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:
Monocenter, 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 male subjects suffering from epilepsy.

Investigator: Professor [redacted], MD

Study Center: Epilepsy Unit, Division of Cardiovascular & Medical Sciences, Western Infirmary, Dumbarton Road, Glasgow G11 6 NT (United Kingdom)

Publication: Not applicable

Studied Period (years):	**Phase of Development:**
Date of first enrolment: 18-Sep-2003 Date of last completed: 04-Dec-2003	Human pharmacology / Phase I

Objectives:
Primary Objective:
The primary objective of this Phase I study in 9 adult male subjects suffering from epilepsy and chronically treated with carbamazepine (CBZ) [redacted] was to evaluate the effect of steady-state ucb 34714 (brivaracetam) administration at 50, 100 mg and 200 mg bid (the highest dose foreseen in phase II/III trials) on the steady-state plasma levels of CBZ and its metabolites CBZE (carbamazepine-10,11 epoxide) and CBZ-diol (carbamazepine-diol).
Secondary Objectives:
The secondary objective of this study was to gain information on the safety of simultaneous administration of ucb 34714 and CBZ in subjects including occurrence of seizure.

Methodology:
This was a Phase I (human pharmacology), open-label, unilateral interaction trial between brivaracetam (BRV) and CBZ during multiple oral administrations conducted in one center.

Number of Subjects:
The Investigator selected 9 epileptic male subjects. All the 9 subjects selected were included and received the investigational treatment.

Diagnosis and Main Criteria for Inclusion:
Subjects included in this trial were male subjects aged from 18 to 65 years currently treated with carbamazepine (CBZ) [redacted] (any daily dose ≥ 600 mg was accepted in bid administration). Subjects had to sign and date the written informed consent form; to suffer from well-characterized epileptic syndrome according to ILAE classification; to be on stable carbamazepine dosage for at least 3 months, with carbamazepine plasma levels in the range (4 – 12 µg/mL); to be considered as reliable and capable of adhering to the protocol (e.g. able to understand and complete diaries), visit schedule or medication intake according to the judgment of the Investigator.

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

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ucb 34714	200 mg capsules for oral administration	12610

Duration of Treatment:
For each subject, the trial lasted a maximum of 9 weeks. Subjects included received BRV + CBZ [redacted] (≥600 mg daily):

- 1x50 mg capsule ucb 34714 twice daily from Days 1 to 7 (50 mg bid, up-titration, Period A)
- 2x50 mg capsules ucb 34714 twice daily from Days 8 to 14 (100 mg bid, up-titration, Period B)
- 1x200 mg capsule ucb 34714 twice daily from Days 15 to 21 (200 mg bid, maintenance, Period C)
- 2x50 mg capsules ucb 34714 twice daily from Days 22 to 28 (100 mg bid, down-titration, Period D)

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

Statistical Methods:
Descriptive statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, arithmetic mean, standard deviation [SD], minimum, median and maximum) were tabulated. Coefficient of variation and geometric mean were also presented in the descriptive statistics for pharmacokinetic data.
The pharmacokinetic analysis was performed on the PP population. The possible interaction effect of BRV on the steady state plasma levels of CBZ, CBZE and CBZ-diol was assessed using pair wise comparison of Day 1 (without BRV) and other sampling days: Days 8-15-22-29 (with BRV) and discharge (without BRV).
A regression analysis on individual CBZ, CBZE or CBZ-diol plasma concentrations, as well as CBZE/CBZ and CBZ-diol/CBZ ratios versus BRV plasma levels were performed. Further, the effect on major metabolites of BRV, and the correlation between CBZ, CBZE or CBZ-diol concentrations and BRV doses (via figures) were explored. Finally, the inter- and intra-subject variability of treatment of CBZ, CBZE and CBZ-diol 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:
Following repeated administration of 50, 100 and 200 mg bid BRV + CBZ, there was a dose-proportional increase in through BRV plasma concentrations and its main metabolites ucb 42145, ucb–100406–1 and ucb–107092–1. Compared to those found previously in healthy subjects, BRV through plasma concentrations measured after 100 and 200 mg bid were similar, but higher than those found previously in healthy subjects co-administered CBZ.

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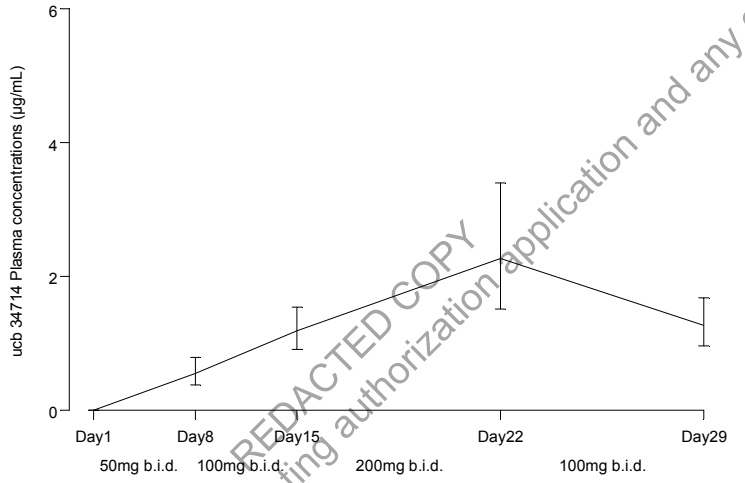
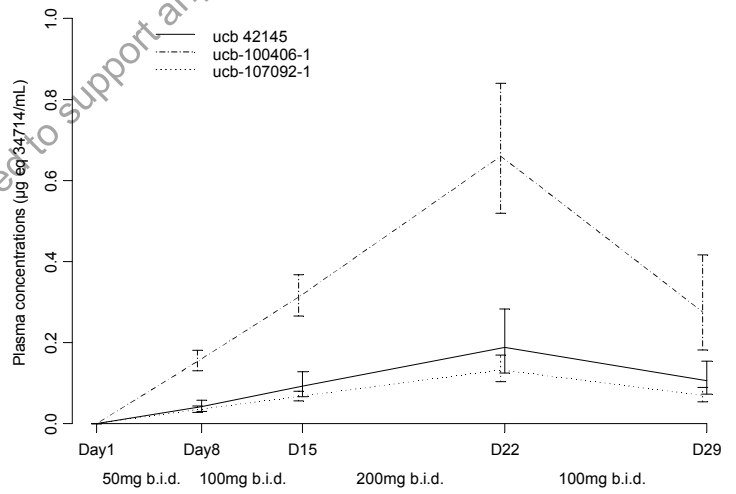
The figures below display the geometric means (± SD on ln-data) of plasma concentrations for BRV (top) and its main metabolites (bottom).





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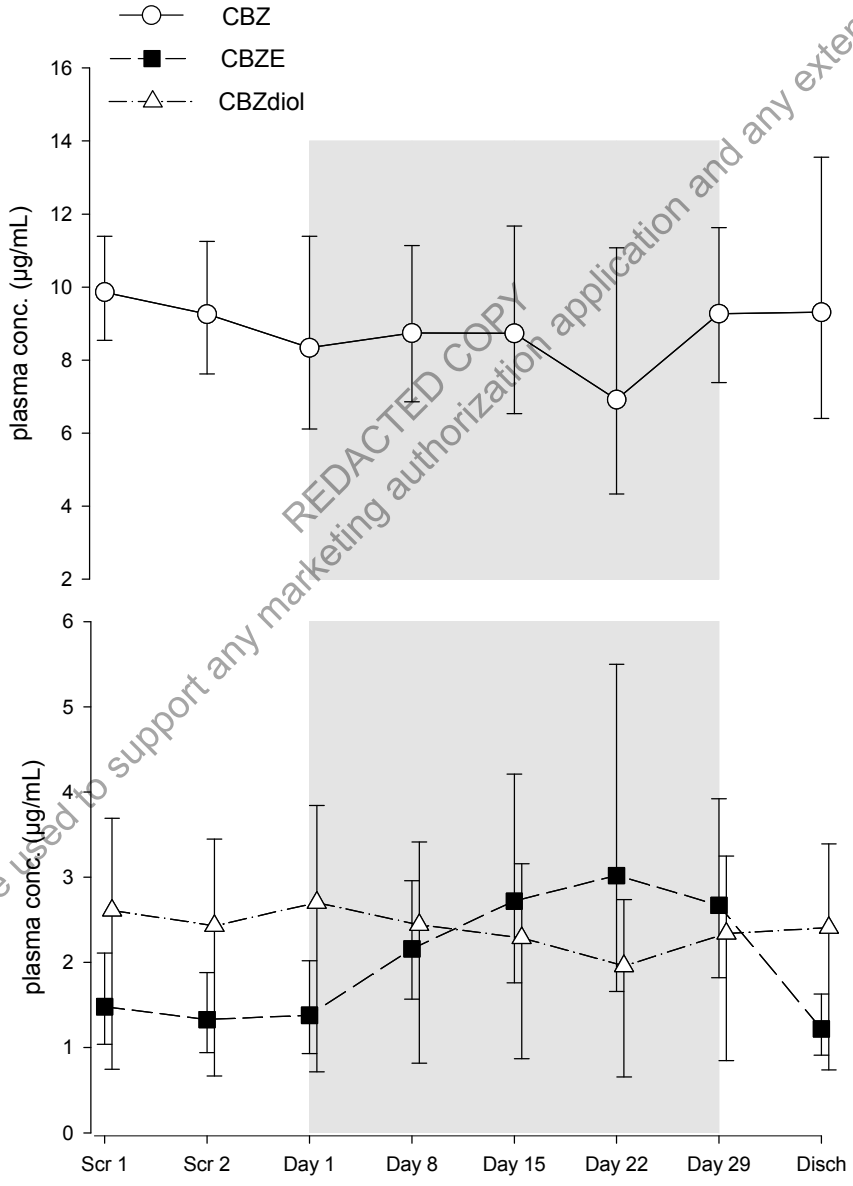
The figures below display the geometric means (± SD on ln-data) of plasma concentrations for CBZ (top) and its metabolites CBZE and CBZ-diol (bottom). The shaded area is the BRV treatment period.



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The inter-subject variability in through concentrations of CBZ was lower than the intra-subject one (CV inter 14.2%, CV intra 18.0%). For CBZ metabolites plasma levels, the inter-subject variability was higher than the intra-subject one (CBZE CV inter 31.5%, CV intra 19.6% and CBZ-diol CV inter 52.5%, CV intra 19.2%). The inter-subject variability observed was low for CBZ and higher for its metabolites. This may be related to the different CBZ dosing regimens between subjects and the consequent different rates of auto-induction.

Day pre-dose	CBZ (µg/mL)		CBZE (µg/mL)		CBZ-diol (µg/mL)	
	Fixed effect[(a)]	Point estimate[(b)]	Fixed effect[(a)]	Point estimate[(b)]	Fixed effect[(a)]	Point estimate[(b)]
Screening 1	9.86 (8.83; 11.02)		1.48 (1.13; 1.94)		2.59 (1.77; 3.80)	
Screening 2	9.26 (7.97; 10.75)		1.33 (1.01; 1.74)		2.41 (1.64; 3.53)	
Day 1	8.34 (6.57; 10.60)		1.38 (1.02; 1.85)		2.65 (1.80; 3.89)	
Day 8	8.74 (7.25; 10.53)	104.8%	2.16 (1.69; 2.75)	156.6%	2.42 (1.65; 3.55)	91.5%
Day 15	8.73 (6.98; 10.91)	104.6%	2.72 (1.94; 3.81)	197.7%	2.27 (1.55; 3.32)	85.7%
Day 22	6.92 (4.83; 9.93)	83.0%	3.02 (1.91; 4.79)	219.6%	1.94 (1.32; 2.84)	73.2%
Day 29	9.27 (7.78; 11.04)	111.1%	2.67 (1.99; 3.59)	194.3%	2.38 (1.62; 3.49)	89.9%
Discharge	9.31 (6.98; 12.43)	111.6%	1.22 (0.97; 1.52)	88.3%	2.39 (1.63; 3.50)	90.2%

[(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

Through plasma CBZ concentrations at the end of BRV up-titration periods did not differ from those observed before BRV administrations. A slight, 17% decrease was observed at the end of the 200 mg bid maintenance period (point estimate 83%). After BRV down-titration with 100 mg bid, CBZ through levels came back to previous levels.
A dose-related increase of mean through CBZE levels was observed, varying from 1.4 µg/mL off-treatment to 2.2, 2.7 and 3.0 µg/mL after 50, 100 and 200 mg bid BRV, respectively. CBZE plasma levels decreased to 2.7 µg/mL after down-titration, and to 1.2 µg/mL at discharge. The geometric LS mean ratio remained in the acceptance range (0–260%) after BRV up-titration. After 200 mg bid BRV, the upper limit was not entirely contained within the acceptance range.
Through plasma CBZ-diol levels at the end of the 50 mg bid period were nearly identical to those observed before BRV administrations (point estimate 91.5%). There was a trend towards a dose-dependent decrease at the two higher doses of BRV (-14% and -27% after 100 and 200 mg bid, respectively). This effect was reversible after down-titration (point estimate 90.2%).
Mean CBZE/CBZ ratios increased from 15% off treatment to 25%, 31% and 44% after 50, 100 and 200 mg bid BRV, respectively. Mean CBZ-diol/CBZE ratios decreased from 179% off treatment to 119%, 83% and 63% after 50, 100 and 200 mg bid BRV, respectively.
The relationship between individual CBZ, CBZE or CBZ-diol through plasma levels or CBZE/CBZ ratio and BRV plasma levels was examined. A linear regression analysis with repeated measurements (Day) was used, with CBZ, CBZE or CBZ-diol through plasma levels or CBZE/CBZ ratio on as dependent variable, BRV through plasma levels as independent variable, and CBZ, CBZE or CBZ-diol through plasma levels or CBZE/CBZ ratio on Day 1 (baseline) as covariate.

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The table below reports pairwise comparisons of CBZ and major metabolites through levels during BRV co-administration versus baseline values (Day 1 pre-dose).

Analyte	Parameter	Estimate	SE	95% CI
CBZ	Intercept	1.496	0.362	(0.637; 2.35)
	Alpha (α)	-0.012	0.029	(-0.079; 0.055)
	Beta (β)	0.363	0.169	(-0.038; 0.764)
CBZE	Intercept	0.518	0.076	(0.343; 0.693)
	Alpha (α)	0.284	0.040	(0.194; 0.375)
	Beta (β)	1.228	0.161	(0.863; 1.59)
CBZ-diol	Intercept	-0.122	0.150	(-0.510; 0.265)
	Alpha (α)	-0.122	0.023	(-0.177; -0.067)
	Beta (β)	0.979	0.134	(0.631; 1.33)
CBZE / CBZ	Intercept	0.521	0.328	(-0.318; 1.36)
	Alpha (α)	0.193	0.056	(0.071; 0.315)
	Beta (β)	0.936	0.181	(0.473; 1.40)

Model: ln(Analyte) = intercept + α ln(BRV) + β ln(Analyte, Day 1 pre-dose) + ε

- Neither BRV through plasma levels nor CBZ baseline values had a statistically significant linear relationship with CBZ through levels (95% CI of the estimate included value "0").
- For CBZE through levels and CBZE/CBZ ratio, a statistically significant positive relationship was observed with BRV through levels.
- CBZ-diol tended to decrease when BRV through levels increased. These results need to be interpreted with caution due to the missing values (2 subjects on Day 1 and 1 subject on Day 29 had a missing value) and the replacement of BLQ values by the limit of quantification value.

SAFETY RESULTS:

Overall, 8 subjects experienced at least one treatment-emergent adverse event (TEAE). The Investigator considered that 6 subjects had drug-related TEAEs. One (1) subject had 2 severe TEAEs which led to hospitalization and were therefore classified as SAEs. These SAEs (post ictal state and aggression preferred terms) occurred two days after the last study drug intake during down-titration and were considered by the Investigator as drug-related. The most frequent TEAEs preferred terms were 'fatigue' (2 subjects), and 'nasopharyngitis' (2 subjects). Nervous system disorders primary system organ class were experienced by 3 subjects overall ('convulsion', 'dizziness' and 'postictal state' preferred terms, 1 subject each). With the exception of the 2 SAEs, all other TEAEs were considered as mild by the Investigator.

The extensive and complete review of clinical laboratory parameters (blood chemistry and hematology) indicated a consistent increase versus time of AST and ALT in only one subject (Subject Nr [redacted]). This increase was mainly observed during follow-up and at discharge, i.e., when the subject was no more treated with BRV. Moreover, this subject had already AST and ALT values above normal range at screening, suggesting an impairment of liver function which could be, at least in part, related to the epileptic pathology or to its treatment. In other subjects, the results of clinical laboratory evaluations did not reveal any clinically relevant findings during treatment periods as well as during follow-up or at discharge. All deviations from normal range were considered as not clinically significant by the Investigator.

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The measurement of blood pressure suggested a moderate decrease of systolic blood pressure. A tendency towards a slight decrease of heart rate was also observed, while diastolic blood pressure was not affected by BRV. However, not any modification of vital signs was considered as clinically relevant by the Investigator.
ECGs did not reveal specific modifications of ventricular rate, PR and QRS intervals. QT intervals corrected for heart rate (QTc) indicated that 3 subjects exhibited borderline increases (from 430 to 450 ms), and 2 subjects showed a prolongation (>450 ms) of QTc, one at 100 mg up-titration Day 8 and one at 100 mg down-titration Day 22.
Compared to screening or Day 1 pre-dose baseline values, 2 subjects showed increases of QTc >60 ms at pre-dose on Day 8 (up titration, 100 mg bid BRV), while 1 subject showed a similar increase of QTc at discharge. Not any modification of ECG parameters was considered as clinically relevant by the Investigator.

CONCLUSIONS:
Overall, the results of this study confirm the findings of the previous CBZ interaction study in healthy subjects. BRV dose-dependently increases CBZE through levels, whereas CBZ through levels were unaffected at the two lower doses (50 and 100 mg bid), and slightly (-17% on average) decreased after 200 mg bid. These effects are related to a dose-dependent and reversible inhibition of epoxide hydrolase, and accessorily to a limited induction of CBZ biotransformation after 200 mg bid BRV. There was a trend towards a decrease of CBZ-diol through plasma concentrations with the increase of exposure to BRV. Despite the modifications of CBZE levels with respect to pre-dose levels, CBZE plasma concentrations remained in the limits of normal range for adults taking other antiepileptic drugs concomitantly (increase from 1.4 to 3.0; normal range 1.4-4.2 µg/mL). The increase of CBZE/CBZ ratios was similar to that observed in the previous CBZ interaction study conducted in healthy subjects. These values remained within normal range for adults subjects administered with other concomitant AEDs.
Brivaracetam undergoes an extensive metabolism, partly CYP-dependent. A previous study in healthy subjects (N01081) indicated that the exposure to BRV is 30% decreased by repeated administrations of CBZ. In this study, BRV through plasma levels increased proportionally to the given dose, and levels observed after the 100 and 200 mg bid dosing steps were similar to those found during the multiple dose study in healthy subjects at the same dose levels, but higher than those found after 200 mg bid administration with CBZ. This difference might be attributed to the different formulations used in the two studies [redacted] in the study N01081) and different populations (i.e. subjects suffering from epilepsy vs. healthy subjects in the study N01081).
The SAEs experienced are likely related to the epileptic pathology or its treatment. The results of clinical laboratory evaluations and those of vital signs and ECG measurements did not suggest the need for any specific precaution associated with co-treatment by BRV and CBZ in epileptic subjects, with the exception of a monitoring of liver and cardiac functions in liver- and cardiac-deficient epileptic subjects, respectively.

Report Date:
06-Jul-2006