2. SYNOPSIS

Name of Sponsor/Company: UCB S.A.	Individual Study Table Referring to Module 5.3.3.4	(For National Authority Use only)
Name of Finished Product: Brivaracetam	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

Title of Study: Multicenter, open label, unilateral metabolic interaction study of ucb 34714 (100, 200 and 400 mg daily) on carbamazepine (≥ 600 mg daily) during a four-week bid administration period in 9 adult subjects suffering from epilepsy and treated with carbamazepine and valproate (≥ 500 mg daily).

Investigators: Pr [redacted] in UK and Dr [redacted] in Poland

Study Center: Three centers (2 in UK and 1 in Poland) participated in the study. Only two centers recruited subjects (center [redacted] in UK and center [redacted] in Poland).

Publication: Not applicable

Studied Period (years): Date of first enrolment: 29-Mar-2004 Date of last completed: 29-Apr-2005	Phase of Development: Human pharmacology / Phase I

Objectives:

Primary Objective:

The primary objective of this Phase I study in 9 adult subjects suffering from epilepsy and chronically treated with a combination of carbamazepine (CBZ) and valproate (VPA) was to evaluate the effect of steady-state brivaracetam (ucb 34714) administration at 50, 100 and 200 mg *b.i.d.* (the highest dose foreseen in phase II/III trials) on steady-state plasma levels of CBZ and its metabolites CBZE and CBZ-diol.

Secondary Objectives:

The secondary objectives of this study were:

- To gain information on the safety of the simultaneous administration of brivaracetam (ucb 34714) and the combination of CBZ and VPA in patients, including occurrence of seizure;
- To confirm that brivaracetam (ucb 34714) does not modify VPA trough levels.

Methodology:

This was a Phase I (human pharmacology), open-label, unilateral interaction, titration trial between brivaracetam and CBZ, in the presence of VPA, during multiple oral administrations conducted in two centers.

Number of Subjects:

The Investigators selected 9 epileptic subjects (4 males and 5 females) who were all included and received the investigational treatment.

Diagnosis and Main Criteria for Inclusion:

Male and female adult subjects (18 - 65 years) suffering from epilepsy and treated with stable CBZ tablets for at least 3 months (any daily dose ≥ 600 mg was accepted) and on stable VPA tablets for at least 3 months (any daily dose ≥ 500 mg was accepted). Subjects with CBZ and VPA plasma level in the target range 4-12 µg/mL and 40 – 100 µg/mL in valproic acid units corresponding to 280-700 µmol/L, respectively.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
ucb 34714	50 mg capsules for oral administration with excipients	12611
ucb 34714	200 mg capsules for oral administration with excipients	12610

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Duration of Treatment:
Treatment duration was 4 weeks for each subject. Subjects included received brivaracetam + CBZ (≥600 mg daily) and VPA (≥500 mg daily):

- 1x50 mg capsule brivaracetam twice daily from Days 1 to 7 (50 mg *b.i.d.*, up-titration)
- 2x50 mg capsules brivaracetam twice daily from Days 8 to 14 (100 mg *b.i.d.*, up-titration)
- 1x200 mg capsule brivaracetam twice daily from Days 15 to 21 (200 mg *b.i.d.*, maintenance)
- 2x50 mg capsules brivaracetam twice daily from Days 22 to 28 (100 mg *b.i.d.*, down-titration)

Criteria for Evaluation:
Pharmacokinetics: Plasma trough concentrations of brivaracetam and CBZ, CBZE and CBZD and VPA.
Safety: Vital signs (systolic and diastolic blood pressure, heart rate and ECG), clinical laboratory evaluations (blood chemistry, hematology and urinalysis), physical and neurological examinations, seizure recording and adverse events.

Statistical Methods:
The pharmacokinetic analysis was performed on the per protocol (PP) population. The possible interaction effect of brivaracetam on the steady state plasma levels of CBZ, CBZE and CBZD was assessed using pairwise comparison between Day 1 pre-dose (without brivaracetam) and Days 8-15-22-29 (with brivaracetam) and discharge (without brivaracetam).
A linear regression analysis on individual CBZ, CBZE or CBZD plasma concentrations, as well as CBZE/CBZ and CBZ-diol/CBZ ratios versus brivaracetam plasma levels was to be performed. Further, the effect on major metabolites of brivaracetam, and the correlation between CBZ or CBZE or CBZD concentrations and brivaracetam doses (via figures) were explored. Finally, the inter- and intra-subject variability of treatment of CBZ, CBZE and CBZD were assessed.
Adverse events (AEs) were summarized descriptively by body system and preferred term. Additional tables summarized AEs by severity and relationship to study drug as well as separate tables for SAEs. Laboratory values and changes from Day 1 were presented descriptively. Vital signs were presented descriptively and graphically by time. Changes were calculated versus Day 1 pre-dose assessment. ECGs were analyzed descriptively on raw data and changes from Day 1 pre-dose. Categorization of changes was performed to detect relevant changes over treatment.

SUMMARY – CONCLUSIONS
ANALYSIS OF PHARMACOKINETICS:
At the end of down-titration (100 mg *b.i.d.* of brivaracetam), trough plasma levels of brivaracetam decreased to values similar to those obtained at the end of the up-titration with the same dose. The between-subject variability of plasma concentration when subjects received 200 mg *b.i.d.* of brivaracetam (maintenance) (CV%=37.8% at Day 22 pre-dose) was larger than that observed at lower doses (CV% = 25.4% and 12.8% at Day 8 pre-dose and Day 15 pre-dose, respectively). For one subject, plasma concentrations at 200 mg *b.i.d.* was lower than at 100 mg *b.i.d.* This subject was considered as an outlier. Mean trough plasma concentrations-time profile without this subject was then performed and showed that trough concentrations of brivaracetam were approximately proportional to the dose between 50 and 200 mg *b.i.d.*

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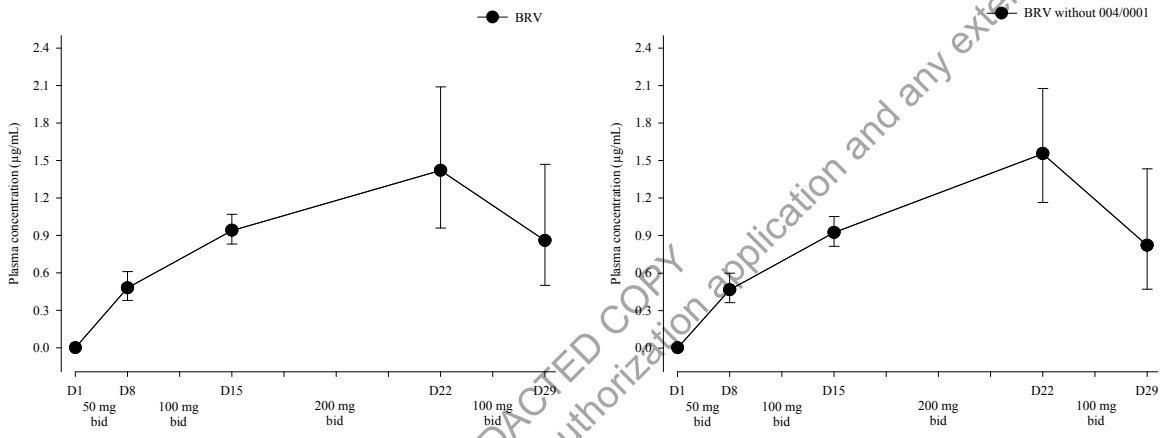
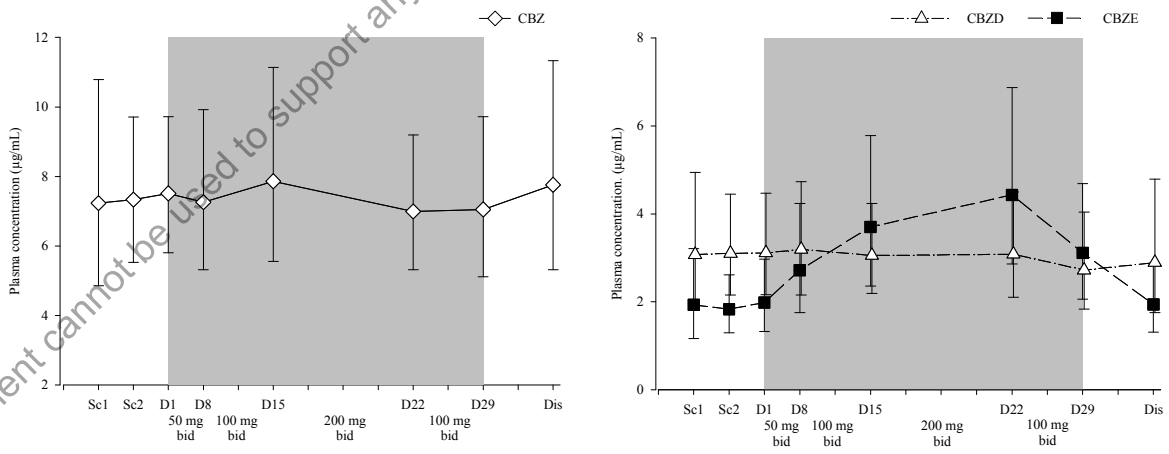
Figures below display the geometric means (± SD on ln-data) of trough plasma concentrations of brivaracetam for PP population (left) and for PP population without data of the outlier subject (right).



Figures below display geometric means (± SD on ln-data,) of trough plasma concentrations of CBZ (left), CBZE and CBZD (right) and VPA (bottom) before, during and after concomitant repeated administration of brivaracetam (shaded area) (PP population).



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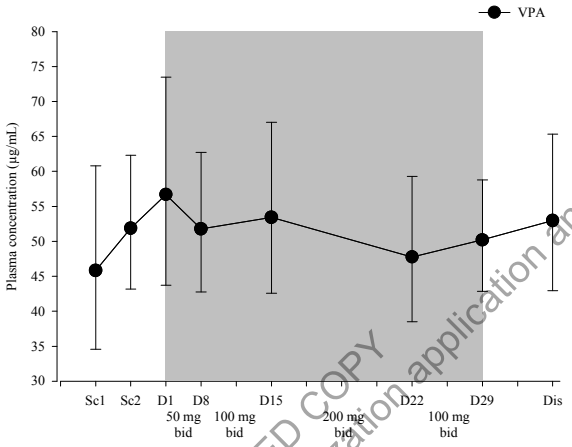

The geometric means of CBZ plasma trough concentrations did not change with brivaracetam dose. The concentration of CBZE increased with brivaracetam dose, but the concentration of CBZD did not change. Mean trough levels of VPA varied from 52.0 µg/mL (mean off-treatments value) to 51.8, 53.4 and 47.8 µg/mL after the 50, 100 and 200 mg *b.i.d.* of brivaracetam periods respectively. Plasma levels increased to 50.2 µg/mL after the down-titration, and to 53.0 µg/mL at discharge.

The interaction effect of brivaracetam on plasma levels of CBZ and its major metabolites was evaluated via an ANOVA model with repeated measurements. The pairwise comparison is presented in the table below.

Day pre-dose	CBZ (µg/mL)		CBZE (µg/mL)		CBZD (µg/mL)	
	Fixed effect[(a)]	Point estimate[(b)]	Fixed effect[(a)]	Point estimate[(b)]	Fixed effect[(a)]	Point estimate[(b)]
Screening 1	7.23 (5.15 - 10.16)		1.93 (1.26 – 2.95)		3.07 (2.14 – 4.40)	
Screening 2	7.33 (5.85 - 9.18)		1.83 (1.38 – 2.43)		3.10 (2.33 – 4.11)	
Day 1	7.51 (6.18 - 9.12)		1.98 (1.46 – 2.69)		3.11 (2.36 – 4.10)	
Day 8	7.26 (5.78 - 9.10)	96.6%	2.72 (1.96 – 3.78)	137.3%	3.19 (2.38 – 4.29)	102.7%
Day 15	7.54 (5.80 - 9.80)	100.4%	3.53 (2.52 – 4.96)	178.3%	2.95 (2.28 – 3.81)	94.9%
Day 22	6.99 (5.71 - 8.56)	93.1%	4.43 (3.20 – 6.15)	223.7%	3.08 (2.32 – 4.08)	99.0%
Day 29	7.27 (5.67 - 9.31)	96.8%	3.22 (2.36 – 4.40)	162.7%	2.87 (2.09 – 3.95)	92.4%
Discharge	7.76 (5.75 - 10.47)	103.4%	1.94 (1.44 – 2.61)	97.9%	2.76 (1.82 – 4.18)	88.8%

[(a)] Values are geometric LS means (95% CI)
[(b)] Point estimate for the Day x / Day 1 pre-dose geometric LS mean ratio (%) derived from ANOVA

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For CBZ, trough plasma concentrations observed at the end of the administration of 50, 100 and 200 mg *b.i.d.* of brivaracetam did not statistically differ from those observed before brivaracetam administration. A statistically significant dose related increase of mean trough CBZE levels was observed, varying from 1.9 µg/mL off-treatment to 2.7, 3.5 and 4.4 µg/mL after 50, 100 and 200 mg *b.i.d.* of brivaracetam, respectively. Plasma levels decreased to 3.2 µg/mL after down-titration with 100 mg *b.i.d.* and to 2.0 µg/mL at discharge. The 90% CI of the geometric LS mean ratio remained within the pre-defined acceptance range (0 – 260%). There was also a signficant dose-related increase of the CBZE/CBZ ratio from 26% off-treatment to 37%, 47% and 63% after 50, 100 and 200 mg *b.i.d.* of brivaracetam doses, respectively. Mean CBZ-diol/CBZE ratio decreased from 162% off-treatment, to 117%, 82% and 69% on the same period.
For VPA, due to an inter-occasion variability observed at baseline (i.e. from 45.8 to 56.7 µg/mL), it appeared more relevant to conduct a pairwise comparison versus mean VPA baseline concentrations; There was no significant difference of VPA levels before and after brivaracetam dosing, at all tested dose levels.
The relationship between individual CBZ, CBZE, CBZ-diol, CBZE/CBZ ratio, VPA trough plasma levels and brivaracetam plasma levels was examined through a linear regression analysis with repeated measurements (Day). Table below presents the pairwise comparisons of CBZ, its major metabolites, CBZE/CBZ ratio and VPA trough levels during brivaracetam co-administration versus baseline.

Analyte	Parameter	Estimate	95% CI
CBZ (µg/mL)	Intercept	-0.268	(-1.179; 0.642)
	ln(brivaracetam)	0.002	(-0.072; 0.076)
	ln(CBZ, Day 1 PD)	1.115	(0.667; 1.563)
CBZE (µg/mL)	Intercept	0.661	(0.401; 0.920)
	ln(brivaracetam)	0.350	(0.242; 0.456)
	ln(CBZE, Day 1 PD)	0.970	(0.639; 1.300)
CBZD	Intercept	0.048	(-0.312; 0.408)
	ln(brivaracetam)	-0.070	(-0.154; 0.015)
	ln(CBZD, Day 1 PD)	0.940	(0.637; 1.244)
CBZE / CBZ (µg/mL)	Intercept	0.666	(0.052; 1.280)
	ln(brivaracetam)	0.221	(0.080; 0.363)
	ln(CBZE / CBZ, Day 1 PD)	1.074	(0.622; 1.526)
VPA (µg/mL)	Intercept	2.351	(0.579; 4.122)
	ln(brivaracetam)	-0.071	(-0.147; 0.004)
	ln(VPA, Day 1 PD)	0.379	(-0.057; 0.815)

Model: $\ln(\text{Analyte}) = \text{intercept} + \alpha \ln(\text{brivaracetam}) + \beta \ln(\text{Analyte, Day 1 pre-dose}) + \varepsilon$
Brivaracetam in mg/day, pre-dose levels in µg/mL

For CBZE trough levels and the associated metabolic ratio, CBZE/CBZ, a statistically significant positive relationship was observed with brivaracetam trough levels. Brivaracetam trough plasma levels have no significant impact on CBZD levels. The metabolic ratio CBZ-diol/CBZE tended to decrease significantly when brivaracetam trough levels increased.
Although an inter-occasion variability is observed for VPA baseline values before brivaracetam dosing, brivaracetam trough plasma levels have no significant effect on VPA trough levels.

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SAFETY RESULTS:

Overall, 7 subjects (78%) reported treatment-emergent adverse events (TEAEs) and 3 subjects (33%) reported TEAEs considered as drug-related by the Investigator. The most frequent TEAEs belong to 'Nervous system disorders' primary system organ class. Two subjects (22%) experienced serious adverse events (SAEs) during follow-up, consisting in 'Feeling abnormal' and 'Epilepsy', respectively. These SAEs were considered by the Investigator as severe and possibly related to study drug; they led to hospitalization and were therefore considered as SAEs.

A limited, not medically relevant but consistent increase of SGOT, GGT and to a less extent SGPT levels was observed when subjects received brivaracetam + CBZ/VPA. Other liver function tests (bilirubin and alkaline phosphatase) did not suggest any modification of liver function and the other blood chemistry parameters did not indicate any relevant modification. Hematology parameters did not indicate any clinically relevant modification.

Vital signs (systolic and diastolic blood pressure SBP and DBP, heart rate) indicated a tendency towards a limited decrease of SBP during brivaracetam administration which is not medically relevant. This tendency did not seem to be dose-related and tended to attenuate with the repetition. DBP exhibited the same trend at a lower extent. No clinically relevant modification of heart rate was observed.

Standard 12-lead ECG measurements indicated normal parameters for most subjects. No value of QTc was >500 msec, whatever the correction applied. Two QTc measurements exhibited values considered as prolonged, both when subjects received 200 mg *b.i.d.* of brivaracetam. These prolongations were nevertheless of limited extent (460 and 456 msec, respectively) and were calculated for the Bazzett's correction, but not for the Fridericia's and the Framingham's ones which indicated only borderline QTc. This was confirmed by the examination of QTc changes from baseline, which indicated no change > 60 msec.

CONCLUSIONS:

Trough plasma CBZ levels observed at the end of the administration of 50, 100 and 200 mg b.i.d. of brivaracetam did not statistically differ from those observed before brivaracetam administration. A dose related increase of mean trough CBZE levels was observed. The 90% CI of the geometric LS mean ratio remained within the acceptance range. However, CBZE plasma concentrations exceeded the normal range reported for patients under other AEDs at the higher dose of brivaracetam. There was no significant difference of VPA levels before and after brivaracetam dosing, at all tested dose levels.

The measurements of vital signs suggest a limited tendency of brivaracetam to decrease SBP without affecting significantly DBP or heart rate. The results of ECG measurements did not suggest a need for any special warning in epileptic subjects treated with brivaracetam + CBZ/VPA.

The analysis of safety parameters do not allow to conclude definitely on the safety of co-administration of brivaracetam and CBZ/VPA in epileptic male and female subjects. Nevertheless, this study does not suggest a need for specific warnings.

Report Date:
14-Sep-2006