lower concentrations of the active metabolite CBZ-E. For both CBZ dose groups, the decrease CBZ-E was approximately the same for first-dose TPV/r (C_{max}, <10%; Cp_{12h}, approximately 50%; $AUC_{0\text{-}12h}$, approximately 30%) and steady-state TPV/r (C_{max}, approximately 74%; Cp_{12h}, approximately 74%; $AUC_{0\text{-}12h}$, approximately 75%).

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Efficacy results (continued):	The effect of first-dose and steady-state TPV/r on the steady-state C_{max}, Cp_{12h} and AUC_{0-12h} of total carbamazepine (CBZ_{total}; CBZ + CBZ-E) was also determined. For CBZ 100 mg at steady state, the geometric means of C_{max}, Cp_{12h} and AUC_{0-12h} of CBZ_{total} were unchanged (increased 2.5% or less) when first-dose or steady-state TPV/r was co-administered, with the exception of Cp_{12h} with first-dose TPV/r which increased approximately 11%. For CBZ200, changes in CBZ_{total} C_{max}, Cp_{12h} and AUC_{0-12h} were similar to CBZ 100 mg after the first-dose TPV/r; however, at steady-state of CBZ 200 mg co-administration with TPV/r increased the geometric mean C_{max} approximately 13%, the AUC_{0-12h} approximately 16% and the Cp_{12h} approximately 23%. Tipranavir and ritonavir C_{max}, Cp_{12h} and AUC_{0-12h} were 33 to 46% lower in the CBZ 200 mg group than in the CBZ 100 mg group after first dose TPV/r and 18 to 31% lower at steady state. The mechanism by which CBZ affected these pharmacokinetic parameters in a dose-dependent manner is unclear. It is likely that the effect of lower ritonavir plasma concentrations in the CBZ 200 mg group compared with the CBZ 100 mg group contributed substantially to the effect on tipranavir. It is unlikely that this effect can be attributed to CYP 3A4 metabolism or P-glycoprotein transport.
Safety results:	The majority of subjects experienced at least one adverse event (AE) in this study. Most of the AEs were known to be a side effect of one of the drugs used. Irrespective of causality, AEs were experienced by 92.9% (26/28) of subjects treated with any study drug. The total time of exposure of subjects to study drugs was 22 days for CBZ and 8 days for TPV/r, which may explain why more subjects reported AEs during the time of CBZ treatment (92.9%) compared to the time when CBZ was co-administered with TPV/r (76.9%). The number of subjects with AEs in each system organ class was also higher for CBZ treatment alone when compared with CBZ treatment co-administered with TPV/r. No deaths or serious adverse events (SAEs) were reported during the study. Most of the reported AEs were of mild or moderate intensity and did not require treatment. Only two subjects experienced AEs of severe intensity; one subject exhibited a marked increase in ALT levels (DAIDS grade 3) and the other subject experienced severe symptoms of dehydration, nausea and vomiting; the latter AE resulted in study discontinuation. Overall, only two subjects discontinued the study prematurely due to an AE; the second subject experienced marked elevations in AST (DAIDS grade 2) and ALT levels (DAIDS grade 3) and was also prematurely discontinued from the study for safety reasons. The most frequently reported single adverse events were fatigue (19 subjects), nausea (14 subjects), headache (12 subjects), and dizziness (11 subjects).

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Safety results (continued):	Several other subjects showed marked elevations above the reference range in liver enzyme concentration, most notably in AST, ALT and GGT. One subject treated with CBZ 200 mg and TPV/r was noted with DAIDS grade 3 elevations in ALT and triglycerides and one subject had a grade 4 elevation in creatine kinase on day 11 of the study period. Other laboratory parameters showed increases above the reference range for individual subjects, but these were not considered clinically relevant by the investigator. Given that the plasma concentration of CBZ in the CBZ 200 mg group was increased by approximately 20% (based on $AUC_{0\text{-}tz,ss}$ and $C_{max,ss}$) by TPV/r, no additional, or unexpected adverse events were observed. Therapeutic drug monitoring (TDM) of CBZ confirmed that none of the subjects had CBZ levels above the suggested reference range of 8 - 12 µg/mL. Based on the administered doses of CBZ (100 mg and 200 mg) co-administration with TPV/r did not result in any additional or unexpected adverse events; however, caution should be exercised when CBZ is co-administered with TPV/r.
Conclusions:	In the present study, CBZ co-administered with steady-state TPV/r resulted in CBZ trough (Cp_{12h}) concentrations ranging from 2.36 – 5.08 µg/mL in the CBZ 100 mg group and 3.79 – 10.90 µg/mL in the CBZ 200 mg group. With regard to CBZ_{total}, there was little effect on C_{max}, Cp_{12h} and $AUC_{0\text{-}12h}$ by first-dose TPV/r for either CBZ treatment group or when steady-state TPV/r was co-administered with steady-state CBZ 100 mg bid, but these parameters were increased when steady-state TPV/r was co-administered with CBZ 200 mg bid. Caution should be exercised when CBZ is co-administered with TPV/r Concentrations of tipranavir and ritonavir were reduced at steady state with CBZ. Based on the results of this study, both drugs should be used with caution. TPV/r may be less effective due to decreased plasma concentrations in patients taking CBZ concomitantly. The number, type and intensity of reported AEs in this study were not unexpected given the well known side effect profile of both drugs. There were no unexpected AEs and co-administration of TPV/r and CBZ did not appear to result in any additional AEs beyond the known side effect profile; however, caution should be exercised when CBZ is co-administered with TPV/r.