2. SYNOPSIS

Name of Sponsor/Company: UCB, Inc.	Individual Study Table Referring to Module 5.3.3.4	*(For National Authority Use only)*
Name of Finished Product: NA	Volume:	
Name of Active Ingredient: brivaracetam	Page:	

Title of Study: A Multicenter, Open-label, Unilateral Interaction Study of ucb 34714 (400 mg daily) on Stable Phenytoin Monotherapy During a 45 day *b.i.d.* Administration Period in 15 Adult Subjects Suffering from Epilepsy.

Investigators: [redacted], MD; [redacted], MD; and [redacted], PharmD.

Study Centers: The three study centers were located in the following cities in the United States (US): Little Rock, AR (Dr. [redacted]), Charlottesville, VA (Dr. [redacted]), and Madison, WI (Dr. [redacted]).

Publication: Not applicable.

Studied Period (years):	**Phase of Development:**
Date of Inclusion of First Subject: 06-Apr-2005 Date of Completion of Last Subject: 22-Jun-2006	Human pharmacology / Phase I

Objectives:

Primary Objective:

The primary objective of this Phase I study in 15 adult subjects suffering from epilepsy and chronically treated with phenytoin (PHT) monotherapy was to evaluate the effect of steady-state brivaracetam (BRV) administration at 200 mg *b.i.d.* on the steady-state plasma levels of PHT.

Secondary Objective:

The secondary objective was to gain information on the tolerability and safety of the simultaneous administration of BRV and PHT in subjects.

Methodology:

This was a Phase I (human pharmacology), open-label, unilateral interaction study of BRV and PHT during multiple oral administration conducted at three centers in the US. At Visits 2 (Day -1) and 7 (Day 24), blood samples for PHT concentration were obtained pre-dose and 1, 2, 4, 6, 8, and 12 hours after the morning dose of PHT. For subjects taking PHT once daily, an additional blood sample was obtained 24 hours after the morning dose of PHT. Trough concentrations of BRV and PHT were determined on Days 3 (PHT only), 4, 5, 6, 8 and 11.

Number of Subjects:

Twenty-seven subjects were screened, 19 (12 females, 7 males) were allocated and received study medications; all 19 completed the study.

Diagnosis and Main Criteria for Inclusion:

Male and female adult subjects (18 - 65 years) suffering from epilepsy (no restriction on seizure frequency) on stable PHT monotherapy for at least 3 months were eligible for inclusion. All subjects had at least one plasma measurement of PHT within the target range of 7 – 23 µg/mL during the screening period.

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Test Product: Brivaracetam	**Dose and Mode of Administration:** 50 mg capsules for oral administration	**Batch Number:** 12839, 13397, 13720

Duration of Treatment:
The duration of treatment with BRV was 45 days. In addition to continuing their stable doses of PHT, subjects received BRV administered as follows:

1. 2 x 50 mg capsules of BRV twice a day from Day 1 through Day 3 (100 mg *b.i.d.*, up-titration).
2. 4 x 50 mg capsules of BRV twice a day from Day 4 through Day 24 (200 mg *b.i.d.*, maintenance).
3. 3 x 50 mg capsules of BRV twice a day from Day 25 through Day 31 (150 mg *b.i.d.*, down-titration).
4. 2 x 50 mg capsules of BRV twice a day from Day 32 through Day 38 (100 mg *b.i.d.*, down-titration).
5. 1 x 50 mg capsule of BRV twice a day from Day 39 through Day 45 (50 mg *b.i.d.*, down-titration).

Reference Therapy: None.	**Dose and Mode of Administration:**	**Batch Number:**

Criteria for Evaluation:

Pharmacokinetics:
The following PK parameters for PHT were calculated and compared between Visit 2 (Day -1) and Visit 7 (Day 24): C_{max}, AUC_{τ}, t_{max}, C_{av}, and CL_{ss}/F.

Efficacy:
Although the protocol was not designed to evaluate efficacy, seizure frequency per week was calculated from the information the subjects provided on their Daily Record Cards (DRCs).

Safety:
Safety assessments included physical and neurological examinations, vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR)], electrocardiograms (ECGs), standard laboratory tests (hematology, biochemistry, urinalysis), DRCs, and adverse events (AEs).

Statistical Methods:
The pharmacokinetic analysis was performed using the per-protocol (PP) population. Plasma concentrations of PHT and BRV were summarized descriptively for each collection time. For PHT, descriptive statistics were calculated for each PK parameter: C_{max}, t_{max}, AUC_{τ}, C_{av} and CL_{ss}/F. Trough BRV and PHT concentrations at Visits 3 (PHT only), 4, 5, 6, 8, and 11 were summarized descriptively and displayed graphically to verify steady state conditions. The drug interaction on PHT was assessed by comparison of AUC_{τ} and C_{max} between Visit 2 (PHT alone) and Visit 7 (combination of BRV and PHT). The primary analysis included inferential analysis tables of natural logarithmic (log) transformed parameters AUC_{τ} and C_{max}. These analyses provided the geometric mean (GeoMean) along with the 95% confidence interval (CI) per treatment, the ratio (Test/Reference) of GeoMean along with the 90% CI, where Test is the combination of BRV and PHT, and Reference is PHT alone.

Descriptive statistics for average seizure frequency per week were summarized by study period (Baseline, Treatment, and Follow-Up).

The number and percent of subjects with treatment-emergent AEs (TEAEs) were summarized by Primary System Organ Class, Preferred Term, and study period (Up-titration, Maintenance, Down-titration). Descriptive statistics for observed values and change from baseline (screening visit) were presented for clinical laboratory values, vital signs, and ECG parameters.

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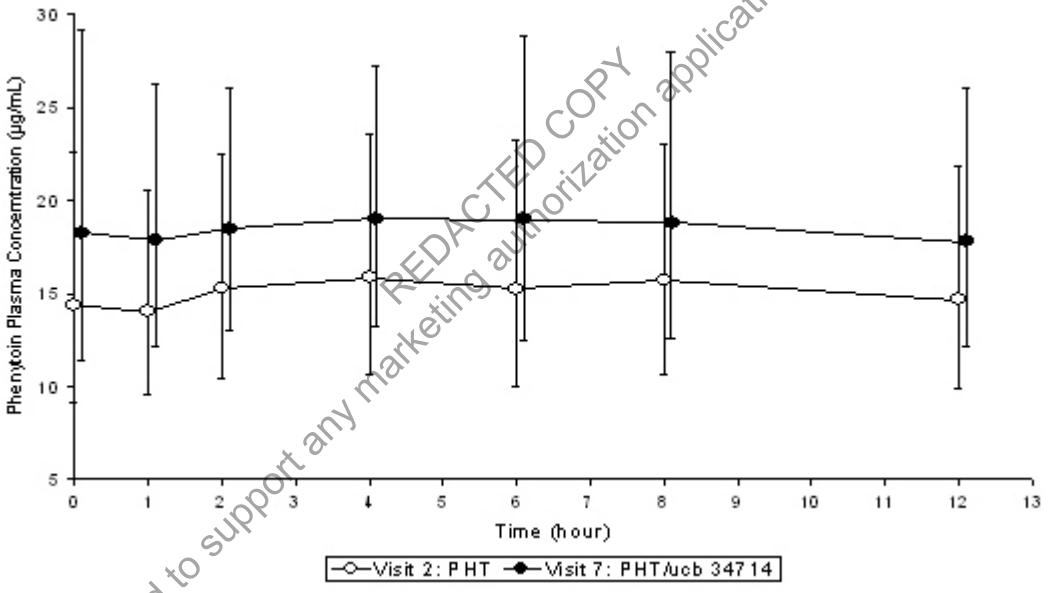
SUMMARY – CONCLUSIONS

Out of the 27 subjects screened, 19 (12 females, 7 males) aged between 21.8 and 55.5 years (mean [SD]: 43.03 [10.10]) were enrolled into the study. All 19 subjects completed the study; they constituted the ITT population. Eighteen subjects were included in the per-protocol (PP) analyses.

PHARMACOKINETIC / EFFICACY RESULTS:

Geometric Means (±SD) of Plasma Concentrations of PHT (µg/mL) in Epileptic Subjects under Stable PHT Treatment before and after Repeated Administration of BRV (PP Population)



The mean PHT concentration increased from approximately 15µg/mL during the baseline period to approximately 18µg/mL at the end of maintenance period, an increase of about 20%.

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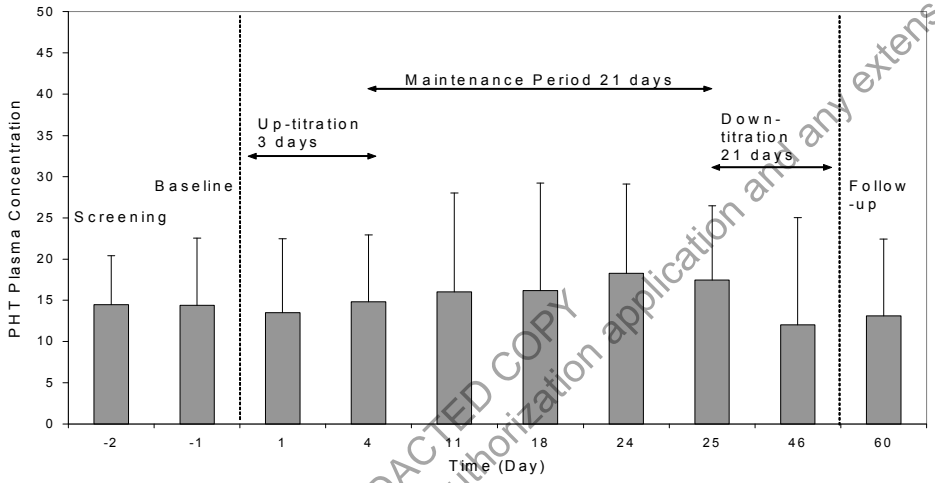
PHT Trough Plasma Concentration: Geometric Means (+SD) (PP Population)



During the treatment period, the mean PHT trough plasma concentration increased gradually as the intake of BRV increased. The mean PHT trough plasma concentration decreased gradually during down-titration reaching a nadir approximately 20% below baseline at the end of down-titration. At Visit 12, two weeks after complete cessation of BRV intake, the mean PHT trough plasma concentration was similar to the baseline mean.

Pharmacokinetic Parameters for PHT Prior to and After Concomitant Administration of BRV for Four Weeks: Geometric Mean (CV%) [PP Population (N=18)]

	Treatment	**C_{max}**	**t_{max} [(a)]**	**AUCτ**	**C_{av}**	**CL_{ss}/F**
Visit 2 (Day -1)	PHT	16.92 (37.5)	4.0 (1.0-12.0)	252.2 (54.8)	14.86 (43.3)	1.063 (51.2)
Visit 7 (Day 24)	PHT/BRV	20.66 (38.1)	4.0 (1.0- 24.0)	305.8 (42.6)	18.39 (39.8)	0.8564 (42.1)

[(a)] median (min-max).

At the end of the maintenance period, the geometric means for C_{max}, C_{av}, and AUC_{τ} increased by approximately 20%, and the geometric mean for CL_{ss}/F decreased by approximately 20%. The median t_{max} did not change.

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Interaction Effect of BRV on PHT [PP Population (N=18)]

Parameter	**Reference[a] (PHT)**	**Test[a] (PHT/BRV)**	**Test/Reference Ratio[b]**	**CV(%)[c]**
C_{max} (µg/mL)	16.92 (14.16 – 20.21)	20.34 (16.96 – 24.38)	1.20 (1.03 – 1.40)	25.2
AUC_τ (h*µg/mL)	252.2 (201.2 – 316.0)	301.4 (239.6 – 379.2)	1.20 (1.01 – 1.42)	29.0
t_{max} (h)	4.0 (1.0 – 12.0)	4.0 (1.0 – 24.0)	0.00 (- 1.98 – 2.00)	

(a) Values are geometric LS means (95% confidence interval), for t_{max}: median (range)
(b) Point estimate (PE) and 90% confidence interval (CI) for Test/Reference geometric LS mean ratio derived from ANOVA. For t_{max}, median point estimate (90% non parametric confidence interval) of the difference between Test and reference (Test – reference)
(c) CV (%): ANOVA residual error, representing intra-subject variability.

After repeated administration of BRV, both C_{max} and AUC_τ of PHT increased by about 20%, and the increase was statistically significant.

The mean (± SD)seizure frequency during baseline was 0.3 ± 1.2 seizures/week and did not change substantially during Treatment (0.3 ± 1.0 seizures/week) or Follow-up (0.4 ± 1.1 seizures/week) periods. Only partial seizures were reported during the study.

SAFETY RESULTS:

A total of 55 TEAEs were reported by 18 (94.7%) subjects, and 45 TEAEs reported by 17 (89.5%) subjects were considered by the investigator to be drug-related. Most of the TEAEs occurred during up-titration (22 TEAEs, 10 subjects) and maintenance (30 TEAEs, 16 subjects). Only 3 TEAEs were reported by 3 (15.8%) subjects during down-titration. Only one TEAE (toothache, not drug-related) was considered to be of severe intensity. No deaths or other SAEs were reported during the study, and no subject discontinued due to TEAEs.

The most frequently reported TEAEs were dizziness (14 subjects) and fatigue (9 subjects). Dizziness was reported for 9 subjects during up-titration and 7 subjects during maintenance. Fatigue was reported for 5, 4, and 1 subject(s) during up-titration, maintenance, and down-titration, respectively. Headache and somnolence, each reported by 2 subjects, were the only other TEAEs reported by more than 1 subject.

Laboratory tests, vital signs, ECGs, and physical and neurological examinations showed no clinically relevant changes during the study.

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CONCLUSIONS:

This study suggests that adding BRV 200 mg *b.i.d*. to an established, stable dosing regimen of PHT being administered to epileptic subjects lead to a statistically significant increase in PHT plasma concentrations. This result should, however, be interpreted with caution since different PHT dosages and regimens were used. Indeed, study subjects were administered PHT once or twice daily [redacted]) with daily doses ranging from 200 mg to 700 mg. In some subjects, dosage regimen was unknown and in some others, morning and evening PHT dosages were different.

The TEAEs observed in this study were consistent with the experience in previous studies involving healthy or epileptic subjects. Overall, the combined therapy of BRV and PHT was well tolerated.

Report Date:
05-Dec-2007