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APPLICATION NUMBER:

205836Orig1s000

205837Orig1s000

205838Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review Addendum

PRODUCT (Generic Name):	Brivaracetam
NDA:	205836, 205837, 205838
PRODUCT (Brand Name):	(b) (4) TM
DOSAGE FORM:	Tablet / IV Solution / Oral Solution
INDICATION:	Adjunctive therapy in the treatment of partial onset seizures in adults 16 years of age and older with epilepsy
SPONSOR:	UCB Inc.
REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	Division 1 (DCP 1)
OND DIVISION:	Neurology (DNP)

The applicant submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) at the same time these three NDAs were submitted to FDA. During its review, EMA requested that new studies be conducted to investigate brivaracetam as an inhibitor of CYPs using a higher concentration (650 μ M); and to investigate brivaracetam as an inhibitor of transporters using concentrations up to 1000 μ M (depending on the transporter tested). The new studies were requested in order to cover the concentration range defined by the EMA guideline on the investigation of drug interactions (June of 2012). The following studies were therefore conducted:

NCD2616: Assessment as a potential inhibitor of human MDRI, BCRP, BSEP, MRP2, MATE1 and MATE2-K Efflux transporters and human OAT1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3 Uptake Transporters

NCD2622: In vitro evaluation as a potential inhibitor of human cytochrome P450 enzymes, in human liver microsomes

Physiologically based pharmacokinetic modeling (PBPK): Quantitative prediction of the potential for brivaracetam as a perpetrator to cause drug-drug interactions with omeprazole and metformin in healthy volunteers

These study reports were provided to EMA to complete the nonclinical data package. To maintain consistency across the applications regarding new data provided to regulatory authorities, the applicant submitted these new reports to NDA 205836 on October 16, 2015, and incorporated for NDA 205837 and NDA 205838 by means of reference to this submission.

We reviewed the study reports for these two *in vitro* studies. The findings from these studies were consistent with the results from the previously conducted studies to

investigate the inhibition potential of brivaracetam on major CYP450 enzymes and transporters. Our conclusion remained the same, i.e., brivaracetam is not expected to cause clinically important inhibition of the following enzymes and transporters at the proposed therapeutic doses: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5; BCRP, BSEP, MATE1, MATE2-K, MDR1 (P-gp), MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3. Please see below for the detailed review of the two *in vitro* studies.

The PBPK report was not reviewed, since it has been concluded that brivaracetam is unlikely to significantly inhibit CYP2C19, OCT1, OCT2, MATE1, or MATE2-K using simple criteria (comparing certain cut-off values with the ratios of total or unbound C_{max} of brivaracetam divided by its measured or anticipated IC_{50} or K_i for these enzyme/transporters).

Study NCD2622: In vitro evaluation of ucb 34714 as a potential inhibitor of human cytochrome P450 enzymes, in human liver microsomes

Objective: The evaluation of ucb 34714 (brivaracetam) as a potential inhibitor *in vitro* of human cytochrome P450 (CYP450) enzymes has already been performed in previous studies (Study number TA0776 and NCD1677). Following a request from Committee for Medicinal Products for Human Use (CHMP), this new study was initiated to evaluate the inhibitory effect of brivaracetam at a higher concentration (650 μ M), in order to cover the concentration range defined by EMA guideline on the investigation of drug interactions (June of 2012).

Method:

1. Evaluation of ucb 34714 as a direct inhibitor of human CYP450 enzymes:
Pooled human liver microsomes (n=200) at a concentration depending on the CYP450 investigated were incubated in triplicate with the CYP450 marker substrate (at the K_m concentration), with and without ucb 34714 (650 μ M). Reactions were initiated with the addition of a NADPH regenerating system.

CYP450 enzyme	Marker reaction	K_m (μ M)	HLM cc (mg/mL)	Incubation time (min)
CYP1A2	Phenacetin O-deethylation	60	0.1	20
CYP2A6	Coumarin 7-hydroxylation	0.7	0.05	5
CYP2B6	Bupropion hydroxylation	100	0.2	20
CYP2C8	Rosiglitazone 5-hydroxylation	5	0.1	20
CYP2C9	Diclofenac 4'-hydroxylation	9	0.05	5
CYP2C19	S-Mephenytoin 4'-hydroxylation	60	0.25	15
CYP2D6	Dextromethorphan O-demethylation	5	0.05	5
CYP3A4	Midazolam 1'-hydroxylation	3	0.05	5
	Testosterone 6 β -hydroxylation	40	0.2	10

Positive controls with reference inhibitors were also performed at inhibitor concentrations of 10-fold K_i value, except for montelukast and benzylnirvanol which were incubated at a higher concentration in order to obtain more than 80% of inhibition.

CYP450 reference direct inhibitors

CYP	Inhibitor	Ki on major target CYP (μM)
1A2	furafylline ^a	0.6
2A6	tranylcypromine	0.2
2B6	thio-tepa	2.8
2C8	montelukast	0.014
2C9	sulfaphenazole	0.3
2C19	benzylrivanol	0.25
2D6	quinidine	0.4
3A4	ketoconazole	0.015

a. 15min pre-incubation (mechanism-based inhibitor).

2. Evaluation of ucb 34714 as a mechanism-based inhibitor of human CYP450 enzymes: Human liver microsomes (1mg/mL) were pre-incubated in triplicate with ucb 34714 (0 and 650 μM), in presence and in absence of a NADPH regenerating system, for 30 minutes. After this pre-incubation, an aliquot was removed and added to incubations containing the CYP450 probe substrate (at Km), NADPH and buffer. This resulted in a dilution of the HLM to the required protein concentration.

CYP450	Marker reaction	Dilution factor
CYP1A2	Phenacetin O-deethylation	10
CYP2A6	Coumarin 7-hydroxylation	20
CYP2B6	Bupropion hydroxylation	5
CYP2C8	Rosiglitazone 5-hydroxylation	10
CYP2C9	Diclofenac 4'-hydroxylation	20
CYP2C19	S-Mephenytoin 4'-hydroxylation	4
CYP2D6	Dextromethorphan O-demethylation	20
CYP3A4	Midazolam 1'-hydroxylation	20
	[¹⁴ C]-Testosterone 6β-hydroxylation	5

Positive controls with reference inhibitors were also performed in parallel, at the inhibitors concentrations specified below. These concentrations were selected in order to obtain more than 25% of mechanism-based inhibition.

CYP450 reference mechanism-based inhibitors

CYP	Inhibitor	Concentration (μM)
1A2	furafylline	0.5
2A6	8-methoxypsoralen	2.5
2B6	ticlopidine	1
2C8	gemfibrozil glucuronide	20
2C9	tienilic acid	1
2C19	S-fluoxetine	100
2D6	paroxetine	5
3A4	azamulin	0.1

The metabolite of each marker substrate was quantified by LC/MS-MS (except for testosterone, for which the metabolite was quantified by radio-HPLC).

3. As ucb 34714 caused significant direct inhibition of CYP2C19 in the initial screening assay, further experiments were performed in order to determine IC₅₀ and Ki values. For the IC₅₀ evaluation, the following ucb 34714 concentrations were applied: 0, 65, 100, 200, 400, 650, 1000, 2000, 6500 and 13000 µM. For the Ki determination, the inhibitory effect of ucb 34714 on CYP2C19 was evaluated at 0, 200, 600, 2000 and 5000 µM, in presence of four concentrations of the CYP2C19 marker substrate, S-Mephenytoin (30, 60, 120 and 240 µM).

4. The microsomal binding of ucb 34714 (650 µM) was also evaluated in human liver microsomes (0.1 and 1 mg/mL), using rapid equilibrium dialysis assay.

Results:

Evaluation of ucb 34714 as a direct inhibitor of human CYP450 enzymes: Among the CYP450 enzymes tested, ucb 34714 caused only an inhibition of CYP2C19 (44% at 650 µM). The IC₅₀ was determined as 909 ± 41.2 µM and Ki was 314 ± 41.2 µM (competitive inhibition). Results for positive controls with CYP reference inhibitors were as expected.

Ucb 34714 as a direct inhibitor of human CYP450s

CYP450 isoform	Marker reaction	Percentage of direct inhibition (%; Mean of 3 values ± SD)	
		ucb 34714 (650µM)	Positive control
CYP1A2	Phenacetin O-deethylation	-3.70 ± 11.6	74.1 ± 1.20 (furafylline 6µM) ²
CYP2A6	Coumarin 7-hydroxylation	6.62 ± 7.16	<u>88.4 ± 3.01</u> (tranylcypromine 2µM)
CYP2B6	Bupropion hydroxylation	-4.95 ± 1.64	87.9 ± 0.496 (thio-tepa 28µM)
CYP2C8	Rosiglitazone 5-hydroxylation	2.19 ± 2.50	84.2 ± 1.16 (montelukast 1.5µM)
CYP2C9	Diclofenac 4'-hydroxylation	-5.77 ± 6.25	85.9 ± 1.07 (sulfaphenazole 3µM)
CYP2C19	S-Mephenytoin 4'-hydroxylation	43.7 ± 4.35 ¹	BLOQ (> 87.9) (benzylmivrianol 4µM)
CYP2D6	Dextromethorphan O-demethylation	3.15 ± 2.21	BLOQ (>79.7) (quinidine 4µM)
CYP3A4	Midazolam 1'-hydroxylation	2.46 ± 8.86	90.5 (n=2) (ketoconazole 0.15µM)
	[¹⁴ C]-Testosterone 6β-hydroxylation	-30.4 ± 35.8	ND (>50) (ketoconazole 0.15µM)

¹: CYP2C19 inhibition: IC₅₀ = 909µM ; Ki = 314µM (competitive mode);

² Mechanism-based inhibition (15-min preincubation);

Underlined: even if the concentration was BLOQ, the value was extrapolated as it was above the S/N;

BLOQ: below limit of quantification;

ND: Not Detected (no peak was detected for 6β-hydroxytestosterone by radio-HPLC).

Evaluation of ucb 34714 as a mechanism-based inhibitor of human CYP450 enzymes: ucb 34714 did not cause any inhibition of all CYP450 enzymes investigated. Results for positive controls with CYP450 reference inhibitors were as expected.

The microsomal protein binding of ucb 34714 (650 µM) was negligible at 0.1 and 1 mg/mL of HLM (i.e., the fu was 1).

Conclusion:

The ratio of the total C_{max} of ucb 34714 at the proposed therapeutic doses divided by its measured or estimated Ki for CYP enzyme (314 µM for CYP2C19, > 325 µM for the

other CYP450 enzymes tested assuming that K_i is equal to half of the IC_{50} values) was less than 0.1. Thus, the conclusion derived from this study is the same as that drawn from the previous studies (TA0776 and NCD1677), i.e., ucb 34714 is not expected to cause clinically important inhibition of the CYP enzymes tested.

Study NCD2616: Assessment of Brivaracetam (UCB34714) as a potential inhibitor of human MDR1, BCRP, BSEP, MRP2, MATE1 and MATE2-K Efflux Transporters and human OATP1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3 Uptake Transporters

Objective: The evaluation of brivaracetam as a potential inhibitor *in vitro* of human efflux and uptake transporters was already performed in a previous study. Following a request from CHMP, this new study was initiated to evaluate the inhibitory effect of brivaracetam at a higher concentration (650 μ M or 1000 μ M, depending on the transporter tested), in order to cover the concentration range defined by EMA guideline on the investigation of drug interactions (June of 2012). IC_{50} was determined if ~50% inhibition was observed at the concentration tested (650 or 1000 μ M).

Methods:

Test article	Transporter	Assay	Applied concentration	Applied concentration range for IC_{50}
brivaracetam	BCRP	MDCKII-BCRP monolayer	650 μ M	-
	MDR1	MDCKII-MDR1 monolayer	650 μ M	-
	BSEP	Vesicular transport assay	650 μ M	-
	MRP2	Vesicular transport assay	650 μ M	-
	MATE1	Uptake transporter assay	650 μ M	-
	MATE2-K	Uptake transporter assay	650 μ M	-
	OATP1B1	Uptake transporter assay	1000 μ M	-
	OATP1B3	Uptake transporter assay	1000 μ M	-
	OAT1	Uptake transporter assay	650 μ M	-
	OAT3	Uptake transporter assay	650 μ M	8.9 - 6500 μ M
	OCT1	Uptake transporter assay	1000 μ M	-
	OCT2	Uptake transporter assay	650 μ M	8.9 - 6500 μ M

1. Vesicular transport assays: were performed using 96-well plates with inside-out membrane vesicles prepared from insect cells (sf9 for MRP2 or Hi5 for BSEP) overexpressing human ABC transporters. Incubations were carried out in the presence of 4 mM ATP or AMP to distinguish between transporter-mediated uptake and passive diffusion into the vesicles. In case of MRP2 the reaction was carried out in the presence of 2 mM glutathione. After stop of the incubation, the amount of substrate inside the filtered vesicles was determined by liquid scintillation counting.

Transporter	Applying protocol	Protein content/well (μg)	Incubation time (min)	Probe substrate	Reference inhibitor
human BSEP	VT-HTS-BSEP-Hi5-TC	50	5	TC (2 μM)	Cyclosporin A (20 μM)
human MRP2	VT-HTS-MRP2-E217 β G	50	8	E ₂ 17 β G (50 μM)	Benzbromarone (100 μM)

TC: taurocholate; E₂17 β G: estradiol-17- β -glucuronide

Relative activities were calculated using the following equation:

$$\text{Relative activity \%} = \frac{A - B}{C - D} \times 100$$

A: amount of translocated substrate in the presence of brivaracetam and ATP

B: amount of translocated substrate in the presence of brivaracetam and AMP

C: amount of translocated substrate in the presence of solvent and ATP

D: amount of translocated substrate in the presence of solvent and AMP

2. Uptake transporter inhibition assays: cells transfected with the specific transporters and the corresponding control cells (e.g., mock-transfected cells) were planted in 96-well plates at a density of 1×10^5 cells/well. After 24-hr culture, the uptake assays were conducted in the conditions described by the table below. The pH of buffer was 7.4 except in case of MATE1 and MATE2-K where the buffer pH was 8.0. Radiolabelled probe substrate transport was measured by liquid scintillation counting.

Transporter	Applying assay protocol	Incubation time (min)	Probe substrate	Reference inhibitor
human MATE1	UPT-MDCKII-MATE1-metformin	15	Metformin (10 μM)	Pyrimethamine (1 μM)
human MATE2-K	UPT-MDCKII-MATE2K-metformin	15	Metformin (10 μM)	Pyrimethamine (10 μM)
human OATP1B1	UPT-HEK293-OATP1B1-E ₂ 17 β G	3	E ₂ 17 β G (1 μM)	Rifampicin (50 μM)
human OATP1B3	UPT-HEK293-OATP1B3-CCK8	10	CCK-8 (0.1 μM)	Rifampicin (50 μM)
human OAT1	UPT-CHO-OAT1-Tenofovir	10	Tenofovir (5 μM)	Probenecid (200 μM)
human OAT3	UPT-HEK293FT-OAT3-MTX	3	Methotrexate (1 μM)	Probenecid (300 μM)
human OCT1	UPT-CHO-OCT1-Metf	20	Metformin (10 μM)	Verapamil (100 μM)
human OCT2	UPT-CHO-OCT2-Metf	10	Metformin (10 μM)	Verapamil (100 μM)

Relative activities were calculated from the equation:

$$\text{Relative activity \%} = \frac{A - B}{C - D} \times 100$$

A: amount of translocated substrate in the presence of brivaracetam in transfected cells
 B: amount of translocated substrate in the presence of brivaracetam in control cells
 C: amount of translocated substrate in the presence of solvent in transfected cells
 D: amount of translocated substrate in the presence of solvent in control cells

3. MDCKII monolayer assays: MDCKII, MDCKII-BCRP and MDCKII-MDR1 cells were seeded into 24-transwell inserts and cultured for 96 hours. Transepithelial electric resistance (TEER) of each well was measured to confirm the confluency of the monolayers prior to the experiments. Values above $120 \Omega\text{cm}^2/\text{plate}$ were accepted. Apical to basolateral permeability of Lucifer yellow (LY) was assessed as a low permeability control, and antipyrine was as a high permeability compound. LY was also incubated in the presence of the test articles in order to assess the effect of the test articles on the monolayer integrity. Assay parameters and treatment groups were summarized in the following table. Samples containing digoxin or prazosin were analyzed by scintillation counting. The donor compartments were sampled before and after incubation to determine the initial concentration (C_0) and recovery (R) of digoxin or prazosin.

Monolayer assay	Applying protocol	Substrate	Direction	Inhibitor	Incubation time (min)
MDCKII, MDCKII-BCRP	ML-MDCKII-BCRP	Prazosin (1 μM)	A-B/B-A	NA	60
		Prazosin (1 μM)	A-B/B-A	brivaracetam 650 μM	60
		Prazosin (1 μM)	A-B/B-A	Ko134 (1 μM)	60
		LY (40 $\mu\text{g}/\text{mL}$)	A-B	NA	120
		Antipyrine (50 μM)	A-B	NA	30
MDCKII, MDCKII-MDR1	ML-MDCKII-MDR1	Digoxin (5 μM)	A-B/B-A	NA	120
		Digoxin (5 μM)	A-B/B-A	brivaracetam 650 μM	120
		Digoxin (5 μM)	A-B/B-A	PSC833 (10 μM)	120
		LY (40 $\mu\text{g}/\text{mL}$)	A-B	NA	120
		Antipyrine (50 μM)	A-B	NA	30

The following equation was used to calculate apparent permeability coefficient (P_{app}):

$$P_{app} = \frac{dQ}{dT} \times \frac{1}{A \times C_0}$$

dQ: amount of transported test drug

dT: incubation time

A: surface of porous membrane in cm^2 (standard: 0.7)

C_0 : initial concentration of the compound in the donor compartment

For MDCKII-MDR1 and MDCKII-BCRP cells, net efflux ratios (ER) were calculated as:

$$\text{net ER} = ER_T - ER_p$$

ER_T: efflux ratios in the transfected cells

ER_P: efflux ratios in the parental cells (used for negative controls)

where ER = P_{app,B->A} / P_{app, A->B}

Recovery (R) was calculated according to the following formula to allow for estimation of metabolism and/or non-specific binding:

$$R(\%) = \frac{Q_{apical} + Q_{basolateral}}{Q_0} \times 100\%$$

Q_{Apical}: amount of test article in the apical chamber in pmol

Q_{Basolateral}: amount of test article in basolateral chamber in pmol

Q₀: amount of test drug detected at t = 0 in pmol

IC₅₀ values were derived from a four parametric logistic equation fitted to the relative activity vs. brivaracetam concentration plot using non-linear regression. Top (maximal response) and Bottom (maximally inhibited response) values were not constrained to constant values of 100 and 0, respectively, unless it is noted otherwise.

$$Y = Bottom + \frac{Top - Bottom}{1 + 10^{(\log IC_{50} - X) \times HillSlope}}$$

Results:

Inhibition results		
Transporter and assay type	maximum inhibition at 650 μM (% of control)	IC ₅₀ (μM)
BCRP ML	NIO	-
MDR1 ML	NIO	-
BSEP VT	NIO (15)	-
MRP2 VT	NIO (-19)	-
MATE1 UPT	28	-
MATE2-K UPT	NIO (-4)	-
OAT1 UPT	NIO (-7)	-
OAT3 UPT	55	541
OATP1B1 UPT	NIO* (11)	-
OATP1B3 UPT	NIO* (4)	-
OCT1 UPT	30*	-
OCT2 UPT	45	740

ML: monolayer assay, VT: vesicular transport assay, UPT: uptake assay

NIO: <20% change of control is not considered as interaction

* at 1000 μM

Brivaracetam inhibited the OAT3-mediated methotrexate accumulation in a dose-dependent manner, with a maximum inhibition of 89% at 6500 μM. The calculated IC₅₀ was 541 μM (95% confidence interval (CI): 293-996 μM).

Brivaracetam inhibited the OCT2-mediated metformin accumulation in a dose-dependent manner, with a maximum inhibition of 92% at 6500 μM . The calculated IC_{50} was 740 μM (95% CI: 450-1218 μM).

In the presence of brivaracetam, the net efflux ratio (ER) of prazosin changed from 25.08 ± 3.8 to 22.53 ± 5.83 , while the net ER of digoxin changed from 8.57 ± 0.34 to 5.64 ± 0.36 . These results indicate that brivaracetam is not an inhibitor of either the BCRP or the MDR1 transporter in the monolayer assay.

MDCKII parental cells				
Compound	Concentration	Papp A-B ($\times 10^{-6}$ cm/s)	Papp B-A ($\times 10^{-6}$ cm/s)	ER
Antipyrine	50 μM	46.61 ± 0.19	NA	ND
LY	40 $\mu\text{g/mL}$	0.84 ± 0.09	NA	ND
LY + Brivaracetam	40 $\mu\text{g/mL}$ + 650 μM	1.21 ± 0.08	NA	ND
Prazosin	1 μM	24.3 ± 1.9	34.7 ± 4.0	1.4 ± 0.2
+ Ko134	+ 1 μM	21.3 ± 4.8	28.8 ± 5.0	1.4 ± 0.4
+ Brivaracetam	+ 650 μM	21.9 ± 5.3	31.6 ± 6.2	1.4 ± 0.4

MDCKII-BCRP cells					Net ER
Compound	Concentration	Papp A-B ($\times 10^{-6}$ cm/s)	Papp B-A ($\times 10^{-6}$ cm/s)	ER	$\text{ER}_T\text{-ER}_P$
Antipyrine	50 μM	43.97 ± 3.93	NA	ND	ND
LY	40 $\mu\text{g/mL}$	0.48 ± 0.01	NA	ND	ND
LY + Brivaracetam	40 $\mu\text{g/mL}$ + 650 μM	1.11 ± 0.04	NA	ND	ND
Prazosin	1 μM	3.1 ± 0.4	81.3 ± 6.0	26.5 ± 3.8	25.1 ± 3.7
+ Ko134	+ 1 μM	18.9 ± 3.0	33.0 ± 2.8	1.7 ± 0.3	0.4 ± 0.4
+ Brivaracetam	+ 650 μM	2.8 ± 0.1	67.6 ± 10.6	24.0 ± 3.8	22.5 ± 5.8

MDCKII parental cells					
Compound	Concentration	Papp A-B ($\times 10^{-6}$ cm/s)	Papp B-A ($\times 10^{-6}$ cm/s)	ER	
Antipyrine	50 μ M	55.00 \pm 3.09	NA	ND	
LY	40 μ g/mL	0.8 \pm 0.0	NA	ND	
LY + Brivaracetam	40 μ g/mL + 650 μ M	0.4 \pm 0.0	NA	ND	
Digoxin	5 μ M	1.0 \pm 0.0	10.3 \pm 0.2	10.0 \pm 0.3	
+ PSC833	+ 10 μ M	1.5 \pm 0.2	2.0 \pm 0.2	1.4 \pm 0.3	
+Brivaracetam	+ 650 μ M	1.0 \pm 0.1	9.0 \pm 0.8	8.7 \pm 1.3	

MDCKII-MDR1 cells					Net ER
Compound	Concentration	Papp A-B ($\times 10^{-6}$ cm/s)	Papp B-A ($\times 10^{-6}$ cm/s)	ER	ER _T -ER _P
Antipyrine	50 μ M	49.31 \pm 2.46	NA	ND	ND
LY	40 μ g/mL	1.1 \pm 0.1	NA	ND	ND
LY + Brivaracetam	40 μ g/mL + 650 μ M	0.8 \pm 0.0	NA	ND	ND
Digoxin	5 μ M	0.9 \pm 0.1	16.0 \pm 0.7	18.6 \pm 3.3	8.6 \pm 0.3
+ PSC833	+ 10 μ M	2.2 \pm 0.3	4.0 \pm 0.3	1.8 \pm 0.3	0.4 \pm 0.3
+ Brivaracetam	+ 650 μ M	0.9 \pm 0.1	13.2 \pm 0.8	14.4 \pm 2.3	5.6 \pm 0.4

Reviewer's Comment: The Drug-Interaction Guidance of FDA recommends calculating the net efflux ratio as ER_T/ER_P. Using this formula, the net ER of digoxin will be 1.86, less than 2, a commonly used threshold indicating efflux transport. This seemed mainly due to the background expression of MDR1 in the parental MDCK-II cells which resulted in an ER of 10. Nevertheless, the positive control worked as expected, greatly inhibiting the ER of digoxin in both parental and MDR1-transfected cells. In contrast, brivaracetam just slightly inhibited the ER of digoxin in either parental or MDR1-transfected cells.

Conclusion:

The findings from this study at higher concentration were consistent with the results from a previously conducted study (NCD2207). Thus, the conclusion previously drawn remains the same, i.e., brivaracetam is not expected to cause clinically important inhibition of BCRP, BSEP, MDR1 (P-gp), OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3.

This study provided new information about the inhibitory potential of brivaracetam on MRP2, MATE1, and MATE2-K. Currently, there is no recommended criterion in the Drug-Interaction Guidance of FDA to judge *in vivo* DDI potential based on *in vitro* data for these transporters. Considering that the location of MRP2 is same as BCRP and P-gp (e.g., lumen membrane of enterocytes, cannalicular membrane of hepatocytes, tubular membrane of kidney cells), the same criteria used for P-gp and BCRP are herein applied to MRP2, and thus brivaracetam is not expected to significantly inhibit MRP2 *in vivo*. For MATE1 or MATE2-K, the International Transporter Consortium (ITC) proposed 0.1 as a cut-off for the ratio of unbound C_{max}/IC₅₀, while EMA recommend 0.02. The

unbound C_{\max} of brivaracetam at proposed therapeutic doses divided by its anticipated IC_{50} ($> 650 \mu\text{M}$) is just on the edge (0.02). Thus, it is not expected that brivaracetam causes clinically important inhibition on MATE1 or MATE2-K.

Xinning Yang, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D. Ph.D. _____

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01/28/2016

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Clinical Pharmacology Review

PRODUCT (Generic Name): Brivaracetam

NDA: 205,836 (0000)
205,837 (0000)
205,838 (0000)

PRODUCT (Brand Name): (b)(4)™

DOSAGE FORM: Tablet / IV Solution / Oral Solution

INDICATION: adjunctive therapy in the treatment of partial onset seizures in adults 16 years of age and older with epilepsy

NDA TYPE: New Molecular Entity

SPONSOR: UCB Inc.

IND : 070205, (b)(4), 103908, 110606

ISR REVIEWERS: Michael Bewernitz, Ph.D.
Xinning Yang, Ph.D.

SECONDARY REVIEWER: Angela Men, M.D., Ph.D.

TEAM LEADER: Angela Men, M.D., Ph.D.

OCP DIVISIONS: Division 1 (DCP 1)

OND DIVISION: Neurology (DNP)

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4.3 Individual Study Review – Non-Clinical

4.3.1 Study PSM0937: *In Vitro* Interspecies Protein Binding and Distribution of [¹⁴C]-ucb 34714 Between Erythrocytes, Plasma and Whole Blood

Objective: to evaluate the *in vitro* blood partitioning of ucb 34714 and the binding percentage of ucb 34714 to plasma proteins in different species (mouse, hamster, rat, rabbit, dog, monkey and human).

Method:

¹⁴C-ucb 34714 was added to blood at final concentrations of 1 and 100 µg/mL (4.7 and 470 µM). After an incubation period of 60 min at room temperature on a rotating agitator to allow drug distribution between plasma and blood cells, aliquots of the suspension were dried, combusted and measured for their content in radioactivity. The remaining blood was immediately centrifuged and aliquots of the supernatant were transferred to counting vials to determine the concentration of ¹⁴C-ucb 34714 in plasma.

The concentration of radioactivity in the blood cells (E) was calculated according to the following equation:

$$E = \frac{WB - [P \times (1 - H)]}{H}$$

where WB, P and H refer to the whole blood concentration, plasma concentration and hematocrit, respectively. The following ratios were calculated:

Blood cell-to-plasma distribution = E/P

Whole blood-to-plasma distribution = WB/P

Binding to plasma proteins was measured by equilibrium dialysis at 37°C. Fresh and frozen plasma samples were brought to pH 7.4 with lactic acid in polypropylene tubes. They were then spiked with 6 different ¹⁴C-ucb 34714 concentrations (0.5-100 µg/mL) and left for homogenization for at least 30 min at room temperature on a rotating agitator before dialysis. 200 µL of the plasma solution were introduced in the “retentate” chamber and dialyzed against 200 µL of the dialysis buffer introduced in the “dialysate” chamber. After dialysis for a period of 4 hrs, aliquots of each chamber were evaluated for ¹⁴C-ucb 34714 concentrations.

The binding percentage of radioactivity to plasma proteins was calculated according to the following standard equation:

$$\text{Binding (\%)} = \frac{C_{\text{retentate}} - C_{\text{dialysate}}}{C_{\text{retentate}}} \times 100$$

where C_{retentate} and C_{dialysate} are the dpm/mL counted by liquid scintillation in the retentate and the dialysate, respectively.

Results:

Throughout all species, blood-to-plasma ratios of ucb 34714 were neither concentration-dependent (over a concentration range of 1-100 µg/mL), nor gender-related. Values ranged

between 0.83 and 0.95 (B/P ratio in humans varied from 0.83 to 0.9). ucb 34714 was stable during incubation. There was no non-specific binding.

Table 1. Blood Partitioning - Interspecies Differences

Species	Gender	H	Concentration (µg/mL)	Time (min)	Plasma (dpm/mL)	Whole blood (dpm/mL)	Blood cells (dpm/mL)	Blood cells / Plasma Ratio	Whole blood / Plasma Ratio
Human	Male	0.443	1	60	28186	23424	17436	0.62	0.83
			100	60	28168	24568	20042	0.71	0.87
	Female	0.368	1	60	27750	24432	18735	0.68	0.88
			100	60	27330	24523	19701	0.72	0.90
Rat	Male	0.366	1	60	27507	23893	17633	0.64	0.87
			100	60	26653	24341	20334	0.76	0.91
	Female	0.349	1	60	27969	24515	18071	0.65	0.88
			100	60	26857	24033	18766	0.70	0.89
Mouse	Male	0.394	1	60	26894	24693	21308	0.79	0.92
			100	60	26569	25169	23015	0.87	0.95
	Female	0.394	1	60	26637	24490	21181	0.80	0.92
			100	60	26261	24633	22124	0.84	0.94
Dog	Female	0.402	1	60	27876	24935	20562	0.74	0.89
			100	60	27175	24274	19958	0.73	0.89
Rabbit	Female	0.347	1	60	27038	25095	21439	0.79	0.93
			100	60	26204	24736	21975	0.84	0.94
Hamster	Male	0.482	1	60	30895	25966	20669	0.67	0.84
			100	60	30211	26012	21498	0.71	0.86
	Female	0.511	1	60	20641	18241	15948	0.77	0.88
			100	60	19041	17154	15351	0.81	0.90

Throughout all species, the binding percentage for ucb 34714 to plasma proteins was constant in the range of 0.5-100 µg/mL. In all cases, the binding capacity for ucb 34714 was low (20.7% with human plasma). No significant gender-related difference was noted in those tested species (human, rat, mouse and hamster). No difference due to freezing was evidenced either with human or rat plasma. There was no fluid shift or non-specific binding during equilibrium dialysis. ucb 34714 was stable during incubation.

Table 2. Protein Binding. Interspecies Differences

	Human		Rat		Mouse		Dog	Rabbit	Monkey	Hamster	
	Male	Female	Male	Female	Male	Female	Female	Female	Male	Male	Female
Protein concentration (g/L)	73.4	81.6	57.1	58.2	44.3	44.3	52.8	49.3	67.3	61.1	66.8
Hematocrit*	0.443	0.368	0.366	0.349	0.394	0.394	0.402	0.347	-	0.482	0.511

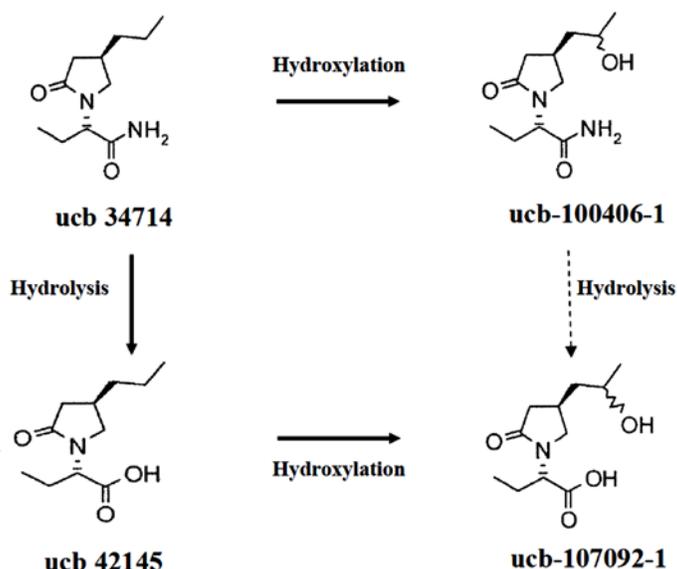
ucb 34714 concentration (µg/mL)	Human		Rat		Mouse		Dog	Rabbit	Monkey	Hamster	
	Male	Female	Male	Female	Male	Female	Female	Female	Male	Male	Female
0.5	20.5	20.5	17.2	20.5	11.8	12.8	10.7	21.1	13.4	27.4	24.9
1	19.3	21.3	19.1	20.2	10.6	15.4	12.7	21.7	11.6	28.4	24.1
5	20.6	20.6	18.3	20.6	11.3	12.6	13.8	21.1	11.8	28.0	25.5
10	19.9	21.7	20.7	19.4	13.4	13.2	10.6	21.5	14.5	27.9	24.8
50	19.8	23.4	19.5	20.9	10.0	11.2	12.1	19.1	10.7	30.4	23.8
100	20.2	20.8	21.2	19.6	12.2	12.0	12.4	19.0	12.3	28.6	24.4

* Pertains to whole blood from which plasma was generated.

4.3.2 Study NCD1674: Determination of Kinetic Parameters for the In Vitro Formation of ucb-107092-1. Identification of the Enzymes Involved in its Biotransformation In Vitro in Human Liver Microsomes and cDNA Expressed Enzymes

Background and Objective: The metabolism of ucb 34714 in human leads to ucb-107092-1 through two possible pathways. The first pathway assumes that ucb 34714 is first converted to ucb-100406-1 via various CYP isoforms. This would be followed by hydrolysis of ucb-100406-1 into ucb-107092-1 via esterase/amidase enzymes. The second pathway assumes that ucb 34714 is hydrolyzed to ucb 42145 via esterase/amidase enzymes, followed by oxidation of ucb 42145 to ucb-107092-1 by CYP450 enzymes. The main objective of this study was to investigate the two hydrolytic reactions in human liver and kidney homogenates, as well as human whole blood. Another purpose was to characterize the CYP isoforms responsible for the biotransformation of ucb 42145 into ucb-107092-1.

Figure 1. Major metabolic pathways of ucb 34714 in human



Method:

1. Pooled human liver homogenate (HLH) and human kidney homogenate (HKH) at 2 mg/ml were incubated with ucb 34714 or ucb-100406-1 (0.1, 1, and 10 mM) in 50 mM potassium phosphate buffer for 6 hours with samples collected at 0.5, 1, 2, 3, 4, and 6 hours to determine the optimum incubation time. Then, HLH and HKH (1, 2, 3, 4, and 5 mg/ml) were incubated with ucb 34714 (0.1, 1, 10, and 100 mM) or ucb-100406-1 (0.1, 1, and 10 mM) in 50 mM potassium phosphate buffer for 60 min to determine the optimal protein concentration. Finally, HLH and HKH (1 mg/mL) were incubated in potassium phosphate buffer with ucb 34714 (10, 25, 50, 100, 150, 200, 250, and 500 mM) or ucb-100406-1 (0.2, 0.5, 1, 2, 5, 10, 15, and 20 mM) for 60 min to determine the kinetic parameters.

2. Human female whole blood was incubated with ucb 34714 or ucb-100406-1 (0.05, 0.5 and 5 mM) in 50 mM potassium phosphate buffer for 6 hours, with samples collected at 0.5, 1, 2, 3, 4 and 6 hours to determine the optimal incubation time. Then, whole blood was incubated with ucb 34714 (0.2, 0.5, 1, 2, 5, 10, 15 and 20 mM) or ucb-100406-1 (0.3, 0.5, 1, 2, 5, 10,

20, 30 mM) in potassium phosphate buffer for 60 min to determine the kinetic parameters. Finally, human female or male whole blood was incubated with 1.6 mM ucb 34714 or 9.6 mM ucb-100406-1 and the inhibitors listed below in potassium phosphate buffer for 60 min.

Esterase	Inhibitor	Concentration to use
Aromatic Esterase	EDTA	1 mM
Choline Esterase	Physostigmine	100 µM
Carboxylesterase	BNPP	100 µM
Choline Esterase / Carboxylesterase	Paraoxon	100 µM
Human Carboxylesterase type 2	Benzil	150 nM
Human Carboxylesterase type 1 & 2	Benzil	500 nM
Acetylcholine esterase	bw284c51	10 µM
Arylesterase	5,5'-Dithiobis(2-nitrobenzoic acid) - DTNB	200 µM
Butyrylcholinesterase	Ethopropazine hydrochloride	10 µM
Serine Esterase & Carboxylesterase (type 1, 2, 3)	Phenylmethanesulfonyl fluoride - PMSF	100 µM
Serine Esterase & carboxylesterase (type 3)	Phenylmethanesulfonyl fluoride - PMSF	2 µM
Carboxylesterase type 2	Loperamide hydrochloride	20 µM
Carboxylesterase type 2	RCL S505-6	10 µM

3. Pooled human liver microsome (HLM, 1 mg/mL) was incubated with ucb 42145 (10, 100 and 1000 µM) for 45 min with samples collected at 5, 10, 20, 30, 45 min to determine the optimal incubation time. Then, HLMs at 0.2, 0.5, 1, 1.5 and 2 mg/mL were incubated with ucb 42145 (10, 100 and 1000 µM) for 30 min to determine the optimal HLM concentration. Following that, HLM (0.2 mg/mL) were incubated for 30 min with ucb 42145 (100, 250, 500, 750, 1000, 2500, 5000 and 10000 µM) to determine the kinetic parameters. For CYP phenotyping, by chemical inhibitors, HLM (0.2 mg/mL) was incubated with 1.6 mM ucb 42145 (corresponding to its K_m) and inhibitors at 10 times their reported K_i for 30 min. In addition, proadifen (100 µM) was used as universal inhibitor of all CYP450s. Incubation mixtures containing furafylline, ticlopidine, diethyldithiocarbamate, and proadifen were pre-incubated in the presence of NADPH and HLM for 10 min, since these inhibitors are mechanism-based. When >50% inhibition was observed, the assay was repeated with several inhibitor concentrations ($0 \times K_i$, $0.1 \times K_i$, $0.3 \times K_i$, $1 \times K_i$, $3 \times K_i$, $10 \times K_i$ and $30 \times K_i$) allowing IC_{50} determination.

(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

CYP450	Inhibitor	Ki (μM) on major target CYP
1A2	furafylline ^a	0.6
2A6	pilocarpine	4
2B6	ticlopidine ^a	0.2
2C8	montelukast	0.15
2C9	sulfaphenazole	0.3
2C19	omeprazole	3.5
2D6	quinidine	0.4
2E1	diethyldithiocarbamate ^a	2
3A4	ketoconazole	0.015
Non specific ("universal")	proadifen	100

For CYP phenotyping using monoclonal antibodies, antibodies specific and highly inhibitory to CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 were pre-incubated with HLM (0.2 mg/mL) for 15 or 20 min before 30-min incubation with ucb 42145 (1.6 mM). Under the experiment conditions, 80% of the target CYP450 was expected to be inhibited.

Finally, supersome™ (0.25 mg protein/mL) for individual CYP1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2, and 3A4 were incubated with 1.6 mM ucb 42145 for 1 hour.

ucb 42145 and ucb-107092-1 were analyzed by LC-MS/MS methods.

4. Calculation of intrinsic clearance

The *in vitro* intrinsic clearance CL_{int} (μL/min/mg homogenate) for the two hydrolytic reactions measured in tissue homogenates (i.e. ucb 34714 into ucb 42145 and ucb-100406-1 into ucb-107092-1) were calculated as follows:

$$CL_{int} = \frac{v}{[substrate]}$$

where v was the reaction rate (pmol formed/min/mg homogenate) and $[substrate]$ was the test item concentration used in the condition of the assay. The above equation is derived from the Michaelis-Menten relationships where the substrate concentration is well below the K_m of the reaction. A mean CL_{int} was obtained from the reaction rates measured in the time linearity assay.

The *in vitro* intrinsic clearance CL_{int} values describing the hydrolytic reactions in blood (i.e. ucb 34714 into ucb 42145 and ucb-100406-1 into ucb-107092-1) and the microsomal oxidation of ucb 42145 into ucb-107092-1 were calculated as follows :

$$CL_{int} = \frac{V_{max}}{Km}$$

The CL_{int} values were derived from the kinetic constants and were expressed as μL/min/mL blood or μL/min/mg microsomal protein.

Intrinsic clearances were also normalized to g tissue and kg bodyweight using the scaling factors listed below.

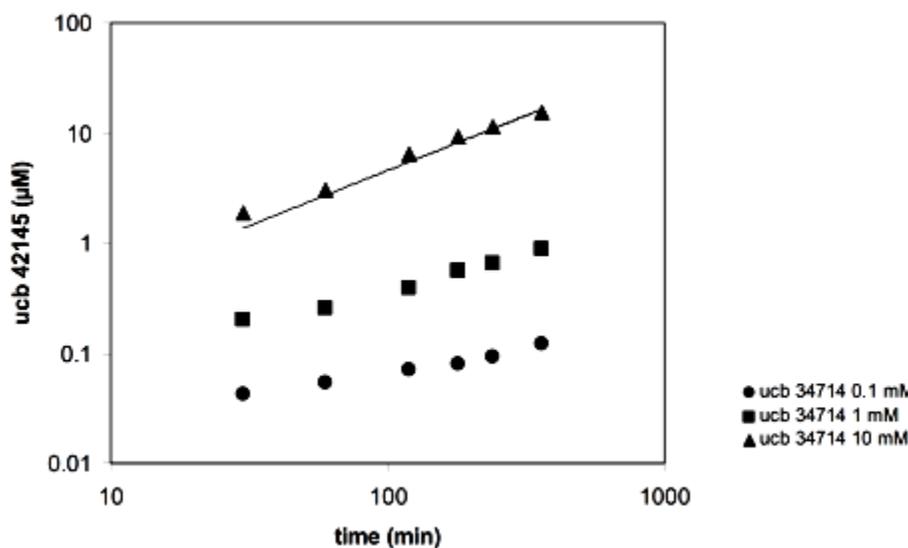
Microsomal protein yield	48.8 mg protein /g liver
Homogenate liver protein yield	80 mg protein /g liver
Homogenate kidney protein yield	72 mg protein /g kidney
Blood volume	0.074 L/kg
Kidney weight	4.4 g kidney/kg body
Liver weight	23 g liver/kg body

Results:

1. Hydrolysis of ucb 34714 to ucb 42145 in HLH

Following incubation of ucb 34714 with HLH (2 mg/ml), a single metabolite known as ucb 42145 was identified. According to the sponsor, the reaction was linear up to 6 hours and the optimal incubation time was set at 60 min for further experiments. The mean reaction rate (0.3, 1.9, and 25.7 pmol/min/mg protein) roughly increased linearly with the substrate concentrations (0.1, 1, and 10 mM).

Figure 2. ucb 42145 Production Versus Incubation Time in Human Liver Homogenates



(Values were corrected for mean signal in the blank controls.)

Reviewer’s Comment: It should be noted that the scales in the above figure are in logarithm. Thus, the formation of ucb 42145 was log-linear to the incubation time but not really linear vs. time (except at 10 mM ucb 34714 the formation of ucb 42145 appeared roughly linear). This is clearly shown by the table below. It is unclear why the sponsor considered 60 min as the optimal incubation time.

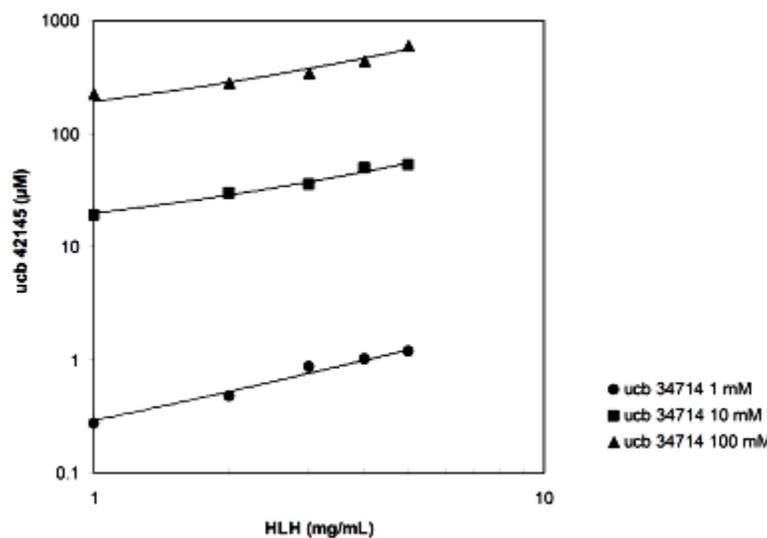
Table 3. ucb 42145 Production Versus Incubation Time in HLH

time (min)	ucb 42145 formed (µM)		
	ucb 34714 [0.1 mM]	ucb 34714 [1 mM]	ucb 34714 [10 mM]
30	0.042	0.203	<u>1.87</u>
60	0.054	0.255	<u>3.05</u>
120	0.070	0.389	<u>6.42</u>
180	0.079	0.559	<u>9.37</u>
240	0.093	0.659	<u>11.31</u>
360	0.120	<u>0.892</u>	<u>15.28</u>

Mean ucb 42145 concentration in zero-protein incubates with 10 mM ucb 34714 was 2.77 µM (2.60 and 2.96 µM at 0 and 360 min, respectively). A fixed value of 0.0277% of test item concentration was used for all the experimental points. Values presented in the table were corrected for mean signal in the blank controls. Underlined value are > upper limit of quantitation.

According to the sponsor, after 60-min incubation, ucb 42145 production increased linearly with HLH protein concentrations (up to 5 mg protein/mL) and 1 mg/mL was set as the optimal protein concentration. The mean reaction rate increased with the substrate concentration (0.85, 4.3, 230, and 2359 pmol/min/mg protein at 0.1, 1, 10 and 100 mM ucb 34714, respectively).

Figure 3. ucb 42145 Production Versus HLH Concentration



(Values were corrected for mean signal in the blank controls.)

Reviewer’s Comment: Similar to the relationship between ucb 42145 formation vs. time, the sponsor presented the log-linear relationship rather than the true linearity. As shown in the table below, ucb 42145 formation did not increase linearly with HLH concentrations except at 1 mM ucb 34714 where the production of ucb 42145 roughly increased in a linear manner with HLHL concentrations.

Table 4. ucb 42145 Production Versus HLH Protein Concentration

HLH concentration mg/mL	ucb 42145 formed (µM)			
	ucb 34714 [0.1 mM]	ucb 34714 [1 mM]	ucb 34714 [10 mM]	ucb 34714 [100 mM]
1	0.095	0.272	<u>19.0</u>	<u>225</u>
2	0.119	0.476	<u>29.7</u>	<u>281</u>
3	0.119	<u>0.858</u>	<u>35.8</u>	<u>340</u>
4	0.133	<u>1.02</u>	<u>49.9</u>	<u>436</u>
5	0.133	<u>1.17</u>	<u>52.6</u>	<u>602</u>

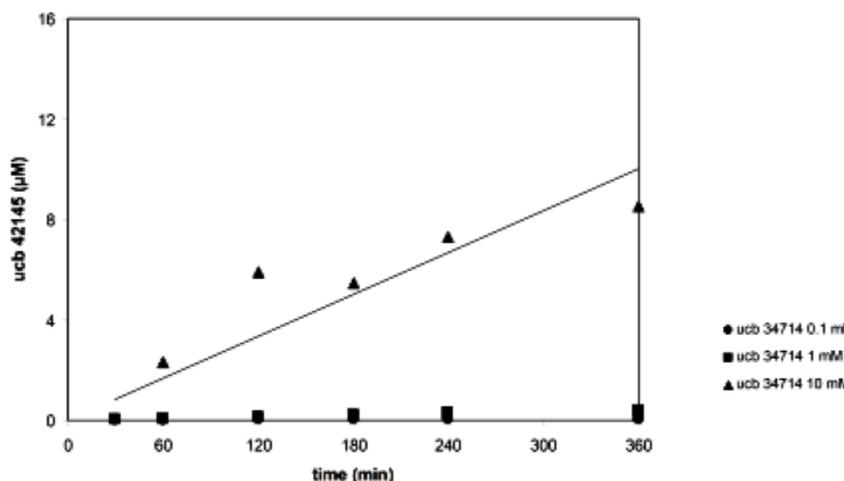
Mean ucb 42145 concentration in zero-protein incubates with 0.1, 1, 10 and 100 mM ucb 34714 was 0.009, 0.094, 0.954 and 8.07 µM. Values presented were corrected for mean signal in the blank controls. (b) (4)

In the assay looking for the kinetic constants, the measured ucb 42145 (b) (4) Thus, no enzymatic reaction could be accurately quantified and no kinetic parameters could be determined. However, the data listed in the table above suggest that the $K_m \geq 100$ mM, since the reaction rate seemed not approaching plateau yet.

2. Hydrolysis of ucb 34714 to ucb 42145 in HKH

When incubated with HKH, ucb 34714 was hydrolyzed into ucb 42145. According to the sponsor, the hydrolytic reaction was roughly linear up to 360 min. The mean reaction rate increased with the substrate concentration (0.1, 0.7 and 14.0 pmol/min/mg protein at 0.1, 1 and 10 mM ucb 34714, respectively). The optimal incubation time was set at 60 min.

Figure 4. ucb 42145 Production Versus Incubation Time in HKH



Values were corrected for mean signal in the blank controls.

Table 5. ucb 42145 Production Versus Incubation Time in HKH

time (min)	ucb 42145 formed (µM)		
	ucb 34714 [0.1 mM]	ucb 34714 [1 mM]	ucb 34714 [10 mM]
30	0.0178	0.063	<u>-0.13</u>
60	0.0171	0.095	<u>2.31</u>
120	0.0231	0.141	<u>5.91</u>
180	0.024	0.204	<u>5.4</u>
240	0.029	0.317	<u>7.3</u>
360	0.043	0.388	<u>8.5</u>

Mean ucb 42145 concentration in zero-protein incubates with 10 mM ucb 34714 was 2.77 µM (2.60 and 2.96 µM at 0 and 360 min, respectively). A fixed value of 0.0277% of test item concentration was used for all the experimental points. Underlined value are > upper limit of quantitation.

Reviewer's Comment: It remains unclear why the sponsor considered the formation of ucb 42145 was linear relative to time in HKH. Nevertheless, considering minimal production of ucb 42145 (after correction by blank control) after 30-min incubation at 10 mM ucb 34714, selection of 60 min for further experiment seemed reasonable.

After 60-min incubation, ucb 42145 production increased linearly with HKH protein concentration (up to 5 mg protein/mL). The mean reaction rate increased linearly with the substrate concentration (0.2, 1.5, 11.8 and 98.0 pmol/min/mg protein at 0.1, 1, 10 and 100 mM ucb 34714, respectively). The optimal protein concentration was set at 1 mg/mL.

Table 6. ucb 42145 Production Versus HKH Concentration

HKH concentration mg/mL	ucb 42145 formed (µM)			
	ucb 34714 [0.1 mM]	ucb 34714 [1 mM]	ucb 34714 [10 mM]	ucb 34714 [100 mM]
1	0.020	0.107	<u>0.9</u>	<u>7</u>
2	0.025	0.179	<u>1.4</u>	ND
3	0.036	0.262	<u>2.0</u>	<u>15</u>
4	0.040	0.33	<u>2.3</u>	<u>24</u>
5	0.041	0.37	<u>3.4</u>	<u>26</u>

Mean ucb 42145 concentration in zero-protein incubates with 0.1, 1, 10 and 100 mM ucb 34714 was 0.009, 0.094, 0.954 and 8.07 µM (ca 0.01%). Values presented were corrected for mean signal in the blank controls.

In the assay looking for the kinetic constants, the ucb 42145 detected (b) (4). Thus, no enzymatic reaction could be accurately quantified and no kinetic constants could be determined. However, the data listed above suggest that the $K_m \geq 100$ mM, since the reaction rate seemed not reaching plateau yet.

3. Hydrolysis of ucb 34714 to ucb 42145 in blood

When incubated with human whole blood, ucb 34714 was transformed into a single identified metabolite, ucb 42145. The extent of conversion was up to 6% (i.e. much higher than the background signal in the blank controls, thus no correction was made). The mean reaction rate increased with the substrate concentration (10, 103 and 371 pmol/min/mL blood at 0.05, 0.5 and 5 mM ucb 34714, respectively). The reaction was in general linear versus time. The optimal incubation time was set at 60 min.

Table 7. ucb 42145 Formation Versus Incubation Time in Whole Blood

time (min)	ucb 42145 formed (µM)		
	ucb 34714 [0.05 mM]	ucb 34714 [0.5 mM]	ucb 34714 [5 mM]
30	0.368	3.27	11.4
60	0.641	6.01	20.7
120	1.11	16.3	51.0
180	1.85	15.4	55.4
240	2.14	19.0	83.1
360	2.77	28.0	113

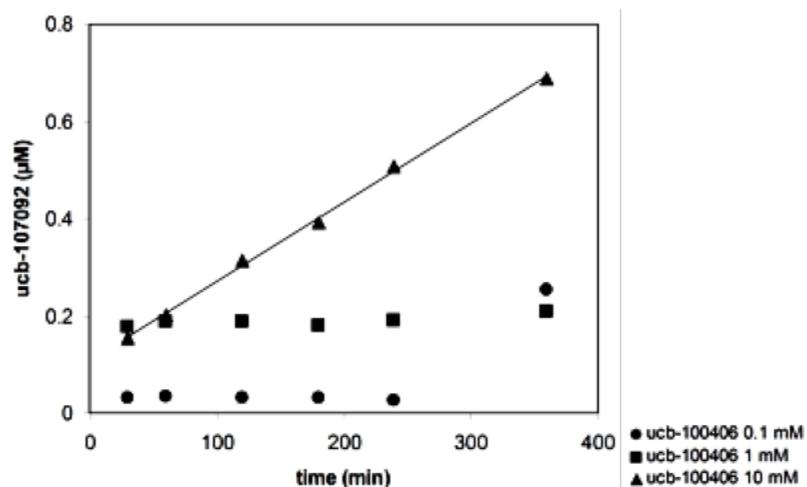
In the assay looking for the kinetic constants, ucb 42145 formation rate started to plateau from 2 mM ucb 34714. The K_m and the V_{max} of the reaction were estimated to be 12.7 ± 0.864 mM and 991 ± 318 pmol/min/mL blood, respectively.

Paraoxon (100 µM), an inhibitor of all serine esterase, inhibited the hydrolysis of ucb 34714 by 68%. All the other tested inhibitors remained without significant effect ($\leq 23\%$ inhibition).

4. Hydrolysis of ucb -100406-1 to ucb ucb-107092-1 in HLH

Following incubation of ucb-100406-1 with HLH, a single metabolite known as ucb-107092-1 was identified. According to the sponsor, the hydrolytic reaction was linear up to 360 min. The test substance ucb-100406-1 was converted by up to 0.007%. The mean reaction rate at 10 mM ucb-100406-1 was 1 pmol/min/mg protein. Because of the very low reaction rate observed (at least 20-fold lower than the one observed for the hydrolysis of ucb 34714 into ucb 42145 at the same concentration of substrate), there was no attempt to further characterize either the protein linearity or the kinetic constants.

Figure 5. ucb-107092-1 Production Versus Incubation Time in Human Liver Homogenates.



Reviewer's Comment: If the relationship between ucb-107092-1 production is linear versus time, the line (at 10 mM ucb-100406-1) should pass the origin point. It should be noted that the data presented here were already corrected for mean signal in blank control. (b) (4)

Table 8. ucb-107092-1 Production versus Incubation Time in HLH

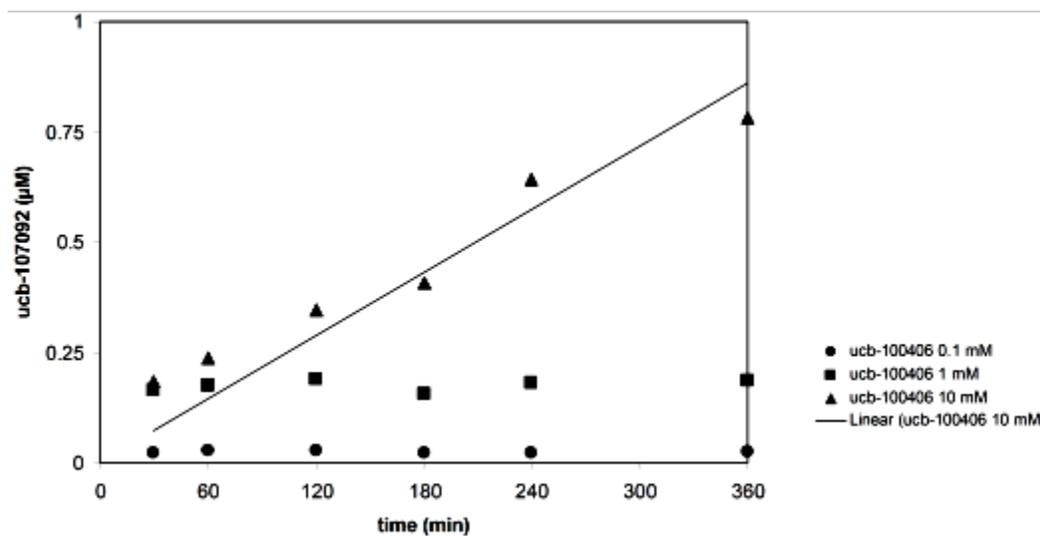
time (min)	ucb-107092-1 formed (µM)		
	ucb-100406-1 [0.1 mM]	ucb-100406-1 [1 mM]	ucb-100406-1 [10 mM]
30	0.0320	0.177	0.15
60	0.0339	0.187	0.20
120	0.0301	0.188	0.31
180	0.030	0.180	0.4
240	0.027	0.191	0.5
360	0.253	0.209	0.7

Mean ucb-107092-1 concentration in zero-protein incubates with 10 mM ucb-100406-1 was 0.41 µM (0.45 and 0.36 µM at 0 and 360 min, respectively). A fixed value of 0.0041% of test item concentration was used for all the experimental points. Values were corrected for mean signal in the blank controls (b) (4)

5. Hydrolysis of ucb -100406-1 to ucb ucb-107092-1 in HKH

When incubated with HKH, ucb-100406-1 was hydrolyzed into ucb-107092-1. According to the sponsor, the hydrolytic reaction was essentially linear up to 360 min. The mean reaction rate at 10 mM was 1 pmol/min/mg protein. Because of the low reaction rate observed (i.e. at least 10-fold lower than the one observed for the hydrolysis of ucb 34714 into ucb 42145), there was no attempt to characterize either the protein linearity or the kinetic constants.

Figure 6. ucb-107092-1 Production Versus Incubation Time in Human Kidney Homogenates



6. Hydrolysis of ucb -100406-1 to ucb ucb-107092-1 in blood

When incubated with human whole blood, ucb-100406-1 was hydrolyzed into a single identified metabolite, ucb-107092-1. The reaction was linear up to 360 min. The test substance was converted by up to 1% (i.e. much higher than the background signal in the blank controls, thus no correction was made). The mean reaction rate increased with the substrate concentration (2.4, 22 and 161 pmol/min/mL blood at 0.05, 0.5 and 5 mM ucb-100406-1, respectively). The optimal incubation time was set at 60 min.

Figure 7. ucb-107092-1 Formation Versus Incubation Time in Whole Blood

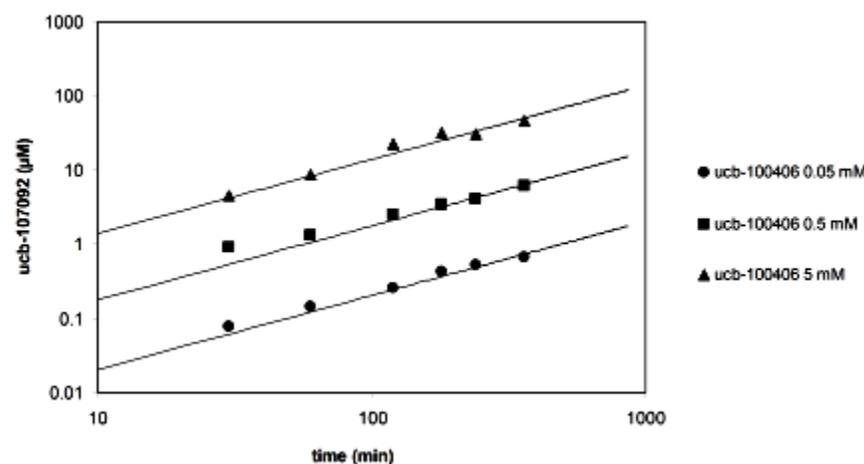


Table 9. ucb-107092-1 Formation Versus Incubation Time in Whole Blood

time (min)	ucb-107092-1 formed (µM)		
	ucb-100406-1 [0.05 mM]	ucb-100406-1 [0.5 mM]	ucb-100406-1 [5 mM]
30	0.0779	0.924	4.59
60	0.141	1.33	8.75
120	0.252	2.50	22.2
180	0.424	3.39	31.9
240	0.520	4.08	30.4
360	0.679	6.19	46.8

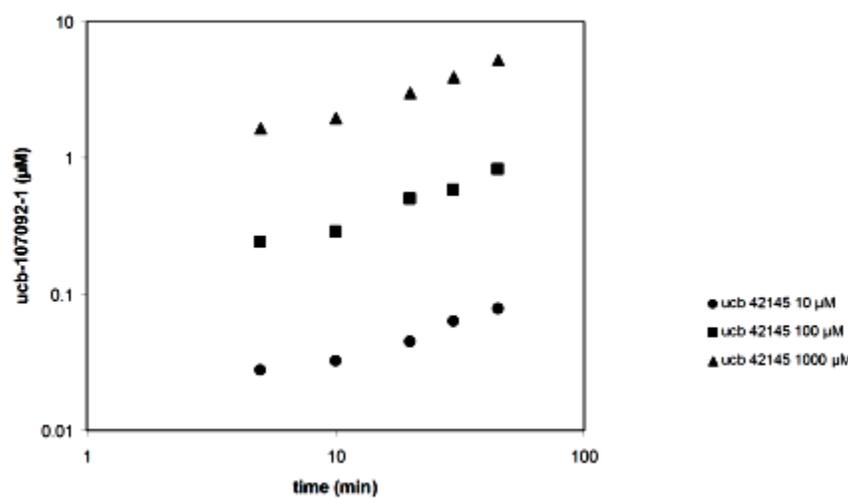
In the assay looking for the kinetic constants, the ucb-107092-1 formation rate started to plateau from 2 mM ucb-100406-1. The K_m and the V_{max} of the reaction were estimated to be 14.7 ± 1.46 mM and 536 ± 274 pmol/min/mL blood, respectively.

Paraoxon (100 µM) inhibited the hydrolysis of ucb-100406-1 by 66%. All the other tested inhibitors remained without significant effect ($\leq 27\%$ inhibition).

7. Conversion of ucb 42145 to ucb-107092-1 in HLMs.

According to the sponsor, when incubated with 1 mg/mL HLMs, ucb 42145 was oxidized into ucb-107092-1 in a reaction that was linear up to 45 min. The mean reaction rate increased with the substrate concentration (3, 28 and 184 pmol/min.mg microsomal protein at 10, 100 and 1000 µM ucb 42145, respectively). The optimal incubation time was set at 30 min.

Figure 8. ucb-107092-1 Formation Versus Incubation Time in Human Liver Microsomes



Reviewer's Comment: Similar to some previous plots, the scales are in logarithm. The relationship between ucb-107092-1 formation and time will be linear only when the slope of

the log-linear line is 1. Based on the following table, it remains unclear why the sponsor considered the reaction was linear up to 45 min.

Table 10. ucb-107092-1 Formation versus Incubation Time in Human Liver Microsomes

time (min)	ucb-107092-1 concentration (µM)		
	ucb 42145 [10 µM]	ucb 342145 [100 µM]	ucb 42145 [1000 µM]
5	0.0278	0.244	<u>1.65</u>
10	0.0326	0.290	<u>1.98</u>
20	0.0448	0.506	<u>2.99</u>
30	0.0636	0.588	<u>3.93</u>
45	0.0778	0.831	<u>5.23</u>

Blank control signal was negligible and thus no correction was made. Underlined value are > upper limit of quantitation.

K_m and V_{max} for ucb-17092-1 formation were calculated to be 1.59 ± 0.201 mM and 460 ± 207 pmol/min/mg, respectively. The reaction was inhibited by 3 µM sulfaphenazole (73%; CYP2C9 inhibitor), and to a lower extent by 40 µM pilocarpine (46%; CYP2A6 inhibitor). The non-specific CYP inhibitor proadifen inhibited the reaction by 68%. All the other inhibitors remained without significant effect ($\leq 25\%$ inhibition). In a subsequent assay, sulfaphenazole was shown to inhibit the reaction with an IC_{50} of 0.597 µM.

Table 11. Effect of Prototypical CYP Inhibitors on ucb-107092-1 Formation in Human Liver Microsomes

ucb-107092-1 (ng/mL)						
Target CYP	Inhibitor [concentration]	average (n=3)	CV	RSD (%)	% of residual activity vs MeOH	% of inhibition vs MeOH
1A2	fufarylline [6 µM]	192	5.1	2.7	93	7.4
2A6	pilocarpine [40 µM]	112	9.9	8.9	54	46
2B6	ticlopidine [2 µM]	201	17	8.3	97	3.1
2C8	montelukast [1.5 µM]	170	9.6	5.7	82	18
2C9	sulfaphenazole [3 µM]	56.6	1.2	2.1	27	73
2C19	omeprazole [35 µM]	170	12	7.3	82	18
2D6	quinidine [4 µM]	221	5.9	2.7	106	-6
2 E1	diethyldithiocarbamate [20 µM]	170	13	7.8	82	18
3A4	ketoconazole [0.15 µM]	213	12	5.7	102	-2
universal	proadifen [100 µM]	67.2	1.0	1.5	32.3	68
NA	methanol (0.1%)	208	19	9.4	100	0
NA	buffer	320	32	10	154	

Monoclonal antibody against CYP2C9 inhibited the conversion of ucb 42145 by 75%. All the other antibodies remained without significant effect (≤ 20% inhibition).

Experiments using recombinant CYPs (Supersomes™) suggested that the oxidation of ucb 42145 to ucb-107092-1 is primarily mediated by CYP2C9 with a minor contribution of CYP2C8 (2.5 and 0.1 pmol/min/pmol CYP, respectively). All the other tested CYP isoforms showed a marginal activity if any.

Table 12. ucb-107092-1 Formation in Recombinants Human CYP Isoforms (Supersomes)

Supersomes	ucb-107092-1 (µM)	velocity (pmol/min/pmol CYP)
1A2	0.013	0.0
1B1	0	0.0
2A6	0.0090	0.0
2B6	0.0098	0.0
2C8	0.27	0.1
2C9	7.5	2.5
2C19	0.021	0.0
2D6	0.017	0.0
2 E 1	0.034	0.0
3A4	0.040	0.0
Control	0	na

The three metabolic reactions described above were compared for their intrinsic clearance. The clearance of ucb 34714 into ucb 42145 was found to be much higher than the hydrolysis of ucb-100406-1 into ucb-107092-1 (26-, 6- and 2-fold difference in liver, kidney

homogenates and blood, respectively). Data expressed on a kg bodyweight basis suggested that blood and liver contribute equally to the hydrolysis of ucb 34714, with a negligible contribution of the kidney. For the hydrolysis of ucb-100406-1, blood seems to play the major role based on data expressed on a kg body weight. The intrinsic clearance associated with the CYP-mediated oxidation of ucb 42145 into ucb-107092-1 was much lower than the hepatic blood flow (i.e. 19 versus 1320 mL/h/kg) and was at least 30 times higher than the clearance of the hydrolysis reactions.

Table 13. Intrinsic Clearances

Substrate	Metabolite	Tissue	Km mM	Vmax	Cl _{int}		
					μL/min/g tissue or μL/min/mL	μL/min/g tissue or μL/min/mL	mL/h/kg bw
ucb 34714	ucb 42145	liver homogenate	> 100	na	0.0026 (c)	0.208	0.287
		kidney homogenate	> 100	na	0.0011 (c)	0.079	0.021
		blood	12.7	991 (a)	0.0780 (d)	0.078	0.346
ucb-100406	ucb-107092	liver homogenate	> 100	na	0.0001 (c)	0.008	0.011
		kidney homogenate	> 100	na	0.0002 (c)	0.014	0.004
		blood	14.7	536 (a)	0.0365 (d)	0.036	0.162
ucb 42145	ucb-107092	liver microsomes	1.59	460 (b)	0.2893 (e)	14.12	19.48

- (a) pmol/min/mL blood
- (b) pmol/min/mg microsomal protein
- (c) μL/min/mg homogenate
- (d) μL/min/mL blood
- (e) μL/min/mg microsomal protein

Conclusions:

1. Overall, the hydrolysis of ucb 34714 into ucb 42145 was found to be much more effective than the hydrolysis of ucb-100406-1 into ucb-107092-1. When scaled-up and expressed on a per kg bodyweight basis, the intrinsic clearance measured in liver, kidney or blood remained < 1 mL/hr/kg.
2. In an attempt to further characterize the enzymes involved, the reactions were measured in the presence of various prototypical inhibitors of arylesterase, aromatic esterase, choline esterase, acetylcholinesterase, butyrylcholinesterase. Only high concentration of the non-specific inhibitor paraoxon showed significant inhibitory effect (> 70% inhibition) of the hydrolysis reactions, suggesting the involvement of serine esterase enzyme(s) other than classical cholinesterase, carboxylesterase or aromatic esterase.
3. Incubations with recombinant enzymes, chemical inhibitors, monoclonal antibodies overall suggested that CYP2C9 is the principal CYP isoform responsible for the conversion of ucb 42145 to ucb-107092-1.

4.3.3 Study NCD2232: Identification of the enzymes involved in ucb 34714 hydrolysis (formation of ucb 42145) in vitro in cNDA expressed enzymes

Objective: to identify the enzymes involved in the hydrolysis of ucb 34714 into ucb 42145.

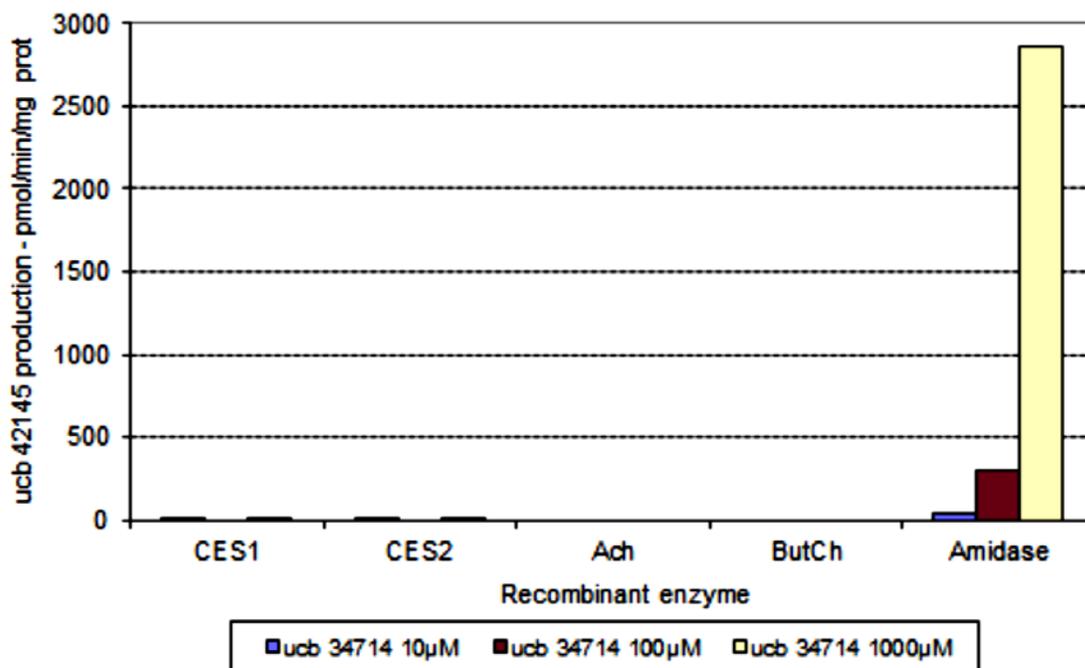
Method: ucb 34714 (10, 100 and 1000 µM) was incubated with each recombinant human enzymes (acetylcholinesterase, amidase, butyrylcholinesterase, and carboxylesterases 1 and 2) at 1, 10 and 100µg/mL in potassium phosphate buffer (50 mM pH 7.4 for amidase and carboxylesterase; 50 mM pH 8.0 for acetylcholinesterase, and 50 mM pH 8.0 containing NaCl 0.15M for butyrylcholinesterase), at 30°C or 37°C (depending on the enzyme). After a 2-min pre-incubation of buffer and recombinant enzymes, reactions were initiated with the addition of test item for 60-min incubation. The formation of ucb 42145 was quantified by a LC/MS-MS method. Zero test item incubation served as blank. The stability of the test item during incubation was assessed using zero-protein incubation.

Results: The hydrolysis of ucb 34714 is only mediated by amidase but not acetylcholinesterase, butyrylcholinesterase, or carboxylesterases 1 and 2. In zero-substrate incubations, ucb 42145 was below limit of quantification whereas small amounts of ucb 42145 were detected in zero-protein incubations. (b) (4)

(b) (4) which remained insignificant with regard to enzymatic hydrolysis.

Kinetic parameters (K_m and V_{max}) for ucb 42145 production by amidase could not be estimated as enzyme saturation was not reached at the highest concentration of ucb 34714 tested (1000 µM), implying that ucb 34714 has a low affinity ($K_m > 1$ mM) for amidase.

Figure 9. ucb 42145 production by recombinant human enzymes (after subtraction of ucb 42145 produced by chemical hydrolysis in zero test system samples)



4.3.4 Study PSM0976: Identification of the CYP450 Isoforms Involved in ucb 34714 Biotransformation In Vitro in Human Liver Microsomes and Supersomes.

Objective: to investigate which cytochrome P450 (CYP) isoforms were responsible for the biotransformation of ucb 34714 into the major hydroxylated metabolite, ucb-100406-1 in pooled human liver microsomes (HLM).

Method: 1) HLM were incubated with ucb 34714 and the production of ucb-100406-1 was determined by LC/MS-MS. The incubation time of ucb 34714 with HLM and the concentrations of HLM were optimized in pilot experiments to ensure that the production of ucb-100406-1 was linear versus time and the relationship between ucb-100406-1 formation and HLM concentration fall in a linear range. A HLM concentration of 0.5 mg/mL and an incubation time of 15 minutes were selected for further experiments. Kinetic parameters (V_{max} and K_m) were determined for the reaction (using a range of ucb 34714 concentrations from 10 μ M to 10 mM). The CYP isoforms implicated in the reaction (at 50 μ M ucb 34714) were investigated by the use of chemical inhibitors and monoclonal antibodies. Each inhibitor was used at 1-fold and 10-fold of its published K_i , so that the inhibition of target CYP450 activity was in the range of 50% and 80-90% respectively, depending on the mechanism of the inhibition. 100 μ M proadifen (a mechanism-based inhibitor) was used as universal inhibitor of all CYPs. Antibodies were used at concentrations expected to give more than 80% inhibition and incubated with HLMs for 15 or 20 min.

CYP	Inhibitor	K_i μ M on major target CYP
1A2	furafylline ^a	0.6
2A6/2C9	pilocarpine	4
2C8/3A4	quercetin	1.3
2C9	sulfaphenazole	0.3
2C19	omeprazole	1, 3.1
2 D6	quinidine	0.4
2E1/2A6/2B6	diethylthiocarbamate ^a	2
3A4	ketoconazole	0.015

a. pre-incubation with HLM for 10 min

The stability of ucb 34714 during incubations and its possible NADPH-independent metabolism were assessed using zero-protein incubations and zero-NADPH incubations, respectively. Zero-substrate incubations served as blanks. In these control conditions, ucb-100406-1 was not detected.

2) Radiolabeled ucb 34714 (100 μ M) was incubated with insect cell microsomes expressing recombinant human CYP isoforms (100 pmol/ml Supersome™, CYP1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) for 2 hours and the extracts analyzed by Radio-HPLC. Selected samples were subjected to further analysis for structural characterization of metabolites. To further confirm the role of CYP2C19 and CYP2C8 in the metabolism of ucb 34714, additional incubations were performed with these CYPs in the presence of inhibitors at 20 x K_i (75 μ M ticlopidine and 20 μ M omeprazole for CYP2C19, and 25 μ M quercetin for CYP2C8).

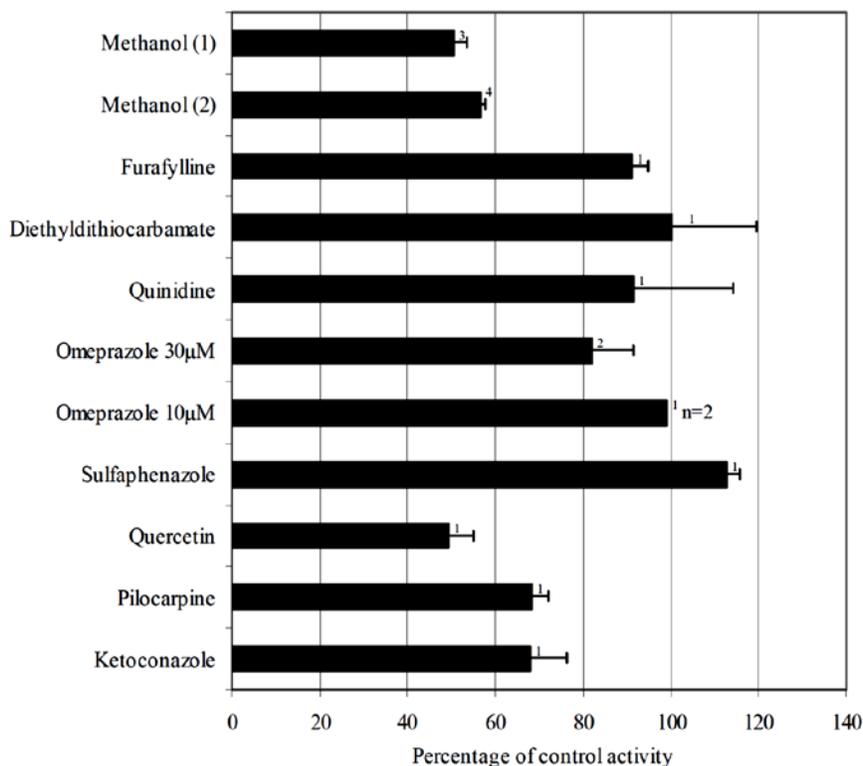
Results:

The K_{mapp} and V_{max} for ucb-100406-1 formation from ucb 34714 by HLM were calculated to be $2438 \pm 147 \mu\text{M}$ (mean \pm SD) and $392 \pm 9 \text{ pmol/min/mg}$, respectively, resulting in an *in vitro* intrinsic clearance (V_{max}/K_{mapp}) of $0.161 \mu\text{L/min/mg}$. This was extrapolated using the well-stirred model and scaling factors (48.8 mg protein/g liver for microsomal protein yield, 23 g liver/kg body for liver weight) to give a predicted *in vivo* hepatic clearance of 0.16 mL/min/kg for ucb 34714.

At 50 μM ucb 34714, the production of ucb-100406-1 in HLMs was inhibited by ketoconazole (32%, CYP3A4 inhibitor), pilocarpine (31.7%, CYP2A6 and 2C9 inhibitor), omeprazole (18%, CYP2C19 inhibitor) at concentrations 10 times of their K_i values compared to quercetin (50.8%, CYP2C8 inhibitor). At their K_i values, only quercetin displayed an inhibition of 21.4%. No inhibition was observed with specific inhibitors for CYP1A2, CYP2C9 and CYP2D6.

In another two following experiments, an IC_{50} of 5.7 or 9.1 μM was further determined for quercetin on inhibition of ucb-100406-1 production. Ticlopidine displayed 14.5 or 20.4% inhibition on ucb-100406-1 formation at 3.7 μM (its literature reported K_i for CYP2C19). However, the IC_{50} of ticlopidine (CYP2B6 and 2C19 inhibitor) exceeded the highest concentrations tested (74 μM).

Figure 10. Effect of Chemical Inhibitors (10 K_i) on the Conversion of ucb 34714 to ucb-100406-1 by Human Liver Microsomes



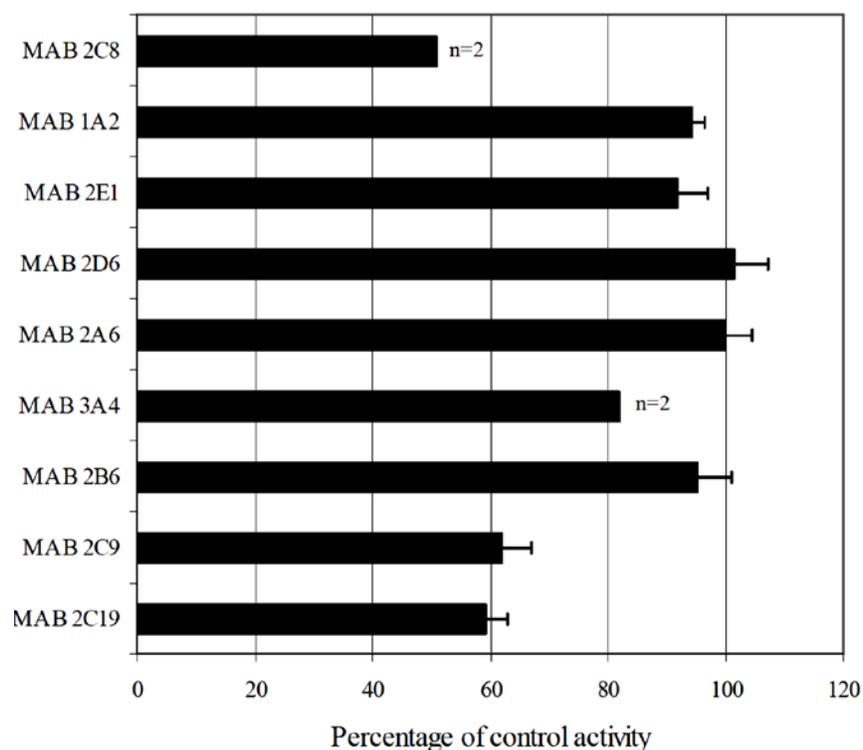
(1. Inhibition effects of the inhibitor drugs were determined with average rate of ucb-100406-1 formation compared to control incubations with methanol (1%, vehicle used to dissolve inhibitor drugs).

2. Inhibition effects of methanol (1%, vehicle) were determined with average rate of ucb-100406-1 formation compared to control incubations with buffer.)

At 50 µM ucb 34714, the CYP2C8 monoclonal antibody inhibited ucb-100406-1 formation in HLM by 49% confirming the result using chemical inhibitor. Inhibition was also observed with monoclonal antibodies to CYP2C9 (37.9%), CYP2C19 (40.8%) and CYP3A4 (18.2%). In the presence of the CYP2B6 monoclonal antibody, weak inhibition was observed at a substrate concentration of 2.5 mM but not at 50 µM.

(Reviewer's comment: The concentration 2.5 mM is much higher than the *in vivo* concentrations after 100 mg bid dosing. Thus, the metabolic profile at this concentration may not be clinically relevant, since there could be shift in metabolic pathways at higher concentrations.)

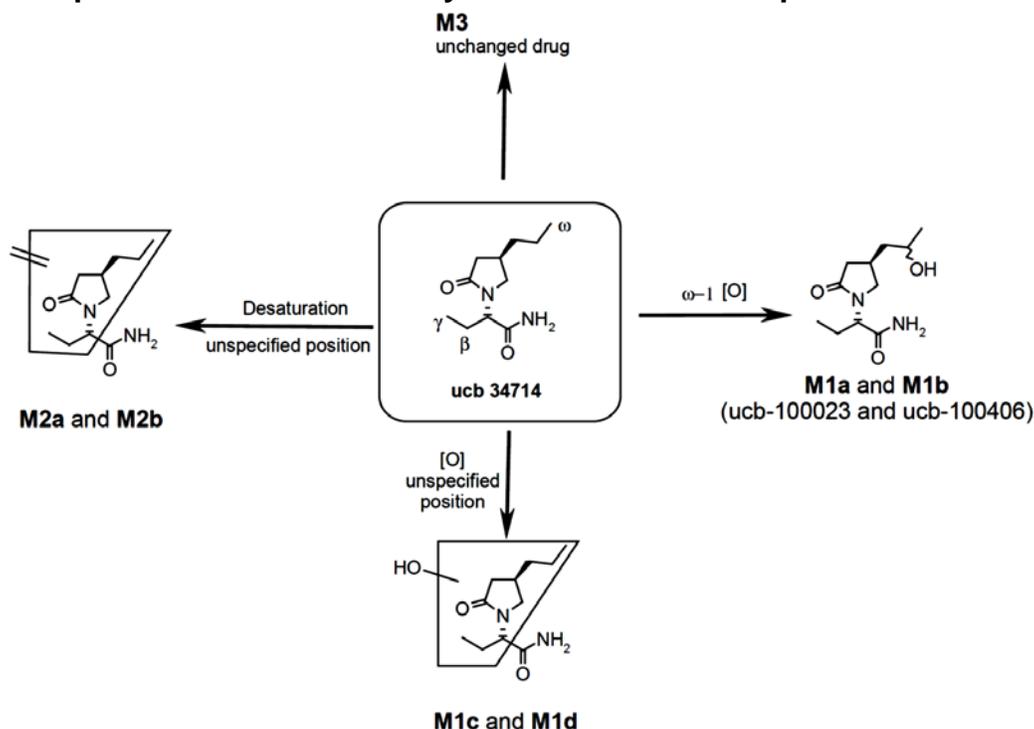
Figure 11. Effect of Monoclonal Antibodies on the Conversion of ucb 34714 (50 µM) to ucb-100406-1 by Human Liver Microsomes



Following the incubation of ucb 34714 with Supersomes, 6 metabolites were identified in addition to the parent drug. The metabolism of ucb 34714 occurred by two initial pathways:

- monohydroxylation, in the ω-1 position of the propyl chain, leading to M1a (ucb-100023-1) and M1b (ucb.100406.1) and in an unspecified position leading to M1c and M1d;
- desaturation leading to M2a and M2b.

Figure 12. Proposed Metabolic Pathways for ucb 34714 in Supersomes.



The formation of ucb-100406-1 was observed with CYP2B6, 2C8, 2C9, 2C19 and 3A4 isoforms. The involvement of CYP2C8 and 2C19 was further confirmed by incubation with chemical inhibitors. The formation of M1b (ucb-100406-1) was inhibited by 90.5% with omeprazole, and ¹⁴C-ucb-100406-1 was not detected in the presence of ticlopidine or quercetin. In the presence of methanol (vehicle used to dissolve inhibitors), an inhibition of 49.7% and 24% was found in incubations with CYP2C19 and CYP2C8, respectively.

Conclusion: Overall, these experiments suggested that the biotransformation of ucb 34714 into ucb-100406-1 was mediated by multiple enzymes, with CYP2C8 being the major isoform, lesser contribution from 2C19, 2C9 and 3A4, and minor contribution from 2B6. It should be noted that the results were preliminary. A clinical drug interaction study showed that gemfibrozil, whose glucuronide metabolite is a potent CYP2C8 inhibitor, did not have significant effect on PK of ucb 34714 and ucb-100406-1 in humans. This was further confirmed by an *in vitro* study (NCD2050) demonstrating that gemfibrozil/gemfibrozil glucuronide only had limited effects on ucb 34714 hydroxylation to ucb-100406-1.

4.3.5 Study NCD1998: Identification of the CYP450 Enzymes Involved in ucb 34714 Hydroxylation (Formation of ucb-100406-1) In Vitro in Human Liver Microsomes and cDNA Expressed Enzymes

Objective: to complete results obtained in a previous study (PSM0976) in order to characterize the human CYP isoform(s) responsible for ucb 34714 hydroxylation into ucb-100406-1.

Method: A HLM concentration of 0.5 mg/mL and an incubation time of 20 minutes were selected based on pilot experiments. ucb-100406-1 was determined by LC-MS/MS. Kinetic parameters (K_m , V_{max} and CL_{int}) of formation of ucb-100406-1 were determined in pooled HLM incubated with 0.2 – 20 mM of ucb 34714. Experiments were further performed with specific CYP inhibitors (chemical inhibitors and monoclonal antibodies). Inhibitors were used at concentrations corresponding to 10 x their respective K_i .

CYP	Inhibitor	K_i μ M on major target CYP
All	proadifen	NA
1A2	furafylline ^a	0.6
2A6	tranylcypromine	0.2
2B6	Thio TEPA	2.8
2C8	montelukast	0.15
2C9	sulfaphenazole	0.3
2C19	omeprazole	3.5
2D6	quinidine	0.4
2E1	diethyldithiocarbamate ^a	2
3A4	ketoconazole	0.015

a. 10 min pre-incubation (metabolism-based inhibitors)

Monoclonal antibodies specific to CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 were used.

Finally, 1-hr incubations were carried out with insect microsomes expressing specific human CYP450 isoforms (Supersomes™, 50 pmol/ml protein CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2, 3A4, 4F12) and 20 μ M ucb 34714 (for CYP3A4, the incubation time was 10 min instead of 1 hr, since the formation was linear up to 20 min). Additional incubations were performed with Supersome™ (CYP2B6, 2C8, 2C9, 2C19 and 3A4) at varied ranges of ucb 34714 concentrations to determine kinetic parameters (K_m , V_{max} and CL_{int}).

Results:

In HLMs, K_m and V_{max} values of ucb 34714 for the formation of ucb-100406-1 were 1.88 ± 0.123 mM (mean \pm SD) and 171 ± 3.6 pmol/min/mg proteins, respectively, resulting in a low intrinsic clearance of 0.091 μ L/min/mg of proteins.

In HLMs, at 100 μ M ucb 34714, significant inhibition was observed with montelukast (CYP2C8, 30.5%), sulfaphenazole (CYP2C9, 20.8%), omeprazole (CYP2C19, 26.4%), and ketoconazole (CYP3A4, 20.3%). The other CYP inhibitors did not exhibit any relevant

(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

inhibition (< 15%). In an additional assay at 2 mM ucb 34714, a cocktail of CYP2C8, 2C9 and 3A4 inhibitors produced 71.9% inhibition, confirming the involvement of multiple isoforms.

For experiments performed with monoclonal antibodies, significant inhibition (i.e. >20% at 100 µM ucb 34714) depended on the sources of antibodies. Inhibition was only observed for CYP2C8 and 2C9 for the supplied from two vendors, while significant inhibition was observed for CYP2C8, 2C9, 2C19 and 3A4 when using the antibodies from another source.

Table 14. Effects of Monoclonal Antibodies on the Formation of ucb-100406-1 in HLM

ucb 34714 :	Monoclonal antibodies					
	% inhibition					
	(b) (4) (1st assay)		(b) (4) (2nd assay)		(b) (4)	
	100 µM	2 mM	100 µM	2 mM	100 µM	2 mM
CYP1A2	-13	-4	\	\	\	\
CYP2A6	0,6	-2	\	\	\	\
CYP2B6	15,6	17,1	\	\	\	\
CYP2C8	26,8	13,9	32,2	16,9	41,8	28,4
CYP2C9	30,1	27,1	37,7	34,9	52,2	39,3
CYP2C19	5,1	-3	7,6	-3	46,3	36,6
CYP2D6	8,5	-4	\	\	\	\
CYP2E1	0	-3	\	\	\	\
CYP3A4	-8	2,1	2,0	-17	24,4	21,7

Kinetic parameters of ucb 34714 for ucb-100406-1 production were further determined for individual CYP isoforms using recombinant CYPs. Relative activity factors (RAF) were used to scale up CL_{int} from recombinant CYPs (Supersomes™) to HLMs and to determine the involvement of each CYP450 in the formation of ucb-100406-1.

Table 15. Summary of Kinetic Parameters in Supersomes™, Predicted Clearances in HLM and Involvement of each CYP450 in Formation of ucb-100406-1 in HLM

CYP	Kinetic Model	K _m mM	V _{max} pmol/min/pmol P450	CL _{int} µL/min/pmol P450	RAF pmol P450/mg prot	CL _{int} pred in HLM µL/min/mg prot	% involment %
2B6	Michaelis Menten	2,64	2,90	0,00110	9,45	0,0104	12,2
2C8	Michaelis Menten	0,897	0,482	0,000537	17,1	0,00918	10,8
2C9	Michaelis Menten	1,27	0,336	0,000265	75,0	0,0198	23,3
2C19	Michaelis Menten	0,0712	0,494	0,00694	2,79	0,0193	22,7
3A4	Hill	1,36	1,89	0,00139	19,1	0,0265	31,1

ucb 34714 showed a high affinity for CYP2C19 (K_m ~ 70 µM) whereas its affinity for CYP2B6, 2C8, 2C9 and 3A4 was much lower (K_m ≥ 900 µM).

(Reviewer's comment: This was consistent with the results obtained from chemical inhibitor experiments. The inhibitory effect of omeprazole (CYP2C19 inhibitor) was only observed at 100 µM and 500 µM but not at 2mM at which CYP2C19 may be already saturated.)

The prediction from recombinant CYPs for the involvement of CYP isoforms in ucb-100406-1 formation was close to the results obtained from chemical inhibitor experiments (in HLMs) except the contribution of CYP2C8.

Table 16. Summary of Results Obtained with Chemical Inhibitors and Supersomes

<i>ucb 34714</i> :	Percentage of involment				Supersomes
	Chemical inhibitors				
	<i>100 μM</i>	<i>500 μM</i>	<i>2 mM</i>		
CYP1A2	(-12)	(-22)	(-6)	-	
CYP2A6	(-1)	(-1)	(-2)	-	
CYP2B6	(14,3)	16,6	(11,3)	12,2	
CYP2C8	30,5	21,9	19,1	10,8	
CYP2C9	20,8	20,2	15,3	23,3	
CYP2C19	26,4	20,3	(4,4)	22,7	
CYP2D6	(4,3)	17,1	(-10)	-	
CYP2E1	(13,4)	(6,6)	(6,7)	-	
CYP3A4	20,3	23,1	17,6	31,1	

Values in parenthesis are not significant

(note: the comma symbol should be decimal point.)

Conclusion: Combined *in vitro* approaches demonstrated that the hydroxylation of ucb 34714 into ucb-100406-1 involved multiple CYP isoforms (CYP2C8, 2C9, 2C19, and CYP3A4).

4.3.6 Study NCD2050: Evaluation of gemfibrozil as a potential inhibitor of ucb 34714 and ucb 42145 hydroxylation (formation of ucb-100406-1 and ucb-107092-1, respectively) in human liver microsomes and human hepatocytes

Background and Objectives: ucb 42145 is the hydrolysis product of ucb 34714. A previous phenotyping study described that CYP2C8 was the main CYP isoform involved in the hydroxylation of brivaracetam. However, a clinical drug-drug interactions study, using gemfibrozil as CYP2C8 inhibitor, showed no statistically significant effect on brivaracetam hydroxylation (formation of ucb-100406-1), while ucb 42145 hydroxylation (formation of ucb-107092-1) was inhibited by ~ 35%. Gemfibrozil is known to be a reversible inhibitor of CYP2C9 (K_i of 5.8 μM), 2C19 (K_i of 24 μM), 1A2 (K_i of 82 μM) and 2C8 (I_{C50} of 120 μM) and gemfibrozil-O-glucuronide is a potent mechanism-based inhibitor of CYP2C8 (K_i of 20 to 52 μM and k_{inact} of 0.21min⁻¹). The aim of this study was to evaluate the ability of gemfibrozil to inhibit hydroxylation of ucb 34714 and ucb 42145 *in vitro*, in order to explain the clinical data and further explore the CYPs involved.

Methods: First, kinetic parameters (K_m and V_{max}) were determined for ucb 34714 and ucb 42145 hydroxylation in pooled HLM (plasma/buffer, 50/50, v/v) and cryopreserved pooled human hepatocytes suspensions (buffer and buffer/plasma (50/50, v/v). ucb 34714 (0.1, 0.3, 0.5, 1, 1.5, 2, 4 and 10 mM) and ucb 42145 (0.15, 0.5, 0.75, 1.5, 3, 6 and 15 mM) were incubated in triplicate with HLM.

Test item	HLM concentration (mg/mL)	Incubation time (min)
ucb 34714	0.5	20
ucb 42145	0.2	30

ucb 34714 (0.4, 1, 2, 4, 8, 16, 40 mM) and ucb 42145 (0.15, 0.5, 0.75, 1.5, 3, 6, 15 mM) were incubated in triplicate with hepatocytes suspensions for 30 min and 60 min, respectively. .

Then, HLM and human hepatocytes suspensions (0.5×10⁶ cells/mL) were incubated with different concentrations of ucb 34714 or ucb 42145 and with varied ranges of gemfibrozil concentrations, to determine inhibitory parameters (I_{C50} and/or K_i).

In addition, the potential of gemfibrozil to act as mechanism-based inhibitor was evaluated in human hepatocytes monolayers (from one donor, 0.75 × 10⁶ cell/mL in 24-well plate cultured overnight) pre-incubated for 3 hrs with gemfibrozil (0, 25, 75, 150, 250, 750, 1500, 2500 μM) for ucb 34714 incubations (3 mM, 1 hour), and 0, 1, 3, 6, 10, 30, 100, 300 μM) for ucb 42145 incubations (2.5 mM, 1 hour).

Finally, gemfibrozil-O-glucuronide (0, 2, 6, 10, 20, 60, 120 and 200 μM) was tested as a direct or metabolism-dependent (pre-incubated for 30 min) inhibitor of ucb 34714 (2 mM) or ucb 42145 (1.5 mM) in HLM. ucb-100406-1 and ucb-107092-1 formed were determined by LC-MS/MS.

Results:

For ucb 34714 hydroxylation, similar K_m values were obtained in all tested conditions, with K_m values of 4.59 ± 0.523 mM, $2.94 \text{ mM} \pm 0.633$, and 5.65 ± 0.663 mM, in HLM (buffer/plasma, 50/50), hepatocytes (buffer), and hepatocytes (buffer/plasma, 50/50), respectively. These values were in accordance with those generated previously from HLM in buffer (1.88 mM or 2.44 mM). The V_{max} values were 312 ± 17.7 pmol/min/mg, 34.0 ± 3.42 pmol/min/ 10^6 hepatocytes, 31.1 ± 2.07 pmol/min/ 10^6 hepatocytes, respectively. These resulted in a low intrinsic clearance (0.068 $\mu\text{L}/\text{min}/\text{mg}$, in HLM, 0.0116 and 0.0055 $\mu\text{L}/\text{min}/10^6$ cells, in hepatocytes with buffer and with buffer/plasma, respectively).

For ucb 42145 hydroxylation, similar K_m values were obtained regardless of the tested conditions: 0.956 ± 0.056 mM, 0.611 ± 0.099 mM, and 1.07 ± 0.123 mM for HLM (buffer/plasma), hepatocytes (buffer) and hepatocytes (buffer/plasma), respectively. Maximal velocity (V_{max}) values were 488 ± 8.1 pmol/min/mg in HLM, 37.8 ± 1.53 pmol/min/ 10^6 cells in hepatocytes (buffer), and 47 ± 1.58 pmol/min/ 10^6 cells in hepatocytes (buffer/plasma). Using the V_{max} to K_m ratio, intrinsic clearance values obtained for ucb 42145 hydroxylation were approximately 5- to 10-times higher than for ucb 34714 hydroxylation.

Gemfibrozil seemed to be a weak mixed inhibitor of ucb 34714 hydroxylation in HLM and hepatocytes suspensions (buffer), with $K_{i,c}$ (competitive) values of 153 ± 33.3 μM and 284 ± 74.4 μM , and $K_{i,u}$ (uncompetitive) values of 451 ± 63.3 μM and 2982 ± 586 μM , respectively. As gemfibrozil displayed a high plasma protein binding (99%), inhibition observed in plasma/buffer (50/50, v/v) was very low ($\text{IC}_{50} = 2.20 \pm 0.12$ mM and > 2.5 mM in HLM and hepatocytes, respectively).

Gemfibrozil caused a more potent inhibition of ucb 42145 hydroxylation in HLM and hepatocytes (buffer), with IC_{50} values of 22.9 ± 0.718 or 19.8 ± 1.87 μM (HLM) and 6.05 ± 2.00 μM (hepatocytes), and K_i values of 11.8 ± 1.86 μM (competitive, in HLM) and 11.5 ± 0.72 μM (non-competitive, in hepatocytes), respectively. Inhibition of ucb 42145 hydroxylation was lower in plasma/buffer (50/50, v/v) due to gemfibrozil protein binding, with IC_{50} value of 464 ± 21.8 μM in HLM and > 500 μM in hepatocytes. K_i values observed in HLM incubated in buffer/plasma were 163 ± 49.6 μM ($K_{i,c}$) or 452 ± 91.8 μM ($K_{i,u}$), and was 801 ± 49.3 μM (non-competitive) in hepatocytes (buffer/plasma), respectively. Gemfibrozil was not a mechanism-based inhibitor of ucb 34714 and ucb 42145 hydroxylation.

Gemfibrozil-O-glucuronide caused a marginal direct inhibition (23.5% at 200 μM) of ucb 34714 hydroxylation in HLM. Similar weak inhibition (24.6%) was observed at lower concentration of gemfibrozil-O-glucuronide (60 μM) when it was pre-incubated 30 minutes as expected from this metabolism-based inhibitor. Gemfibrozil-O-glucuronide did not cause any significant direct or metabolism-dependent inhibition of ucb 42145 hydroxylation.

Conclusion: Limited effect of gemfibrozil-O-glucuronide, a mechanism-based inhibitor of CYP2C8, on ucb 34714 hydroxylation suggested that production of ucb-100406-1 was not primarily mediated by CYP2C8. Gemfibrozil-O-glucuronide did not affect ucb 42145 hydroxylation, indicating that CYP2C8 was not responsible for the reaction. The observed K_i of gemfibrozil on this metabolic pathway is in the same range as its K_i on CYP2C9, suggesting that CYP2C9 may be involved (*reviewer's note*: this was demonstrated by another study NCD1674 which provided firm evidence.)

4.3.7 Study PSM1175: In Vitro Inhibition of ucb 34714 Biotransformation to ucb-100406-1 by AEDs in Human Liver Microsomes

Objective: to investigate the potential for anti-epileptic drugs (AEDs) to inhibit the formation of ucb-100406-1 from ucb 34714 in human liver microsomes.

Method: Inhibition studies were conducted with pooled HLM. A sequential approach was used.

- First, AEDs were tested for their inhibition potential at 100 µM and at a concentration close to the C_{max} in the high range of therapeutic doses.
- In a second step, if inhibition exceeding 25% was observed at either concentration of AED, an IC₅₀ determination would be performed using a range of AED concentration (solubility permitting).

Table 17. AEDs C_{max} at Therapeutic Doses, Actual Concentration Used and Vehicle

AEDs	C _{max} at therapeutic doses	Concentration in incubates	Vehicle
Carbamazepine	12 µg/mL (51 µM) ⁽⁴⁾	50 µM	Methanol
Phenytoin	20 µg/mL (79 µM) ⁽⁴⁾	80 µM	Methanol
Valproic Acid	100 µg/mL (693 µM) ⁽⁴⁾	700 µM	Water
Lamotrigine	14 µg/mL (55 µM) ⁽⁴⁾	55 µM	Methanol
Gabapentin	5 µg/mL (29 µM) ⁽⁵⁾	30 µM	Water
Zonisamide	40 µg/mL (188 µM) ⁽⁴⁾	190 µM	Methanol
Phenobarbital	40 µg/mL (172 µM) ⁽⁴⁾	170 µM	Water
Felbamate	80 µg/mL (336 µM) ⁽⁶⁾	340 µM	Methanol

Direct inhibition and metabolism-dependent (10-min pre-incubation) inhibition were tested for each AED.

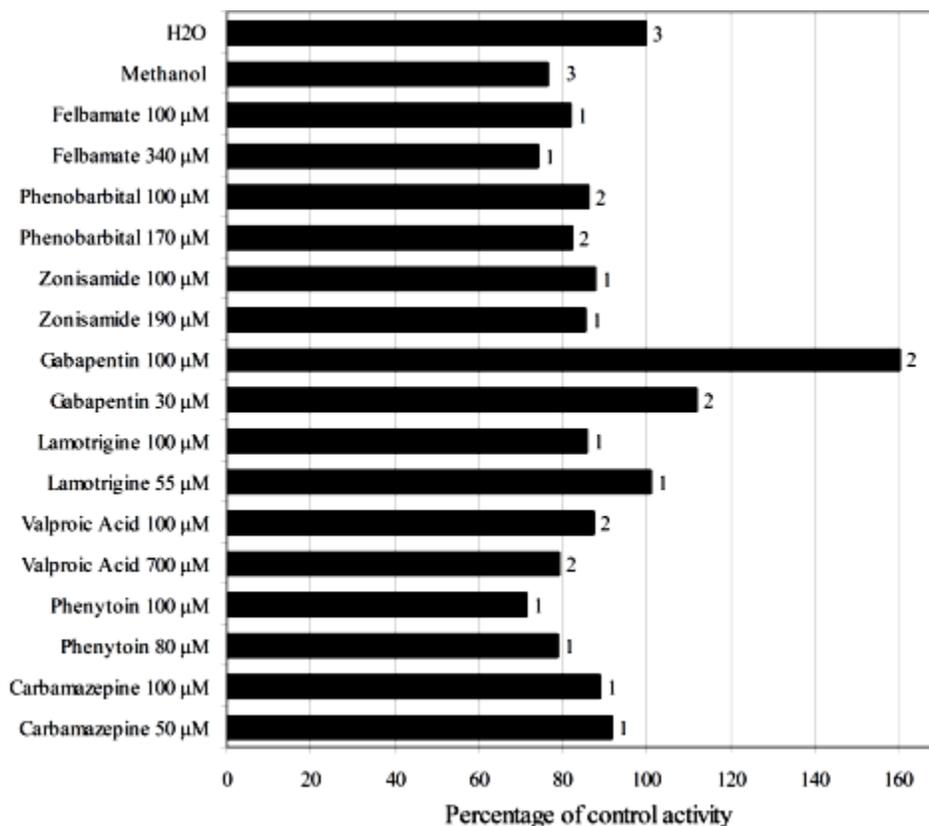
ucb 34714 was used at final concentrations of 2.5 mM (the K_m value for ucb-100406-1 production, from Study PSM0976) and 50 µM (which is a more pharmacologically relevant concentration). Concentration of HLM was 1 mg/mL and incubation time was 15 minutes. The concentrations of ucb-100406-1 were determined by a LC/ESI/MS method.

Results:

In incubations with 50 µM ucb 34714, felbamate inhibited ucb-100406-1 production by 18.1% at 100 µM and by 26.0% at 340 µM. Phenytoin also inhibited ucb-100406-1 production by 21.2% at 80 µM and by 28.5% at 100 µM. The other AEDs tested did not display an inhibition higher than 20.8%. Gabapentin was found to increase ucb-100406-1 production by 11.9% and 60.2% at 30 µM and 100 µM, respectively. Felbamate and phenytoin were not further investigated to determine an IC₅₀ because of their limited solubility which was insufficient.

In incubations with 2.5 mM ucb 34714, none of the AEDs were found to inhibit ucb-100406-1 production by more than 11.4%. Gabapentin was found to increase ucb-100406-1 production by 18.5% and 53.5% at 30 µM and 100 µM, respectively.

Figure 13. Effect of AEDs as Direct Inhibitors on the Conversion of ucb 34714 (50 µM) to ucb-100406-1

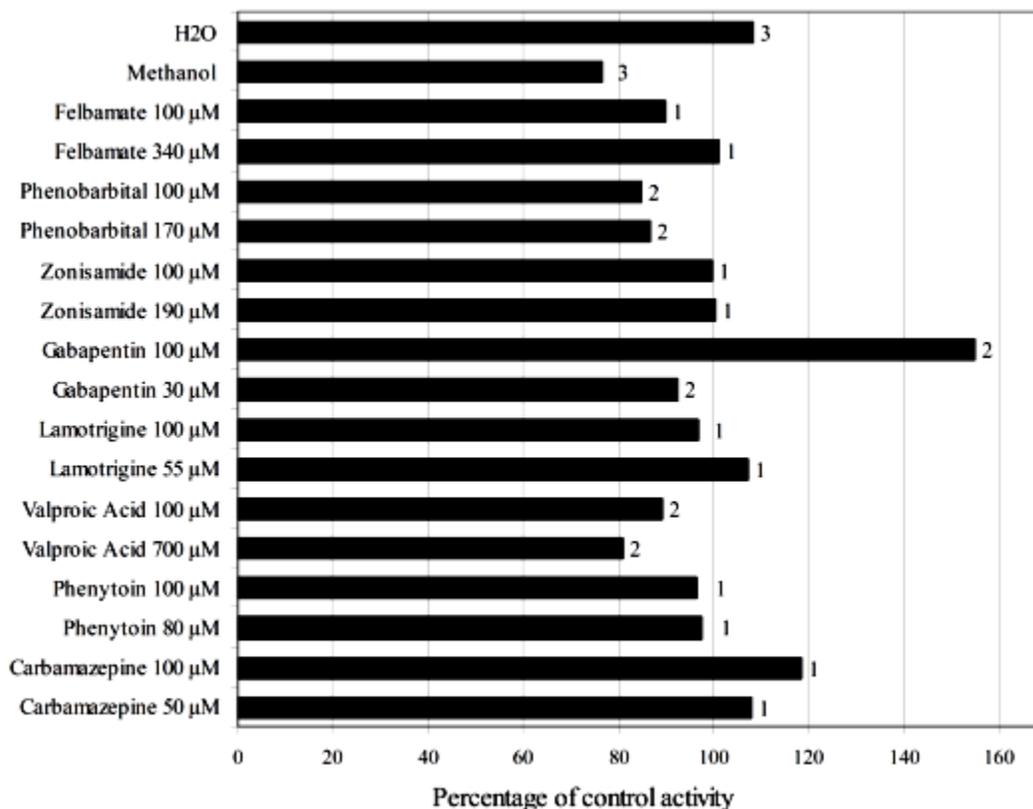


1. inhibition determined with average rate of ucb-100406-1 formation in control incubations with methanol
2. inhibition determined with average rate of ucb-100406-1 formation in control incubations with water
3. inhibition determined with average rate of ucb-100406-1 formation in control incubations with buffer

With per-incubation, at a concentration of 50 µM ucb 34714, no AED was found to inhibit ucb-100406-1 production by more than 19.2%. Gabapentin was found to increase ucb-100406-1 production by 54.8% at 100 µM. There was no evidence that any of the tested AEDs was mechanism-dependent inhibitor for ucb-100406-1 formation.

In incubations with ucb 34714 (2.5 mM), no AED was found to inhibit ucb-100406-1 production by more than 18.2%. Gabapentin was found to increase ucb-100406-1 production by 18.4% at 30 µM and by 47.9% at 100 µM.

Figure 14. Effect of AEDs as Metabolism-Dependent Inhibitors on the Conversion of ucb 34714 (50 µM) to ucb-100406-1



1. inhibition determined with average rate of ucb-100406-1 formation in control incubations with methanol
2. inhibition determined with average rate of ucb-100406-1 formation in control incubations with water
3. inhibition determined with average rate of ucb-100406-1 formation in control incubations with buffer

Reviewer's Comments:

According to literature, felbamate did not inhibit CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4, but inhibited CYP2C19 with a K_i of 225 µM (Glue P, et al. *Clin Pharmacokinet.* 1997 Sep;33(3):214-24). This may explain the observation here. As shown by the previous studies, CYP2C19 was one of the CYP enzymes involved in ucb-100406-1 formation.

Felbamate increased phenytoin plasma concentrations in humans. This may be due to its inhibitory effect on CYP2C19. The effect of felbamate on ucb 34714 PK in humans has not been investigated but is not expected to exceed the effect of CYP2C19 poor metabolizers.

A study in Japanese subjects showed that the clearance of ucb 34714 was reduced from 0.99 mL/min/kg in homozygous CYP2C19 extensive metabolizers to 0.81 mL/min/kg (18% reduction) in heterozygous extensive metabolizers and 0.70 mL/min/kg (30% reduction) in CYP2C19 poor metabolizers, suggesting that there is at most 43% increase of ucb 34714 plasma concentrations (AUC) in lack of CYP2C19 activity in humans. Such change is not considered clinically significant to warrant dose adjustments.

The BRV (brivaracetam, ucb 34714) exposure-safety relationship for the common adverse events (e.g. somnolence, dizziness, and fatigue) indicates a modest increase of adverse event risk with increasing BRV exposures. As such, default starting dose of 50 mg bid (100 mg/day) is acceptable and a reduction of the maximum dose, 100 mg bid (200 mg/day) is unnecessary. For these reasons, it is not necessary to assess the CYP2C19 genotype of patients receiving BRV.

Phenytoin was reported to inhibit several CYPs (2C9, 2C19, and 3A4) *in vitro*, with the most potent inhibitory effects observed for CYP2C9 (K_i ranged from 4.04 to 56 μM). The IC₅₀ of phenytoin for CYP2C19 was reported as 35, 75, and 84 μM in literature. An *in vivo* study in CYP2C19 extensive and poor metabolizers suggested that CYP2C19 is the predominant enzyme responsible for ucb-100406-1 formation in humans. Thus, the inhibitory effect of phenytoin on CYP2C9 may not be relevant. On the other hand, phenytoin is an inducer of multiple enzymes including CYP2Cs. Thus, it has potential to induce metabolism of ucb 34714, which seems to be confirmed by *in vivo* findings, 'The population PK results indicate a 30%, 27%, and 24% reduction in BRV C_{ss} with concomitant carbamazepine, phenytoin, and phenobarbital use'.

Conclusion:

In human liver microsomes, felbamate and phenytoin appeared to be weak direct inhibitors of ucb-100406-1 production at low ucb 34714 concentrations (up to 26% for approximate C_{max} of felbamate, up to 28.5% for 100 μM of phenytoin whose approximate C_{max} is 80 μM). Felbamate is not expected to result in clinically significant change in ucb 34714 PK *in vivo* to warrant dose adjustments. The effect of phenytoin on ucb 34714 PK in humans has been characterized by population PK analysis which showed that phenytoin reduced ucb 34714 concentrations by 27% (due to induction effects of phenytoin).

Carbamazepine, valproic acid, lamotrigine, zonisamide and phenobarbital did not significantly affect the conversion of ucb 34714 to ucb-100406-1.

Gabapentin increased the production of ucb-100406-1 up to 1.6 fold at 100 μM, but by less than 1.2 fold at its C_{max} (30 μM). Therefore, this finding is unlikely to be physiologically relevant at therapeutic concentrations of ucb 34714.

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)

4.3.8 Study TA0776: Evaluation of ucb 34714 as a potential inhibitor of human cytochrome P450 enzymes

Objective: to evaluate the ability of ucb 34714 to inhibit the major P450 enzymes in human liver microsomes (namely CYP1A2, 2A6, 2C9, 2C19, 2D6 and 3A4/5).

Method: To evaluate ucb 34714 as a direct-acting (metabolism-“independent”) reversible inhibitor of CYP450 activity, HLM from a pool of nine individuals were incubated with a marker substrate at a concentration equal to approximately K_m in the presence or absence of ucb 34714 at concentrations equal to 25, 100 and 200 μM (5, 21, 42 $\mu\text{g/mL}$). The metabolites formed were measured by fluorimetric or HPLC methods.

Enzyme	P450 Activity	[Substrate] (μM)	Incubation Volume (μL)	Protein ^a ($\mu\text{g/mL}$)	Incubation Time (min)	ucb 34714	
						Concentration ^b (μM)	Volume ^c (μL)
CYP1A2	7-Ethoxyresorufin <i>O</i> -dealkylase	0.25	1000	100	10	0, 25, 100, 200	10
CYP2A6	Coumarin 7-hydroxylase	0.50	1000	25	5	0, 25, 100, 200	10
CYP2C9	Diclofenac 4'-hydroxylase	4.0	1000	100	5	0, 25, 100, 200	10
CYP2C19	<i>S</i> -Mephenytoin 4'-hydroxylase	35	200	1000	30	0, 25, 100, 200	2
CYP2D6	Dextromethorphan <i>O</i> -demethylase	5.0	1000	100	10	0, 25, 100, 200	10
CYP3A4/5	Testosterone 6 β -hydroxylase	100	500	50	10	0, 25, 100, 200	5

^a The human liver microsomal sample used for these experiments was a pool of nine individuals (samples 71, 72, 76, 79, 99, 101, 105, 140 and 142).

^b ucb 34714 concentrations = 25 μM (5 $\mu\text{g/mL}$), 100 μM (21 $\mu\text{g/mL}$), 200 μM (42 $\mu\text{g/mL}$)

^c Water was the vehicle used to dissolve the test article.

Positive controls were included as

P450 Enzyme	Positive Control	Diluent	Concentration Studied
CYP1A2	α -Naphthoflavone	Methanol	1.0 μM
CYP2A6	Nicotine	Methanol	200 μM
CYP2C9	Sulfaphenazole	Methanol	10 μM
CYP2C19	Modafinil	DMSO	250 μM
CYP2D6	Quinidine	Water	1.0 μM
CYP3A4/5	Ketoconazole	Methanol	0.1 μM

In addition, ucb 34714 was evaluated for its ability to function as a metabolism-dependent “reversible” inhibitor, where ucb 34714 was pre-incubated with HLM and NADPH for 15 min to allow for the generation of metabolites that could inhibit CYP450. Incubations containing no ucb 34714 and incubations that contain ucb 34714 but were not pre-incubated, served as negative controls.

Enzyme	P450 Activity	[Substrate] (μM)	Incubation Volume (μL)	Protein ^a ($\mu\text{g/mL}$)	Pre-incubation Time (min)	Incubation Time (min)	ucb 34714	
							Concentrations ^b (μM)	Volume ^c (μL)
CYP1A2	7-Ethoxyresorufin <i>O</i> -dealkylase	0.25	1000	100	15	10	25, 100, 200	10
CYP2A6	Coumarin 7-hydroxylase	0.5	1000	25	15	5	25, 100, 200	10
CYP2C9	Diclofenac 4'-hydroxylase	4.0	1000	100	15	5	25, 100, 200	10
CYP2C19	<i>S</i> -Mephenytoin 4'-hydroxylase	35	200	1000	15	30	25, 100, 200	2
CYP2D6	Dextromethorphan <i>O</i> -demethylase	5.0	1000	100	15	10	25, 100, 200	10
CYP3A4/5	Testosterone 6 β -hydroxylase	100	500	50	15	10	25, 100, 200	5

^a Human liver microsomal sample used for these experiments was a pool of nine individuals (samples 71, 72, 76, 79, 99, 101, 105, 140 and 142).

^b ucb 34714 concentrations = 25 μM (5 $\mu\text{g/mL}$), 100 μM (21 $\mu\text{g/mL}$), 200 μM (42 $\mu\text{g/mL}$)

^c Water was the vehicle used to dissolve the test article.

ucb 34714 was also evaluated for its ability to function as a metabolism-dependent “irreversible” inhibitor, where ucb 34714 was pre-incubated with HLM and NADPH for 15 min. Then, aliquots of the pre-incubated solutions (typically 100 μL) were removed and added to triplicate incubations. The marker substrate (at a concentration equal to approximately K_m)

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)

was added to these incubation mixtures and the additional incubations were carried out to measure the marker CYP450 activity. This experimental design allowed ucb 34714 to be diluted by a factor of 10 for the final incubation with the marker substrate, thereby minimizing any “reversible” inhibitory effects. Pre-incubations containing no ucb 34714 and incubations that contain ucb 34714 but were not pre-incubated, served as negative controls.

Enzyme	P450 Activity	PRE-INCUBATION			INCUBATION WITH MARKER SUBSTRATE						
		Protein ^a (µg/mL)	Volume (µL)	Time (min)	ucb 34714		Protein (µg/mL)	Volume (µL)	Time (min)	ucb 34714 Concentration (µM)	Substrate (µM)
					Concentration ^b (µM)	Volume ^c (µL)					
CYP1A2	7-Ethoxyresorufin <i>O</i> -dealkylase	1000	1000	15	200	10	100	1000	10	20	0.25
CYP2A6	Coumarin 7-hydroxylase	250	1000	15	200	10	25	1000	5	20	0.5
CYP2C9	Diclofenac 4'-hydroxylase	1000	1000	15	200	10	100	1000	5	20	4.0
CYP2C19	<i>S</i> -Mephenytoin 4'-hydroxylase	10000	200	15	200	2	1000	200	30	20	35
CYP2D6	Dextromethorphan <i>O</i> -demethylase	1000	1000	15	200	10	100	1000	10	20	5.0
CYP3A4/5	Testosterone 6β-hydroxylase	500	50	15	200	5	50	500	10	20	100

^a Human liver microsomal sample used for these experiments was a pool of nine individuals (samples 71, 72, 76, 79, 99, 101, 105, 140 and 142).
^b ucb 34714 concentrations = 20 µM (4 µg/mL), 200 µM (42 µg/mL)
^c Water was the vehicle used to dissolve the test article.

Positive controls were included as following,

P450 Enzyme	Positive Control	Diluent	Concentration Studied
CYP1A2	Furafylline	DMSO	10 µM
CYP2A6	8-Methoxypsoralen	Methanol	0.5 µM
CYP3A4/5	Troleandomycin	Acetonitrile	50 µM

Results: As a reversible inhibitor, ucb 34714 at 200 µM (42 µg/mL) inhibited CYP2C19 (46% inhibition) and CYP3A4/5 (12% inhibition). ucb 34714 did not inhibit CYP1A2, 2A6, 2C9 or 2D6. ucb 34714 has little or no capacity to function as a “reversible” or “irreversible” metabolism-dependent inhibitor of any of the CYPs examined.

The IC₅₀ of ucb 34714 for CYP2C19 was estimated to be about 230 µM. Thus, the approximate Ki value could theoretically be as low as 115 µM if the mechanism of inhibition was competitive, or as high as 230 µM if the mechanism of inhibition was noncompetitive.

Table 18. Evaluation of ucb 34714 as an inhibitor of human P450 enzymes

Enzyme	P450 Activity	Metabolism-“independent” inhibition	Metabolism-dependent inhibition ^b	
		Percent inhibition at 200 µM (42 mg/mL)	“Reversible”	“Irreversible”
CYP1A2	7-Ethoxyresorufin <i>O</i> -dealkylase	<10%	Little or no inhibition	Little or no inhibition
CYP2A6	Coumarin 7-hydroxylation	<10%	Little or no inhibition	Little or no inhibition
CYP2C9	Diclofenac 4'-hydroxylase	<10%	Little or no inhibition	Little or no inhibition
CYP2C19	<i>S</i> -Mephenytoin 4'-hydroxylase	46% ^a	Little or no inhibition	Little or no inhibition
CYP2D6	Dextromethorphan <i>O</i> -demethylase	<10%	Little or no inhibition	Little or no inhibition
CYP3A4/5	Testosterone 6β-hydroxylase	12%	Little or no inhibition	Little or no inhibition

^a The estimated IC₅₀ value for the reversible (metabolism-“independent”) inhibition of CYP2C19 by ucb 34714 was approximately 230 µM. Therefore, the approximate Ki value theoretically could be as low as 115 µM if the mechanism of inhibition was competitive, or as high as 230 µM if the mechanism of inhibition was noncompetitive.

^b Metabolism-dependent inhibition:

Little or no inhibition : 0 – 10% Inhibition; Weak inhibition : 11 – 20% Inhibition
Moderate inhibition : 21 – 40% Inhibition; Marked inhibition : > 40% Inhibition

Reviewer’s Comment: At therapeutic dose, the steady-state C_{max} of ucb 34714 was expected to be around 16 µM (3.5 µg/mL). Since the ratio of total C_{max}/Ki was 0.14, just marginally above the cut-off of 0.1, it is less likely for ucb 34714 to have clinically significant inhibitory effect on CYP2C19 *in vivo*.

4.3.9 Study NCD1677: Evaluation of ucb 34714 as a Potential Inhibitor of Human Cytochrome P450 2C8 and 2B6

Objective: to evaluate the ability of ucb 34714 to inhibit cytochrome P450 (CYP) 2C8 and 2B6 enzyme in human liver microsomes.

Method: To evaluate ucb 34714 as reversible inhibitor of CYP2C8, pooled HLM (0.3 mg/ml) were incubated with 20 µM paclitaxel for 10 min in the presence or absence of ucb 34714 at concentrations of 25, 100 and 200 µM. The formed metabolite (6α-hydroxypaclitaxel) was quantitated with Radio-HPLC. To evaluate ucb 34714 as reversible inhibitor of CYP2B6, pooled HLM (0.5 mg/ml) were incubated with 100 µM bupropion for 20 min with or without ucb 34714 (25, 100, and 200 µM). The amount of hydroxybupropion formed was determined by a LC/MS/MS method. The concentrations of marker substrates were their K_m values determined for CYP2C8 and 2B6, respectively. Montelukast (1.5 µM) and ticlopidine (2 µM) were used as positive controls for CYP2C8 and 2B6, respectively. The concentrations used were 10 times of their K_i for corresponding enzymes.

To evaluate ucb 34714 as metabolism-dependent inhibitor of CYP2C8 and 2B6, ucb 34714 (200 µM) was pre-incubated with HLM and NADPH for 15 min. Then, marker substrates (paclitaxel and bupropion) were added and the incubation continued to measure residual CYP450 activities.

Results: ucb 34714 was neither a direct nor a metabolism-dependent inhibitor of CYP2C8 and 2B6.

Table 19. ucb 34714 as a Direct Inhibitor of CYP2C8 and 2B6: Initial Screening Results

	Mean percentage velocity of control	
	CYP2C8 Paclitaxel 6α-hydroxylation	CYP2B6 Bupropion hydroxylation
ucb 34714 25 µM	110%	102%
ucb 34714 100 µM	125%	101%
ucb 34714 200 µM	116%	99.0%
Positive Control	25.5% (Montelukast 1.5 µM)	8.46% (Ticlopidine 2 µM)

Table 20. Evaluation of ucb 34714 as a Metabolism-Dependent Inhibitor of CYP2C8

Group Name	Velocity (pmol/min/mg protein)	Mean Velocity (pmol/min/mg protein)	% Velocity of Control	Mean % Velocity of Control	%CV
Control w/o pre-incub Paclitaxel 20 µM	254	230	110	100	10
	231		100		
	207		89.7		
ucb 34714 200 µM w/o pre-incub Paclitaxel 20 µM	196	208	85.1	90.4	5.6
	219		95.2		
	209		90.8		
Control w pre-incub Paclitaxel 20 µM	165	189	87.6	100	11
	194		103		
	207		110		
ucb 34714 200 µM w pre-incub Paclitaxel 20 µM	204	206	108	109	13
	179		95.1		
	235		124		
Control for Positive Reference Paclitaxel 20 µM	196	204	96.0	100	5.1
	201		98.3		
	216		106		
Montelukast 1.5 µM Paclitaxel 20 µM	68.0	56.4	33.3	27.6	20
	56.0		27.4		
	45.3		22.2		

¹ : Control velocity determined with average rate of paclitaxel 6α-hydroxylation in “Control w/o pre-incub” incubations;

² : Control velocity determined with average rate of paclitaxel 6α-hydroxylation in “Control w pre-incub” incubations;

³ : Control velocity determined with average rate of paclitaxel 6α-hydroxylation in “Control for positive reference” incubations.

Table 21. Evaluation of ucb 34714 as a Metabolism-Dependent Inhibitor of CYP2B6

Group Name	Velocity (pmol/min/mg protein)	Mean Velocity (pmol/min/mg protein)	% Velocity of Control	Mean % Velocity of Control	%CV
Control w/o pre-incub Bupropion 100 µM	248	241	103	100	2.9
	240		99.7		
	234		97.2		
ucb 34714 200 µM w/o pre-incubation Bupropion 100 µM	222	214	92.2	88.9	4.9
	218		90.6		
	202		83.9		
Control w pre-incub Bupropion 100 µM	204	191	107	100	6.1
	181		94.9		
	188		98.3		
ucb 34714 200 µM w pre-incubation Bupropion 100 µM	161	170	84.5	88.8	4.6
	171		89.3		
	177		92.6		
Control for Positive Reference Bupropion 100 µM	220	224	98.2	100	3.1
	220		98.2		
	232		104		
Ticlopidine 2 µM Bupropion 100 µM	7.50	7.46	3.35	3.33	11
	8.26		3.69		
	6.62		2.96		

¹ : Control velocity determined with average rate of bupropion hydroxylation in “Control w/o pre-incub” incubations;

² : Control velocity determined with average rate of bupropion hydroxylation in “Control w pre-incub” incubations;

³ : Control velocity determined with average rate of bupropion hydroxylation in “Control for positive reference” incubations.

4.3.10 Study NCD1678: Evaluation of ucb 34714, ucb 42145 and ucb-100406-1 as Potential Inhibitors of Phenytoin 4-Hydroxylation Activity In Vitro

Background and Objective: During a clinical study (UCB N01172), co-administration of ucb 34714 and phenytoin was associated with 20% increase in the steady-state concentration of phenytoin. This study was designed to investigate the *in vitro* potential of ucb 34714 and its major metabolites to inhibit the conversion of phenytoin to its major metabolite 4-hydroxyphenytoin, which was exclusively mediated by CYP2C9 and 2C19, with 2C9 playing the major role.

Method: Recombinant human rhCYP2C9 and rhCYP2C19 enzymes were used (Supersomes™). Kinetic parameters were first determined for both enzymes to provide suitable incubation conditions for subsequent evaluation of inhibition. For CYP2C9, [¹⁴C]-phenytoin concentrations were 1.5, 4, 6, 8, 12, 15, 20, 30, 50, 90 and 150 µM. For CYP2C19, [¹⁴C]-phenytoin concentrations were 4, 8, 15, 20, 30, 50, 90, 150, 240 and 400 µM. The incubation time (40 min) and CYP2C9 and 2C19 Supersome™ concentrations (200 pmol/mL for both) were selected based on pilot experiments to ensure the formation of 4-hydroxyphenytoin was linear vs. time and vs. supersome concentrations.

To evaluate ucb 34714, ucb 42145 and ucb-100406-1 as direct inhibitors of phenytoin 4-hydroxylation, rCYP2C9 and rCYP2C19 were initially incubated with phenytoin in the presence or absence of test items at concentrations of 25, 100 and 200 µM. The concentrations of phenytoin were 15 µM for CYP2C9 and 45 µM for 2C19 (approximate values of K_m as determined *prior*). Positive controls (sulfaphenazole for CYP2C9, $K_i = 0.3$ µM; omeprazole for CYP2C19, $K_i = 3.0$ µM) were also performed with an inhibitor concentration of $10 \times K_i$.

To evaluate ucb 34714, ucb 42145 and ucb-100406-1 as metabolism-dependent inhibitors of phenytoin 4-hydroxylation, test items were pre-incubated with both rCYP2C9 and rCYP2C19 for 15 min. ucb 42145 and ucb-100406-1 concentrations were 200 µM. ucb 34714 concentration was 100 µM for CYP2C19 and 200 µM for CYP2C9.

The samples were analyzed by Radio-HPLC method.

Results:

K_m and V_{max} for 4-hydroxyphenytoin production via rhCYP2C9 isoform were calculated to be 16.5 µM and 0.315 pmol/min/pmol CYP450, respectively. K_m and V_{max} for 4-hydroxyphenytoin production via rCYP2C19 isoform were 46.2 µM and 0.355 pmol/min/pmol CYP450, respectively.

ucb 34714, ucb 42145 and ucb-100406-1 did not cause significant inhibition of phenytoin 4-hydroxylation mediated by rhCYP2C9. For rhCYP2C19, ucb 42145 did not significantly inhibit phenytoin 4-hydroxylation. ucb-100406-1 weakly (< 20%) inhibited this activity when incubated at 200 µM. ucb 34714 (200 µM) was found to inhibit this activity by 50.4% in the presence of ucb 34714, which was consistent with the result from Study TA0776. Results for

positive control were as expected (73.7% and 76.1% inhibition for rhCYP2C9 and rhCYP2C19, respectively).

The basal activity of phenytoin 4-hydroxylation was increased following pre-incubation with vehicle for both enzymes. Due to this reason, compared to incubations in the presence of vehicle, there was some extent of inhibition observed for ucb 34714, ucb 42145, or ucb-100406-1. However, the inhibition in general was small (< 20%), except CYP2C19 inhibition by ucb 34714 (25.4%). Yet, the magnitude of this inhibition was similar to that without pre-incubation (31.8%), suggesting that ucb 34714 was not a time-dependent inhibitor for CYP2C19, which was also consistent with the result from Study TA0776.

Table 22. Evaluation of ucb 34714, ucb 42145 and ucb-100406-1 as Metabolism-Dependent Inhibitors of Phenytoin 4-Hydroxylation via CYP450 2C9

Group Name	Velocity (pmol/min/pmol P450)	Mean Velocity (pmol/min/pmol P450)	% Velocity of Control	Mean % Velocity of Control	%CV
Control Phenytoin 15 µM wo pre-incub	0.138	0.146	94.3	100	7.1
	0.143		97.7		
	0.158		108		
ucb 34714 200 µM Phenytoin 15 µM wo pre-incub	0.138	0.140	94.3	96.3	4.4
	0.148		101		
	0.136		93.4		
ucb 42145 200 µM Phenytoin 15 µM wo pre-incub	0.146	0.142	100	97.4	4.3
	0.135		92.6		
	0.145		99.4		
ucb-100406-1 200 µM Phenytoin 15 µM wo pre-incub	0.130	0.153	89.1	105	15
	0.175		120		
	0.153		105		
Control Phenytoin 15 µM w pre-incub	0.156	0.196	79.6	100	19
	0.231		118		
	0.201		103		
ucb 34714 200 µM Phenytoin 15 µM w pre-incub	0.203	0.170	103	86.8	19
	0.173		87.9		
	0.136		69.4		
ucb 42145 200 µM Phenytoin 15 µM w pre-incub	0.183	0.179	93.0	91.3	16
	0.206		105		
	0.149		75.8		
ucb-100406-1 200 µM Phenytoin 15 µM w pre-incub	0.130	0.163	66.2	83.0	20
	0.195		99.4		
	0.164		83.4		
Zero-Inhibiteur Phenytoin 15 µM	0.121	0.126	95.8	100	7.1
	0.136		108		
	0.121		96.1		
Sulfaphenazole 3 µM Phenytoin 15 µM	0.0184	0.0171	14.6	13.6	9.5
	0.0153		12.1		
	0.0176		14.0		

1. Control velocity determined with average rate of phenytoin 4-hydroxylation in Control without pre- incubation;
2. Control velocity determined with average rate of phenytoin 4-hydroxylation in Control with pre-incubations;
3. Control velocity determined with average rate of phenytoin 4-hydroxylation in Zero Inhibitor incubations.

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)

Table 23. Evaluation of ucb 34714, ucb 42145 and ucb-100406-1 as Metabolism-Dependent Inhibitors of Phenytoin 4-Hydroxylation via CYP450 2C19

Group Name	Velocity (pmol/min/pmol P450)	Mean Velocity (pmol/min/pmol P450)	% Velocity of Control	Mean % Velocity of Control	%CV
Control Phenytoin 15 µM wo pre-incub	0.143	0.152	93.7	100	5.6
	0.155		102		
	0.159		104		
ucb 34714 100 µM Phenytoin 15 µM wo pre-incub	0.117	0.104	76.9	68.2	11
	0.0968		63.6		
	0.0974		64.0		
ucb 42145 200 µM Phenytoin 15 µM wo pre-incub	0.140	0.152	92.1	100	8.2
	0.165		108		
	0.151		99.5		
ucb-100406-1 200 µM Phenytoin 15 µM wo pre-incub	0.155	0.158	102	104	8.5
	0.173		113		
	0.146		96.2		
Control Phenytoin 15 µM w pre-incub	0.208	0.183	114	100	13
	0.179		97.9		
	0.161		88.4		
ucb 34714 100 µM Phenytoin 15 µM w pre-incub	0.146	0.136	80.1	74.6	9.2
	0.140		76.7		
	0.122		66.9		
ucb 42145 200 µM Phenytoin 15 µM w pre-incub	0.171	0.171	93.8	93.8	1.5
	0.169		92.5		
	0.174		95.2		
ucb-100406-1 200 µM Phenytoin 15 µM w pre-incub	0.144	0.153	78.8	84.0	5.8
	0.155		84.9		
	0.161		88.4		
Zero-Inhibiteur Phenytoin 15 µM	0.166	0.143	116	100	15
	0.138		96.2		
	0.125		87.4		
Omeprazole 30 µM Phenytoin 15 µM	0.0479	0.0402	33.5	28.1	26
	0.0445		31.1		
	0.0281		19.7		

1. Control velocity determined with average rate of phenytoin 4-hydroxylation in Control without pre-incubation;
2. Control velocity determined with average rate of phenytoin 4-hydroxylation in Control with pre-incubations;
3. Control velocity determined with average rate of phenytoin 4-hydroxylation in Zero Inhibitor incubations.

Conclusion:

ucb 42145 was neither a direct nor a metabolism-dependent inhibitor of phenytoin 4-hydroxylation by rCYP2C9 and rCYP2C19. ucb-100406-1 was a weak direct inhibitor of rCYP2C19 mediated phenytoin 4-hydroxylation but had no effect on the reaction mediated by rCYP2C9 and was not a metabolism-dependent inhibitor of either enzyme. ucb 34714 is a direct inhibitor of phenytoin 4-hydroxylation via CYP2C19 (IC_{50} estimated to be around 200 µM) but has no direct inhibition effect on this activity via rCYP2C9. ucb 34714 was not a metabolism-dependent inhibitor of rCYP2C9 or rCYP2C19.

(Reviewer's comment: Though the IC_{50} of ucb 34714 on CYP2C19-mediated phenytoin-4-hydroxylation was not formally determined, it was estimated to be around 200 µM since phenytoin hydroxylation was inhibited by about 50% at this concentration. The ratio of total C_{max} of ucb 34714 at steady state after 100 mg bid, the recommended therapeutic dose, divided by its IC_{50} will be 0.16 which is marginally above the cut-off of 0.1. Thus, ucb 34714 is less likely to cause significant DDI due to CYP2C19 inhibition *in vivo*. It should be noted that, though Study N01172 showed that ucb 34714 increased phenytoin AUC by approximately 20%, the other Study N01082 reported that ucb 34714 reduced phenytoin AUC by about 13%.)

4.3.11 Study PSM0815: In Vitro Induction of CYP1A and CYP3A4 in Human Hepatocytes

Objective: to determine the ability of ucb 34714 to induce CYP1A and CYP3A4 in human hepatocytes *in vitro*.

Method: Human hepatocytes were prepared from liver tissues and planted on 9 cm tissue culture dishes at a density of 5×10^6 cells/dish. After 24 hrs, hepatocytes were exposed to phenobarbital (0.75 mM), 3-methylcholanthrene (3-MC, 10 μ M), omeprazole (10 μ M), rifampicin (25 μ M), and the test substance ucb 34714 (25, 200, and 500 μ M) for 72 hrs with renewal of medium containing test and reference substances (dissolved in 0.5% DMSO) at 24 h intervals. After 72-hr incubation, the cells were collected and homogenized. The homogenates were used for enzyme assays. 7-Ethoxyresorufin-O-deethylase (EROD) activity mediated by CYP1A was measured using a spectrofluorometer in the presence of 1.5 μ M 7-ethoxyresorufin, 10 μ M dicumarol (a Phase II enzyme inhibitor), and 6 mM NAD. The testosterone hydroxylation activity mediated by CYP3A4 was measured using HPLC after 10-minute incubation with 1.33 mM testosterone.

Results: The viability of hepatocytes was 84%, 70%, 87.4%, and 93% for donors 1, 2, 3, 4, respectively, as determined by Trypan blue method. Results from Donor 2 were not presented as unexpected data were obtained for testosterone 6 β -hydroxylase activity with reference substances (i.e., induction activity in the presence of 3-MC but not with phenobarbital).

Little or no induction of CYP 1A activity was observed with ucb 34714. CYP1A activities at all concentrations of ucb 34714 tested were at least 15-fold less than those observed in the presence of 10 μ M omeprazole.

(Reviewer's Comment: It is unknown why 3-MC, one of the positive controls for CYP1A, did not show induction effect. Per the Drug Interaction Guidance (2006 version), 6-26 fold induction of CYP1A2 is generally achieved with 1 or 2 μ M 3-MC. According to the sponsor, higher concentrations of 3-MC may compromise induction of CYP1A based on personal communication with a researcher in academic. Nevertheless, omeprazole exerted induction effect as expected.

It should be noted that the CYP1A activities were below the detection limit in a number of treatments including solvent controls for Donor 3.)

Table 24. Induction factors of EROD activities in hepatocyte cultures of donors No. 1 – 4

Donor No.	Induction factor of EROD activity versus solvent control		
	1	3**	4
PB (0.75 mM)	0.3*	1.0	0.4*
3-MC (10 µM)	0.8	1.0	0.4*
Omeprazole (10 µM)	16.9	42.3	17.1
Rifampicin (25 µM)	0.3*	2.0	0.8
ucb 34714 (500µM)	0.5	1.2	0.4*
ucb 34714 (200µM)	1.0	2.8	0.4*
ucb 34714 (25µM)	0.3*	1.0	0.4*

* activity below detection limit

** activity of the solvent control below detection limit

In all cases (* and **) the detection limit (1.0 pmol × mg⁻¹ × min⁻¹) was used to calculate the induction factors

At 25 µM, ucb 34714 had little or no effect on CYP 3A4 activity. The effect increased in a concentration-dependent manner with an induction factor between 1.4 and 3.0 at 500 µM. Yet, for all the three donors, the increase in CYP 3A4 activity in the presence of ucb 34714 was less than (< 40% of) that observed with the positive controls rifampicin and phenobarbital, suggesting that the induction effect of ucb 34714 on CYP3A is weak.

Table 25. Induction factors of formation of 6β-Hydroxytestosterone in hepatocyte cultures of donors No. 1 – 4

Induction factor of 6β-Hydroxytestosterone activity versus solvent control			
Donor No.	1	3	4
PB (0.75 mM)	3.5	4.2	14.5
3-MC (10 μM)	0.3	0.1	0.2
Omeprazole (10 μM)	1.1	1.2	1.5
Rifampicin (25 μM)	5.5	4.5	17.3
ucb 34714 (500μM)	1.4	2.0	3.0
ucb 34714 (200μM)	1.0	1.7	2.4
ucb 34714 (25μM)	0.6	1.3	1.1

4.3.12 Study NCD1710: In Vitro Evaluation as Cytochrome P450 Inducer in Cultured Human Hepatocytes

Objective: to evaluate the ability of ucb 34714 to induce cytochrome P450s (CYPs).

Method: Fresh human hepatocytes from 4 donors were supplied at a density of 1.5×10^6 viable cells per well in a 6-well plate pre-coated with a single film of collagen. The hepatocytes were treated with ucb 34714 or controls for 72 hrs with medium renewed every 24 hrs. The potential induction of CYP1A1/2, CYP2B6 or CYP3A4/5 by ucb 34714 (10, 30 and 100 μ M) was determined by measuring specific marker activities (ethoxyresorufin O-dealkylase, bupropion hydroxylase and midazolam 1'-hydroxylase activity, respectively) in microsomes freshly prepared from hepatocytes after 72-hr incubation. The O-dealkylation of ethoxyresorufin by CYP1A was measured by a fluorimetric method after incubating microsomes (100 μ g/mL) with 10 μ M ethoxyresorufin for 60 min. Bupropion hydroxylation activity was determined by a LC/MS/MS method after incubating 0.5 mg/mL microsomes with 200 μ M bupropion for 20 min. Midazolam 1'-hydroxylation activity was determined by a LC/MS/MS method after incubating 0.05 mg/mL microsomes with 3 μ M midazolam for 5 min. β -Naphthoflavone (β -NF, 25 μ M) and omeprazole (OMP, 30 μ M) were used as reference inducers of CYP1A. Phenobarbital (PB, 500 μ M) and phenytoin (PHE, 50 μ M) were used as reference inducers of CYP2B6 while rifampicin (1 μ M) was used as reference inducer of CYP3A4.

Results: The activity of CYP1A was reduced by around half in the presence of ucb 34714 compared to vehicle control.

(Reviewer's comment: It is unknown why the activity of CYP1A was reduced in the presence of ucb 34714. According to Study TA0776, ucb 34714 at concentrations up to 200 μ M did not inhibit CYP1A2. In addition, Study NCD1902 showed that ucb 34714 at concentrations up to 10 μ M did not alter mRNA expression of CYP1A2. Thus, the effect observed here with 10 μ M ucb 34714 cannot be explained by down regulation of CYP1A2 expression.)

Table 26. Effect of ucb 34714 on CYP1A1/2 Activity in Human Hepatocytes (expressed as fold-induction of vehicle-treated cells, mean data of triplicate)

Treatment	Concentration	Fold-induction of vehicle-treated cells		
		Hepatocytes Preparation		
		FHH-021	FHH-023	FHH-032
Vehicle : DMSO	0.1% (v/v)	1.00	1.00	1.00
ucb 34714	10 μ M	0.573	0.522	0.496
ucb 34714	30 μ M	0.432	0.443	0.591
ucb 34714	100 μ M	0.620	0.322	0.357
β -NF	25 μ M	9.11	15.7	7.00
OMP	30 μ M	7.45	14.4	4.09
PB	500 μ M	1.69	1.84	1.04
PHE	50 μ M	NP	NP	0.936
RIF	1 μ M	1.46	1.58	0.756

NP: not performed.

The activity of CYP2B6 was slightly induced by ucb 34714 in a dose-dependent manner (2.6-fold induction at the highest tested concentration – 100 µM). Nevertheless, the increase in CYP 2B6 activity in the presence of ucb 34714 was less than (< 40% of) that observed with the positive control phenobarbital, suggesting that the induction effect of ucb 34714 on CYP2B6 is weak.

Table 27. Effect of ucb 34714 on CYP2B6 Activity in Human Hepatocytes (expressed as fold-induction of vehicle-treated cells, mean data of triplicate)

Treatment	Concentration	Fold-induction of vehicle-treated cells		
		Hepatocytes Preparation		
		FHH-021	FHH-023*	FHH-025**
Vehicle : DMSO	0.1% (v/v)	1.00	<u>1.00</u>	<u>1.00</u>
ucb 34714	10 µM	1.63	1.42	<u>1.23</u>
ucb 34714	30 µM	1.92	1.85	<u>1.80</u>
ucb 34714	100 µM	2.67	2.61	<u>2.52</u>
β-NF	25 µM	2.84	2.95	3.76
OMP	30 µM	2.36	4.64	4.30
PB	500 µM	8.29	5.81	36.5
PHE	50 µM	NP	NP	13.9
RIF	1 µM	2.50	4.68	8.45

* single value; ** : mean of duplicate; NP: not performed;
 BLQ (below level of quantification) but > LOD (the limit of detection)

The activity of CYP3A4/5 was not induced by ucb 34714.

Table 28. Effect of ucb 34714 on CYP3A4/5 Activity in Human Hepatocytes (expressed as fold-induction of vehicle-treated cells, mean data of triplicate)

Treatment	Concentration	Fold-induction of vehicle-treated cells		
		Hepatocytes Preparation		
		FHH-021	FHH-023	FHH-025
Vehicle : DMSO	0.1% (v/v)	1.00	1.00	1.00
ucb 34714	10 µM	1.33	1.37	1.56
ucb 34714	30 µM	1.39	1.49	1.20
ucb 34714	100 µM	1.42	1.51	1.48
β-NF	25 µM	0.614	0.508	0.344
OMP	30 µM	1.02	1.22	1.97
PB	500 µM	2.12	4.16	8.02
PHE	50 µM	NP	NP	3.60
RIF	1 µM	2.08	4.36	6.00

NP: not performed.

4.3.13 Study NCD1902: In Vitro Evaluation of the Potential of ucb 34714 to Interfere with Induction of Cytochrome P450 and Related Gene Expression by Phenytoin in Cultured Human Hepatocytes

Objective: to investigate the potential of ucb 34714 to interfere with induction of cytochrome P450 and related gene expression by phenytoin in primary cultures of human hepatocytes.

Method: Cultured hepatocytes from three separate human livers were treated once daily for three consecutive days with DMSO (0.1% v/v, vehicle control), phenytoin control, ucb 34714 (0.5, 2, or 10 μ M) with and without phenytoin, or known human CYP inducers, namely, β -naphthoflavone (33 μ M), phenobarbital (750 μ M), CITCO (1 μ M) and rifampin (10 μ M). After treatment, cultures were treated with TRIzol reagent to isolate RNA, which was analyzed by RT-PCR to assess the effect of ucb 34714 on CYP1A2, 2B6, 2C9, 2C19, 3A4, microsomal epoxide hydrolase (EPHX1), RXR, AhR, CAR, PXR, GR and HNF- α mRNA levels. The relative quantity of the target cDNA compared with that of the control cDNA (GAPDH) was determined by the $\Delta\Delta$ CT method. Relative quantification measures the change in mRNA expression in a test sample relative to that in a control sample (e.g., DMSO). Calculations are as follows:

1. Δ Ct = Ct (target) – Ct (endogenous control)
2. $\Delta\Delta$ Ct = Δ Ct (treated sample) - Δ Ct (untreated control)
3. Fold change in expression = $2^{-\Delta\Delta$ Ct}

Results: Treatment of human hepatocytes with ucb 34714 alone (up to 10 μ M) caused little or no change in the mRNA levels of any of the transcripts examined.

Treatment of human hepatocytes with phenytoin alone increased CYP2B6, 2C9, 2C19, 3A4, and EPHX1 mRNA levels. The extent of induction observed with the combination of ucb 34714 and phenytoin was similar to that of phenytoin alone.

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)

Table 29. The effects of treating cultured human hepatocytes with ucb 34714 (with and without phenytoin) or prototypical inducers on mRNA expression: Fold increase (treated/ vehicle control)

Treatment	Concentration	Fold increase ^a					
		(CYP1A2)	(CYP2B6)	(CYP2C9)	(CYP2C19)	(CYP3A4)	Epoxyde hydrolase (EPHX1)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Phenytoin	50 µM	0.792 ± 0.280	6.75 ± 3.44	2.11 ± 0.48 †	2.10 ± 0.60	3.41 ± 1.50	2.68 ± 0.94 †
ucb 34714	0.5 µM	0.987 ± 0.232	1.11 ± 0.19	1.06 ± 0.26	1.01 ± 0.15	1.05 ± 0.23	1.29 ± 0.28
ucb 34714	2 µM	0.900 ± 0.192	1.04 ± 0.11	0.974 ± 0.119	1.01 ± 0.16	0.890 ± 0.177	1.10 ± 0.32
ucb 34714	10 µM	1.03 ± 0.06	1.47 ± 0.21	1.25 ± 0.21	1.16 ± 0.13	1.10 ± 0.22	1.22 ± 0.16
ucb 34714 + 50 µM phenytoin	0.5 µM	1.27 ± 0.91	8.56 ± 5.29 †	2.29 ± 0.51 † *	2.44 ± 0.83	3.73 ± 1.27	2.85 ± 1.18 † *
ucb 34714 + 50 µM phenytoin	2 µM	1.22 ± 0.55	8.40 ± 5.22 †	2.23 ± 0.42 † *	2.30 ± 1.06	3.90 ± 1.66	2.82 ± 0.85 † *
ucb 34714 + 50 µM phenytoin	10 µM	0.830 ± 0.374	6.45 ± 3.87	2.12 ± 0.31 †	2.35 ± 0.88	3.79 ± 1.47	2.42 ± 0.63
β-Naphthoflavone	33 µM	123 ± 172	1.75 ± 1.06	1.09 ± 0.32	1.39 ± 0.38	0.361 ± 0.207	1.22 ± 0.31
Phenobarbital	750 µM	1.29 ± 1.17	7.74 ± 3.48 *	3.18 ± 1.01 *	5.41 ± 2.82 *	7.21 ± 3.79	3.42 ± 1.02 *
CITCO	1 µM	1.90 ± 1.37	9.62 ± 6.44 *	2.01 ± 0.18	1.42 ± 0.40	1.62 ± 0.76	2.54 ± 0.95
Rifampin	10 µM	1.06 ± 0.67	6.20 ± 3.12	3.17 ± 0.77 *	6.12 ± 3.51 *	8.89 ± 6.66	2.90 ± 0.70 *

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H868, H876 and H877).

Data are shown graphically in Figures 2 – 13.

* Significantly different from the vehicle control (dimethyl sulfoxide) as a result of One-way Analysis of Variance ($p < 0.05$) with all treatment groups included in the statistical analysis.

† Significantly different from the vehicle control (dimethyl sulfoxide) as a result of One-way Analysis of Variance ($p < 0.05$) with the positive control groups (β-naphthoflavone, phenobarbital, CITCO and rifampin) excluded from the statistical analysis.

Treatment	Concentration	Fold increase ^a					
		Retinoid X receptor (RXR)	Aryl hydrocarbon receptor (AHR)	Constitutive androstane receptor (CAR)	Pregnane X receptor (PXR)	Glucocorticoid receptor (GR)	Hepatocyte nuclear factor-α (HNF-α)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Phenytoin	50 µM	0.803 ± 0.060	1.27 ± 0.11	0.603 ± 0.125	1.07 ± 0.40	1.46 ± 0.30	1.15 ± 0.26
ucb 34714	0.5 µM	1.06 ± 0.18	1.01 ± 0.10	1.39 ± 0.23	1.31 ± 0.29	1.29 ± 0.23	1.15 ± 0.06
ucb 34714	2 µM	0.959 ± 0.143	0.862 ± 0.196	1.05 ± 0.23	0.993 ± 0.119	1.18 ± 0.44	1.09 ± 0.09
ucb 34714	10 µM	0.995 ± 0.026	0.922 ± 0.203	1.36 ± 0.21	1.17 ± 0.07	1.11 ± 0.31	1.23 ± 0.18
ucb 34714 + 50 µM phenytoin	0.5 µM	0.906 ± 0.074	1.22 ± 0.42	0.913 ± 0.243	1.21 ± 0.51	1.35 ± 0.20	1.14 ± 0.29
ucb 34714 + 50 µM phenytoin	2 µM	0.882 ± 0.094	1.22 ± 0.31	1.08 ± 0.18	1.42 ± 0.54	1.87 ± 0.70	1.22 ± 0.27
ucb 34714 + 50 µM phenytoin	10 µM	0.791 ± 0.052	1.18 ± 0.34	0.821 ± 0.208	1.18 ± 0.38	1.50 ± 0.39	1.16 ± 0.27
β-Naphthoflavone	33 µM	0.747 ± 0.112	0.889 ± 0.218	1.32 ± 1.18	1.95 ± 0.50	0.829 ± 0.368	1.58 ± 0.63
Phenobarbital	750 µM	0.768 ± 0.188	1.73 ± 0.80	1.25 ± 0.83	1.44 ± 0.58	2.61 ± 0.37 *	1.23 ± 0.23
CITCO	1 µM	0.936 ± 0.113	1.11 ± 0.30	1.22 ± 0.21	1.35 ± 0.41	1.70 ± 0.66	1.22 ± 0.34
Rifampin	10 µM	0.676 ± 0.025 *	1.57 ± 0.47	0.749 ± 0.418	1.23 ± 0.46	2.04 ± 0.76	1.14 ± 0.35

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H868, H876 and H877).

Data are shown graphically in Figures 2 – 13.

* Significantly different from the vehicle control (dimethyl sulfoxide) as a result of One-way Analysis of Variance ($p < 0.05$) with all treatment groups included in the statistical analysis.

On average, treatment of cultured human hepatocytes with ucb 34714, phenytoin or ucb 34714 in combination with phenytoin, caused little or no change (< 2-fold) in transcription factor/nuclear hormone receptor mRNA levels (RXR, AhR, CAR, PXR, GR, or HNF-α). In contrast, the prototypical inducers phenobarbital and rifampin increased GR mRNA levels, on average, by 2.61- and 2.04-fold, respectively.

4.3.14 Study PSM1033: In Vitro Evaluation as a Potential Inhibitor of Human Liver Microsomal Epoxide Hydrolase

Objective: to evaluate the ability of ucb 34714 and its metabolites (ucb 42145, ucb 47074 and ucb-100406-1) to inhibit microsomal epoxide hydrolase (mEH) *in vitro*, as a result of reports of elevated levels of carbamazepine-10,11-epoxide after co-administration of ucb 34714 and carbamazepine (CBZ) in healthy subjects. mEH plays an important role in the hydrolysis of electrophilic epoxides (including carbamazepine-10,11-epoxide).

Method: The mEH activity was investigated using pooled HLM. Styrene oxide (SO) was used as the marker substrate for mEH that catalyses the hydrolysis of SO to phenylethanediol (PED). It was reported that carbamazepine-10,11-epoxide and SO are substrates for the same isoform of epoxide hydrolase and that *in vitro* inhibition of this enzyme is unaffected by the choice of the substrate. Progabide, valpromide and sodium valproate were used as reference items for inhibition of the mEH activity. HLM (30 µg/mL) were incubated with SO (10 µM) for 10 minutes at 37°C in 0.1M tris buffer (pH 9) and test items or reference items (250 µM) in a final volume of 1 mL. For the evaluation of ucb 34714 as a metabolism-dependent inhibitor, HLM (30 µg/mL) were pre-incubated with ucb 34714 (250 µM) for 15 min before adding SO. ucb 34714 concentration-dependent inhibition was evaluated by incubating SO (at 5, 10, 15 or 20 µM) and ucb 34714 (at 50, 150, 300, 600 and 900 µM) with 10 µg/mL HLM for 10 minutes. Formation of PED was measured by HPLC-UV analysis.

Results:

Maximal inhibition of mEH activity was obtained for valpromide (88.2%) and progabide (86.1%). No significant mEH inhibition was observed for sodium valproate, ucb 42145, ucb 47074 and ucb-100406-1. These results for the reference compounds were in general agreement with the K_i values reported in similar test systems.

The activity of mEH was inhibited by 50.2% with ucb 34714. A similar inhibition (50.8%) was observed when HLM were pre-incubated with ucb 34714, indicating that no metabolism-dependent inhibition of mEH occurred.

Table 30. Inhibition Screening of Microsomal Epoxide Hydrolase (mEH)

	Inhibition of mEH activity (%)	
	Mean (n = 3)	SD
ucb 34714	50.2	4.0
ucb 34714 (with a 15 min preincubation)	50.8	2.0
ucb 42145	16.1	14.0
ucb 47074	21.6	8.4
ucb-100406-1	9.8	4.8
sodium valproate	19.0	9.2
valpromide	88.2*	-
progabide	86.1	1.4

* n = 2

The IC_{50} of ucb 34714 for mEH was calculated to be 92 µM when SO was used at 5 µM which is close to its K_m ($4.1 \pm 0.6\mu M$). Thus, the K_i of ucb 34714 may be estimated to be 46 µM if competitive or uncompetitive inhibition is assumed or 92 µM if non-competitive inhibition is anticipated.

4.3.15 Study NCD2328: In vitro Evaluation of ucb 34714 and ucb-100406-1 as Potential Inhibitors of Epoxide Hydrolase using Carbamazepine Epoxide as Probe Substrate

Objective: to evaluate the potential of ucb 34714 and its hydroxylated metabolite, ucb-100406-1, to inhibit epoxide hydrolase using carbamazepine epoxide as a clinically more translatable probe substrate.

Method: Pooled HLM (0.5mg/mL) and cryopreserved human hepatocyte suspensions (0.5×10^6 cells/mL) were incubated with carbamazepine 10, 11-epoxide (400 μ M) for 30 min and 60 min, respectively, in the presence or absence of ucb 34714 and ucb-100406-1. The formation of trans 10, 11-dihydroxycarbamazepine was quantified using a LC/MS-MS method. Progabide was used as a positive control at concentrations of 10 μ M and 200 μ M, which corresponded to 10-fold of its IC_{50} values, in human hepatocytes and human liver microsomes, respectively. An initial screening was performed with 0, 10, 100 and 500 μ M of ucb 34714 or ucb-100406-1. As ucb 34714 caused a significant inhibition of epoxide hydrolase activity, another experiment was performed in order to determine its IC_{50} values. The concentrations of ucb 34714 used for this experiment were 0, 0.7, 2, 4, 7, 10, 20, 40, 70 and 140 μ M in human hepatocytes suspensions and 0, 8, 25, 50, 80, 120, 240, 500 and 800 μ M in HLM.

Results: Epoxide hydrolase is inhibited by ucb 34714 in HLM ($IC_{50} = 108 \pm 14.5$ μ M, mean \pm standard error) and human hepatocytes suspensions ($IC_{50} = 8.2 \pm 1.0$ μ M, mean \pm SE), while ucb-100406-1 did not cause significant inhibition of epoxide hydrolase activity (21% and 9% of inhibition, in HLM and human hepatocytes, respectively, at 500 μ M).

4.3.16 Study NCD1663: Transport Through the Caco-2 (HTB-37) Model

Objectives

Objectives	Final concentration of working solutions (µM)
i) A>B and B>A transport	5, 10, 20, 50, 100
ii) A>B and B>A transport in the presence of a prototypic P-gp inhibitor	20
iii) A>B transport in the presence of BSA	20

The concentrations referred to ¹⁴C- ucb 34714.

Method: Caco-2 cell monolayers (passage numbers between 29 and 31) were grown for 20 days to confluence on 1.0 µM pore size inserts (12-well plate). Monolayers were pre-incubated with transport medium (0.5 mL, pH 6.5 in A compartment and 1.5 mL, pH 7.4 in B compartment) for 1 hr. Cells were then incubated with test and reference items for 3 hrs for transport studies. For A to B transport, 100 µL of transport medium from the B compartment were sampled at pre-specified timepoints (e.g., 0.5 h, 1 h, 2 h and 3 h) and replaced with 100 µL fresh medium. For B to A transport, 50 µL of transport medium from the A compartment were sampled at pre-determined incubation time (e.g., 0.5 h, 1 h, 2 h and 3 h) and replaced with 50 µL fresh medium. Except lucifer yellow (LY) which was measured using fluorimeter, all the other test and reference items were quantitated using scintillate counting.

Monolayers were analyzed for their integrity before treatment by measuring the transepithelial electrical resistance (TEER) and after treatment by measuring the passage of LY (20 µg/mL). ¹⁴C-Antipyrine (20 µM) and ¹⁴C-mannitol (20 µM) were used as high and low permeability reference items, respectively. ¹⁴C-PEG 4000 (20 µM) was used as zero permeability marker. ³H-Digoxin (5 µM) was used as marker for the P-gp mediated transport. ¹⁴C-Urea (20 µM) was used as a marker for the reduced paracellular transport in the presence of BSA.

Transport of test and reference items was expressed as P_{app} according to the following equation:

$$P_{app} \text{ (cm/s)} = (dc/dt) * (V_r/A) * (1/3600 * C_i)$$

where dc/dt = the slope of cumulative receiver concentration versus time plot (dpm/mL/h) (the slope was calculated from the linear part of the curve);

V_r = the volume of transport medium in the receiver compartment (mL);

A = the surface area of monolayer (0.9 cm²);

C_i = the initial measured concentration in donor compartment (dpm/mL).

Results: The A-to-B transport of ucb 34714 did not vary as a function of concentration (5 to 100 µM) and was similar to the B-to-A transport (P_{app} values around 15 x 10⁻⁶ cm/s). The permeability was comparable to that of the high permeability marker antipyrine (P_{app, A-to-B} of 16.7 x 10⁻⁶ cm/s, P_{app, B-to-A} of 18.4 x 10⁻⁶ cm/s).

The efflux ratio ($P_{app, A-to-B}/P_{app, B-to-A}$) of ucb 34714 approximated 1.0 and was not significantly modified by the presence of quinidine (100 μ M), a P-gp inhibitor, suggesting that P-gp is not involved in the transport of ucb 34714.

Table 31. A-to-B and B-to-A Transport of ucb 34714 and Digoxin through Caco-2 Cell Monolayers in the Absence and in the Presence of Quinidine

Results expressed as P_{app} (10^{-6} cm/s) (Mean \pm SD, n=6 for ucb 34714, n=3 for Digoxin)

Transport direction	Item (μ M)	Presence of quinidine (100 μ M)	P_{app} (10^{-6} cm/s)		
A>B	ucb 34714	-	12.1	\pm	0.50
	(20)	+	11.6	\pm	1.01
	digoxin	-	0.629	\pm	0.04
	(5)	+	1.71	\pm	0.32
B>A	ucb 34714	-	9.89	\pm	0.86 ⁽¹⁾
	(20)	+	11.3	\pm	0.85
	digoxin	-	2.78	\pm	0.15
	(5)	+	2.32	\pm	0.18

⁽¹⁾ n=5 (LY > 2%/h)

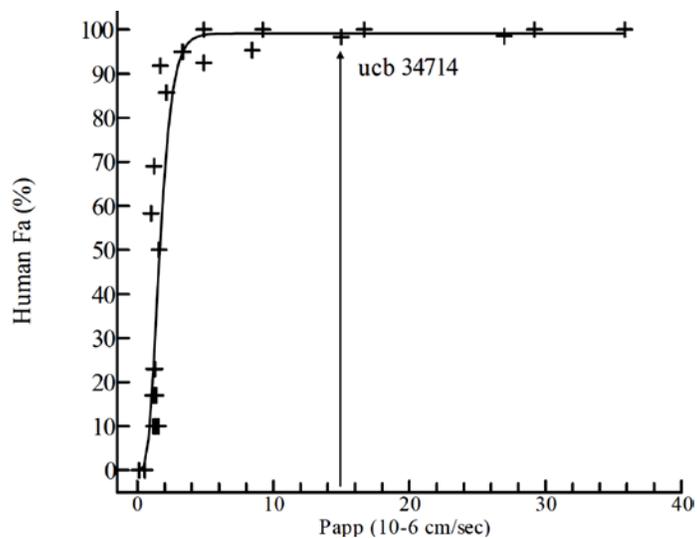
Results expressed as efflux ratio

Item (μ M)	Presence of quinidine	Efflux ratio
ucb 34714	-	0.81
(20)	+	0.98
digoxin	-	4.42
(5)	+	1.35

In the presence of BSA, the transport of ucb 34714 was not modified indicating that the permeation of ucb 34714 occurs principally via the transcellular rather than the paracellular route. In contrast, the passage of the paracellular markers urea, mannitol, and PEG 4000 was decreased in the presence of BSA.

On the basis of comparison of the permeability with reference compounds with a known fraction absorbed in humans, ucb 34714 may be classified as highly permeable according to the biopharmaceutical classification system.

Figure 15. Caco-2 Curve in the Culture Conditions Used in the Laboratory



(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

4.3.17 Study NCD2207: Assessment of ucb 34714 and its metabolites (ucb 42145, ucb-100406-1, and ucb-107092-1) as potential inhibitors of human OAT1-, OAT3-, OCT1-, OCT2-, OATP1B1-, OATP1B3-, BCRP-, BSEP- and P-gp-mediated transport

Objective: to determine if ucb 34714 (200 µM) or its metabolites (10 µM ucb 42145, 10 µM ucb-100406-1, or 2 µM ucb-107092-1) tested at a single concentration corresponding to 10-fold total C_{max} following repeat administration of 100 mg BID, potentially inhibit the transport of substrate by OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, P-gp, or BSEP.

Method: Polarized monolayers of MDCK-II cells transfected with individual transporters were used to measure uptake by OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3. The cells (passage numbers 22-40) were plated at 1.5×10^5 cells/well in 24-well transwell plates for approximate 24 hours before being transfected. Transport assays were performed about 24 hours after transfection. MDCK-MDR1 cells were used for P-gp assay, in which the cells (passage numbers 5-90) were seeded at 1.5×10^5 cells/well in 24-well transwell plates for approximate 3 days before the assays were conducted. For BCRP, the experimental system was monolayer of Caco-2 cells which relied on the endogenous expression of BCRP. The cells (passage numbers 7-20) were seeded at 1.5×10^5 cells/well in 24-well transwell plates for about 7 days before the assays were carried out. For BSEP, the membrane vesicles prepared from transfected Sf9 cells (an insect cell line) were applied as a suspension onto a 96-well plate. Substrate transport (see below) is determined by radiometric detection.

OCT1: 10 µM [14 C]-metformin
 OCT2: 10 µM [14 C]-metformin
 OAT1: 2 µM [3 H]-p-aminohippurate
 OAT3: 0.75 µM [3 H]-estrone-3-sulfate
 OATP1B1: 2 µM [3 H]-estradiol-17β-d-glucuronide
 OATP1B3: 2 µM [3 H]-bromosulphothalein
 BCRP: 25 nM [3 H]-genistein
 P-gp: 100 nM [3 H]-digoxin
 BSEP: 1 µM [3 H]-taurocholic acid

Positive control groups:

OCT1: 100 µM quinidine + 10 µM [14 C]-metformin
 OCT2: 100 µM quinidine + 10 µM [14 C]-metformin
 OAT1: 100 µM probenecid + 2 µM [3 H]-p-aminohippurate
 OAT3: 100 µM probenecid + 0.750 µM [3 H]-estrone-3-sulfate
 OATP1B1: 100 µM rifampicin + 2 µM [3 H]-estradiol-17β-d-glucuronide
 OATP1B3: 100 µM rifampicin + 2 µM [3 H]-bromosulphothalein
 BCRP: 100 µM chrysin + 25 nM [3 H]-genistein
 P-gp: 100 µM verapamil + 100 nM [3 H]-digoxin; 50 µM ketoconazole + 100 nM [3 H]-digoxin (to determine background)
 BSEP: 300 µM rifampicin + 1 µM [3 H]-taurocholic acid

Incubation time of substrates with corresponding experimental system:

5 for OAT1, OAT3, OCT2, OATP1B1 and OATP1B3
 120 for BCRP and P-gp
 15 for BSEP

Calculations for uptake transporter assays:

$$\text{Net Transporter-mediated Substrate Uptake} = \left[\begin{array}{c} \text{Cellular accumulation} \\ \text{(in the presence of transporter)} \end{array} \right] - \left[\begin{array}{c} \text{Mean cellular accumulation} \\ \text{(in the absence of transporter)} \end{array} \right]$$

Percent inhibition is calculated by dividing the net transporter mediated substrate uptake in the presence of the test article or reference inhibitor by the net transporter mediated substrate uptake in the absence of inhibitor:

$$\text{Percent Inhibition} = 100 - \left[\frac{100 \times (\text{transporter-mediated uptake})_{\text{inhibitor}}}{(\text{transporter-mediated uptake})_{\text{substrate}}} \right]$$

Calculations for BCRP and P-gp assays:

The net basal (B) to apical (A) flux of substrate transported by BCRP is calculated by subtracting A → B flux from B → A flux:

$$\text{Net (B} \rightarrow \text{A) flux} = (\text{B} \rightarrow \text{A) flux} - (\text{A} \rightarrow \text{B) flux}$$

The net (B → A) flux of substrate transported by P-gp is calculated as follows:

$$\text{Net (B} \rightarrow \text{A) flux} = [(\text{B} \rightarrow \text{A})_{\text{substrate flux}} - (\text{A} \rightarrow \text{B})_{\text{substrate flux}}] - [\text{mean (B} \rightarrow \text{A)}_{\text{substrate+keto flux}} - \text{mean (A} \rightarrow \text{B)}_{\text{substrate+keto flux}}]$$

where (B → A)substrate flux or (A → B) substrate flux is the appearance of substrate in the receiver compartment as a function of time and mean (B → A) substrate+keto flux and mean (A → B) substrate+keto flux represent the chemical abrogation of transport in the presence of ketoconazole to determine background transporter activity.

Percent inhibition is calculated by dividing the net (B → A) flux in the presence of the test article or reference inhibitor by the net (B → A) flux in the absence of inhibitor:

$$\text{Percent Inhibition} = 100 - [100 * (\text{Net B} \rightarrow \text{A flux})_{\text{inhibitor}} / (\text{mean Net B} \rightarrow \text{A flux})_{\text{substrate}}]$$

Calculations for BSEP (Vesicle) assays:

ATP-dependent substrate accumulation in Sf9 control vesicles and vesicles containing BSEP is calculated by subtracting the mean substrate accumulation in vesicles treated with AMP from the substrate accumulation in vesicles treated with ATP:

$$\text{Vesicular Accumulation (ATP-dependent)} = (\text{Vesicular accumulation})_{\text{ATP}} - (\text{Mean vesicular accumulation})_{\text{AMP}}$$

Net, ATP-dependent, BSEP-mediated transport is then calculated by subtracting the mean, ATP-dependent substrate accumulation in control vesicles from that in Sf9 vesicles containing BSEP:

$$\text{Net Transporter-mediated Vesicular Accumulation (ATP-dependent)} = (\text{Mean ATP-dependent vesicular accumulation})_{\text{BSEP vesicle}} - (\text{Mean ATP-dependent vesicular accumulation})_{\text{Sf9 control vesicle}}$$

$$\text{Percent Inhibition} = 100 - \left[\frac{100 \times (\text{Net ATP-dependent, transporter-mediated accumulation})_{w/ \text{inhibitor}}}{(\text{Net ATP-dependent, transporter-mediated accumulation})_{w/out \text{inhibitor}}} \right]$$

Results:

- At a concentration of 200 μM, ucb 34714 showed statistically significant inhibition of OAT3 (18.1%), OATP1B1 (29.6%), and OCT1 (21.7%).
- At a concentration of 10 μM, ucb 42145 showed statistically significant inhibition of OATP1B1 (24.8%), OATP1B3 (18.4%), BCRP (12.3%), and OCT1 (20.5%).
- At a concentration of 10 μM, ucb-100406-1 showed statistically significant inhibition of BCRP (14.5%) and OCT1 (38.5%).
- At a concentration of 2 μM, ucb-107092-1 showed statistically significant inhibition of OATP1B1 (28.8%) and BCRP (11.8%).

Table 32. *In vitro* data for the inhibition of OAT1-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Cellular Accumulation (transporter) (pmol/min/cm ²)	Cellular Accumulation (control) (pmol/min/cm ²)	Net Transporter-Mediated Cellular Accumulation (pmol/min/cm ²)	Inhibition (%)
2 μM PAH ^a	1.55 ± 0.104	0.176 ± 0.00257	1.37 ± 0.104	0.00 ± 7.60
2 μM PAH + 100 μM Probenecid	0.336 ± 0.113	0.141 ± 0.0661	0.195 ± 0.113	85.8 ± 8.22
2 μM PAH + 200 μM ucb 34714	1.48 ± 0.0511	0.118 ± 0.0263	1.36 ± 0.0511	0.840 ± 3.72
2 μM PAH + 10 μM ucb 42145	1.54 ± 0.152	0.0812 ± 0.0128	1.46 ± 0.152	-6.67 ± 11.1
2 μM PAH + 10 μM ucb-100406-1	1.46 ± 0.0755	0.129 ± 0.0219	1.33 ± 0.0755	2.96 ± 5.50
2 μM PAH + 2 μM ucb-107092-1	1.59 ± 0.0809	0.112 ± 0.0373	1.48 ± 0.0809	-7.64 ± 5.89

Table 33. *In vitro* data for the inhibition of OAT3-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Cellular Accumulation (transporter) (pmol/min/cm ²)	Cellular Accumulation (control) (pmol/min/cm ²)	Net Transporter-Mediated Cellular Accumulation (pmol/min/cm ²)	Inhibition (%)
750 nM E3S ^a	0.883 ± 0.0455	0.259 ± 0.0539	0.624 ± 0.0455	0.00 ± 7.30
750 nM E3S + 100 μM Probenecid	0.495 ± 0.130	0.594 ± 0.0493	-0.0981 ± 0.130	116 ± 20.8
750 nM E3S + 200 μM ucb 34714	0.815 ± 0.0364	0.304 ± 0.0242	0.511 ± 0.0364	18.1 ± 5.83
750 nM E3S + 10 μM ucb 42145	0.869 ± 0.0317	0.325 ± 0.0357	0.544 ± 0.0317	12.8 ± 5.08
750 nM E3S + 10 μM ucb-100406-1	0.849 ± 0.0371	0.248 ± 0.0526	0.601 ± 0.0371	3.69 ± 5.95
750 nM E3S + 2 μM ucb-107092-1	0.854 ± 0.0454	0.285 ± 0.0652	0.569 ± 0.0454	8.74 ± 7.28

a. E3S = Estrone-3-Sulfate

Table 34. *In vitro* data for the inhibition of OATP1B1-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Cellular Accumulation (transporter) (pmol/min/cm ²)	Cellular Accumulation (control) (pmol/min/cm ²)	Net Transporter-Mediated Cellular Accumulation (pmol/min/cm ²)	Inhibition (%)
2 μM E217G ^a	1.72 ± 0.0833	0.322 ± 0.00757	1.40 ± 0.0833	0.00 ± 5.97
2 μM E217G + 100 μM Rifampicin	0.384 ± 0.0414	0.309 ± 0.0289	0.0752 ± 0.0414	94.6 ± 2.96
2 μM E217G + 200 μM ucb34714	1.31 ± 0.0600	0.326 ± 0.0151	0.982 ± 0.0600	29.6 ± 4.30
2 μM E217G + 10 μM ucb42145	1.36 ± 0.0813	0.305 ± 0.0447	1.05 ± 0.0813	24.8 ± 5.83
2 μM E217G + 10 μM ucb100406-1	1.60 ± 0.129	0.286 ± 0.0580	1.31 ± 0.129	5.99 ± 9.22
2 μM E217G + 2 μM ucb107092-1	1.30 ± 0.0984	0.309 ± 0.0393	0.993 ± 0.0984	28.8 ± 7.06

a. E17βG = Estradiol-17β-d-Glucuronide

Table 35. *In vitro* data for the inhibition of OATP1B3-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Cellular Accumulation (transporter) (pmol/min/cm ²)	Cellular Accumulation (control) (pmol/min/cm ²)	Net Transporter-Mediated Cellular Accumulation (pmol/min/cm ²)	Inhibition (%)
10 μM BSP ^a	3.07 ± 0.0751	1.69 ± 0.136	1.38 ± 0.0751	0.00 ± 5.44
10 μM BSP + 100 μM Rifampicin	1.72 ± 0.0726	1.79 ± 0.0549	-0.0727 ± 0.0726	105 ± 5.26
10 μM BSP + 200 μM ucb 34714	2.78 ± 0.109	1.60 ± 0.132	1.18 ± 0.109	14.6 ± 7.92
10 μM BSP + 10 μM ucb 42145	2.81 ± 0.0758	1.69 ± 0.0676	1.13 ± 0.0758	18.4 ± 5.48
10 μM BSP + 10 μM ucb-100406-1	2.93 ± 0.0904	1.72 ± 0.0440	1.21 ± 0.0904	12.5 ± 6.55
10 μM BSP + 2 μM ucb-107092-1	3.10 ± 0.0827	1.71 ± 0.0797	1.39 ± 0.0827	-0.965 ± 5.99

a. BSP = Bromosulfophthalein

Table 36. *In vitro* data for the inhibition of OCT1-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Cellular Accumulation (transporter) (pmol/min/cm ²)	Cellular Accumulation (control) (pmol/min/cm ²)	Net Transporter-Mediated Cellular Accumulation (pmol/min/cm ²)	Inhibition (%)
10 μM Metformin	5.29 ± 0.145	1.44 ± 0.307	3.85 ± 0.145	0.00 ± 3.77
10 μM Metformin + 100 μM Quinidine	1.75 ± 0.0415	1.23 ± 0.239	0.515 ± 0.0415	86.6 ± 1.08
10 μM Metformin + 200 μM ucb 34714	4.31 ± 0.190	1.29 ± 0.346	3.02 ± 0.190	21.7 ± 4.93
10 μM Metformin + 10 μM ucb 42145	4.35 ± 0.400	1.28 ± 0.290	3.06 ± 0.400	20.5 ± 10.4
10 μM Metformin + 10 μM ucb-100406-1	4.24 ± 0.471	1.87 ± 0.343	2.37 ± 0.471	38.5 ± 12.2
10 μM Metformin + 2 μM ucb-107092-1	4.87 ± 0.510	1.49 ± 0.0254	3.38 ± 0.510	12.3 ± 13.2

Table 37. *In vitro* data for the inhibition of OCT2-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Cellular Accumulation (transporter) (pmol/min/cm ²)	Cellular Accumulation (control) (pmol/min/cm ²)	Net Transporter-Mediated Cellular Accumulation (pmol/min/cm ²)	Inhibition (%)
10 μM Metformin	10.9 ± 0.689	2.92 ± 0.460	7.94 ± 0.689	0.00 ± 8.67
10 μM Metformin + 100 μM Quinidine	4.08 ± 0.849	2.32 ± 0.275	1.76 ± 0.849	77.8 ± 10.7
10 μM Metformin + 200 μM ucb 34714	10.1 ± 0.854	2.16 ± 0.0360	7.98 ± 0.854	-0.453 ± 10.7
10 μM Metformin + 10 μM ucb 42145	9.60 ± 0.525	2.29 ± 0.170	7.31 ± 0.525	8.01 ± 6.60
10 μM Metformin + 10 μM ucb-100406-1	9.78 ± 0.728	2.93 ± 0.540	6.85 ± 0.728	13.7 ± 9.16
10 μM Metformin + 2 μM ucb-107092-1	10.4 ± 0.0749	2.29 ± 0.198	8.12 ± 0.0749	-2.27 ± 0.943

Table 38. *In vitro* data for the inhibition of BSEP-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Net Accumulation, transporter (ATP – AMP) (pmol/min/mg)	Net Accumulation, control (ATP – AMP) (pmol/min/mg)	Net Accumulation, transporter – control (pmol/min/mg)	Inhibition (%)
1 μM Taurocholate	21.2 ± 4.67	0.370 ± 0.0148	20.9 ± 4.67	0.00 ± 22.4
1 μM Taurocholate + 300 μM Rifampicin	0.559 ± 0.0499	0.0546 ± 0.0212	0.505 ± 0.0499	97.6 ± 0.239
1 μM Taurocholate + 200 μM ucb 34714	20.4 ± 2.95	0.449 ± 0.0525	19.9 ± 2.95	4.44 ± 14.2
1 μM Taurocholate + 10 μM ucb 42145	22.4 ± 3.37	0.395 ± 0.141	22.0 ± 3.37	-5.66 ± 16.2
1 μM Taurocholate + 10 μM ucb-100406-1	18.6 ± 2.69	0.341 ± 0.0891	18.3 ± 2.69	12.3 ± 12.9
1 μM Taurocholate + 2 μM ucb-107092-1	19.9 ± 0.723	0.381 ± 0.00924	19.6 ± 0.723	6.21 ± 3.47

Table 39. *In vitro* data for the inhibition of BCRP-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Papp B→A (nm/s)	Papp A→B (nm/s)	Efflux Ratio (B→A)/(A→B)	Mean Net B→A Flux (pmol/hr/cm ²) [^]	Inhibition (%)
25 nM Genistein	463 ± 12.3	81.2 ± 7.07	5.70	3.44 ± 0.137	0.00 ± 3.97
25 nM Genistein + 100 μM Chrysin	314 ± 8.26	257 ± 13.8	1.22	0.511 ± 0.0790	85.2 ± 2.30
25 nM Genistein + 200 μM ucb 34714	459 ± 20.6	64.2 ± 0.363	7.15	3.55 ± 0.186	-3.33 ± 5.40
25 nM Genistein + 10 μM ucb 42145	413 ± 24.7	77.6 ± 19.7	5.32	3.02 ± 0.172	12.3 ± 5.00
25 nM Genistein + 10 μM ucb-100406-1	408 ± 14.6	80.9 ± 11.0	5.04	2.94 ± 0.161	14.5 ± 4.67
25 nM Genistein + 2 μM ucb-107092-1	402 ± 9.37	65.3 ± 5.18	6.16	3.03 ± 0.0667	11.8 ± 1.94

The mean net B→A flux values were based on a membrane surface area of 0.7 cm².

Table 40. *In vitro* data for the inhibition of P-gp-mediated transport by ucb 34714, ucb 42145, ucb-100406-1, and ucb-107092-1

Test Conditions	Papp B→A (nm/s)	Papp A→B (nm/s)	Efflux Ratio (B→A)/(A→B)	Mean Net B→A Flux (pmol/hr/cm ²) ^a	Inhibition (%)
100 nM Digoxin	112 ± 7.25	6.82 ± 0.240	16.4	3.61 ± 0.268	0.00 ± 7.41
100 nM Digoxin + 100 μM Verapamil	38.7 ± 1.60	23.2 ± 0.676	1.67	0.381 ± 0.0587	89.5 ± 1.62
100 nM Digoxin + 50 μM Ketoconazole	36.7 ± 1.89	31.8 ± 0.831	1.16	0 ± 0.0433	100 ± 1.20
100 nM Digoxin + 200 μM ucb 34714	113 ± 4.96	7.11 ± 0.370	15.9	3.65 ± 0.167	-0.889 ± 4.62
100 nM Digoxin + 10 μM ucb 42145	112 ± 1.46	6.91 ± 0.160	16.2	3.61 ± 0.0534	0.0868 ± 1.48
100 nM Digoxin + 10 μM ucb-100406-1	112 ± 3.20	6.99 ± 0.399	16.0	3.59 ± 0.109	0.740 ± 3.02
100 nM Digoxin + 2 μM ucb-107092-1	109 ± 2.97	7.01 ± 0.246	15.5	3.48 ± 0.104	3.78 ± 2.88

The mean net B→A flux values were based on a membrane surface area of 0.7 cm².

Reviewer’s Comments:

For BCRP, the efflux ratio of genistein was slightly altered in the presence of ucb 34714 or its metabolites, suggesting that these compounds did not inhibit BCRP at tested concentrations. For P-gp, since MDCK cells were used, supposedly wild-type MDCK cells should have been included, so that the efflux ratio values can be adjusted to derive net efflux ratios. Nevertheless, the efflux ratio for digoxin in MDCK-MDR1 cells was as expected, and the directional transport was inhibited by positive controls (ketoconazole and verapamil), indicating that the system was reasonably established. Since the efflux ratios of digoxin were not altered in the presence of ucb 34714 or its metabolites, these compounds did not inhibit P-gp at tested concentrations. For the potential of inhibition of BCRP or P-gp in intestinal tract, the metabolites are not relevant, since they are formed after absorption of ucb 34714. The recommended dose of ucb 34714 will be 100 mg BID. At the dose of 100 mg, the estimated gut concentrations of ucb 34714 is 1.88 mM (Dose/250 mL), thus the [I]₂/IC₅₀ ratio will be at most 9.4 (using 200 μM as IC₅₀. It should be noted that the true IC₅₀ has not been determined and will be surely larger than 200 μM for BCRP or P-gp). Since the ratio is less than a cut-off of 10, ucb 34714 at the recommended therapeutic dose is not expected to inhibit BCRP or P-gp at intestine. As to the potential of inhibition of BCRP or P-gp at systemic level (e.g., liver, kidney, etc.), the ratios of total C_{max} at steady state/IC₅₀ (i.e., [I]₁/IC₅₀) are less than 0.1, indicating that ucb 34714 or its metabolites unlikely inhibit BCRP or P-gp in liver, kidney, or brain.

For uptake transporters, overall, the effects of ucb 34714 and its metabolites were weak, with IC₅₀ values larger than the tested concentrations. For renal uptake transporters, the ratios of unbound plasma C_{max} at steady state/IC₅₀ will be less than a threshold of 0.1. For liver uptake transporters, the ratios of unbound liver inlet C_{max} at steady state/IC₅₀ will be less than a threshold of 0.25. Thus, ucb 34714 and its metabolites are not expected to inhibit these transporters *in vivo* at the recommended therapeutic dose.

As to BSEP, there is no recommended criterion in the Guidance to judge *in vivo* DDI potential based on *in vitro* data. Considering that the location of BSEP is same as BCRP and P-gp on

cannalicular membrane of hepatocytes, ucb 34714 and its metabolites may not inhibit BSEP *in vivo*.

4.3.18 Study NCD2061: Involvement of MDR1, MRP1 and MRP2 in the Transport of ¹⁴C-ucb 34714 using LLC-PK1 Cells and Membrane Vesicles

Objective: to investigate the potential interaction properties of ucb 34714 with P-glycoprotein (P-gp or MDR1) and MRPs (MRP1 and MRP2) *in vitro* and plasma membrane vesicles expressing MRP1 or MRP2.

Method:

→ Using LLC-PK1 cell line expressing human MDR1 (and the corresponding Mock/LLC-PK1 cells):

- ability of ucb 34714 (at 1, 10, 100 µM) to inhibit the transport of a reference MDR1 substrate, ³H-digoxin (10 µM), measured over an incubation period of 6 hours.
- ability of ¹⁴C-ucb 34714 (at 1, 10, 100 µM) to act as a substrate of MDR1 *in two* different incubation conditions, i.e., concentration equilibrium (drug added at the same initial concentration in the donor and receiver compartments, incubated for 6 hours) and concentration gradient (drug added in the donor compartment only, incubated for 5 hours).

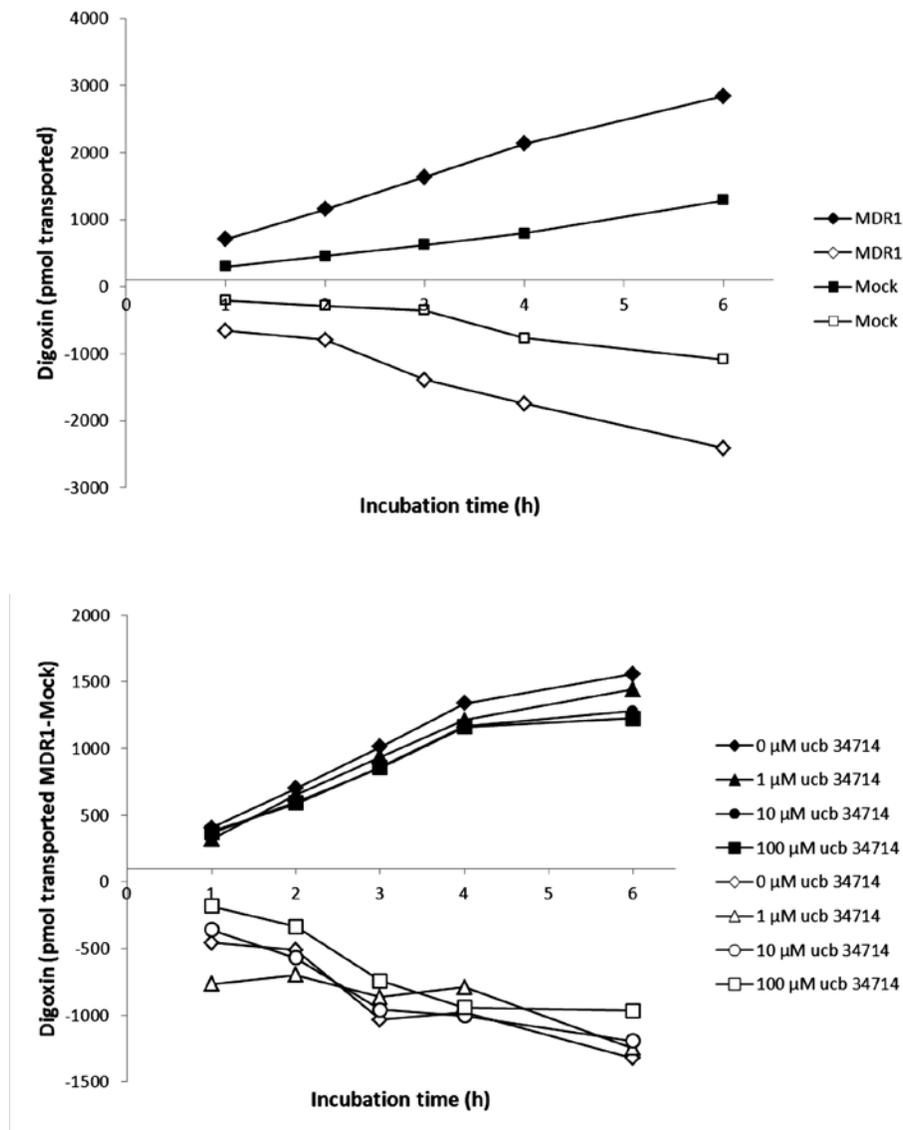
→ Using membrane vesicles prepared from sf9 cells transfected by human MRP1 and MRP2:

- after determination of the suitable experimental conditions, assessment of the ability of ¹⁴C-ucb 34714 (at 1, 10 and 100 µM), incubated with vesicles for 2 hours to be transported by MRP1 and MRP2.

Results:

1. ucb 34714 at concentrations up to 100 µM did not inhibit P-gp-mediated transport of digoxin.

Figure 16. Effect of ucb 34714 on the active transport of digoxin in MDR1 transfected cells (concentration equilibrium conditions). Mean data presented.

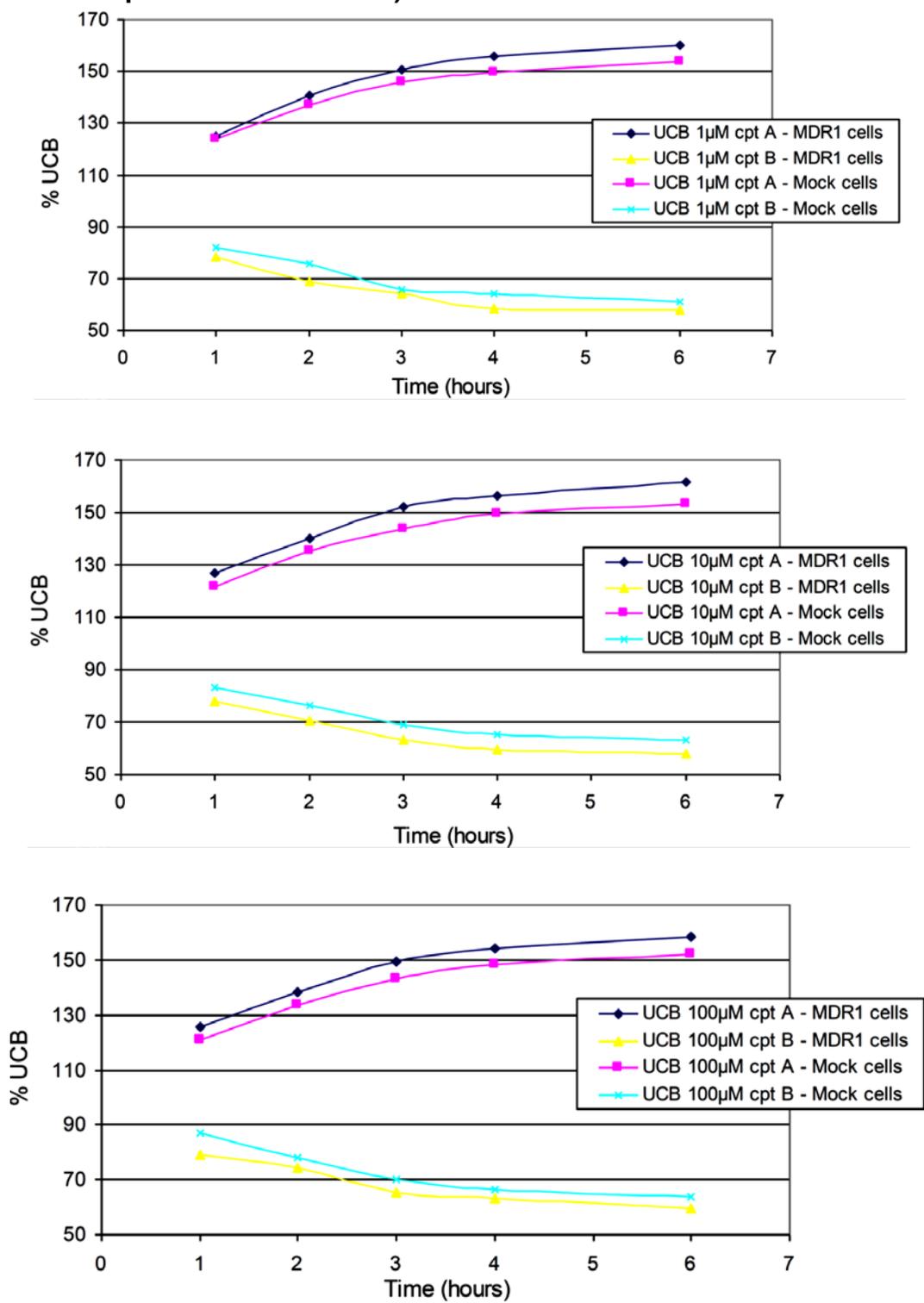


Top graph: Radiolabelled digoxin was added to the basolateral compartment in the concentration equilibrium conditions (10 μM cold digoxin in both compartments). Radioactive material in the apical (solid symbols) and basolateral (open symbols) compartments was measured in MDR1-transfected LLCPK1 cells and in mock cells.

Bottom graph: as above except that ucb-34714 was added at the indicated concentrations in both compartments. Data reported as digoxin transported in MDR1-cells minus transport in mock cells.

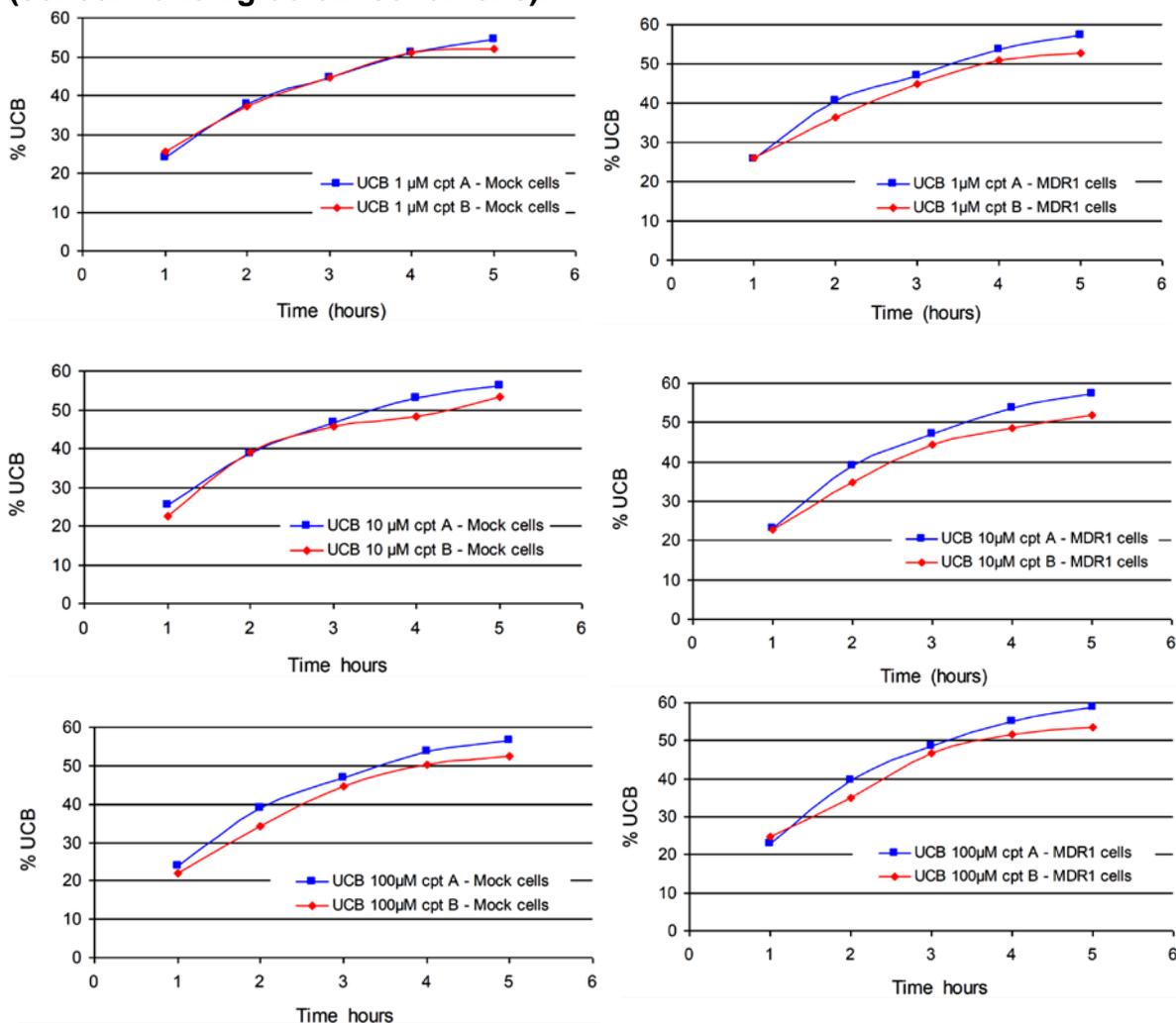
2. ucb 34714 did not show evidence of P-gp-mediated transport irrespective of the final concentration (from 1 to 100 μM). Absence of P-gp substrate activity was demonstrated both in the conventional concentration gradient conditions and in the concentration equilibrium conditions. In contrast, there was active transport of digoxin.

Figure 17. Ability of ¹⁴C-ucb 34714 to be actively transported in MDR1 transfected cells (concentration equilibrium conditions).



Radiolabelled ucb 34714 was added to the basolateral compartment in the concentration equilibrium conditions (indicated final concentrations in both compartments). Radioactive material in the apical (A) and basolateral (B) compartments was measured at different incubation times in MDR1-transfected LLCCK1 cells and in mock cells. Digoxin was tested as positive control (10 µM).

Figure 18. Ability of ¹⁴C-ucb 34714 to be actively transported in MDR1 transfected cells (concentration gradient conditions).



Radiolabelled ucb 34714 was added to the donor compartment in the concentration gradient conditions (no test substance in the receiver compartment). Basolateral to apical (A) and apical to basolateral (B) transports were measured at different incubation times in MDR1-transfected LLCPK1 cells and in mock cells. Digoxin was tested as positive control (10 μM).

3. Assays in membrane vesicles showed that ucb 34714 (1-100 μM) was not a substrate of either MRP1 or MRP2. In contrast, the positive controls (³H-Estradiol-17-β-D-glucuronide, 10 μM for MRP1 and 50 μM for MRP2) provided the expected response.

Table 41. Ability of ¹⁴C-ucb 34714 to be transported by human MRP1 expressed on purified plasma membrane vesicles

ucb 34714 1µM

MRP1	ucb 34714 uptake			
	ATP		AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
5	0.6	12	0.5	10
10	0.6	12	0.7	14
20	0.6	12	0.6	12
40	0.6	12	0.7	14
60	0.7	14	0.6	12
120	0.5	10	0.7	14

ucb 34714 10µM

MRP1	ucb 34714 uptake			
	ATP		AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
5	0.9	18	0.7	14
10	0.6	12	0.7	14
20	0.6	12	0.6	12
40	0.8	16	0.7	14
60	0.5	10	1.0	20
120	0.6	12	1.3	26

ucb 34714 100µM

MRP1	ucb 34714 uptake			
	ATP		AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
5	1.6	32	1.0	20
10	1.3	26	1.0	20
20	1.2	24	1.0	20
40	1.8	36	1.3	26
60	1.5	30	1.1	22
120	1.3	26	1.2	24

MRP1	Estradiol-17-β-D-glucuronide uptake					
	ATP		AMP		ATP-AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
1.5	6.4	127.5	0.9	17.4	5.5	110.2
3	10.4	208.3	1.5	29.3	9.0	179.0
5	11.6	232.0	1.7	33.9	9.9	198.1

(Reviewer's note: At a concentration of 100 µM, ucb 34714 seemed to have more accumulation in the vesicles in the presence of ATP than AMP. However, the differences were much smaller than the ones observed for the positive control. In addition, active transport was not observed at lower concentrations which are more clinically relevant considering the location of MRP1 in tissues. It should also be noted that control vesicles (from sf9 cells not transfected with MRP1) were not included in the experiments.)

Table 42. Ability of ¹⁴C-ucb 34714 to be transported by human MRP2 expressed on purified plasma membrane vesicles

ucb 34714 1μM

MRP2	ucb 34714 uptake			
	ATP		AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
5	0.7	14	0.4	8
10	0.7	14	0.6	12
20	0.6	12	0.5	10
40	0.8	16	0.5	10
60	0.5	10	0.5	10
120	0.6	12	0.5	10

ucb 34714 10μM

MRP2	ucb 34714 uptake			
	ATP		AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
5	0.6	12	0.7	14
10	0.6	12	0.7	14
20	0.6	12	0.7	14
40	0.6	12	0.7	14
60	0.6	12	1.0	20
120	0.6	12	0.7	14

ucb 34714 100μM

MRP2	ucb 34714 uptake			
	ATP		AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
5	0.90	18	0.9	18
10	1.20	24	1.1	22
20	1.00	20	1.0	20
40	1.10	22	1.0	20
60	1.00	20	1.0	20
120	1.20	24	1.1	22

MRP2	Estradiol-17-β-D-glucuronide uptake					
	ATP		AMP		ATP-AMP	
Time (min)	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹	pmol.well ⁻¹	pmol.mg prot ⁻¹
1.5	31.1	622.9	3.5	69.9	27.6	553.0
3	74.1	1482.4	5.1	102.0	69.0	1380.4
5	125.5	2509.2	6.6	131.2	118.9	2378.0

Conclusion: ucb 34714 was neither a substrate nor an inhibitor of P-gp. ucb 34714 was not transported by MRP1 or MRP2.

4.4 Individual Study Review - Clinical

4.4.1 N01066: SAD of BRV Capsules: Phase 1

Study Report#	RPCE01E3101 / N01066																				
Title	<i>Randomized, monocenter, double-blind, placebo-controlled, 3-alternating panel, 3-period rising single oral dose (10 to 1400 mg), safety, tolerability, pharmacokinetic and pharmacodynamic study of ucb 34714 (capsule without excipient) in 27 healthy male volunteers.</i>																				
Objectives	<u>Primary:</u> Assess safety and tolerability, determined MTD <u>Secondary:</u> 1. Determine plasma and urinary PK of BRV 2. Assess proportionality of AUC and C _{max} 3. Assess dose-dependence of t _{max} , λ _z , CL/f, V _z /f, f _e , and CL _R <u>Exploratory:</u> Assess CNS PD and relationship to dose																				
Study Design	Randomized, monocenter, double-blind, placebo-controlled, 3-alternating panel, 3-period rising single oral dose.																				
Duration	3 days of confinement in the CRU																				
Dosage and Administration	3-alternating panel study where healthy volunteers were administered 3 single doses (10, 20, 40, 80, 150, 300, 600, 1000, or 1400 mg) in 3 periods as a BRV capsule. <u>Panel 1 (n=9):</u> Placebo, 10, 80, 600 mg <u>Panel 2 (n=9):</u> Placebo, 20, 150, 1000 mg <u>Panel 3 (n=9):</u> Placebo, 40, 300, 1400 mg Each period was separated by a 28-day washout period. At each occasion, n=6 received BRV capsules and n=3 received placebo. Within each of the 3 dosing periods, n=2 received BRV oral capsules and n=1 received placebo.																				
PK Assessment	<u>Plasma Samples:</u> pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, and 48 hours <u>Urine Samples:</u> predose, 0-3h, 3-6h, 6-9h, 9-12h, 12-24h <u>PK Analyses:</u> AUC, AUC _{0-t} , C _{max} , t _{max} , λ _z , t _{1/2} , MRT, CL/f, V _z /f, A _e , f _e , CL _R and CL _{NR} . A power model was used to assess dose proportionality of AUC, AUC _{0-t} , C _{max} . A power model was also used to assess dose independence of λ _z , t _{1/2} , MRT, CL/f, V _z /f, A _e , f _e , CL _R . The median t _{max} values were compared between dose groups.																				
Bioanalytical Methods	<p style="text-align: center;">HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-2.3 to 3.1%</td> </tr> <tr> <td>Standards precision</td> <td>2.1 to 4.6%</td> </tr> <tr> <td>QC concentrations</td> <td>152, 607, 1769 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-2.9 to 1.7%</td> </tr> <tr> <td>QC Precision</td> <td>5.6 to 6.8%</td> </tr> <tr> <td>LLOQ</td> <td>50 ng/mL</td> </tr> </table> <p>[Reviewer comment: The validation of analytical assay for BRV is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL	Standards accuracy	-2.3 to 3.1%	Standards precision	2.1 to 4.6%	QC concentrations	152, 607, 1769 ng/mL	QC Accuracy	-2.9 to 1.7%	QC Precision	5.6 to 6.8%	LLOQ	50 ng/mL
Analyte Name	Brivaracetam																				
Analyte ID	ucb 34714																				
Internal Standard (IS)	(b) (4)																				
Standard curve concentrations	50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL																				
Standards accuracy	-2.3 to 3.1%																				
Standards precision	2.1 to 4.6%																				
QC concentrations	152, 607, 1769 ng/mL																				
QC Accuracy	-2.9 to 1.7%																				
QC Precision	5.6 to 6.8%																				
LLOQ	50 ng/mL																				

HPLC-MS/MS Analytical Methods for Urine Concentrations				
Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite 1 (stereoisomer)	Hydroxy Metabolite 2 (stereoisomer)
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-100023-1
Internal Standard (IS)	(b) (4)	(b) (4)		
Standard curve concentrations	0.25, 0.5, 1, 2.5, 5, 10, 25, 50 µg/mL	0.25, 0.5, 1, 2.5, 5, 10, 25, 50 µg/mL	1, 2.5, 5, 10, 25, 50, 100 µg/mL	1, 2.5, 5, 10, 25, 50, 100 µg/mL
Standards accuracy	- 4.6 to 5.6%	-8.7 to 9.2%	-9.6 to 7.8%	-9.7 to 6.6%
Standards precision	3.5 to 6.4%	Not reported		
QC concentrations	0.75, 7.5, 40 µg/mL	0.75, 7.5, 50 µg/mL	1.5, 15, 75 µg/mL	1.5, 15, 75 µg/mL
QC Accuracy	-3.8 to 6.4%	1.4 to 4.8%	-4.7 to 5.7%	-4.9 to 3.7%
QC Precision	3.4 to 5.3%	4.3 to 10.8%	Sponsor did not report QC precision for these metabolites in urine (one run each).	
20-fold dilution QC Concentration	n/a	n/a	77.0 µg/mL	75.8 µg/mL
20-fold dilution Accuracy	n/a	n/a	14.4%	11.3%
20-fold dilution Precision	n/a	n/a	1.7%	1.6%
LLOQ	0.25 µg/mL	Sponsor did not provide a LLOQ for the metabolites in urine.		
<p><i>*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).</i></p> <p>IS (b) (4)</p> <p>IS (b) (4) (b) (4)</p> <p>[Reviewer comment: The urine assay is validated for BRV. However, Sponsor indicates that the urine assays for ucb 42145, ucb-100406-1, and ucb-100023-1 (aka ucb 100023-1) were partially-validated. Precision estimates and LLOQ values were not provided for the metabolites. As such, the measurements of metabolites in the urine may not be reliable.]</p>				
Population / Demographics	<p>N=27 healthy male volunteers age 18 to 55 years with BMI 19 – 27 kg/m²</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male subjects age 18 to 55 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 			

Exclusion Criteria:

1. Female subjects
2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug
3. Concomitant or chronic acute illness
4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical trial
5. Current smoker or had given up smoking in the last 6 months

PK Results

Figure N01066-1: BRV Mean PK Profile After Single Doses for 48 Hours

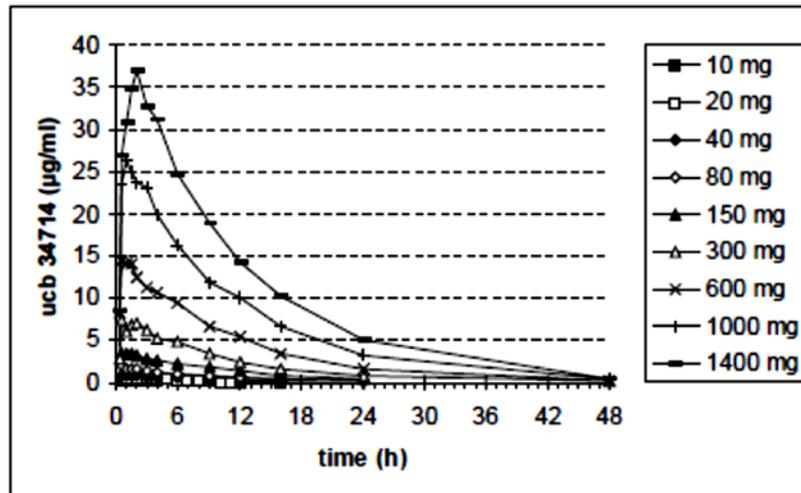
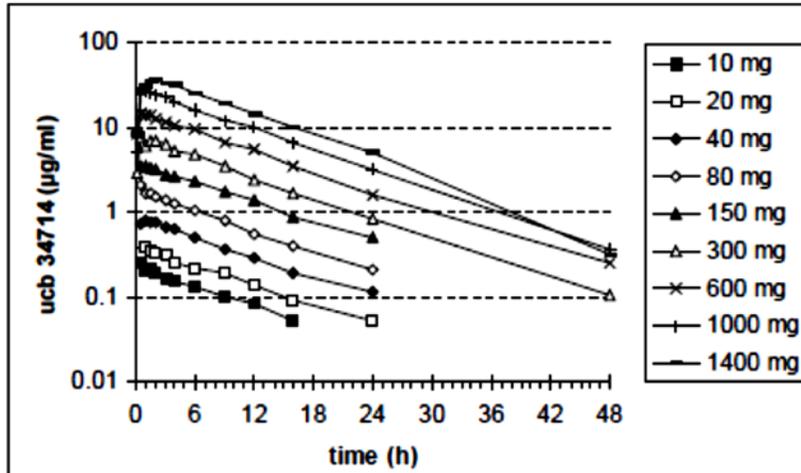


Table N01066-1: Mean ± SD BRV Plasma PK Parameters After Single Oral Capsule Administration

Parameter Unit	ucb 34714 dose (mg) ^(b) (N=6)								
	10	20	40	80	150	300	600	1000	1400
C _{max} (µg/mL)	0.305 (0.118)	0.429 (0.071)	0.945 (0.227)	2.18 (0.37)	4.24 (0.85)	8.58 (1.36)	16.2 (2.0)	28.5 (4.6)	41.3 (10.0)
t _{max} ^(h) (h)	0.58 (0.50-2.02)	1.00 (0.50-3.00)	1.26 (0.50-2.00)	0.51 (0.50-1.50)	0.75 (0.50-3.00)	1.01 (0.25-2.00)	0.75 (0.25-1.50)	1.27 (0.50-4.00)	1.75 (1.02-4.00)
AUC(0-t) (µg·h/mL)	1.79 (0.40)	3.65 (1.20)	8.35 (1.04)	17.3 (2.1)	37.2 (4.1)	81.2 (16.3)	165 (33)	313 (49)	432 (58)
AUC (µg·h/mL)	2.54 (0.38)	4.50 (1.48)	9.74 (1.62)	19.7 (2.5)	43.1 (6.0)	84.3 (15.1)	170 (30)	317 (52)	465 (87)
t _{1/2} (h)	8.06 (0.87)	8.18 (1.56)	8.05 (1.38)	7.71 (0.96)	8.04 (1.04)	7.43 (1.09)	7.26 (1.02)	7.41 (1.26)	7.31 (1.25)
CL _f (mL/min)	66.9 (10.8)	81.7 (28.5)	70.0 (10.9)	68.8 (8.8)	59.0 (8.5)	60.9 (10.6)	60.5 (11.2)	53.7 (8.5)	51.9 (11.1)
CL _f (mL/min/kg)	0.876 (0.086)	1.07 (0.32)	0.954 (0.163)	0.945 (0.080)	0.822 (0.088)	0.858 (0.097)	0.831 (0.103)	0.725 (0.064)	0.696 (0.151)
CL _f (mL·min ⁻¹ ·73m ⁻²)	59.5 (7.5)	72.0 (23.5)	62.8 (10.5)	62.5 (6.6)	53.9 (6.1)	56.9 (7.6)	55.3 (8.3)	48.1 (4.7)	46.7 (10.0)
V _d /f (L)	46.5 (8.4)	55.1 (10.8)	47.8 (4.0)	45.6 (6.5)	40.5 (3.3)	38.4 (3.3)	37.6 (6.1)	33.9 (4.3)	32.4 (6.1)
V _d /f (L/kg)	0.610 (0.079)	0.730 (0.112)	0.649 (0.025)	0.628 (0.065)	0.568 (0.064)	0.545 (0.028)	0.518 (0.062)	0.461 (0.058)	0.436 (0.090)

Table N012066-2: Mean ± SD BRV PK Parameters After Single Oral Capsule Administration

Parameter Unit	ucb 34714 dose (mg) (N=6)								
	10	20	40	80	150	300	600	1000	1400
f _e (%)	3.2 (1.7)	4.0 (0.9)	5.7 (1.3)	5.5 (1.8)	6.1 (1.8)	8.0 (4.1)	6.9 (2.0)	5.8 (1.8)	7.5 (1.4)
CL _R (mL/min/kg)	0.0700 (0.0553)	0.0521 (0.0226)	0.0634 (0.0161)	0.0594 (0.0218)	0.0570 (0.0117)	0.0805 (0.0478)	0.0657 (0.0223)	0.0488 (0.0162)	0.0614 (0.0230)
CL _{NR} (mL/min/kg)	0.806 (0.105)	1.02 (0.30)	0.890 (0.155)	0.886 (0.074)	0.765 (0.096)	0.778 (0.063)	0.765 (0.093)	0.676 (0.073)	0.635 (0.132)

[Reviewer comment: BRV CL_{NR} appears to be ~10-fold greater than BRV CL_{Ren} across the full dose range. The BRV fraction excreted in the urine appears to vary from 3 – 7% across the full dose range.]

Figure N01066-2: Dose-AUC Relationship Following Single Doses to HV

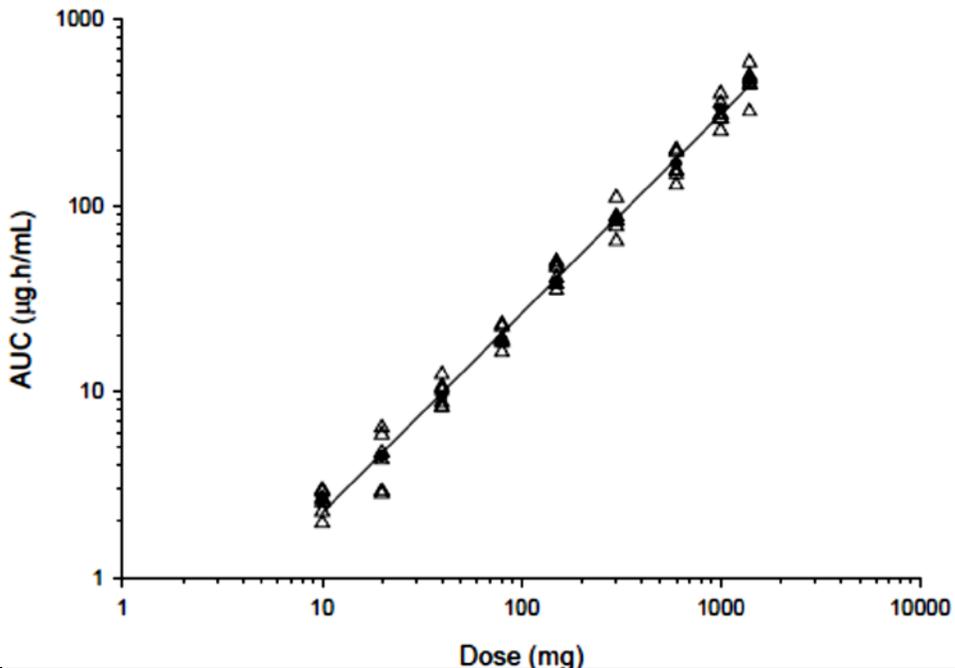
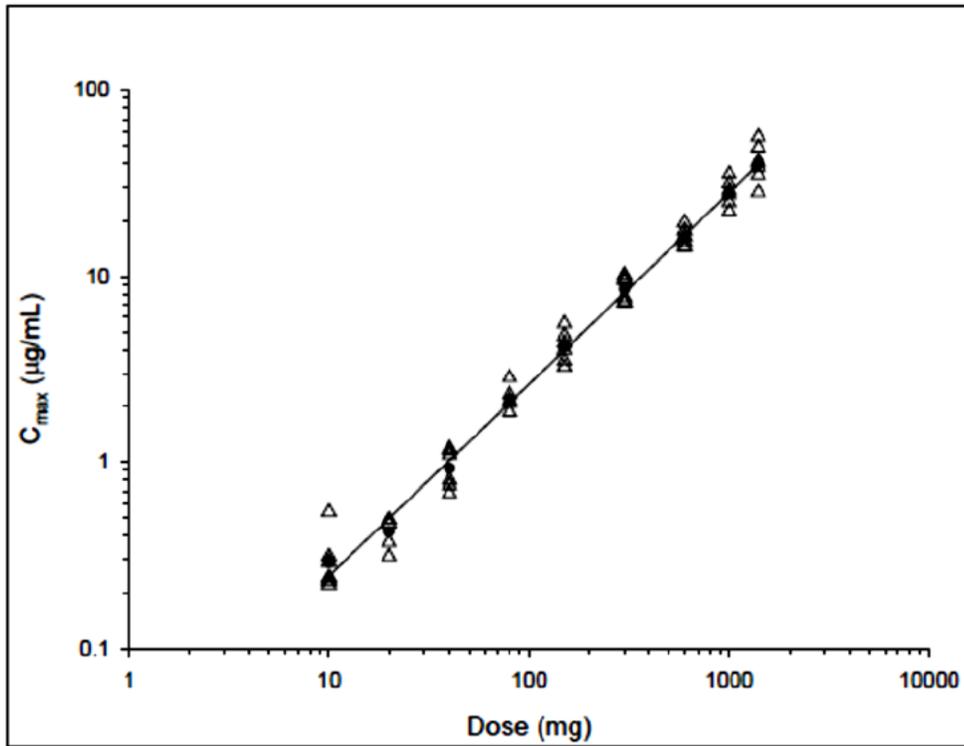


Figure N01066-3: Dose-C_{max} Relationship Following Single Doses to HV



Sponsor assessed dose-proportionality using the power model according to Smith et al., 2000 (PMID: 11145235). For equivalence boundaries of 70%-143%, using the power-model, Sponsor could conclude dose-proportionality if the 90% CI of the slope was contained within the acceptance interval of {0.928, 1.072}.

Table N01066-3: Dose-Proportionality of AUC and C_{max} from 10-1400 mg

Parameter	Estimate slope	SE	90% CI
AUC (µg.h/mL)	1.0693	0.0127	{1.048 ; 1.091}
C _{max} (µg/mL)	1.0301	0.0177	{1.000 ; 1.060}

Sponsor indicated that the AUC value exceeded upper limit of the no-effect boundary for dose-proportional. Sponsor re-conducted the analysis for AUC on a subset of doses where the highest two dose values were eliminated

Table N01066-4: Dose-Proportionality of AUC from 10-600 mg (Excluding Highest Two Dose levels; 1000 mg and 1400 mg)

Parameter	Estimate	SE	90% CI
AUC (µg.h/mL)	1.0287	0.0123	{1.006 ; 1.051}

Table N01066-5: Non-Dose-Proportionality of AUC at 1000 mg and 1400 mg

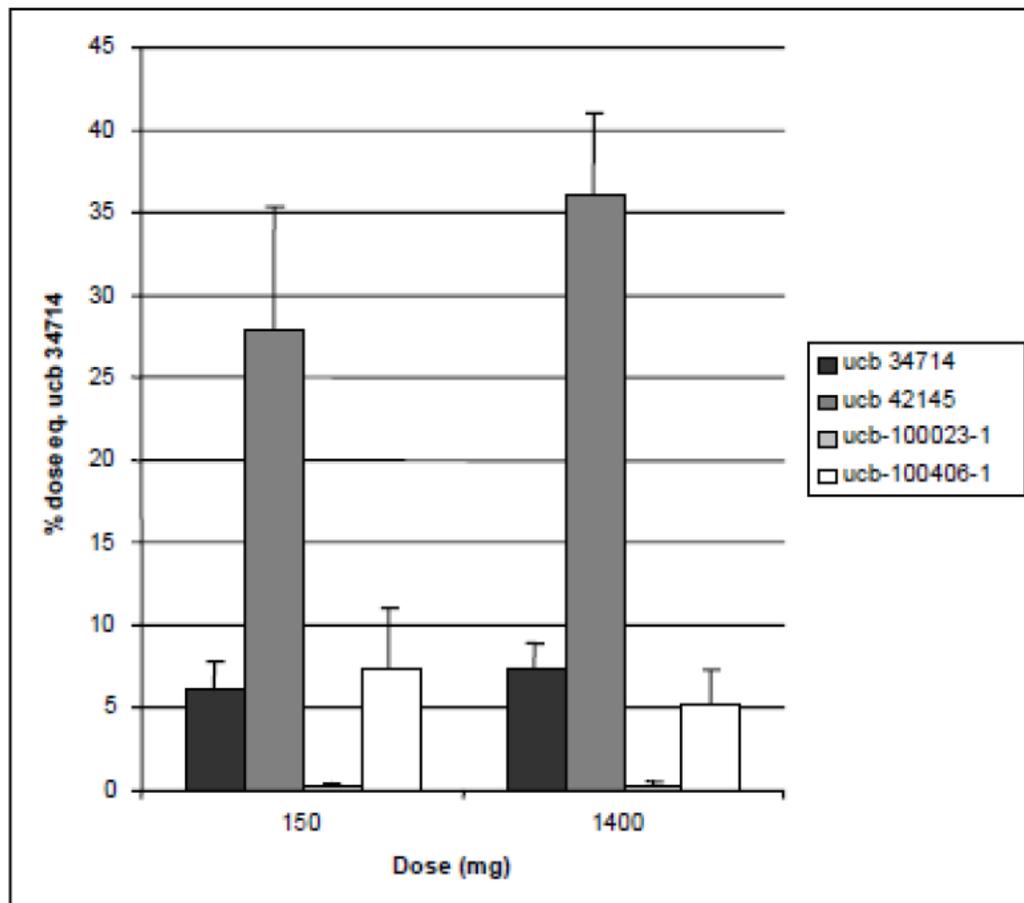
Parameter	Dose	Ratio	90% CI
AUC (µg.h/mL)	1000 mg	1.28	{1.13 ; 1.67}
	1400 mg	1.24	{0.98 ; 1.48}

Table N01066-6: Exploratory Estimation of Dose-Proportionality of Other BRV Plasma and Urinary PK Parameters

Parameter	Estimate slope	SE	90% CI
CL/f (mL/min/kg)	-0.0652	0.0124	{-0.086 ; -0.044}
CL _{NR} (mL/min/kg)	-0.0675	0.0129	{-0.089 ; -0.046}
CL _R (mL/min/kg)	0.0030	0.0338	{-0.054 ; 0.060}
λ _z (h ⁻¹)	0.0229	0.0102	{0.006 ; 0.040}
f _z (%)	0.1385	0.0294	{0.089 ; 0.188}
V _z /f (L/kg)	-0.0864	0.0115	{-0.105 ; -0.067}

The dose-dependent increase in CL/F was mainly due to CL_{NR}.

Figure N01066-4: Mean 24-Hour Urinary Excretion of BRV and Major Metabolites Following 150 and 1400 mg Single Oral Doses



[Reviewer Comment: Sponsor reports that The hydroxylation at the ω-1 position of the propyl chain was stereoselective and led to 2 (b)(4) ucb-100023-1 and ucb-100406-1. However, the hydroxy metabolite ucb-100023-1 was found in negligible amount in urine.]

	<p>Table N01066-7: Mean 24-Hour Urinary Excretion of BRV and Metabolites</p> <p>Cumulative urinary excretion (expressed in % of the dose given)</p> <table border="1" data-bbox="591 260 1247 653"> <thead> <tr> <th rowspan="2">Compound</th> <th colspan="2">Dose (mg)</th> </tr> <tr> <th>150</th> <th>1400</th> </tr> </thead> <tbody> <tr> <td>Parent compound</td> <td></td> <td></td> </tr> <tr> <td>ucb 34714</td> <td>6.1</td> <td>7.5</td> </tr> <tr> <td>Metabolites</td> <td></td> <td></td> </tr> <tr> <td>ucb 42145</td> <td>27.9</td> <td>36.1</td> </tr> <tr> <td>ucb-100023-1</td> <td>0.3</td> <td>0.4</td> </tr> <tr> <td>ucb-100406-1</td> <td>7.5</td> <td>5.4</td> </tr> <tr> <td>Total</td> <td>35.7</td> <td>41.8</td> </tr> <tr> <td>Parent compound + metabolites</td> <td></td> <td></td> </tr> <tr> <td>Total excreted</td> <td>41.9</td> <td>49.3</td> </tr> </tbody> </table> <ul style="list-style-type: none"> • 3-7% of BRV is excreted unchanged into the urine during 24 hours. • Systemic BRV clearance (58 mL/min) was lower than hepatic blood flow (1450 mL/min) 	Compound	Dose (mg)		150	1400	Parent compound			ucb 34714	6.1	7.5	Metabolites			ucb 42145	27.9	36.1	ucb-100023-1	0.3	0.4	ucb-100406-1	7.5	5.4	Total	35.7	41.8	Parent compound + metabolites			Total excreted	41.9	49.3
Compound	Dose (mg)																																
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<p>Safety</p>	<p><u>Assessments:</u> Physical examination, vital signs, respiratory rate, ECG, clinical EEG, safety laboratory tests, AEs</p> <p><u>Results:</u> TEAEs were reported in 92.6% of subjects. The main TEAE were dizziness (44.4%) and somnolence (33.3%), especially at higher dose levels. Both events resolved within 1 day. One SAE (severe drowsiness) occurred at 1400 mg.</p>																																
<p>Sponsor's Conclusions</p>	<ul style="list-style-type: none"> • Due to the SAE (severe drowsiness) observed at 1400 mg, 1000 mg was determined to be the MTD. • C_{max} increased proportionally dose from 10 to 1400 mg and AUC increased proportionally from 10 to 600 mg. • AUC increase was less than proportional above 600 mg. • Parent drug was the major circulating species at 16 hours post-dose • BRV is a low-extraction drug and non-renal clearance is the major part of the total body clearance (CL_{renal} of unchanged BRV is 5-10% of total CL). • UCB 34714 is mainly metabolized into ucb 42145 and to a lesser extent into ucb-100406-1. These metabolites were detected in the urine. 																																
<p>Reviewer's Comments</p>	<ul style="list-style-type: none"> • <i>This reviewer concurs that the single-dose MTD of BRV capsules in healthy volunteers is at least 1000 mg based on the current study.</i> • <i>The actual BRV CL_{renal} (4 mL/min) is far less than what would be expected if CL_{renal} depended only on GFR (CL_{renal} = GFR * fu = 125 mL/min * 0.8 = 100 mL/min). This reviewer agrees with the Sponsor that this finding suggests that extensive tubular resorption of BRV is taking place.</i> • <i>Total BRV CL (58 mL/min) is far less than hepatic blood flow (1100 mL/min). This reviewer agrees with the Sponsor this is finding suggests that BRV is a low-extraction drug.</i> • <i>This reviewer agrees that the dose-proportionality can be concluded from 10 to 1400 mg for C_{max}, and 10 to 600 mg for AUC.</i> 																																

4.4.2 N01067: Multiple-Dose PK and CYP3A4 Induction

Study Report#	RPCE02C0101 / N01067																																	
Title	Randomized, monocenter, double blind, placebo-controlled, parallel group, 2 weeks repeated oral dose, safety, tolerability, pharmacokinetic and pharmacodynamic study of ucb 34714 100 mg, 200 mg and 400 mg (100 and 200 mg (b) (4)) twice daily in 36 healthy male volunteers.																																	
Objectives	<p><u>Primary:</u> Assess safety and tolerability of repeat BRV doses for 2 weeks</p> <p><u>Secondary:</u></p> <ul style="list-style-type: none"> Assess Plasma PK of BRV, urinary PK of BRV and metabolites Assess metabolism induction potential Assess dose proportionality Assess PD effect effects Assess feasibility of BRV monitoring through saliva 																																	
Study Design	Monocenter, randomized, double-blind, placebo-controlled, parallel-group, single-2-week-period, repeat dose study.																																	
Duration	2 weeks of treatment																																	
Dosage and Administration	There were 4 treatment groups with n=9 subjects per group. Subjects received placebo (bid), 200 mg/day (100 mg bid), 400 mg/day (200 mg bid), or 800 mg/day (400 mg bid) as oral capsules for 2 weeks.																																	
PK Assessments	<p>Plasma BRV, urinary BRV, urinary metabolites, as well as urinary 6-beta-hydroxycortisol and cortisol (as an indicator of whether BRV induces CYP3A4) were measured.</p> <p><u>Plasma PK Samples:</u></p> <ul style="list-style-type: none"> Pre-dose, 0.5, 1, 2, 3, 4, 6, 9, 12 and 16 hours, on Day 1 and 14. Pre-dose, 0.5, 1, 2, 3, 4, 6, 9 and 12 hours post-dose on Day 7. Pre-dose on Day 2, 5, 6, 8, 12 and 13 (morning only). 24, 36 and 48 after the last dosing on Day 15 and 16 <p><u>Urine PK Samples:</u> Pre-dose, 0-12h and 12-24h on Day 1 and 7. At Day 14, urine will be collected up to 48h after the last dose, in 12 hours fractions. Urine will be used to assess BRV, metabolites, cortisol, and 6-beta-hydroxycortisol.</p> <p><u>Saliva PK Samples:</u> pre-dose and 0.5, 1, 2, 3, 4, 6, 9 and 12 hours post-dose on Day 7.</p>																																	
Bioanalytical Methods	<p>urinary 6-beta-hydroxycortisol and cortisol were measured using commercially-available kits.</p> <p style="text-align: center;">HPLC-MS/MS Analytical Methods for BRV in Plasma and Saliva</p> <table border="1"> <thead> <tr> <th>Analyte Name</th> <th colspan="2">Brivaracetam</th> </tr> <tr> <th>Analyte ID</th> <td colspan="2">ucb 34714</td> </tr> <tr> <th>Internal Standard (IS)</th> <td colspan="2">(b) (4)</td> </tr> <tr> <th>Media</th> <th>Plasma</th> <th>Saliva</th> </tr> </thead> <tbody> <tr> <td>Standard curve concentrations</td> <td>50, 100, 250, 400, 750, 1000, 1500, 2000 ng/mL</td> <td>50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-1.4 to 3.5%</td> <td>-2.4 to 1.9%</td> </tr> <tr> <td>Standards precision</td> <td>3.2 to 6.1%</td> <td>2.4 to 5.4%</td> </tr> <tr> <td>QC concentrations</td> <td>151, 605, 1764 ng/mL</td> <td>150, 600, 1750 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>0.3 to 2.1%</td> <td>-6 to -2.5%</td> </tr> <tr> <td>QC Precision</td> <td>5.0 to 7.0%</td> <td>6.4 to 8.0%</td> </tr> <tr> <td>LLOQ</td> <td>50 ng/mL</td> <td>50 ng/mL</td> </tr> </tbody> </table>	Analyte Name	Brivaracetam		Analyte ID	ucb 34714		Internal Standard (IS)	(b) (4)		Media	Plasma	Saliva	Standard curve concentrations	50, 100, 250, 400, 750, 1000, 1500, 2000 ng/mL	50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL	Standards accuracy	-1.4 to 3.5%	-2.4 to 1.9%	Standards precision	3.2 to 6.1%	2.4 to 5.4%	QC concentrations	151, 605, 1764 ng/mL	150, 600, 1750 ng/mL	QC Accuracy	0.3 to 2.1%	-6 to -2.5%	QC Precision	5.0 to 7.0%	6.4 to 8.0%	LLOQ	50 ng/mL	50 ng/mL
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LLOQ	50 ng/mL	50 ng/mL																																

[Reviewer comment: The plasma and saliva assays for BRV are validated.]

HPLC-MS/MS Analytical Methods for BRV and Metabolites in Urine

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1
Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)
Standards Concentrations	0.252, 0.504, 1.26, 2.52, 3.83, 5.04, 7.55, 10.1 µg/mL	0.250 0.500 1.25 2.50 3.80 5.00 7.50 10.0 µg/mL	0.253 0.506 1.27 2.53 3.85 5.06 7.59 10.1 µg/mL
Standards Accuracy	-2.3 to 4.7%	-2.9 to 2.5%	-1.6 to 2.6%
Standards Precision	1.3 to 6.8%	1.7 to 5.7%	1.6 to 6.2%
QC Concentrations	0.755 3.02 8.86 µg/mL	0.752 3.01 8.83 µg/mL	0.765 3.06 8.98 µg/mL
QC Accuracy	-5.8 to -4.3%	-3.7 to 0.4%	-8.9 to -6.5%
QC Precision	5.5 to 8.0%	3.6 to 5.6%	4.5 to 4.8%
LLOQ	0.25 µg/mL.	0.25 µg/mL.	0.25 µg/mL.

[Reviewer comment: The urine assays for BRV and metabolites are validated.]

Population/
Demographics

N=36 healthy male volunteers age 18 to 55 with normal ECG, EEG, and clinical laboratory parameters

Inclusion Criteria:

1. Male subjects age 18 to 55 years
2. Good physical and mental health
3. ECG is normal or abnormal but not clinically significant
4. Laboratory test results are within the reference range

Exclusion Criteria:

5. Female subjects
6. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug
7. Concomitant or chronic acute illness
8. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical trial
9. Current smoker or had given up smoking in the last 6 months

PK Results

Figure N01067-1: Mean \pm SD PK Profile for BRV On Days 1, 7, and 14 of Repeat 100 mg bid Administration

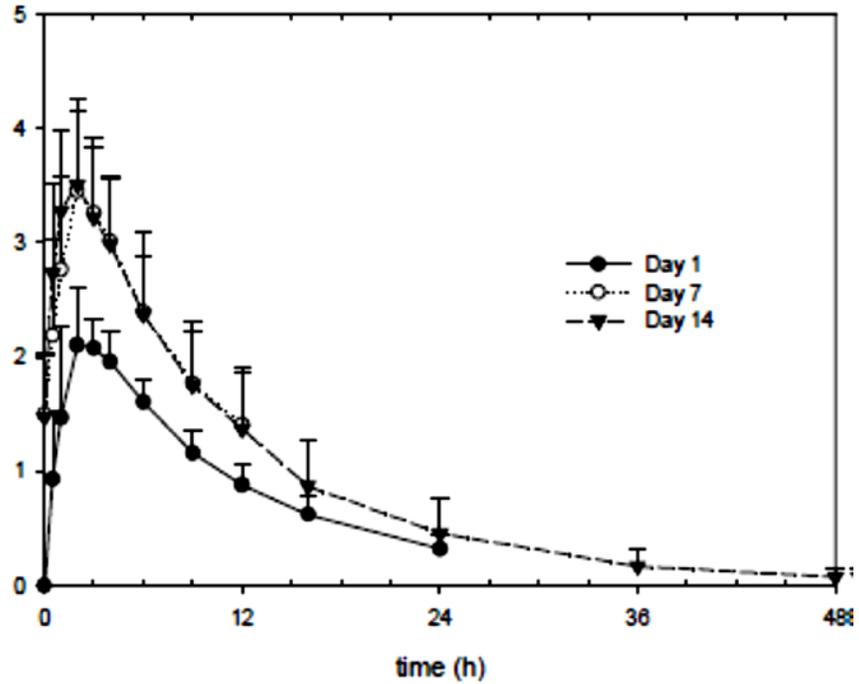


Figure N01067-2: Mean \pm SD PK Profile for BRV On Days 1, 7, and 14 of Repeat 200 mg bid Administration

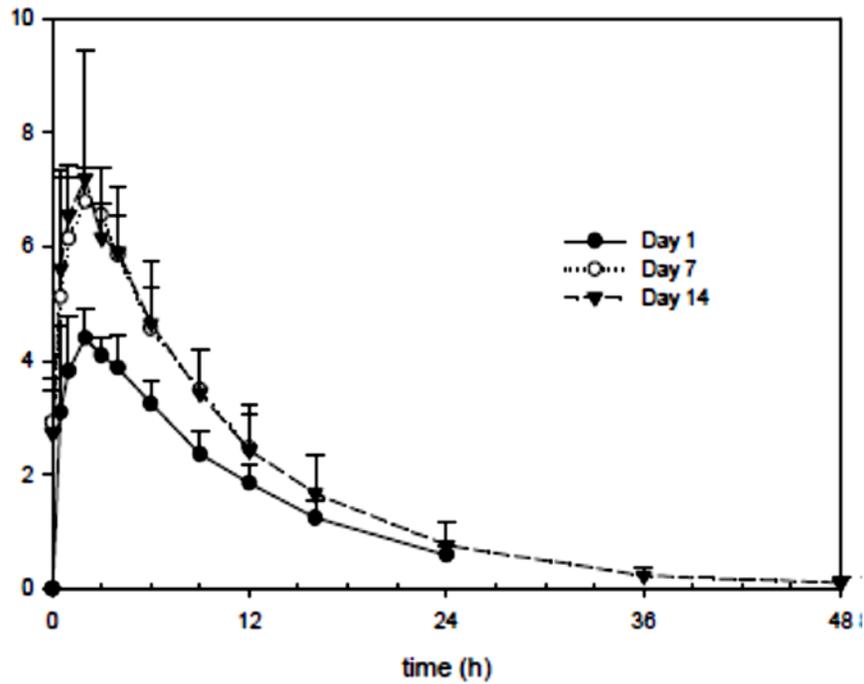
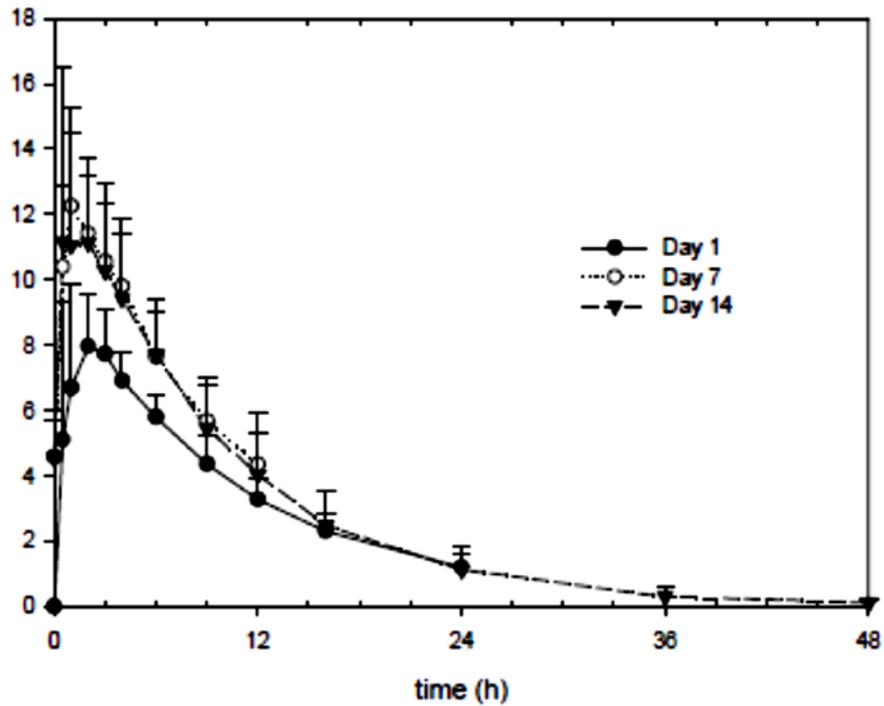


Figure N01067-3: Mean ± SD PK Profile for BRV On Days 1, 7, and 14 of Repeat 400 mg bid Administration



[Reviewer comment: Steady State PK appears to be achieved by Day 7 for all 3 dosing regimens.]

Figure N01067-4: Mean ± SD Trough Concentration In Morning and Evening for BRV On Days 1, 7, and 14 of Repeat 100, 200, and 400 mg bid Administration

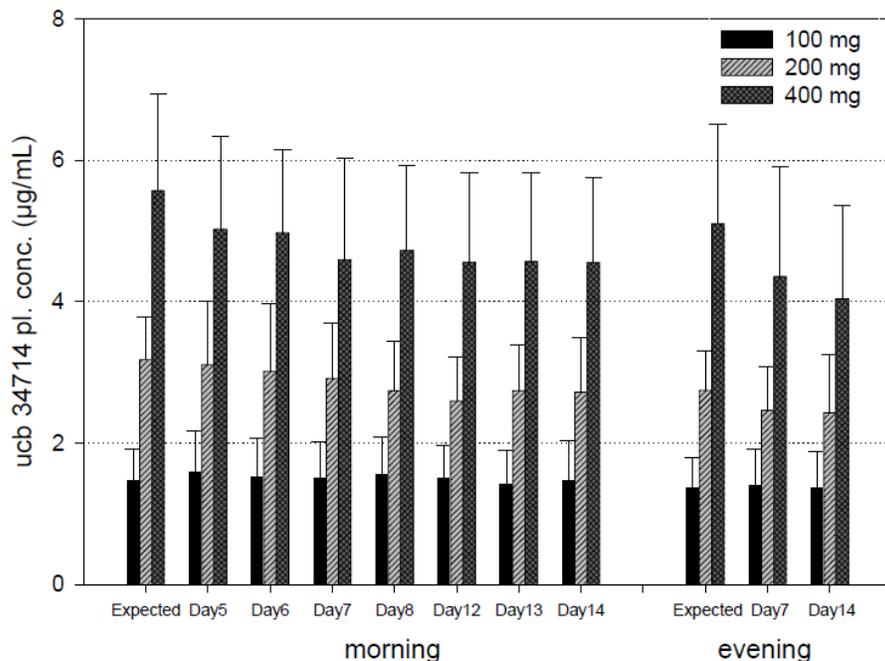


Table N01067-1: Geometric Mean (%CV) Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 100 mg bid Administration

		ucb 34714 100 mg bid		
		Day 1	Day 7	Day 14
t_{max} (h)	Median	2.00	2.00	2.00
	Range	(1.02-4.03)	(0.98-3.00)	(1.00-2.00)
C_{max} ($\mu\text{g/mL}$)	G. mean	2.23	3.50	3.54
	CV%	14.1	21.5	19.6
$AUC_{\tau}^{(a)}$ ($\mu\text{g}\cdot\text{h/mL}$)	G. mean	17.33	27.65	27.99
	CV%	15.8	21.1	24.1
$AUC(0-t)$ ($\mu\text{g}\cdot\text{h/mL}$)	G. mean	23.94	-	-
	CV%	18.1	-	-
AUC ($\mu\text{g}\cdot\text{h/mL}$)	G. mean	27.53	-	-
	CV%	22.8	-	-
λ_z (1/h)	G. mean	0.09	-	0.094
	CV%	19.4	-	26.3
$t_{1/2}$ (h)	G. mean	7.67	-	7.33
	CV%	19.9	-	25.7
$CL/F^{(b)}$ (mL/min/kg)	G. mean	0.833	0.827	0.817
	CV%	20.5	21.3	22.6
V_z/F (L/kg)	G. mean	0.551	-	0.518
	CV%	8.7	-	11.3

[Reviewer comment: AUC_{tau} increases 60-62% by Day 7 and Day 14 compared to Day 1 for the 100 mg bid regimen.]

Figure N01067-5: Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 100 mg bid Administration

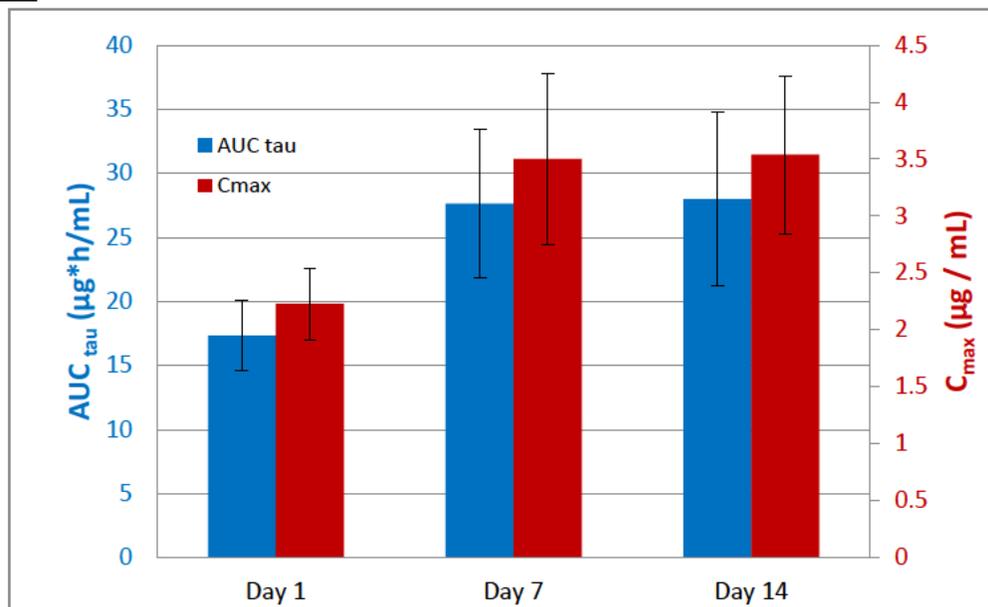


Table N01067-2: Geometric Mean (%CV) Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 200 mg bid Administration

		ucb 34714 200 mg bid		
		Day 1	Day 7	Day 14
t_{max} (h)	Median	2.00	2.00	2.00
	Range	(0.50-2.05)	(0.50-3.00)	(0.52-4.00)
C_{max} ($\mu\text{g}/\text{mL}$)	G. mean	4.74	7.26	7.65
	CV%	10.3	10.5	26.2
$AUC_{\tau}^{(a)}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	G. mean	36.51	55.19	55.38
	CV%	10.8	14.4	18.3
$AUC(0-t)$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	G. mean	49.78	-	-
	CV%	12.8	-	-
AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)	G. mean	56.04	-	-
	CV%	15.2	-	-
λ_z (1/h)	G. mean	0.095	-	0.10
	CV%	15.0	-	17.5
$t_{1/2}$ (h)	G. mean	7.27	-	6.82
	CV%	15.8	-	19.7
$CL/F^{(b)}$ ($\text{mL}/\text{min}/\text{kg}$)	G. mean	0.818	0.831	0.828
	CV%	14.0	16.2	19.4
V_z/F (L/kg)	G. mean	0.515	-	0.488
	CV%	7.7	-	6.1

[Reviewer comment: AUC_{τ} increases 51-52% by Day 7 and Day 14 compared to Day 1 for the 200 mg bid regimen.]

Figure N01067-6: Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 200 mg bid Administration

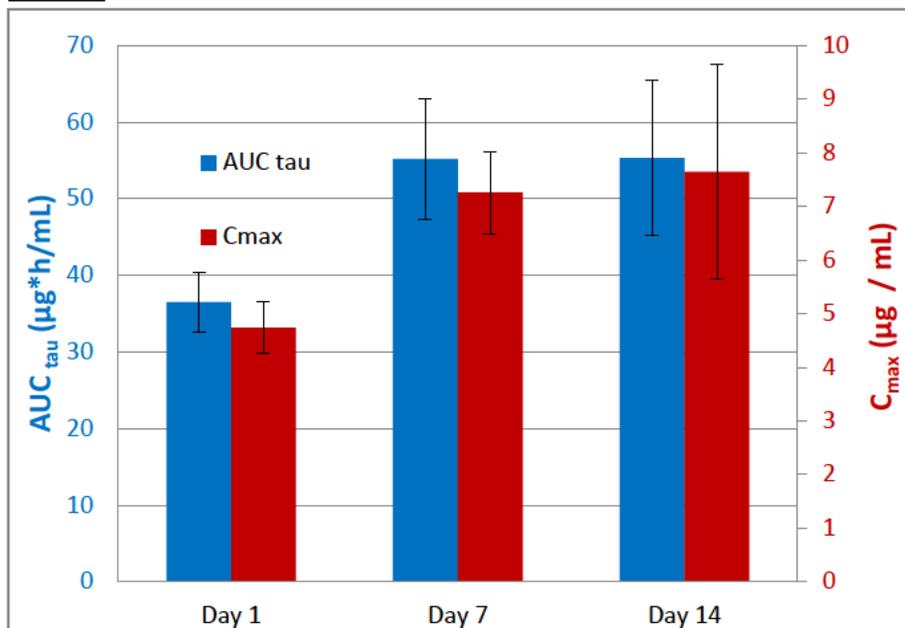


Table N01067-3: Geometric Mean (%CV) Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 400 mg bid Administration

		ucb 34714 400 mg bid		
		Day 1	Day 7	Day 14
t_{max} (h)	Median	2.00	1.00	1.00
	Range	(0.50-3.03)	(0.50-2.00)	(0.50-3.00)
C_{max} ($\mu\text{g/mL}$)	G. mean	8.95	12.39	13.32
	CV%	22.7	21.0	24.5
$AUC_{\tau}^{(a)}$ ($\mu\text{g}\cdot\text{h/mL}$)	G. mean	65.61	93.10	90.79
	CV%	14.0	22.1	19.6
$AUC(0-t)$ ($\mu\text{g}\cdot\text{h/mL}$)	G. mean	90.34	-	-
	CV%	14.7	-	-
AUC ($\mu\text{g}\cdot\text{h/mL}$)	G. mean	104.1	-	-
	CV%	17.9	-	-
λ_z (1/h)	G. mean	0.088	-	0.109
	CV%	16.9	-	18.6
$t_{1/2}$ (h)	G. mean	7.80	-	6.32
	CV%	17.7	-	20.5
$CL/F^{(b)}$ (mL/min/kg)	G. mean	0.829	0.925	0.948
	CV%	16.3	18.0	15.4
V_z/F (L/kg)	G. mean	0.558	-	0.519
	CV%	8.9	-	10.4

[Reviewer comment: AUC_{τ} increases 39-42% by Day 7 and Day 14 compared to Day 1 for the 400 mg bid regimen.]

Figure N01067-7: Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 400 mg bid Administration

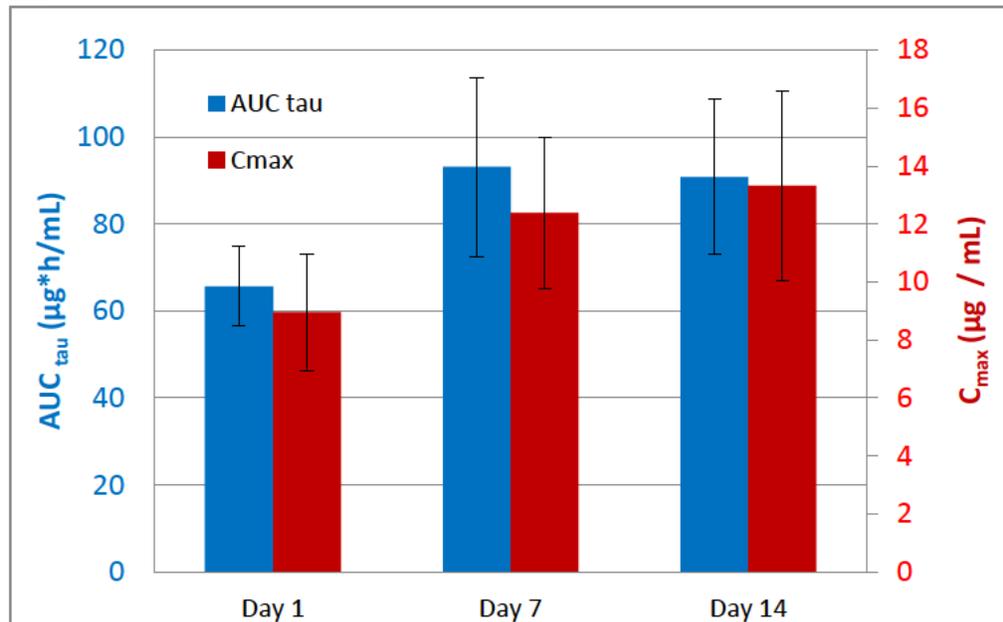


Table N01067-4: Geometric Mean (%CV) Urinary PK Parameters BRV and Metabolites On Days 1, 7, and 14 of Repeat 100, 200, and 400 mg bid Administration

Dose level: 100 mg bid				
Parameter	Units	Day 1	Day 7	Day 14
$f_{e\text{ ucb } 34714}$	%	4.62 (0.296)	5.13 (0.474)	5.74 (0.486)
$f_{e\text{ ucb } 42145}$	%	16.5 (0.390)	17.6 (0.422)	22.3 (0.422)
$f_{e\text{ ucb-100406-1}}$	%	11.4 (0.620)	15.1 (0.662)	20.6 (0.552)
CL_R	mL/min/kg	0.038 (0.303)	0.042 (0.421)	0.047 (0.389)
CL_{NR}	mL/min/kg	0.790 (0.209)	0.780 (0.234)	0.765 (0.242)
$CL_{fm\text{ ucb } 42145/F}$	mL/min/kg	0.158 (0.367)	0.145 (0.416)	0.182 (0.351)
$CL_{fm\text{ ucb-100406-1}/F}$	mL/min/kg	0.109 (0.677)	0.125 (0.705)	0.169 (0.660)
Dose level: 200 mg bid				
Parameter	Units	Day 1	Day 7	Day 14
$f_{e\text{ ucb } 34714}$	%	5.37 (0.381)	8.18 (0.232)	6.78 (0.324)
$f_{e\text{ ucb } 42145}$	%	21.7 (0.342)	28.4 (0.398)	26.7 (0.277)
$f_{e\text{ ucb-100406-1}}$	%	11.4 (0.505)	21.8 (0.358)	22.3 (0.401)
CL_R	mL/min/kg	0.043 (0.421)	0.068 (0.300)	0.056 (0.359)
CL_{NR}	mL/min/kg	0.753 (0.125)	0.762 (0.163)	0.769 (0.198)
$CL_{fm\text{ ucb } 42145/F}$	mL/min/kg	0.196 (0.335)	0.236 (0.309)	0.222 (0.277)
$CL_{fm\text{ ucb-100406-1}/F}$	mL/min/kg	0.103 (0.557)	0.181 (0.451)	0.184 (0.493)
Dose level: 400 mg bid				
parameter	units	Day 1	Day 7	Day 14
$f_{e\text{ ucb } 34714}$	%	6.00 (0.384)	6.62 (0.405)	5.46 (0.443)
$f_{e\text{ ucb } 42145}$	%	24.3 (0.248)	25.6 (0.299)	25.4 (0.370)
$f_{e\text{ ucb-100406-1}}$	%	9.64 (0.405)	19.2 (0.383)	21.3 (0.476)
CL_R	mL/min/kg	0.050 (0.451)	0.061 (0.305)	0.051 (0.460)
CL_{NR}	mL/min/kg	0.774 (0.163)	0.859 (0.197)	0.864 (0.162)
$CL_{fm\text{ ucb } 42145/F}$	mL/min/kg	0.231 (0.327)	0.237 (0.272)	0.236 (0.393)
$CL_{fm\text{ ucb-100406-1}/F}$	mL/min/kg	0.092 (0.448)	0.177 (0.408)	0.198 (0.504)

[Reviewer comment: The $CL_{formation,ucb-100406-1}/F$ increases over two weeks as dose the fraction excreted in the urine. In the 400 mg bid arm, both of these parameters are doubled on Day 14 compared to Day 1. In addition, the non-renal clearance increases ~11% between Day 1 and Day 14. Taken together, the Sponsor concludes that CYP induction occurs over this time period. However, the Sponsor does not clarify which enzyme or enzymes are likely to be induced. Please refer to the discussion at the end of this ISR for additional comments.]

Dose Proportionality: Sponsor assessed dose-proportionality using the power model according to Smith et al., 2000 (PMID: 11145235). For equivalence boundaries of 80%-125%, using the power-model, Sponsor could conclude dose-proportionality if the 90% CI of the slope was contained with the acceptance interval of {0.831, 1.161}.

Table N01067-5: Dose-Proportionality Assessment Via Slope Estimation Using the Power Model

	Day	Estimate	SE	DF	90% CI
AUC	Day 1	0.959	0.061	25	(0.855 ; 1.063)
AUC _τ	Day 7	0.876	0.064	25	(0.767 ; 0.985)
[μg*h/mL]	Day 14	0.850	0.067	25	(0.735 ; 0.963)
C _{max}	Day 1	1.002	0.056	25	(0.908 ; 1.097)
[μg/mL]	Day 7	0.912	0.061	25	(0.808 ; 1.017)
	Day 14	0.956	0.073	25	(0.830 ; 1.081)

The data provided in this table are derived from Table 14.2.1.4.

Table N01067-6: Dose-Proportionality Assessment Via Slope Estimation Using the Anova Model

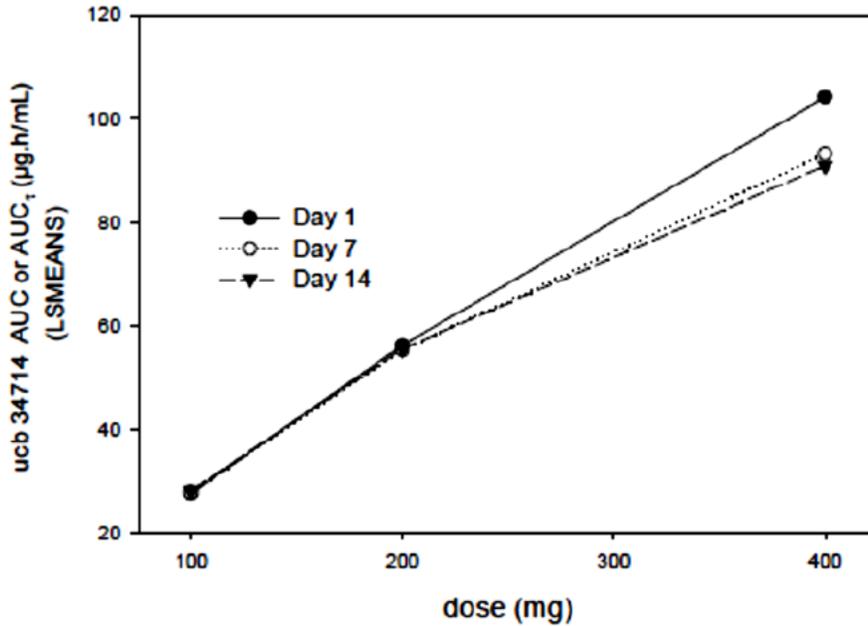
		200/100 mg bid Ratio (90% CI)	
AUC	Day 1	1.018	(0.880; 1.178)
AUC _τ	Day 7	0.998	(0.858; 1.161)
[μg*h/mL]	Day 14	0.989	(0.845; 1.158)
C _{max}	Day 1	1.062	(0.930; 1.212)
[μg/mL]	Day 7	1.038	(0.900; 1.196)
	Day 14	1.079	(0.908; 1.282)

		400/100 mg bid Ratio (90% CI)	
AUC	Day 1	0.945	(0.817; 1.094)
AUC _τ	Day 7	0.842	(0.724; 0.979)
[μg*h/mL]	Day 14	0.811	(0.693; 0.950)
C _{max}	Day 1	1.003	(0.879; 1.145)
[μg/mL]	Day 7	0.886	(0.768; 1.021)
	Day 14	0.940	(0.792; 1.117)

		400/200 mg bid Ratio (90% CI)	
AUC	Day 1	0.928	(0.802; 1.075)
AUC _τ	Day 7	0.843	(0.725; 0.981)
[μg*h/mL]	Day 14	0.820	(0.700; 0.959)
C _{max}	Day 1	0.945	(0.828; 1.078)
[μg/mL]	Day 7	0.854	(0.740; 0.984)
	Day 14	0.871	(0.733; 1.035)

[Reviewer comment: Both the ANOVA model and the power model demonstrate that C_{max} as well as AUC_{tau} increases less than proportionally on Day 7 and Day 14 compared to Day 1. Inspection of the PK data demonstrates that the less than proportional increase on Days 7 and 14 only manifests in the 400 mg bid arm, and is not evident in the 100 mg bid arm or 200 mg bid arm (see the figure below). The reduced exposures in the 400 mg bid group on Days 7 and 14 may be due to auto-induction (see the discussion at the end of this review for additional details).]

Figure N01067-8: LS Mean BRV AUC During Single and Repeated Doses of 100, 200, and 400 mg BRV Capsules



[Reviewer comment: The reduced exposures in the 400 mg bid group on Days 7 and 14 (see the figure above) may be due to auto-induction.]

Table N01067-7: Assessment of BRV Auto-Induction by Pairwise Comparisons

		Day 7/Day 1 (90% CI)	
CL/F [mL/min/kg]	100 mg bid	0.993	(0.958; 1.030)
	200 mg bid	1.015	(0.950; 1.085)
	400 mg bid	1.116	(1.080; 1.152)
		Day 14/Day 1 (90% CI)	
CL/F [mL/min/kg]	100 mg bid	0.981	(0.946; 1.018)
	200 mg bid	1.012	(0.947; 1.082)
	400 mg bid	1.144	(1.108; 1.181)
		Day 14/Day 7 (90% CI)	
CL/F [mL/min/kg]	100 mg bid	0.988	(0.953; 1.025)
	200 mg bid	0.997	(0.933; 1.065)
	400 mg bid	1.025	(0.993; 1.059)

[Reviewer comment: In the 400 mg bid group, there appears to be an increase of about 12% in BRV CL/F by Day 7 (compared to Day 1) and an increase of about 14% BRV in CL/F by Day 14 (compared to Day 1).]

Table N01067-8: CYP3A4 Induction Activity Over Time As Determined by Ratios of Urinary 6-Beta-Hydroxycortisol/Cortisol Ratios

Treatment	Day	N	Arithmetic mean	(SD)	Minimum	Median	Maximum
Placebo	Day 1	9	8.091	(3.145)	3.88	7.11	12.02
	Day 7	9	7.537	(2.599)	2.80	8.06	10.14
	Day 14	9	6.541	(2.542)	4.43	6.41	12.83
100 mg	Day 1	9	10.832	(4.550)	4.16	10.36	19.44
	Day 7	8	10.674	(5.765)	4.49	10.61	17.64
	Day 14	9	10.000	(6.703)	4.56	9.82	26.77
200 mg	Day 1	9	7.284	(2.803)	3.89	6.82	11.18
	Day 7	9	8.449	(4.820)	4.62	6.06	19.11
	Day 14	9	8.352	(2.426)	4.16	7.94	12.37
400 mg	Day 1	9	10.996	(5.597)	4.38	10.10	21.30
	Day 7	9	13.175	(5.953)	4.74	14.15	23.79
	Day 14	9	13.046	(5.593)	7.50	11.04	22.18

[Reviewer comment: The mean ratio and median ratio of 6-Beta-Hydroxycortisol/Cortisol is greater on Day 7 than Day 1 and greater on Day 14 than Day 1 for both the 200 mg bid group and the 400 mg bid group. However, considering the magnitude of the variability in the ratio, these results do not confirm a CYP3A4 induction (e.g. the increase in means may be due to random chance).]

Table N01067-9: BRV Renal Clearance Over Time Assess by Pairwise Comparisons

		Day 7/Day 1 Geometric means (90% CI)	Day 14/Day 1 Geometric means (90% CI)	Day 14/Day 7 Geometric means (90% CI)
CL _R [mL/min/kg]	100 mg bid	1.108 (0.859; 1.429)	1.223 (0.949; 1.577)	1.104 (0.856; 1.424)
	200 mg bid	1.612 (1.323; 1.963)	1.332 (1.094; 1.622)	0.827 (0.684; 0.999)
	400 mg bid	1.232 (0.891; 1.704)	1.036 (0.740; 1.453)	0.841 (0.600; 1.179)

Sponsor indicates that, while CL_R is slightly increased overall, due to the magnitude of variability in the 90% CI, interpretations should be made with caution.

[Reviewer comment: It is not clear why the renal CL of brivaracetam increases over time. However, renal CL is a minor pathway of BRV elimination and represents ~10% of total BRV clearance (see study N01066). So the observed change in BRV CL_R observed over the 14-day duration is not likely to be clinically significant.]

Table N01067-10: Change in BRV Non-Renal Clearance Over Time Assessed by Pairwise Comparisons

		Day 7/Day 1 Geometric means (90% CI)	Day 14/Day 1 Geometric means (90% CI)	Day 14/Day 7 Geometric means (90% CI)
CL _{NR} [mL/min/kg]	100 mg bid	0.988 (0.949; 1.028)	0.968 (0.930; 1.008)	0.980 (0.942; 1.021)
	200 mg bid	0.996 (0.924; 1.073)	1.005 (0.932; 1.083)	1.009 (0.939; 1.084)
	400 mg bid	1.110 (1.064; 1.158)	1.145 (1.096; 1.197)	1.032 (0.987; 1.078)

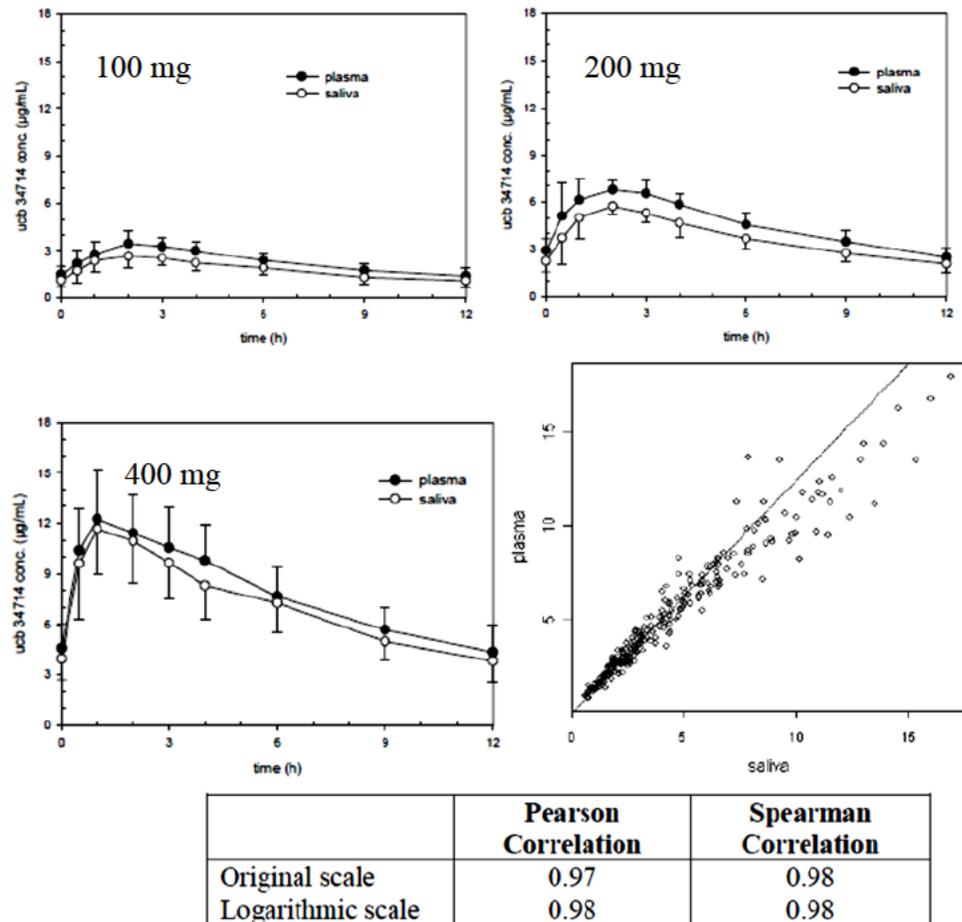
[Reviewer comment: There was a 10% increase in BRV CL_{NR} starting at Day 7 and persisting through Day 14.]

Table N01067-11: Change in Metabolite CL of Formation Over Time Assessed by Pairwise Comparisons

	Dose of ucb 34714	Day 7/Day 1 Geometric means (90% CI)	Day 14/Day 1 Geometric means (90% CI)	Day 14/Day 7 Geometric means (90% CI)
$CL_{fm\ ucb\ 42145/F}$ [mL/min/kg]	100 mg bid	0.920 (0.740; 1.144)	1.155 (0.929; 1.435)	1.255 (1.010; 1.560)
	200 mg bid	1.201 (0.973; 1.483)	1.125 (0.911; 1.389)	0.937 (0.765; 1.148)
	400 mg bid	1.022 (0.824; 1.268)	1.013 (0.810; 1.267)	0.991 (0.792; 1.239)
$CL_{fm\ ucb\ 100406-1/F}$ [mL/min/kg]	100 mg bid	1.149 (0.896; 1.474)	1.553 (1.211; 1.991)	1.351 (1.053; 1.732)
	200 mg bid	1.649 (1.338; 2.032)	1.681 (1.364; 2.072)	1.019 (0.834; 1.245)
	400 mg bid	1.931 (1.518; 2.456)	2.172 (1.690; 2.793)	1.125 (0.875; 1.446)

[Reviewer comment: There is no consistent change in the $CL_{formation\ ucb42145/F}$ across doses or across the two week period. However, the $CL_{formation\ ucb100406-1/F}$ shows an increase that is apparent across all 3 dose levels at Day 7 (15% - 93% increase) as well as Day 14 (55% to 117% increase).]

Figure N01067-9: Relationship Between Day 7 BRV Plasma PK and Day 7 BRV Saliva PK



Safety

TEAE occurred in 77.8%, 66.7%, 88.9%, and 100% of subjects in placebo, 100 mg bid, 200 mg bid, and 400 mg bid groups respectively. All AEs were mild or moderate. Dizziness or euphoric mood appeared to increase in frequency with increasing dose. All AEs resolved within during the first day of treatment except for 1 dizziness event (100 mg bid group) and 2 events of somnolence (200 and 400 mg bid groups).

<p>Sponsor's Conclusions</p>	<ol style="list-style-type: none"> 1. The MTD was not reached after 14 days of 400 mg bid dosing 2. Vz/F was 0.5 to 0.55 L/kg (slightly less than total body water) 3. Cmax and AUC increased proportionally with dose after a single dose 4. Cmax was hypo-proportional on Day 7 and 14. 5. CLss/F (Day 7 or Day 14) / CL/F Day 1 suggests auto-induction of the metabolism for the 400 mg bid dose. The observed auto-induction does not warrant an increase in dosing frequency. 6. The effect of BRV on CYP3A4 activity did not show statistical significance 7. Steady state was reached within 1 week 8. CL_{Ren} was 5-10% of the total CL/F 9. Saliva and plasma BRV concentrations were correlated 10. The increase in BRV CL_{NR} over 2-weeks and 2-fold increase of CL_{formation}/F of ucb-100406-1 metabolite is likely due to induction of oxidative enzymes for ucb-100406-1 formation (but not for ucb 42145 metabolite).
<p>Reviewer Comment</p>	<ul style="list-style-type: none"> • <i>Observed BRV accumulation, based on AUC_{tau}, was 1.62 to 1.60 (Days 7 and 14) for the 100 mg bid group, 1.52 to 1.51 (Days 7 and 14) for the 200 mg bid arm, and 1.39 to 1.42 (Days 7 to 14) for the 400 mg bid arm.</i> • <i>The CL_{formation,ucb-100406-1}/F increases over 14 days in this in-vivo study. Sponsor indicates that BRV likely induces its own metabolism at 400mg but does not specify which enzyme or enzymes may be induced. Based on in-vitro studies, 2C19 is the enzyme responsible for creation of ucb-100406-1 and BRV is not expected to induce CYP2C19. As such possible self-induction occurs at 400mg, not at the proposed doses (up to 200mg/day), no further investigation is needed.</i> • <i>There was an increase in the mean ratio of 6-beta-hydroxycortisol / cortisol on Day 7 compared to Day 1, and Day 14 compared to Day 1, for the 200 mg bid arm and the 400 mg bid arm. However, considering the magnitude of the variability in the ratio, possibility that the increase in the ratio was due to random chance (rather than an actual CYP3A4 induction) cannot be ruled out. As such, this reviewer agrees with the Sponsor that a 3A4 induction effect was not demonstrated by the data in this study.</i> • <i>Results from study N01261 are consistent with these findings as the midazolam AUC values were not statistically significantly different from before BRV treatment compared to 21 days on BRV treatment</i> • <i>The AE profile appears to be consistent with the AE profile reported in other trials.</i> • <i>This reviewer concurs with the Sponsor that saliva and plasma concentrations were correlated in study N01067.</i>

4.4.3 N01068: Mass Balance Study (Phase 1)

Study Report#	RPCE02A3001 / N01068																				
Title	Open-label, monocenter, excretion balance, pharmacokinetics and metabolism of [¹⁴ C]-labelled ucb 34714 after single 150 mg oral dose administration in 6 healthy male volunteers																				
Objectives	<p><u>Primary objectives:</u></p> <ul style="list-style-type: none"> Assess PK of radioactivity after single oral dose of [¹⁴C]-ucb 34714 ([¹⁴C]-BRV) Assess excretion balance of [¹⁴C]-ucb 34714 (BRV, parent drug, aka M7 in this study) Assess PK of parent compound and known major metabolites (M9[ucb 42145, carboxylic acid metabolite], M1b[ucb 100406-1, hydroxyl metabolite], M4b[ucb-107029-1, hydroxyl acid metabolite]) <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> Further identify and quantify metabolites Further characterize safety of ucb 34714 																				
Study Design	Phase 1, monocenter, open-label, single oral dose ADME study																				
Duration	Single-dose study																				
Dosage and Administration	Subjects received a single dose of 150 mg of BRV as a capsule containing 2.775 MBq (75 µCi) of [¹⁴ C]-ucb 34714.																				
PK Assessment	<p><u>Plasma PK Samples:</u> pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h post-dose</p> <p><u>Urine PK Samples:</u> 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hour intervals</p> <p><u>Expired Air Samples:</u> pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 h post dose</p> <p><u>PK Analyses:</u> C_{max}, t_{max}, AUC_{0-t}, λ_z, t_{1/2z}, AUC, CL/f, A_e</p>																				
Bioanalytical Methods	<p>Metabolite profiling in plasma and urine was performed using radio-HPLC. Sponsor assessed specific radioactivity using liquid scintillation counter directly (plasma, urine) or after combustion (whole blood, feces). Unchanged BRV in plasma was measured using LC-MS.</p> <p style="text-align: center;">HPLC-MS Analytical Methods for Plasma Concentrations</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>50.1 100 251 501 752 1002 1503 2004 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.4 to 6.6%</td> </tr> <tr> <td>Standards precision</td> <td>0.6 to 5.1%</td> </tr> <tr> <td>QC concentrations</td> <td>150 601 1752</td> </tr> <tr> <td>QC Accuracy</td> <td>-1.7 to 7.4%</td> </tr> <tr> <td>QC Precision</td> <td>2.9 to 5.5%</td> </tr> <tr> <td>LLOQ</td> <td>2 ng/mL</td> </tr> </table> <p>[Reviewer comment: The plasma and assay for BRV is acceptable.]</p> <p>The Sponsor utilized NMR spectroscopy to identify parent and metabolites in the urine. The following figures show the chromatograms for M7 (parent, BRV), M9(ucb 42145, carboxylic acid metabolite), M1b(ucb 100406-1, hydroxyl metabolite), M4b(ucb-107029-1, hydroxyl acid metabolite).</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50.1 100 251 501 752 1002 1503 2004 ng/mL	Standards accuracy	-4.4 to 6.6%	Standards precision	0.6 to 5.1%	QC concentrations	150 601 1752	QC Accuracy	-1.7 to 7.4%	QC Precision	2.9 to 5.5%	LLOQ	2 ng/mL
Analyte Name	Brivaracetam																				
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QC Accuracy	-1.7 to 7.4%																				
QC Precision	2.9 to 5.5%																				
LLOQ	2 ng/mL																				

Figure N01068-1: Radiochromatogram (a) and Parallel Mass Chromatogram for the MH+ ions (m/z 213) of M7 (Parent Drug, BRV) in Urine (b). Mass Chromatogram for the MH+ ions (m/z 213) of the Reference Standards ucb 34714 and ucb 34713 (c). Recorded Using the TFA Mobile Phase.

PSM0963 : RSRR C8019 : urine human ucb 34714; 150 mg; PO 12-24h sujet 003

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Agilent 1100 53/HP/014
FSA- [14C]
An1
1.57e5

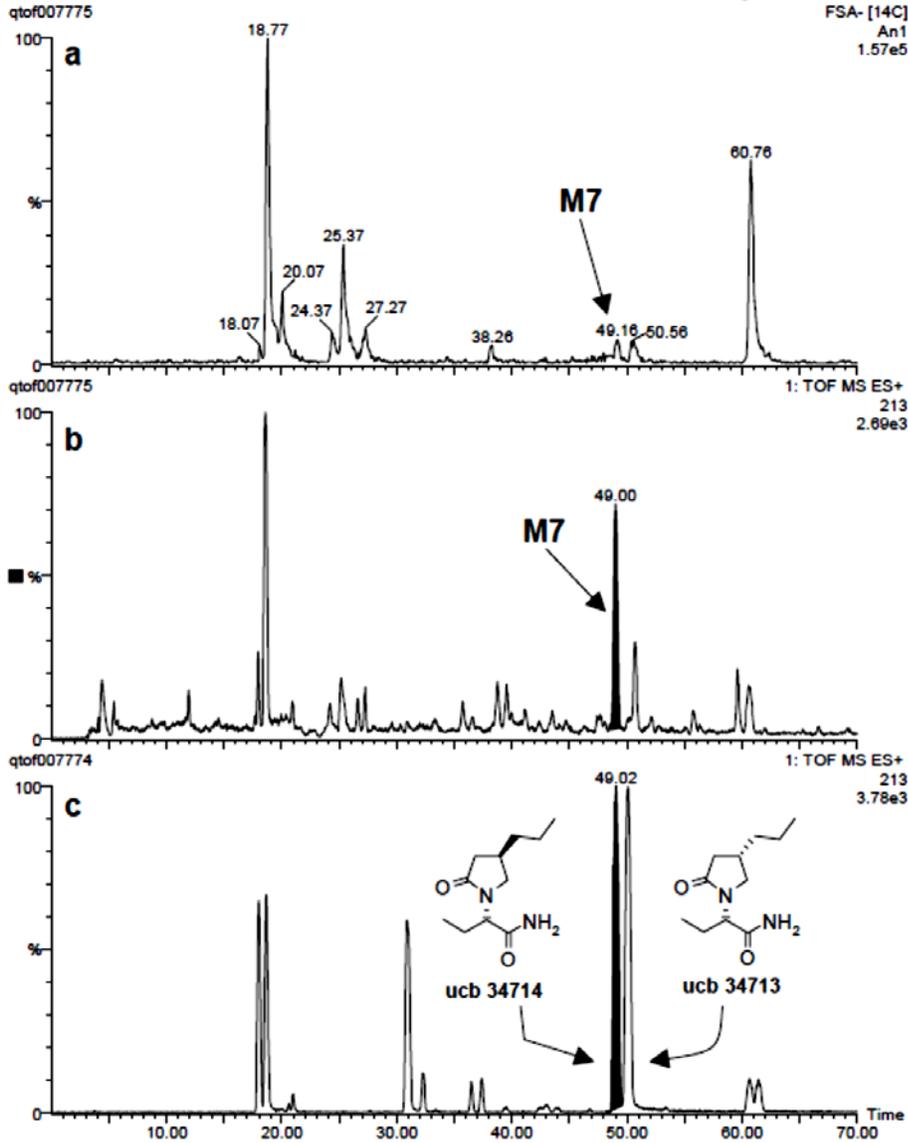


Figure N01068-2: Radiochromatogram (a) and Parallel Mass Chromatogram for the MH+ Ions (m/z 214) of Metabolite M9 (ucb 42145) in Urine (b). Mass Chromatogram for the MH+ Ions (m/z 214) of the Reference Standards ucb 42145 and ucb 42144 (c). Recorded Using the TFA Mobile Phase.

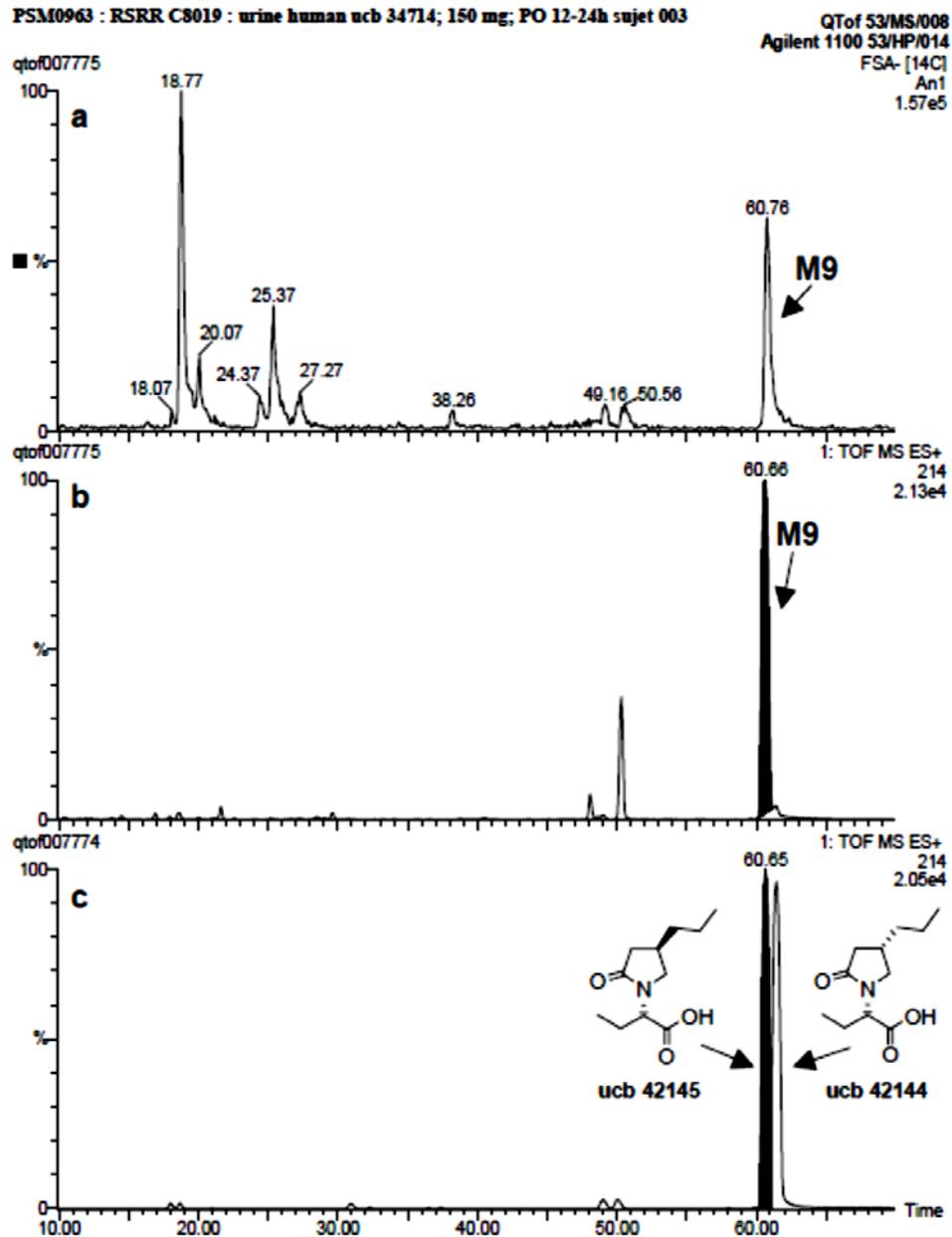


Figure N01068-3: Radiochromatogram (a) and Parallel Mass Chromatogram for the MH+ ions (m/z 229) of Metabolites M1a and M1b (ucb 100406-1) in Urine (b). Mass Chromatogram for the MH+ ions (m/z 229) of the Reference Standards ucb-100023-1, ucb-100406-1 and ucb-102993-1 (c). Recorded Using the TFA Mobile Phase.

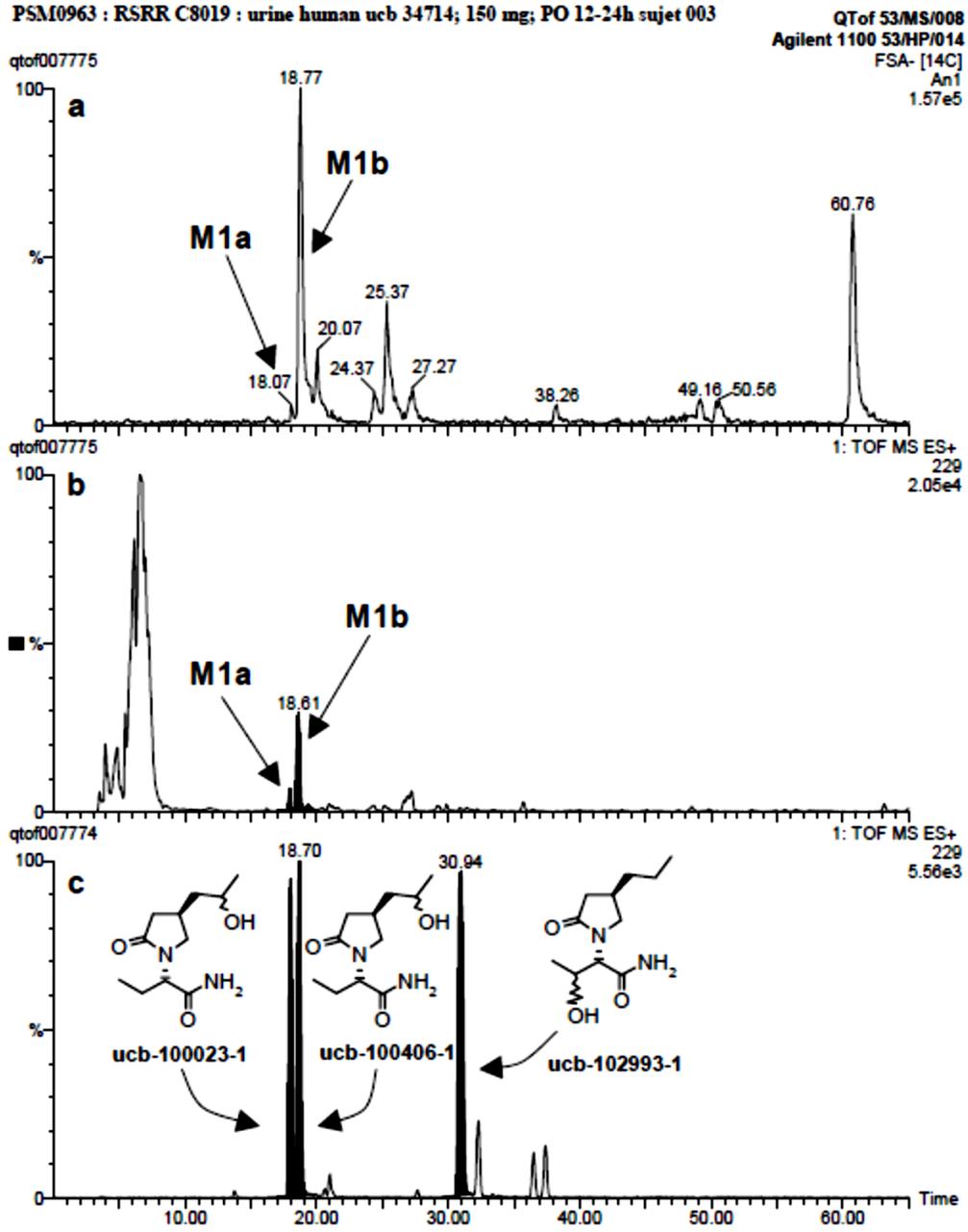
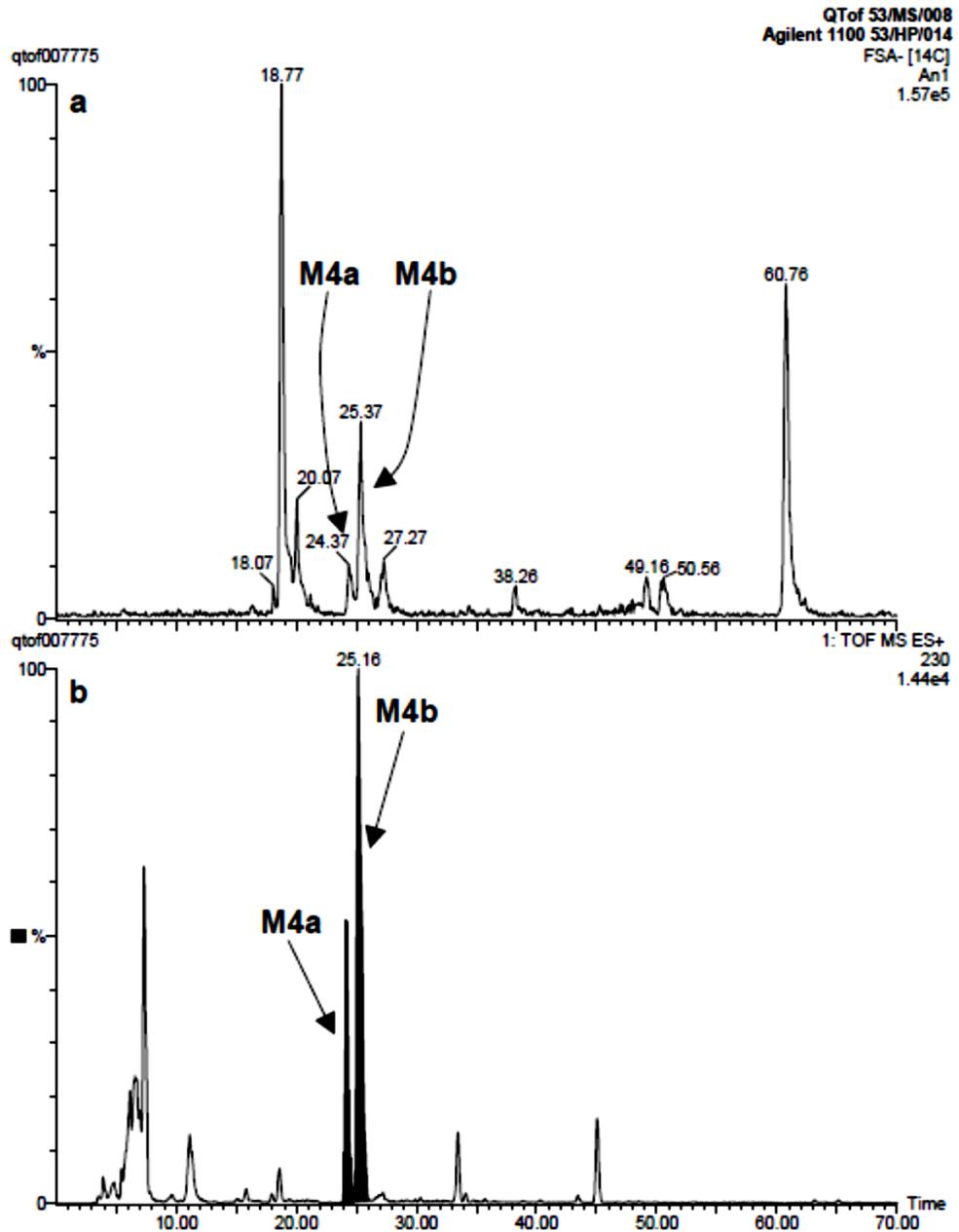


Figure N01068-4: Radiochromatogram (a) and Parallel Mass Chromatogram for the [M-H]⁻ Ions (m/z 228) of Metabolites M4a and M4b (ucb-107029-1) in Urine (b). Recorded Using the AcNH₄ Mobile Phase.

PSM0963 : RSRR C8019 : urine human ucb 34714; 150 mg; PO 12-24h sujet 003



Population/
Demographics

N=6 healthy male volunteers

Inclusion Criteria:

1. Male subjects age 18 to 55 years
2. Good physical and mental health
3. Regular intestinal transit
4. ECG is normal or abnormal but not clinically significant
5. Laboratory test results are within the reference range

	<p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Female subjects 2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness 4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical trial 5. Current smoker or had given up smoking in the last 6 months 																																																																																																																								
<p>PK Results</p>	<p>Ex-vivo protein binding results indicate protein binding of BRV and metabolites was 18.7 ± 1.7% at 1 hour, 17.6 ± 2.0% at 12 hours, and 16.2 ± 3.5% at 24 hours after administration.</p> <p>Table N01068-1: PK Parameters of Plasma Radioactivity</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>[unit]</th> <th>N</th> <th>Mean</th> <th>SD</th> <th>Median</th> <th>Minimum</th> <th>Maximum</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>[µg-eq/g]</td> <td>6</td> <td>3.61</td> <td>0.427</td> <td>3.56</td> <td>3.09</td> <td>4.25</td> </tr> <tr> <td>t_{max}</td> <td>[h]</td> <td>6</td> <td>1.22</td> <td>0.68</td> <td>1.51</td> <td>0.27</td> <td>2.02</td> </tr> <tr> <td>AUC_(0-t)</td> <td>[µg-eq.h/g]</td> <td>6</td> <td>48.9</td> <td>7.92</td> <td>47.4</td> <td>40.5</td> <td>58.7</td> </tr> <tr> <td>AUC</td> <td>[µg-eq.h/g]</td> <td>6</td> <td>49.8</td> <td>8.30</td> <td>48.5</td> <td>41.4</td> <td>60.5</td> </tr> <tr> <td>t_{1/2z}</td> <td>[h]</td> <td>6</td> <td>8.82</td> <td>1.45</td> <td>8.97</td> <td>6.96</td> <td>11.0</td> </tr> <tr> <td>Protein binding</td> <td>[%]</td> <td>6</td> <td>17.5</td> <td>1.43</td> <td>17.2</td> <td>15.7</td> <td>19.4</td> </tr> </tbody> </table> <p>Table N01068-2: PK Parameters of Plasma BRV</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>[unit]</th> <th>N</th> <th>Mean</th> <th>SD</th> <th>Median</th> <th>Minimum</th> <th>Maximum</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>[µg/mL]</td> <td>6</td> <td>4.04</td> <td>0.539</td> <td>4.12</td> <td>3.24</td> <td>4.60</td> </tr> <tr> <td>t_{max}</td> <td>[h]</td> <td>6</td> <td>1.39</td> <td>0.58</td> <td>1.52</td> <td>0.27</td> <td>2.00</td> </tr> <tr> <td>AUC_(0-t)</td> <td>[µg.h/mL]</td> <td>6</td> <td>43.4</td> <td>10.8</td> <td>43.1</td> <td>31.6</td> <td>57.7</td> </tr> <tr> <td>AUC</td> <td>[µg.h/mL]</td> <td>6</td> <td>44.6</td> <td>11.3</td> <td>43.9</td> <td>32.4</td> <td>59.4</td> </tr> <tr> <td>t_{1/2z}</td> <td>[h]</td> <td>6</td> <td>7.61</td> <td>1.67</td> <td>7.38</td> <td>5.69</td> <td>10.1</td> </tr> <tr> <td>CL/f</td> <td>[mL/min/1.73 m²]</td> <td>6</td> <td>51.6</td> <td>11.6</td> <td>49.5</td> <td>40.8</td> <td>67.9</td> </tr> <tr> <td>Vz/f</td> <td>[L/kg]</td> <td>6</td> <td>0.487</td> <td>0.0529</td> <td>0.499</td> <td>0.397</td> <td>0.552</td> </tr> </tbody> </table> <p>[Reviewer comment: The mean half-life of the radioactivity is comparable to the half-life of BRV in plasma.]</p>	Parameter	[unit]	N	Mean	SD	Median	Minimum	Maximum	C _{max}	[µg-eq/g]	6	3.61	0.427	3.56	3.09	4.25	t _{max}	[h]	6	1.22	0.68	1.51	0.27	2.02	AUC _(0-t)	[µg-eq.h/g]	6	48.9	7.92	47.4	40.5	58.7	AUC	[µg-eq.h/g]	6	49.8	8.30	48.5	41.4	60.5	t _{1/2z}	[h]	6	8.82	1.45	8.97	6.96	11.0	Protein binding	[%]	6	17.5	1.43	17.2	15.7	19.4	Parameter	[unit]	N	Mean	SD	Median	Minimum	Maximum	C _{max}	[µg/mL]	6	4.04	0.539	4.12	3.24	4.60	t _{max}	[h]	6	1.39	0.58	1.52	0.27	2.00	AUC _(0-t)	[µg.h/mL]	6	43.4	10.8	43.1	31.6	57.7	AUC	[µg.h/mL]	6	44.6	11.3	43.9	32.4	59.4	t _{1/2z}	[h]	6	7.61	1.67	7.38	5.69	10.1	CL/f	[mL/min/1.73 m ²]	6	51.6	11.6	49.5	40.8	67.9	Vz/f	[L/kg]	6	0.487	0.0529	0.499	0.397	0.552
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Figure N01068-5: BRV Plasma Mean PK Profile and Radioactivity Mean Profile.

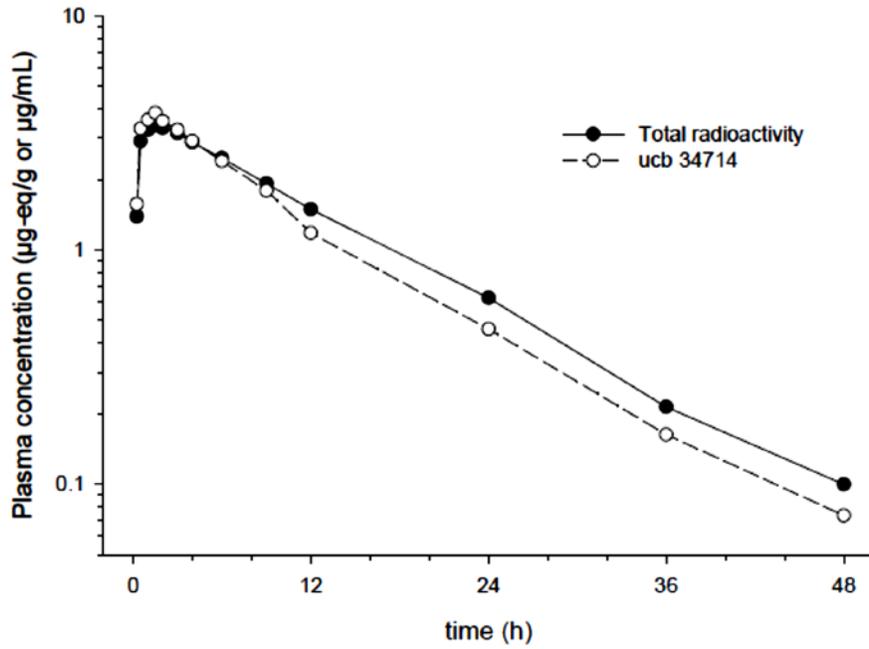


Figure N01068-6: Urinary Metabolite PK Profiles

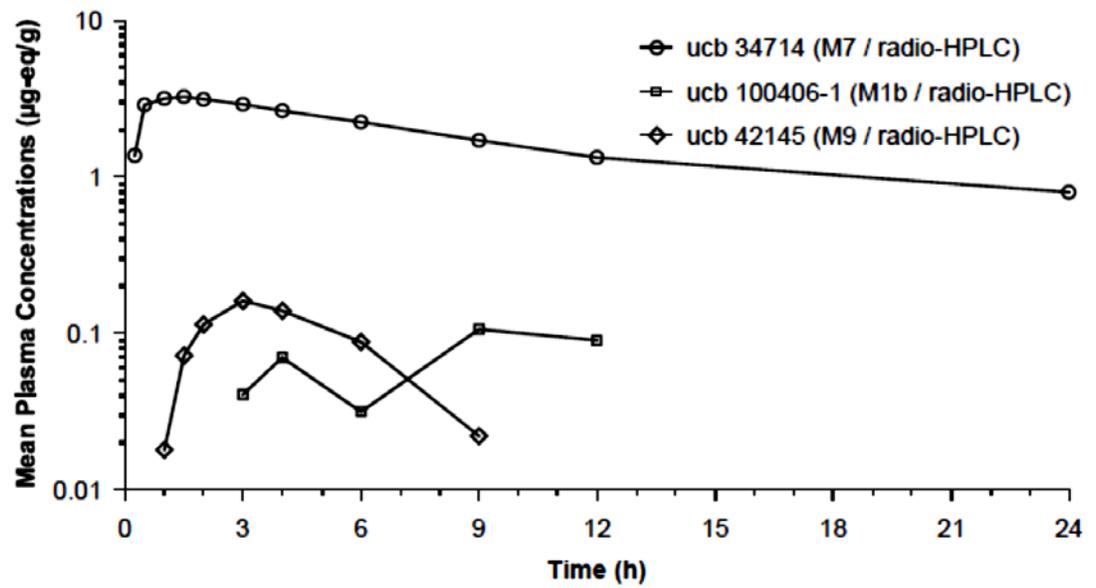


Figure N01068-7: Cumulative Urinary Excretion of BRV (ucb 34714, M7) and Metabolites

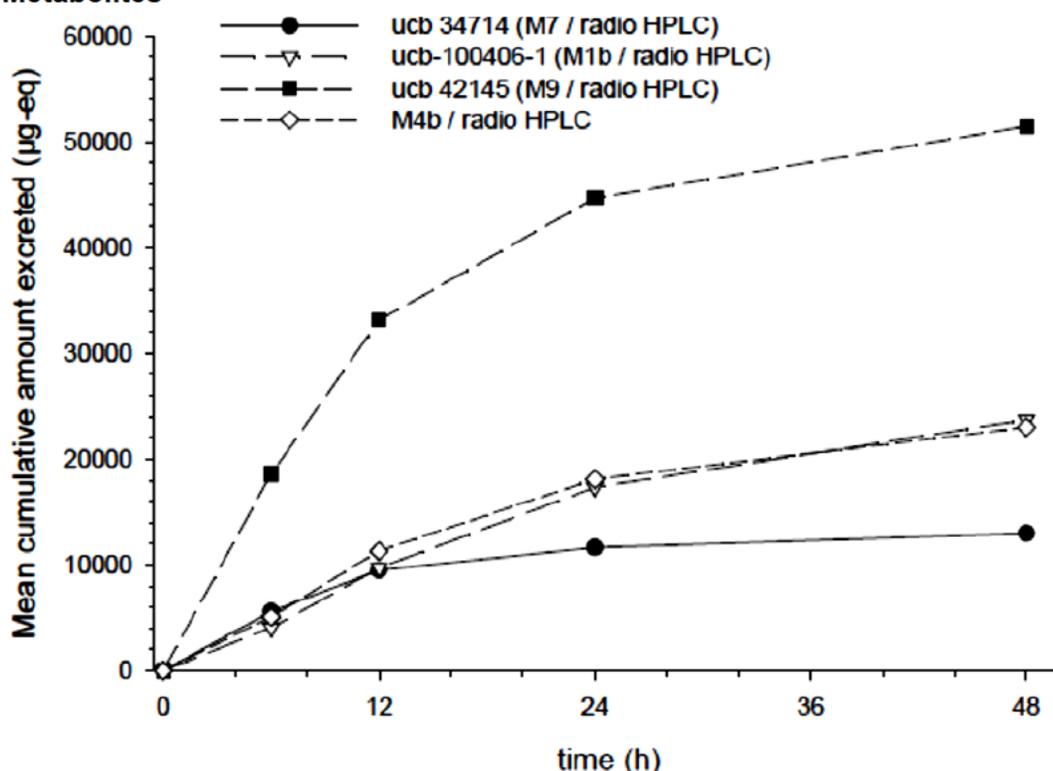


Table N01068-3: Cumulative Radioactivity Excretion (% Dose)

Excretion route	N	Mean	SD	Minimum	Median	Maximum
Urine (0-48 h): Total Radioactivity	6	92.2	1.2	90.8	92.2	93.5
ucb 34714 (M7)	6	8.7	3.7	5.2	7.9	14.9
ucb 42145 (M9)	6	34.2	6.1	26.5	32.3	44.4
ucb 100406-1 (M1b)	6	15.9	7.4	6.35	17.3	23.7
M4b	6	15.2	2.4	12.8	15.0	18.5
Other metabolites ^(a)	6	18.3	1.9	15.4	18.5	20.7
Urine (0-144 h): Total Radioactivity	6	96.8	0.7	96.1	96.5	97.9
Feces: Total Radioactivity	6	0.7	0.2	0.5	0.6	1.0
Total	6	97.5	0.7	96.7	97.5	98.5

Individual expired air concentrations of total radioactivity was negligible (quantifiable concentrations only found in 3 samples, h post-dose in subject 001-004, and 3 and 12 h post-dose in subject 001-006)

Safety

TEAEs were experienced by 100% of subjects (n=6). The TEAEs were mild and started within 9 hours after administration, and included dizziness (100%), fatigue (50%). Dizziness resolved within a few hours and fatigued resolved within 24 hours.

Sponsor's Conclusions

- T_{max} was generally 1.5 and mean half-life was about 7.6 hours
- Mean protein binding was $17.5 \pm 2.6\%$ for ucb 34714 and related metabolites at 1 h, 12 h or 24 h post-dose
- Renal BRV CL represents 5-15% of total body BRV CL (suggests tubular resorption).
- 90% of the radioactivity was excreted into the urine after 48 hours after a dose 150 mg. Fecal excretion accounted for < 1% of the radioactive dose.
- The 48 hour cumulative urinary excretion of parent compound BRV 8.7%, M9

	<p>(ucb 42145, carboxylic acid) was 34.2%, M1b (ucb 100406-1, hydroxyl metabolite) was 15.9%, and M4b (ucb-107029-1, hydroxyl acid metabolite) was 15.2% of the dose, respectively.</p> <ul style="list-style-type: none">• The parent drug, BRV (M7), was the main radioactivity compound in the plasma up to 24 hours (represented ~80% of the circulating radioactivity).•
<i>Reviewer Comment</i>	<ul style="list-style-type: none">• <i>Though the mean protein binding for BRV and metabolites, when considered together, appeared to be < 20% protein bound, these results do not clarify the protein binding of BRV alone, or any particular metabolite alone.</i>• <i>The safety profile is consistent with other studies.</i>• <i>This reviewer concurs with the other PK conclusions listed above.</i>

4.4.4 N01075: Food Effect Study With Oral Capsule (Phase 1)

Study Report#	RPCE01K0101 / N01075																				
Title	Randomized, monocenter, open label, two-way cross-over, food interaction pilot study of a single dose (150 mg) of ucb 34714 (oral capsule (b) (4)) in 8 healthy male volunteers																				
Objectives	<u>Primary:</u> Assess the effect of food (high-fat breakfast) on rate and extent of BA after single 150 mg dose of BRV as an oral capsule <u>Secondary:</u> Further characterize safety and tolerability																				
Study Design	Randomized, open-label, 2-way cross-over, single dose, food-effect study																				
Duration	Single dose																				
Dosage and Administration	Subjects were randomized to receive a single 150 mg dose of BRV as an oral capsule in a fed state (standard high-fat breakfast) or a fasted state with ≥ 7 day washout duration between doses.																				
PK Assessment	<u>Plasma PK Samples:</u> before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36 and 48 h after dosing <u>Urine PK Samples:</u> pre-dose, 0-3 h, 3-6 h, 6-9 h, 9-12 h, 12-24, 24-36 and 36-48 h. <u>PK Analyses:</u> AUC, AUC _{0-t} , C _{max} , t _{max} , t _{1/2} , λ _z , V _z /f, CL/f, MRT, A _e , CL _R , CL _{NR} and fe derived from the 48-hour plasma and urine ucb 34714 (BRV) profiles. Food-effect bioavailability comparisons were made using a univariate ANOVA, adaptive to cross-over design. The model included period sequence and treatment as fixed effects and subjects nested in sequence as a random effect. The ANOVA analysis was conducted using C _{max} , AUC, and AUC _{0-t}																				
Bioanalytical Methods	<p style="text-align: center;">HPLC-MS Analytical Methods for Plasma Concentrations</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>50.3 101 251 503 754 1005 1508 2010 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-2.4 to 1.9%</td> </tr> <tr> <td>Standards precision</td> <td>5.0 to 6.5%</td> </tr> <tr> <td>QC concentrations</td> <td>155 619 1806 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-3.9 to 1.8%</td> </tr> <tr> <td>QC Precision</td> <td>4.3 to 7.4%</td> </tr> <tr> <td>LLOQ</td> <td>2 ng/mL</td> </tr> </table> <p>[Reviewer comment: The plasma assay for BRV is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50.3 101 251 503 754 1005 1508 2010 ng/mL	Standards accuracy	-2.4 to 1.9%	Standards precision	5.0 to 6.5%	QC concentrations	155 619 1806 ng/mL	QC Accuracy	-3.9 to 1.8%	QC Precision	4.3 to 7.4%	LLOQ	2 ng/mL
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LLOQ	2 ng/mL																				
Population/ Demographics	N=8 healthy male volunteers age 18 to 55 years <u>Inclusion Criteria:</u> 1. Healthy males age 18 to 55 years 2. Good physical and mental health 3. ECG normal or without clinically significant abnormalities <u>Exclusion Criteria:</u> 1. Female subjects 2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness																				

4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake
5. Current smoker or had given up smoking in the last 6 months

PK Results

Table N01075-1: Mean ± SD BRV PK Parameters After a Single Oral Capsule of 150 mg BRV Administered Under Fed and Fasted Conditions

Parameter	Fasting		Fed	
	Mean (SD)	*Median (Range)	Mean (SD)	*Median (Range)
C _{max} (µg/mL)	4.41 (0.64)		3.16 (0.15)	
t _{max} (h) *	0.51 (0.5-2)		3.50 (1-6)	
AUC _(0-∞) (µg.h/mL)	40.4 (8.2)		40.2 (8.5)	
AUC (µg.h/mL)	41.7 (8.6)		41.4 (9.2)	
t _{1/2} (h)	7.61 (1.62)		7.98 (1.81)	
CL/f (mL/min/kg)	0.79 (0.19)		0.80 (0.22)	
V _z /f (L/kg)	0.50 (0.07)		0.53 (0.06)	
Ae (mg)	10.2 (3.3)		9.8 (1.8)	
fe (%)	6.80 (2.19)		6.55 (1.22)	
Cl _R (mL/min/kg)	0.0536 (0.0180)		0.0533 (0.0168)	
Cl _{NR} (mL/min/kg)	0.736 (0.180)		0.749 (0.207)	

Figure N01075-1: Mean BRV PK Profile After a Single Oral Capsule of 150 mg BRV Administered Under Fed and Fasted Conditions

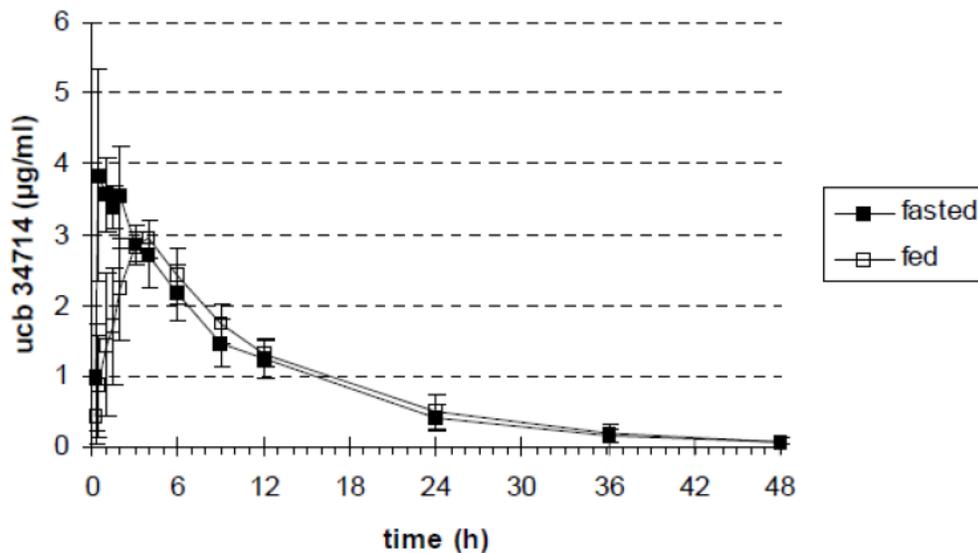


Figure N01075-2: Forest Plot Of Bioavailability Comparison Between Fasted and Fed States

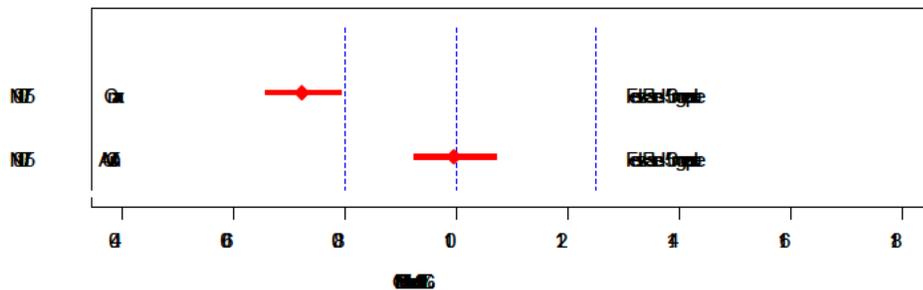


Table N01075-2: Table of Geometric Mean PK Parameters and Bioavailability Comparison Results Between Fasted and Fed State				
Parameter (unit)		AUC (µg.h/mL)	AUC0-t (µg.h/mL)	C _{max} (µg/mL)
Number of Evaluable Subjects		8	8	8
Analysis of log transformed data				
Geometric Mean (a) Fasted		40.8618	39.6260	4.36549
95% CI	35.9053	46.5025	34.9746 44.8961	4.04695 4.70910
Geometric Mean (a) Fed		40.5342	39.4304	3.15279
95% CI	35.6174	46.1297	34.8019 44.6745	2.92270 3.40100
Geometric Mean (a) Fasted / Fed		0.99198	0.99506	0.72221
90% CI	0.91764	1.07235	0.92927 1.06552	0.66160 0.78837
Safety	TEAE occurred in 60% (5 of 8) subjects. All TEAEs were mild. One AE occurred pre-treatment (pharyngolaryngeal pain). Upon administration in fed state, 2 AEs occurred (fatigue and vasovagal attack). Upon administration in the fasted state, 4 AEs occurred (3 dizziness, and somnolence). None of the AEs lead to discontinuation.			
Sponsor's Conclusions	<ul style="list-style-type: none"> Food decreases C_{max} 28% (GM C_{max} = 3.15 µg/mL in a fed state, GM C_{max} = 4.37 µg/mL in a fasted state, GMR was 0.722). Food delays T_{max} by 3 hours (median t_{max} in fasted state is 0.51 h, median t_{max} in fed state is 3.50 hours). Food did not affect the extent of absorption as measured by AUC0-t and AUC_{inf} values (which were contained within the 0.8 – 1.25) Other PK parameters were not affected by Food BRV was well-tolerated in both the fasted and fed state 			
Reviewer Comment	<ul style="list-style-type: none"> <i>This reviewer concurs with the BA comparison results between fasted and fed state and that food does not significantly affect the extent of BRV absorption. The effect of food on C_{max} and T_{max} do not warrant a dose adjustment.</i> <i>Other than the vasovagal attack, the AE profile is consistent with BRV use in other studies. Overall, the safety profile favors BRV administration in fasted and fed state.</i> <i>The oral capsule formulation used in this study is not being pursued for marketing. Study N01287 conducts a food-effect study using a tablet formulation. Sponsor ultimately selected a tablet formulation for marketing.</i> 			

4.4.5 N01080: DDI – LVN + EES (Phase 1)

Study Report#	RPCE02E0201 / Study N01080
Title	Randomized, monocenter, open label, two-way crossover, multiple oral dose interaction study between ucb 34714, 200 mg (oral capsule (b) (4) twice daily and oral contraceptive (ethinylestradiol 30 µg and levonorgestrel 150 µg) once daily in 24 healthy female volunteers.
Objectives	<ul style="list-style-type: none"> Assess PK interaction potential BRV (200 mg twice daily) during 20 days with oral contraceptive (ethinylestradiol 30 µg and levonorgestrel 150 µg) given once daily during 21 days. Assess the impact of BRV on follicular and luteal activity (LH, FSH, 17β-estradiol, progesterone, sex hormone binding globulin and daily episodes of spotting/bleeding) Assess steady-state plasma BRV PK and relate it to oral contraceptive exposure change. Assess BRV safety in female subjects Assess the CYP3A4 activity and induction potential of BRV (by measuring the urinary 6β-hydroxycortisol/cortisol excretion). Assess potential neurological effects of BRV
Study Design	Open-label, randomized, two-way crossover, multiple oral doses interaction study
Duration	16 weeks (from screening to discharge)
Dosage and Administration	<p>N= 24 healthy female volunteers were randomized to undergo the following two treatment regimens in a randomized cross-over manner</p> <p>A: ethinylestradiol 30 µg and levonorgestrel 150 µg + BRV 200 mg bid B: ethinylestradiol 30 µg and levonorgestrel 150 µg</p> <p>Over two 28-day contraceptive cycles, subjects received oral contraceptives (OC) either alone (Treatment B) or in combination with BRV (200 mg b.i.d., Treatment A), with treatment commencing on Day 1 of the first contraceptive cycle after randomization.</p> <p>OC tablets were taken at approximately 8 AM from Day 1 to Day 21 of both 28-day contraceptive cycles, followed by 7 days without oral contraceptive. BRV was taken orally at approximately 8 AM and 8 PM from Day 1 to Day 20 of one cycle only. After the two treatment periods, subjects were followed up during the next 28-day contraceptive cycle during which OC was taken as normal for 21 days.</p>
PK Assessment	<p><u>Plasma PK samples:</u></p> <ul style="list-style-type: none"> Days 1, 3, 8 and 15 at pre-dose in the morning and in the evening Day 20, at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours after the morning dose. <p><u>Urine PK Samples (cortisol, cortisol metabolite):</u> 24-hour urine collection was conducted on Day 20 and Day 21 of both treatment periods</p> <p><u>PK Analyses:</u> <i>EES + LEV:</i> AUCtau, Cmax, tmax, Cmin. <i>BRV:</i></p> <ul style="list-style-type: none"> Days 1, 3, 8, 15, 20: Cmin at morning and evening Day 20, AUCtau, Cmax, tmax, Cmin, λz, t½, CL/F <p><i>CYP3A4 Activity:</i> urinary 6β-hydroxycortisol/cortisol ratio</p>

	<p>Lack of pharmacokinetic interaction in this study was concluded if 90% confidence intervals for the LEV+EES AUC and Cmax ratios (with/without ucb 34714) were included in the standard 80-125% no-effect boundary.</p>																				
<p>Bioanalytical Methods</p>	<p>The cortisol assay was performed using a commercially available radioimmunoassay kit (CIS bio international). The 6β-hydroxycortisol assay was performed using a commercially available enzyme-immunoassay kit (STABILIGEN).</p> <p>HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1" data-bbox="370 466 1372 892"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>50.0 100 250 500 750 1000 1500 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-0.6 to 1.2%</td> </tr> <tr> <td>Standards precision</td> <td>2.6 to 5.6%</td> </tr> <tr> <td>QC concentrations</td> <td>150 600 1750 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-0.4 to 0.7%</td> </tr> <tr> <td>QC Precision</td> <td>3.8 to 6.6%</td> </tr> <tr> <td>LLOQ</td> <td>0.05 µg/mL</td> </tr> </table> <p>[Reviewer comment: The assay for brivaracetam is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL	Standards accuracy	-0.6 to 1.2%	Standards precision	2.6 to 5.6%	QC concentrations	150 600 1750 ng/mL	QC Accuracy	-0.4 to 0.7%	QC Precision	3.8 to 6.6%	LLOQ	0.05 µg/mL
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QC Precision	3.8 to 6.6%																				
LLOQ	0.05 µg/mL																				
<p>Population/ Demographics</p>	<p>N=24 (n=23 included in PK analyses)</p> <p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Healthy, nonsmoking, premenopausal, non-pregnant and non-lactating female subjects at 18 to 45 years 2. Good physical and mental health 3. Receiving OC of interest (EES 30µg and LVN 150µg, Microgynon30®, or Ovrnette®) for at least 3 consecutive cycles prior to Cycle 1 4. Use of additional appropriate birth control method 5. ECG considered normal or abnormal but not clinically significant 6. Clinical laboratory tests within reference range or outside range but not clinically significant. <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Hepatic, renal, gastrointestinal or other disorder capable of altering ADME of drugs (or causing a risk factor for use of the medication) 2. Clinically significant chronic or acute illness 3. Contraindication to prescription Minidril 4. Any prescription or OTC medications including herbs within 14 days before study drug administration in cycle 1 (paracetamol [acetaminophen] up to 2 g/day is permitted) 5. Blood pressure and heart rate outside normal range (unless clinically not significant) 6. Current tobacco smoker 7. Heavy caffeine drinker 																				

PK Results

Table N01080-1: BRV PK Parameters After 20 Days of 200 mg BID Administration

C_{max} ($\mu\text{g/mL}$)	$t_{max}^{(a)}$ (h)	$AUC\tau^{(b)}$ ($\mu\text{g}\cdot\text{h/mL}$)	C_{min} ($\mu\text{g/mL}$)	CL_{ss}/F ($\text{mL}/\text{min}/\text{kg}$)	CL_{ss}/F (mL/min)
9.23 (13)	1.5 (0.5-3.1)	69.51 (17)	3.22 (27)	0.77 (16)	47.60 (20)

CV = 100 x SD / Arithmetic Mean.
 (a) Values presented for t_{max} are median and range.
 (b) τ = 12 h.

Figure N01080-1: Comparison of Day 20 Mean \pm SD EES Exposure With BRV versus Without BRV (200 mg bid for 20 days)

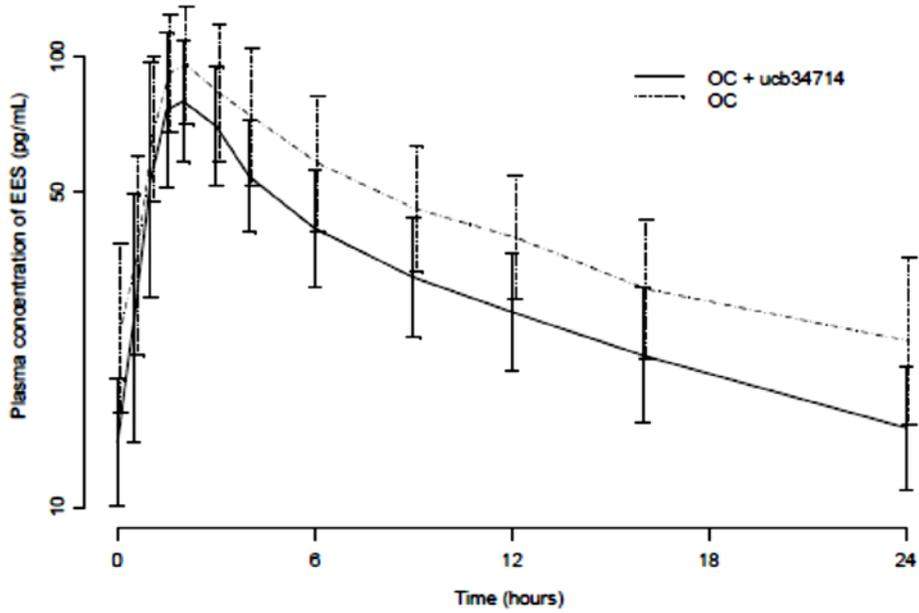


Figure N01080-2: Comparison of Day 20 Mean ± SD LVN Exposure With BRV versus Without BRV (200 mg bid for 20 days) on Day 20

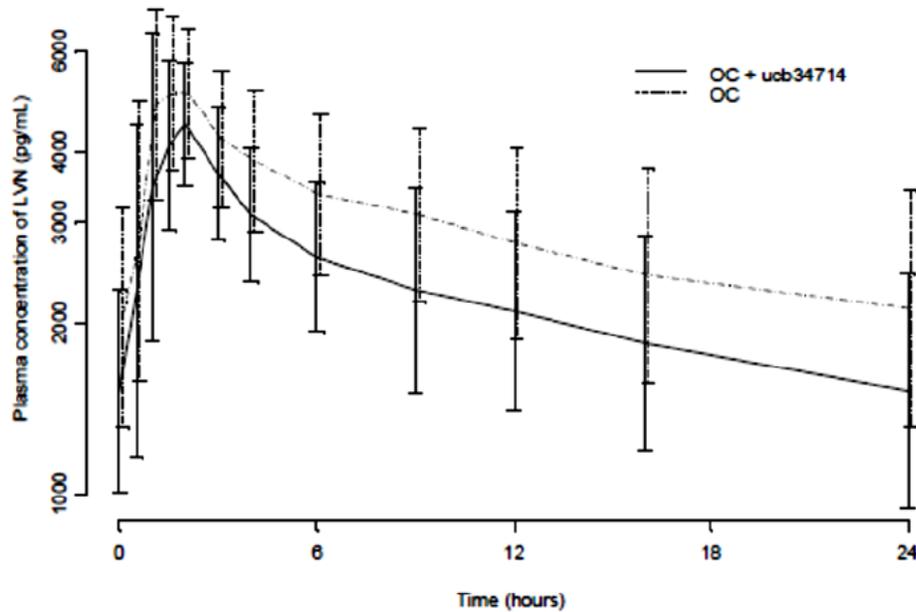


Table N01080-2: PK Parameters of EES and LVN With BRV and Without BRV

Parameter	Ethinylestradiol		Levonorgestrel	
	Without ucb 34714	With ucb 34714	Without ucb 34714	With ucb 34714
C _{max} (pg/mL)	102.52 (29)	88.29 (33)	5897 (24)	5296 (27)
t _{max} (h) ^(a)	2.0 (1.0-3.3)	1.5 (1.0-3.1)	1.5 (1.0-2.0)	1.5 (0.5-3.1)
AUC _τ (pg*h/mL) ^(b)	1077 (33)	788 (29)	71524 (34)	55433 (33)
C _{min} (pg/mL)	22.22 (47)	13.25 (38)	1944 (46)	1373 (42)
CL _{ss} /F (mL/min/kg)	7.50 (26)	10.25 (25)	0.56 (42)	0.73 (48)

CV = 100 x SD / Arithmetic Mean.
^(a) Values presented for t_{max} are median and range.
^(b) τ = 24 h.

Table N01080-3: BE Analyses Results of EES With BRV versus EES Without BRV

Parameter	Reference ^(a) : Oral Contraceptive	Test ^(a) : 200 mg ucb 34714 + Oral Contraceptive	CV ^(b) (%)	Test versus Reference ^(c)	
				Point estimate	90% CI
C _{max} (pg/mL)	102.85 (90.73 - 116.58)	88.63 (78.19 - 100.47)	17.5	86.2	78.9 - 94.1
AUC _τ (pg*h/mL)	1077.13 (948.99 - 1222.58)	789.71 (695.76 - 896.35)	12.5	73.3	68.8 - 78.1
t _{max} (h)	2.00 (1.00 - 3.25)	1.50 (1.00 - 3.05)	NA	-0.23	-0.50 - 0.25

^(a) Values are geometric LS means (95% confidence interval), for t_{max}: median (range).
^(b) Intra-individual coefficient of variation (%).
^(c) Point estimate and 90% confidence interval (90% CI) for the Test/Reference geometric LS mean ratio (%) derived from ANOVA for continuous parameter, for t_{max}: median point estimate and 90% non-parametric confidence interval of the difference Test-Reference (h).

Table N01080-4: BE Analyses Results of LVN With BRV versus EES Without BRV

Parameter	Reference ^(a) : Oral Contraceptive	Test ^(a) : 200 mg ucb 34714 + Oral Contraceptive	CV ^(b) (%)	Test versus Reference ^(c)	
				Point estimate	90% CI
C _{max} (pg/mL)	5896.38 (5234.56 - 6641.87)	5294.05 (4699.85 - 5963.39)	10.1	89.8	85.3 - 94.5
AUC _τ (pg*h/mL)	71206.9 (61575.4 - 82344.9)	55189.2 (47724.3 - 63821.7)	13.9	77.5	72.2 - 83.2
t _{max} (h)	1.47 (0.97 - 2.02)	1.50 (0.50 - 3.05)	NA	0.25	-0.01 - 0.28

(a) Values are geometric LS means (95% confidence interval), for t_{max}: median (range).
 (b) Intra-individual coefficient of variation (%).
 (c) Point estimate and 90% confidence interval (90% CI) for the Test/Reference geometric LS mean ratio (%) derived from ANOVA for continuous parameter, for t_{max}: median point estimate and 90% non-parametric confidence interval of the difference Test-Reference (h).

Figure N01080-3: BE Assessment of EES With and Without BRV and LVN With and Without BRV

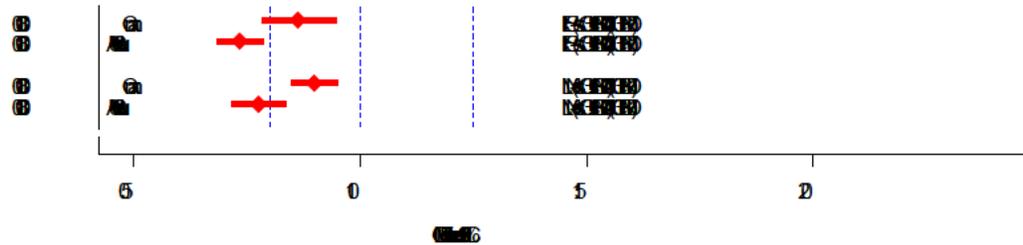


Figure N01080-4: Correlation of AUC_{tau} Ratios for EES with BRV AUC_{tau}

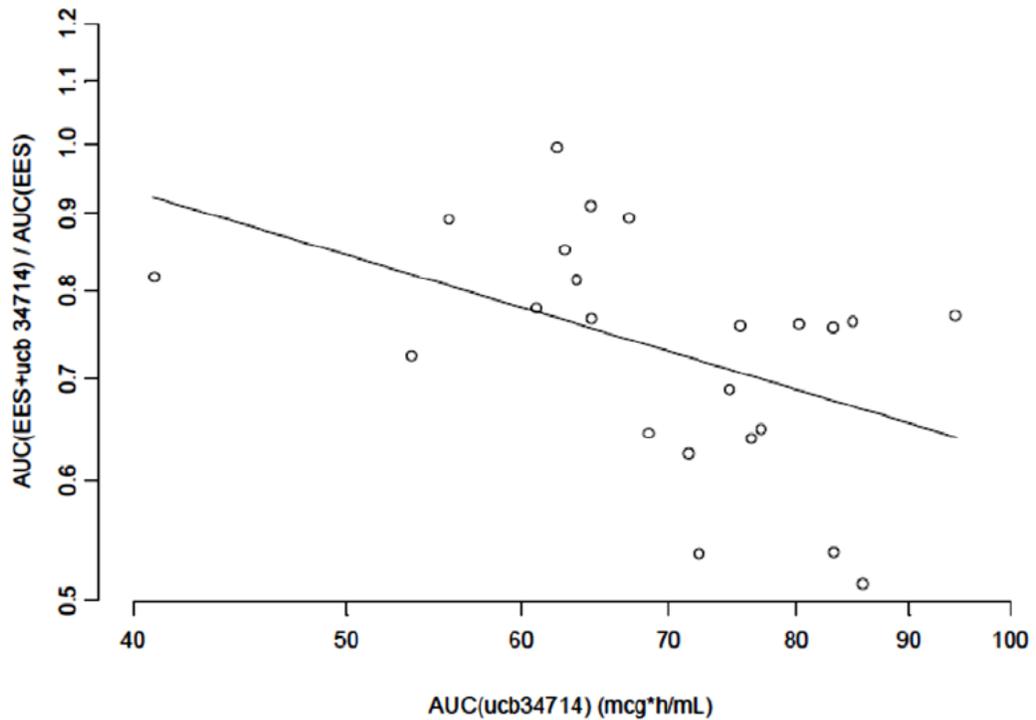


Figure N01080-5: Correlation of AUCtau Ratios for LVN with BRV AUCtau

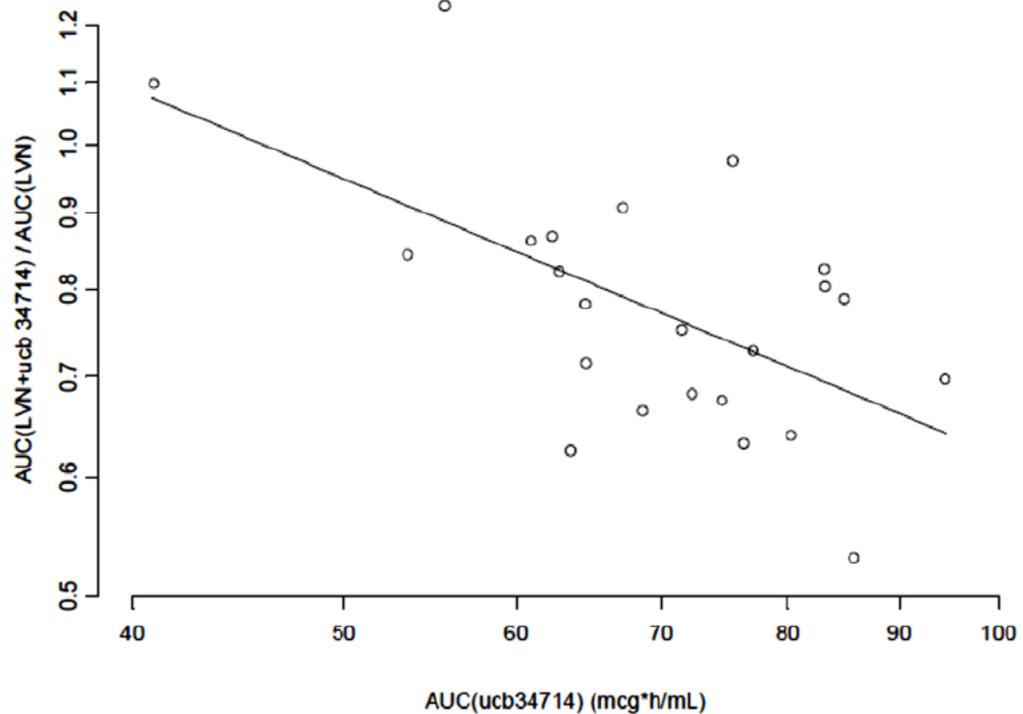


Table N01080-5: Assessment of BRV on CYP3A Activity In Terms of 6-Beta-Hydroxycortisol / Cortisol Ratio

Parameter	Reference ^(a) : Oral Contraceptive	Test ^(a) : 200 mg ucb 34714 + Oral Contraceptive	CV ^(b) (%)	Test versus Reference ^(c)	
				Point estimate	90% CI
6β-HCTL/CTL	6.38 (4.20 - 9.67)	10.48 (6.44 - 17.04)	31	161.55	137.86 - 189.31

^(a) Values are geometric means (Exponential (mean ± SD, computed on ln-transformed data)).

^(b) Intra-individual coefficient of variation (%).

^(c) Point estimate and 90% confidence interval (90% CI) for the Test/Reference geometric LS mean ratio (%) derived from ANOVA for continuous parameter.

Safety

- All subjects experienced at least 1 TEAE.
- All subjects experienced at least one TEAE following administration of ucb34714 plus OC.
- 58.3% and 73.9% experienced at least one TEAE following OC and Follow-up, respectively
- Most TEAEs were moderate and related to study treatment
- The most common TEAEs were dizziness and headache, nausea, and fatigue.
- 4 Severe TEAEs were reported in BRV + OC arm (headache, dysmenorrhea, night sweats and pruritus)
- more subjects reported spotting and bleeding pattern following administration of ucb 34714 plus OC compared to OC alone and Follow-up

[Reviewer comment: The increased spotting and bleeding in patients with BRV+OC

	<p><i>compared to OC alone may be due to the reduced OC exposures associated with concomitant BRV treatment. However, this is not considered clinically significant AE per the safety reviewer's conclusion.]</i></p>
<p>Sponsor's Conclusions</p>	<ul style="list-style-type: none"> • 6-beta-hydroxycortisol/cortisol ratio, an endogenous biomarker of CYP3A4 activity, was too variable in study N01067 to conclude an effect. In the current study, this ratio increased during BRV co-treatment by 62%. • Compared to male volunteers (e.g. study N01067), exposure to BRV is higher in this population of female subjects • The higher exposure to parent drug could explain the induction of CYP3A4, confirmed by the increased 6β-hydroxycortisol/cortisol ratio in females, not observed in the population of male volunteers (e.g. study N01067) • Concomitant BRV administration with OC seemed safe and well-tolerated
<p>Reviewer Comment</p>	<ul style="list-style-type: none"> • <i>BRV 200 mg bid for 20 days resulted in decreases of 14% and 27% in Cmax and AUC of EES, respectively.</i> • <i>BRV 200 mg bid for 20 days resulted in decreases of 10% and 22% in Cmax and AUC of LVN, respectively.</i> • <i>The current labels of two products containing levonorgestrel and ethinyl estradiol (Seasonique label, 07-29-2010 version and Quartette label, 03-28-2013 version) both include the following statement regarding drug interactions such as those caused by BRV:</i> <p style="margin-left: 40px;"><i>“Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of combination oral contraceptives (COCs) or increase breakthrough bleeding. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with COCs”</i></p> • <i>Study N01082 indicated a 26% and 22% decrease in EES and LVN, respectively, from BRV 200 mg bid (400 mg/day). However, study N01282 demonstrated a 10% and 7% AUC decrease in EES and LVN, respectively from BRV 50 mg bid (100 mg/day). This finding suggests that the reduction in EES and LVN exposure may increase with increasing BRV dose. It should be noted that the 200 mg bid dose utilized in study N01082 2-fold greater than the (b) (4) proposed dose for the label, 100 mg bid. It is not clear what the change in EES and LVN exposure is at the BRV 100 mg bid.</i> <p style="margin-left: 40px;"><i>At the time of this review, there is no exposure-response data to assess the effect these reductions in EES + LVN on oral contraceptive efficacy. As such, from a PK/PD standpoint, it is not clear whether a dose increase in combined oral contraceptive products is required when used with concomitant BRV.</i></p> <p style="margin-left: 40px;"><i>The medical officers have reviewed the safety data from the brivaracetam clinical trials and concluded that a dose adjustment of combined oral contraceptives is not necessary.</i></p> • <i>A 61% increase in 6-beta-hydroxycortisol/cortisol ratio with BRV treatment was observed in the current trial, suggesting that BRV may increase CYP3A4 activity. However, this finding is inconsistent with other trials conducted by the Sponsor:</i> <ul style="list-style-type: none"> ○ <i>In study N01081, BRV 200 mg bid did not alter the 6-beta-hydroxycortisol/cortisol ratio, yet carbamazepine 300 mg bid (a CYP3A4 inducer) increased the ratio 3-fold.</i> ○ <i>A smaller increase in the mean 6-beta-hydroxycortisol/cortisol ratio was observed in study N01067 (compared to the current study), but the</i>

	<p><i>variability was too large to conclude an effect of BRV on 3A4 activity.</i></p> <ul style="list-style-type: none">○ <i>In Study N01261, BRV 75 mg bid did not significantly alter the concentration of midazolam or 1-hydroxymidazolam plasma concentrations.</i>● <i>Overall, BRV does not appear to have a consistent effect on 3A4 activity as assessed by the 6β-hydroxycortisol/cortisol ratio.</i>
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4.4.6 N01081: DDI – Carbamazepine (Phase 1)

Study Report#	RPCE02G0401 / N01081
Title	Monocenter, open label, bilateral pharmacokinetic interaction study of ucb 34714 (200 mg oral capsules b.i.d.) and carbamazepine (100 mg oral tablets/300 mg b.i.d.) during single and multiple oral administrations in 14 healthy male subjects
Objectives	Assess effect of steady-state BRV on the steady-state carbamazepine PK Assess effect of steady-state carbamazepine on the single dose and steady-state BRV PK
Study Design	Monocenter, open label, bilateral pharmacokinetic interaction study
Duration	35 days on treatment
Dosage and Administration	N=14 healthy male subjects each received the same treatment sequence: <u>BRV:</u> <ul style="list-style-type: none"> • single dose of ucb 34714 (200 mg) on Days 1, 22 and 35 • multiple doses of ucb 34714 (200 mg b.i.d) on Days 24 to 34. <u>CBZ:</u> CBZ (Tegretol®) twice daily from Day 4 to Day 35, in a dose escalation manner <ul style="list-style-type: none"> • 100 mg b.i.d on Days 4 to 7, • 200 mg b.i.d on Days 8 to 14 • 300 mg b.i.d on Days 15 to 35
PK Assessment	<u>Plasma samples:</u> <ul style="list-style-type: none"> • Days 1, 22, and 35 (for the determination of BRV and BRV metabolite plasma concentrations) • Days 9, 12, 16, 19, 23, 26, 30, and 33 (for predose carbamazepine plasma concentrations only) • Days 21 and 35 (for the determination of carbamazepine plasma concentrations up to 12h). <u>PK Analyses:</u> Observed Cmax and tmax, plus: <u>BRV:</u> AUC(0-t), AUC, AUCτ, λz, t1/2, Vz/F, CL/F, Ae, CLR <u>BRV metabolites:</u> AUC(0-t), AUC, AUCτ, λz, t½, Ae, CLR <u>CBZ:</u> Cmin, AUCtau, CL/F <u>CBZ-10,11-epoxide:</u> Cmin, AUCtau <u>CYP3A4 Enzyme Activity:</u> Urinary 6-β-hydroxycortisol/cortisol ratio on 24 h urine collection.
Bioanalytical Methods	The cortisol analysis was performed using a commercial radio-immunoassay (RIA) kit. The 6-β-hydrocortisol analysis was performed using a commercial enzyme-immunoassay kit.

HPLC-MS/MS Analytical Methods for Plasma Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1
Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)
Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL	1.99 4.98 19.9 49.8 100 498 995 1991 ng/mL*	1.86 4.65 18.6 46.5 93.0 465 930 1860 ng/mL*
Standards accuracy	-7.3 to 9.2%	-4.1 to 1.8%	-2.4 to 2.5%
Standards precision	2.8 to 6.5%	0.9 to 5.1%	1.2 to 3.2%
QC concentrations	150 600 1750 ng/mL	10.0 74.7 1792 ng/mL*	9.30 69.7 1674 ng/mL*
QC Accuracy	-1.8 to 1.1%	-5.3 to 2.7%	-4.6 to -0.5%
QC Precision	6.2 to 8.5%	5.4 to 14.3%	5.6 to 13.7%
LLOQ	0.05 µg/mL	2 ng/mL*	2 ng/mL*

*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).

IS (b) (4)

IS (b) (4)

HPLC-MS/MS Analytical Methods for Urine Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1
Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)
Standard curve concentrations	0.250 0.500 1.25 2.50 3.80 5.00 7.50 10.0 µg/mL	0.250 0.500 1.25 2.50 3.80 5.00 7.50 10.0 µg/mL*	0.253 0.506 1.27 2.53 3.85 5.06 7.59 10.1 µg/mL*
Standards accuracy	-2.0 to 2.5%	-2.0 to 1.6%	-3.4 to 3.5%
Standards precision	1.0 to 3.7%	1.9 to 6.0%	1.8 to 5.3%
QC concentrations	0.750 3.00 8.80 µg/mL	0.752 3.01 8.83 µg/mL*	0.765 3.06 8.98 µg/mL*
QC Accuracy	-4.6 to -3.1%	-3.8 to -0.7%	-7.6 to -6.2%
QC Precision	4.8 to 6.9%	3.9 to 6.3%	4.1 to 5.4%
LLOQ	0.25 µg/mL	0.25 µg/mL *	0.25 µg/mL *

*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).

IS (b) (4)

IS (b) (4)

[Reviewer comment: The assays are acceptable.]

<p>Population/ Demographics</p>	<p>Key Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male subjects age 18 to 55 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range <p>Key Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Female subjects 2. disorders capable of altering the ADME of drugs, or constituting a possible risk factor when taking the study medication 3. Any concomitant chronic or acute illness. 4. Any drug treatment, including prescribed or OTC medicines, taken in the 14 days (2 months for enzyme-inducing drugs, including St John's Wort – Hypericum perforatum) preceding the first intake of the study drug, with the exception of occasional paracetamol (max dose of 2 g/day and max dose of 10 g/2 weeks). 5. Heavy coffee drinkers (≥ 5 cups/day), or equivalent caffeinated beverages. 6. Subjects who smoked or had given up smoking for less than 6 months. 																																								
<p>PK Results</p>	<p>Figure N01081-1: Geometric Mean \pm SD BRV Concentration Profile Following Single 200 mg (Day 1 and 22) and Repeated (Day 35) Administration of Oral 200 mg bid BRV Capsules</p> <table border="1"> <caption>Approximate data points from Figure N01081-1</caption> <thead> <tr> <th>Time (h)</th> <th>Day 1 (µg eq ucb 34714/mL)</th> <th>Day 22 (µg eq ucb 34714/mL)</th> <th>Day 35 (µg eq ucb 34714/mL)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0.00</td> <td>0.00</td> <td>0.00</td> </tr> <tr> <td>1</td> <td>0.05</td> <td>0.02</td> <td>0.15</td> </tr> <tr> <td>2</td> <td>0.10</td> <td>0.05</td> <td>0.20</td> </tr> <tr> <td>3</td> <td>0.15</td> <td>0.10</td> <td>0.25</td> </tr> <tr> <td>4</td> <td>0.20</td> <td>0.15</td> <td>0.30</td> </tr> <tr> <td>6</td> <td>0.25</td> <td>0.20</td> <td>0.35</td> </tr> <tr> <td>9</td> <td>0.20</td> <td>0.15</td> <td>0.25</td> </tr> <tr> <td>12</td> <td>0.15</td> <td>0.10</td> <td>0.20</td> </tr> <tr> <td>24</td> <td>0.05</td> <td>0.03</td> <td>0.04</td> </tr> </tbody> </table>	Time (h)	Day 1 (µg eq ucb 34714/mL)	Day 22 (µg eq ucb 34714/mL)	Day 35 (µg eq ucb 34714/mL)	0	0.00	0.00	0.00	1	0.05	0.02	0.15	2	0.10	0.05	0.20	3	0.15	0.10	0.25	4	0.20	0.15	0.30	6	0.25	0.20	0.35	9	0.20	0.15	0.25	12	0.15	0.10	0.20	24	0.05	0.03	0.04
Time (h)	Day 1 (µg eq ucb 34714/mL)	Day 22 (µg eq ucb 34714/mL)	Day 35 (µg eq ucb 34714/mL)																																						
0	0.00	0.00	0.00																																						
1	0.05	0.02	0.15																																						
2	0.10	0.05	0.20																																						
3	0.15	0.10	0.25																																						
4	0.20	0.15	0.30																																						
6	0.25	0.20	0.35																																						
9	0.20	0.15	0.25																																						
12	0.15	0.10	0.20																																						
24	0.05	0.03	0.04																																						

Table N01081-1: Geometric Mean (CV%) Pharmacokinetic Parameters of BRV after Single (Days 1 and 22) and Repeated (Day 35) Administration of 200 mg BRV b.i.d.

Parameter / N=13	Day 1	Day 22	Day 35
C _{max} (µg/mL)	4.51 (37.31)	3.92 (21.39)	5.07 (20.36)
t _{max} (h) ^(a)	1.50 (0.27 – 3.00)	1.05 (0.50 – 3.02)	1.03 (0.47 – 3.00)
AUC (µg.h/mL)	48.30 (15.43)	34.19 (11.06)	-
AUC(0-t) (µg.h/mL)	42.77 (14.74)	31.67 (11.69)	-
AUCτ (µg.h/mL)	-	-	33.73 (13.07)
C _{min} (µg/mL)	-	-	1.25 (16.44)
t _{1/2} (h)	7.51 (14.55)	6.37 (7.51)	6.06 (8.14)
V _Z /F (L/kg)	0.60 (12.49)	0.72 (13.33)	0.69 (13.95)
CL/F (mL/min/kg)	0.92 (13.20)	1.30 (12.06)	1.32 (13.12)
CL _R (mL/min/kg)	0.0564 (32.3)	-	0.0435 (60.2)
Ac(0-48) (mg)	12.249 (32.4)	-	-
Aet (mg)	-	-	6.882 (63.4) ^(b)

CV = 100 x arithmetic mean / SD

^(a) Values presented for t_{max} are median and range

^(b) N = 11

Table N01081-2: Single Dose Pharmacokinetics of 200 mg BRV With and Without 300 mg b.i.d. Carbamazepine

Parameter / N = 13	Reference ^(a) : ucb 34714 single dose (Day 1)	Test ^(a) : ucb 34714 single dose + CBZ 300 mg b.i.d. (Day 22)	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
AUC (µg.h/mL)	48.30 (46.56-50.11)	34.19 (32.96-35.47)	7.55	70.79	67.16-74.62
AUC(0-t) (µg.h/mL)	42.77 (41.27-44.33)	31.67 (30.56-32.83)	5.92	74.05	71.05-77.17
C _{max} (µg/mL)	4.51 (4.20-4.84)	3.92 (3.65-4.21)	23.09	86.96	74.15-101.98
CL/F (mL/min/kg)	0.92 (0.89-0.95)	1.30 (1.25-1.35)	7.55	141.25	134.00-148.89

^(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data)).

^(b) Intra-individual coefficient of variation (%)

^(c) Point estimate and 90% confidence interval for the expected Test/Reference geometric mean ratio (%), derived from

[Reviewer comment: CBZ resulted in a 41% increase in BRV CL on Day 22 compared to BRV single-dose CL on Day 1. BRV AUC was reduced by 29%.]

Table N01081-3: Single-Dose BRV PK (Day 22) and Multiple-Dose BRV PK (Day 35) With 300 mg b.i.d. Carbamazepine

Parameter / N= 13	Reference ^(a) : ucb 34714 single dose + CBZ 300 mg b.i.d. (Day 22)	Test ^(a) : ucb 34714 bid + CBZ 300 mg b.i.d. (Day 35)	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
CL/F (mL/min/kg) ^(d)	1.30 (1.26-1.35)	1.32 (1.27-1.36)	4.29	101.36	98.37 – 104.44

^(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data)).

^(b) Intra-individual coefficient of variation (%)

^(c) Point estimate (PE) and 90% confidence interval (90% CI) for the expected Test/Reference geometric mean ratio (%), derived from ANOVA for continuous parameters

^(d) CL_{SS}/F on Day 35

[Reviewer comment: The increase in BRV clearance caused by CBZ was consistent on Day 22 (single dose of BRV administer while at SS CBZ) as well as Day 35 (14 days of BRV administration while at SS CBZ).]

Table N01081-3: Geometric Mean (CV%) Pharmacokinetic Parameters of ucb 42145 (carboxylic-acid metabolite) after Single (Days 1 and 22) and Repeated (Day 35) Administration of 200 mg BRV b.i.d.

Parameter / N=13	Day 1	Day 22	Day 35
C _{max} (µg eq 34714/mL)	0.29 (22.42)	0.21 (26.73)	0.36 (27.72)
t _{max} (h) ^(a)	4.00 (2.00 – 9.00)	3.02 (1.98 – 4.07)	3.00 (1.00 – 6.02)
AUC (µg eq 34714.h/mL)	-	2.31 (21.45) ^(b)	-
AUC(0-t) (µg eq 34714.h/mL)	3.41 (19.50)	2.10 (19.90)	3.53 (22.69)
AUC _τ (µg eq 34714.h/mL)	-	-	2.62 (24.42)
t _½ (h)	-	6.85 (12.17) ^(b)	6.48 (13.06) ^(b)
Ae(0-48) (mg)	43.843 (26.4)	-	-
Ae _τ (mg)	-	-	22.989 (31.4) ^(c)

CV= 100 x arithmetic mean / SD

^(a) Values presented for t_{max} are median and range

^(b) N = 9

^(c) N = 11

Table N01081-4: Interaction Effect of 300 mg b.i.d. Carbamazepine on the Single Dose Pharmacokinetic Parameters of ucb 42145 (carboxylic-acid metabolite) after Administration of 200 mg ucb 34714

Parameter / N = 13	Reference ^(a) : ucb 34714 200 mg single dose (Day 1)	Test ^(a) : ucb 34714 200 mg single dose and carbamazepine 300 mg b.i.d. (Day 22)	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
AUC(0-t) (µg eq 34714.h/mL)	3.41 (3.22 – 3.61)	2.10 (1.98 – 2.22)	10.89	61.64	57.13 – 66.50
C _{max} (µg eq 34714/mL)	0.29 (0.27 – 0.31)	0.21 (0.20 – 0.23)	15.31	72.64	65.31 - 80.80

^(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data)).

^(b) Intra-individual coefficient of variation (%).

^(c) Point estimate and 90% confidence interval for the expected Test/Reference geometric mean ratio (%), derived from ANOVA for continuous parameters.

[Reviewer comment: Concomitant CBZ administration is associated with a 39% decrease in ucb 42145 (carboxylic-acid metabolite).]

Table N01081-5: Geometric Mean (CV%) Pharmacokinetic Parameters of ucb-100406-1 (hydroxy metabolite) after Single (Days 1 and 22) and Repeated (Day 35) Administration of 200 mg BRV b.i.d.

Parameter / N=13	Day 1	Day 22	Day 35
C _{max} (µg eq 34714/mL)	0.25 (42.40)	0.30 (20.31)	0.74 (20.66)
t _{max} (h) ^(a)	9.00 (9.00 – 12.00)	6.00 (3.98 – 9.00)	3.00 (1.00 – 6.02)
AUC(0-t) (µg eq 34714.h/mL)	4.55 (42.70)	5.31 (20.23)	11.72 (20.82)
AUCτ (µg eq 34714.h/mL)	-	-	7.43 (21.63)
t _{1/2} (h)	NE ^(b)	NE ^(b)	9.68 (12.38) ^(c)
Ae(0-48) (mg)	37.310 (46.5)	-	-
Aeτ (mg)	-	-	38.048 (47.0) ^(c)

CV= 100 x arithmetic mean / SD

^(a) Values presented for t_{max} are median and range

^(b) Not Estimable

^(c) N = 11

Table N01081-6: Interaction Effect of 300 mg b.i.d. Carbamazepine on the Single Dose Pharmacokinetic Parameters of ucb-100406-1 (hydroxy metabolite) after Administration of 200 mg ucb 34714

Parameter / N = 13	Reference ^(a) : ucb 34714 200 mg single dose (Day 1)	Test ^(a) : ucb 34714 200 mg single dose + CBZ 300 mg b.i.d. (Day 22)	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
AUC(0-t) (µg eq 34714.h/mL)	4.55 (4.04 – 5.13)	5.31 (4.71 – 5.98)	32.92	116.52	93.12 – 145.81
C _{max} (µg eq 34714/mL)	0.25 (0.22 – 0.28)	0.30 (0.27 – 0.34)	34.45	123.26	97.53 – 155.77

^(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data)).

^(b) Intra-individual coefficient of variation (%).

^(c) Point estimate and 90% confidence interval for the expected Test/Reference geometric mean ratio (%), derived from ANOVA for continuous parameters

[Reviewer comment: Concomitant CBZ administration is associated with a 16% increase in ucb-100406-1 (hydroxy metabolite) AUC. However, the AUC increases about 3-fold on Day 35 compared to Day 1.]

Table N01081-7: Geometric Mean (CV%) Pharmacokinetic Parameters of Carbamazepine and Carbamazepine-Epoxide after Repeated Administration of 300 mg Bid without (Day 21) and with (Day 35) 200 mg b.i.d. BRV

Parameter / N = 13	Carbamazepine		Carbamazepine-epoxide	
	Day 21	Day 35	Day 21	Day 35
C _{max} (µg/mL)	8.33 (14.10)	7.44 (10.79)	1.15 (14.95)	3.03 (13.90)
t _{max} (h) ^(a)	4.00 (1.98-7.78)	3.78 (1.02-8.00)	4.00 (0.28-8.00)	6.00 (2.00-8.03)
AUCτ (µg.h/mL)	85.81 (14.48)	75.23 (14.54)	12.48 (15.97)	32.12 (16.00)
C _{min} (µg/mL)	5.79 (19.52)	4.56 (27.53)	0.87 (21.51)	2.10 (22.48)
CL _{SS} /F (mL/min/kg)	0.78 (15.14)	0.89 (16.61)	-	-

CV= 100 x arithmetic mean / SD
 (a) Values presented for t_{max} are median and range

Table N01081-8: Effect of 200 mg b.i.d. BRV on the Steady State CBZ PK

Parameter / N= 13	Reference ^(a) : CBZ 300 mg b.i.d. (Day 21)	Test ^(a) : ucb 34714 200 mg bid and CBZ 300 mg b.i.d. (Day 35)	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
C _{max} (µg/mL)	8.33 (8.04-8.62)	7.44 (7.19-7.70)	5.33	89.33	86.06-92.72
AUCτ (µg.h/mL)	85.81 (82.39-89.36)	75.23 (72.24-78.35)	4.10	87.68	85.20-90.22
CL _{SS} /F (mL/min/kg)	0.78 (0.74-0.81)	0.89 (0.85-0.93)	4.10	114.06	110.8 - 117.4
C _{min} (µg/mL)	5.79 (5.37-6.24)	4.56 (4.23-4.92)	15.99	78.74	70.47-87.99

(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data)).
 (b) Intra-individual coefficient of variation (%).
 (c) Point estimate and 90% confidence interval for the expected Test/Reference geometric mean ratio (%), derived from

[Reviewer comment: Other than C_{min} slightly dropping below the standard 80-125% boundary, the CBZ exposures when co-administered with CBZ can be considered bioequivalent with CBZ exposures without BRV.]

Table N01081-9: Effect of 200 mg b.i.d. BRV on the Steady State CBZ-Epoxide PK

Parameter / N = 13	Reference ^(a) : CBZ 300 mg b.i.d. (Day 21)	Test ^(a) : ucb 34714 200 mg bid + CBZ 300 mg b.i.d. (Day 35)	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
C _{max} (µg/mL)	1.15 (1.10-1.19)	3.03 (2.91-3.15)	12.99	264.00	241.18-288.98
AUCτ (µg.h/mL)	12.48 (11.94-13.05)	32.12 (30.73-33.57)	9.08	257.31	241.51-274.13
C _{min} (µg/mL)	0.87 (0.81-0.92)	2.10 (1.97-2.24)	15.72	242.73	217.62-270.74

(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data)).
 (b) Intra-individual coefficient of variation (%).
 (c) Point estimate and 90% confidence interval for the expected Test/Reference geometric mean ratio (%), derived from ANOVA for continuous parameters.

[Reviewer comment: Co-administration of CBZ with BRV results in 2.5-fold increase in C_{max}, C_{min}, and AUCtau of CBZ-epoxide. This is likely due to inhibition of epoxide-hydrolase by BRV.]

Table N01081-10: Treatment Related Increases of the <u>6-β-Hydroxycortisol/Cortisol Ratios</u> Compared to Day 1			
Day / N = 13	Test Values ^(a)	Test versus Reference ^(c)	
		Point Estimate	90% CI
Screening	10.59 (9.27-12.10)	101.97	76.33-136.23
Day 21	30.80 (27.10-35.00)	296.53	223.37-393.65
Day 35	29.83 (26.25-33.90)	287.21	216.35-381.27

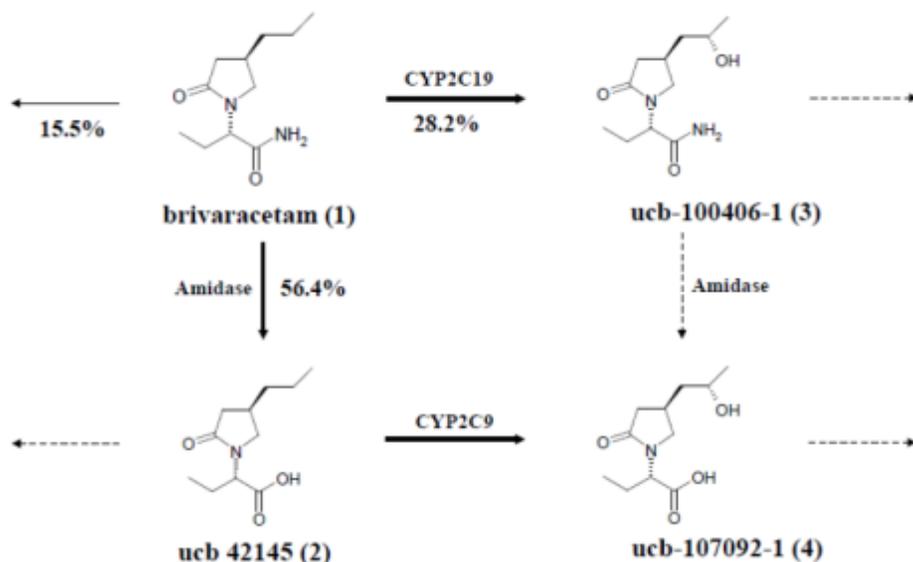
^(a) Values are least squares means (Exponential (LS-mean+/-SD computed on ln-transformed data))
^(b) Reference value = 10.39 (9.14-11.80); Intra-individual coefficient of variation = 44.76%
^(c) Point estimate and 90% confidence interval for the expected Test/Reference geometric mean ratio (%).

[Reviewer comment: Though variability in the 6-β-Hydroxycortisol/Cortisol ratio is high, the results suggest that BRV alone had a minor impact on the ratio (Screening visit compared to Day 1). After 21 days CBZ treatment (without concomitant BRV), the ratio increases 196.53%. By Day 35 of CBZ treatment (with 14 days of concomitant BRV treatment), the ratio increases slightly to 187.21% increase from Day 1.]

Safety	<ul style="list-style-type: none"> All included subjects experienced at least one TEAE The most frequently reported TEAEs were dizziness, fatigue, somnolence, and headache. Most AEs were mild or moderate in intensity, although 3 of them were rated severe (one headache, one somnolence and one dizziness); all 3 occurred during the CBZ titration period Three subjects presented clinically significant increases in hepatic enzymes which tended to return to normal values under continuing treatment safety profile in this study is consistent with the safety profile observed in the previously performed phase I studies with ucb 34714 AE profile observed during the study gives no indication that the concomitant administration of both drugs would increase the incidence of any event compared to the administration of each drug separately.
Sponsor's Conclusions	<ul style="list-style-type: none"> When co-administered with CBZ, <ul style="list-style-type: none"> BRV plasma concentrations were decreased, ucb 42145 (carboxylic acid metabolite) were decreased, and ucb-100406-1 (hydroxy metabolite) were increased. This suggests that CBZ increases the metabolic clearance of BRV through an increase of the oxidative biotransformation CBZ-E/CBZ Cmax and AUCtau ratios increased from 14% at baseline to 42% after two weeks of coadministration The decrease in CBZ concentrations is likely due to CYP3A4 induction The increase of CBZ-epoxide is most likely due a decrease in its elimination (inhibition of the epoxide hydrolase, as previously observed in vitro). The 6-β-hydroxycortisol/cortisol ratio was greatly increased under CBZ steady state, due to induction of CYP 3A4 by CBZ, but no further increase was seen under co-administration of BRV. The co-administration of ucb 34714 and carbamazepine was well tolerated.
Reviewer Comment	<ul style="list-style-type: none"> CBZ is a weak inhibitor of 2C19, a moderate inducer of 2C9, a strong inducer of 3A4, and an inducer of P-gp. Co-administration of CBZ resulted in <ul style="list-style-type: none"> decrease of BRV concentration, decrease in ucb 42145 (carboxylic acid metabolite) 16% increase in ucb-100406-1 (hydroxy metabolite) AUC CYP2C19 metabolizes BRV into ucb-100406-1 (hydroxy metabolite). As CBZ is a 2C19 inhibitor, then 2C19 inhibition is expected to contribute to an increase in

- BRV and a decrease in ucb-100406-1 (hydroxy metabolite). However, the observation was the opposite (BRV decreases, and ucb-100406-1 increases when CBZ is co-administered).*
- *As amidase metabolizes BRV into ucb42145 (carboxylic acid metabolite) and amidase also metabolizes ucb100406-1 (hydroxy metabolite) into ucb-107092-1 (hydroxyacid metabolite), the observation that BRV decreases while ucb-100406-1 increases is not likely due to induction of amidase*
 - *The reduction of ucb 42145 (carboxylic acid metabolite) is likely due to 2C9 induction by CBZ*
 - *Overall, the mechanism by which CBZ affects BRV PK is complicated, involves several CYP isoenzymes, and is not fully understood*
 - **No BRV dose adjustment is necessary when co-administering with CBZ**

Figure N01081-2: Main Metabolic Pathways for BRV in Humans



A “positive control” (CBZ, a strong 3A4 inducer) produced a 3-fold increase (+196.53%) in the 6-β-hydroxycortisol/cortisol ratio yet BRV produced only a 1.97% change in this ratio. Though variability was high in the ratio estimates, this study suggests that BRV does not substantially induce 3A4 activity.

The observed 157.31% increase in CBZ-E AUC_{tau} is likely due to BRV's inhibition of epoxide hydrolase. While the potential for increased toxicity is possible with increased carbamazepine-epoxide, it may also result in increased efficacy.

A carbamazepine dose reduction should be considered if tolerability issues arise. Please see section 3.0 of the QBR for details.

4.4.7 N01082: DDI – Phenytoin (Phase 1)

Study Report#	RPCE02G402 / N01082																				
Title	Monocenter, open label, interaction study between ucb 34714 at steady state (200 mg oral capsules, twice daily) and single dose phenytoin 600 mg (2 x 300 mg oral capsules) in 20 healthy male volunteers																				
Objectives	<p><u>Primary</u>: assess whether BRV at steady state alters the single dose PK of phenytoin.</p> <p><u>Secondary</u>:</p> <ul style="list-style-type: none"> • assess the effect of BRV on the metabolic pathways of phenytoin. • assess safety of concomitant BRV and phenytoin administration 																				
Study Design	Monocenter, open label, interaction study																				
Duration	15 days of treatment																				
Dosage and Administration	<p>N=20 healthy male subjects underwent the same treatment regimen, consistent of 3 phases:</p> <p>1) phenytoin alone (Day 1-3), 2) BRV alone (Day 4 to 13), 3) BRV + phenytoin (Day 13-15):</p> <p><u>BRV</u>: 200 mg bid oral capsules from Day 4 to Day 15 morning (11.5 days) <u>Phenytoin</u>: a single 600 mg dose (2 x 300 mg capsules), was administered on Day 1 and Day 13.</p>																				
PK Assessment	<p><u>Plasma Samples</u>:</p> <p><u>BRV</u>: Trough levels on Days 7, 10, and 13. <u>Phenytoin</u>: Day 1 and 13 at pre-dose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 48 and 72 hours after the morning dose</p> <p><u>Urine Samples</u>:</p> <p><u>p-HPPH</u>: predose, 0-24, 24-48, 48-72 hours post-dose on Day 1 and Day 13</p> <p><u>PK Analyses</u>:</p> <p><u>Phenytoin (after Day 1 and Day 13 doses)</u>: C_{max}, t_{max}, AUC(0-t), partial metabolic clearance to produce (R) and (S)-HPPH, Ae and fe of total, conjugated and unconjugated (R) and (S)-HPPH.</p>																				
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>50.0 100 250 500 750 1000 1500 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-3.1 to 2.6%</td> </tr> <tr> <td>Standards precision</td> <td>1.1 to 6.1%</td> </tr> <tr> <td>QC concentrations</td> <td>150 600 1750 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>2.7 to 3.5%</td> </tr> <tr> <td>QC Precision</td> <td>3.7 to 8.6%</td> </tr> <tr> <td>LLOQ</td> <td>0.05 µg/mL</td> </tr> </table> <p>[Reviewer comment: The assay is acceptable]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL	Standards accuracy	-3.1 to 2.6%	Standards precision	1.1 to 6.1%	QC concentrations	150 600 1750 ng/mL	QC Accuracy	2.7 to 3.5%	QC Precision	3.7 to 8.6%	LLOQ	0.05 µg/mL
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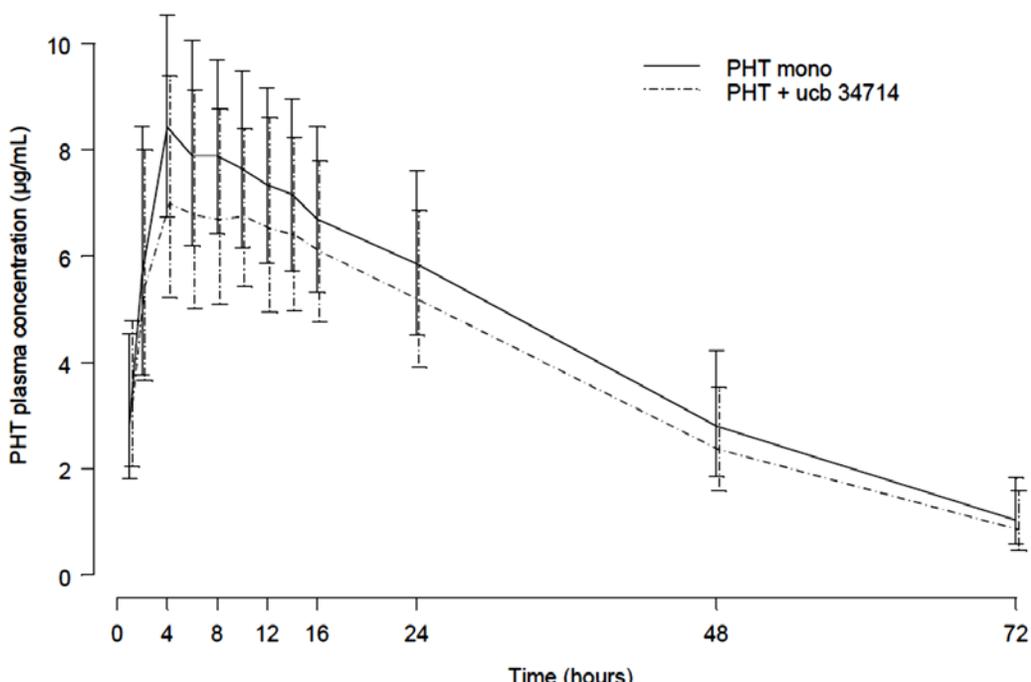
<p>Population/ Demographics</p>	<p>Key inclusion criteria:</p> <ol style="list-style-type: none"> 1. Healthy male subjects age 18 to 55 years 2. Good physical and mental health with 3. no abnormal cardiovascular findings (or “abnormal but not clinically relevant”) 4. No abnormal clinical laboratory tests <p>Key exclusion criteria:</p> <ol style="list-style-type: none"> 1. Female subjects 2. Presents of disorders capable of altering the ADME of drugs or posing a possible risk factor when taking the study medication(s) 3. Any concomitant chronic or acute illness. 4. Any drug treatment, including prescribed or OTC medicines and vitamin and mineral salt supplements, taken in the 14 days (2 months for enzyme-inducing drugs, including St John’s Wort – Hypericum perforatum) preceding the first dose of the study drug, with the exception of occasional paracetamol (acetaminophen) 5. Heavy caffeine drinkers (≥ 5 cups/day), or equivalent caffeinated beverages. 6. Subjects who currently smoke or have given up smoking for less than 6 months. 																																
<p>PK Results</p>	<p>Table N01082-1: BRV Plasma Trough Concentrations After Repeat Oral 200 mg BID Administration</p> <table border="1" data-bbox="381 924 1396 1123"> <thead> <tr> <th>Day</th> <th>N</th> <th>Geometric mean</th> <th>SD</th> <th>CV</th> <th>Min</th> <th>Median</th> <th>Max</th> </tr> </thead> <tbody> <tr> <td>Day 7</td> <td>19</td> <td>2.85</td> <td>0.656</td> <td>22.45</td> <td>1.73</td> <td>2.92</td> <td>4.58</td> </tr> <tr> <td>Day 10</td> <td>19</td> <td>2.91</td> <td>0.675</td> <td>22.66</td> <td>1.82</td> <td>2.93</td> <td>4.36</td> </tr> <tr> <td>Day 13</td> <td>19</td> <td>2.98</td> <td>0.788</td> <td>25.58</td> <td>1.77</td> <td>2.94</td> <td>4.38</td> </tr> </tbody> </table> <p>Figure N01081-1: Geometric Mean ± SD Phenytoin Plasma Concentration Profile With Brivaracetam and Without Brivaracetam</p>  <p>The graph plots PHT plasma concentration (µg/mL) on the y-axis (0 to 10) against Time (hours) on the x-axis (0 to 72). Two data series are shown: 'PHT mono' (solid line) and 'PHT + ucb 34714' (dashed line). Both series show an initial rapid increase in concentration, peaking around 4 hours, followed by a gradual decline. The 'PHT + ucb 34714' group consistently maintains a lower plasma concentration than the 'PHT mono' group throughout the 72-hour period. Vertical error bars at each time point represent the standard deviation (SD) for the geometric mean.</p>	Day	N	Geometric mean	SD	CV	Min	Median	Max	Day 7	19	2.85	0.656	22.45	1.73	2.92	4.58	Day 10	19	2.91	0.675	22.66	1.82	2.93	4.36	Day 13	19	2.98	0.788	25.58	1.77	2.94	4.38
Day	N	Geometric mean	SD	CV	Min	Median	Max																										
Day 7	19	2.85	0.656	22.45	1.73	2.92	4.58																										
Day 10	19	2.91	0.675	22.66	1.82	2.93	4.36																										
Day 13	19	2.98	0.788	25.58	1.77	2.94	4.38																										

Table N01082-2: Phenytoin PK after a Single Administration of Phenytoin 600 mg (Reference) or after Administration of Both Phenytoin 600 mg and ucb 34714 200 mg b.i.d. in 19 Healthy Subjects

Parameters	Reference ^(a) : phenytoin 600 mg	Test ^(a) : phenytoin 600 mg and ucb 34714 200 mg b.i.d.	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
C _{max} (µg/mL)	8.833 (8.386-9.304)	7.519 (7.138-7.920)	13.8	85.12	78.8 – 91.9
AUC(0-t) (µcg.h/mL)	313.7 (294.6-334.1)	272.7 (256.1-290.4)	12.3	86.93	81.1 – 93.1
t _{max} (h)	6.00 (4.0-24.0)	4.10 (2.0-16.0)	-	-	-

[Reviewer comment: Though BRV is known to inhibit CYP2C19, an enzyme that metabolizes phenytoin, the phenytoin exposures appear to decrease upon concomitant administration with BRV.]

Table N01082-2: Effect of Concomitant BRV Administration on Phenytoin Metabolite Formation

Parameters	Reference ^(a) : phenytoin 600 mg	Test ^(a) : phenytoin 600 mg and ucb 34714 200 mg b.i.d	CV ^(b) (%)	Test versus Reference ^(c)	
				Point Estimate	90% CI
fe(0-72) free (S)-p-HPPH (%)	0.354 (0.313-0.400)	0.379 (0.335-0.428)	22.96	107.0	94.2-121.5
fe(0-72) free (R)-p-HPPH (%)	0.095 (0.084-0.109)	0.100 (0.088-0.114)	25.69	104.9	91.0-120.9
fe(0-72) conj. (S)-p-HPPH (%)	44.83 (41.63-48.27)	47.05 (43.69-50.67)	21.32	105.0	93.2-118.2
fe(0-72) conj. (R)-p-HPPH (%)	1.284 (1.118-1.474)	1.337 (1.164-1.535)	30.13	104.1	88.2-122.9
CL _{fm} /F (R)-p-HPPH (mL/min/kg)	0.00670 (0.00602-0.00745)	0.00775 (0.00697-0.00862)	24.60	115.7	100.9-132.6
CL _{fm} /F (S)-p-HPPH (mL/min/kg)	0.202 (0.182-0.224)	0.244 (0.220-0.270)	18.78	120.8	108.7-134.1

[Reviewer comment: Formation of (S) and (R)-p-HPPH was increased by 21% and 16%, respectively, when phenytoin is co-administered with BRV (versus phenytoin administration alone).]

Safety

- Most AEs were mild and related to study medication, none were severe
- Dizziness, somnolence, and fatigue were the most common AEs. Most of these AEs occurred after the first dose, lasted less than 24 hours, and did not re-appear after the next doses.
- More AEs of dizziness (6 vs 4) and somnolence (2 vs 1) occurred after the 2nd phenytoin dose (administered with BRV) compared to the 1st phenytoin dose (administered without BRV)
- Sleep disorders were reported in 3 subjects 2-3 days after the 2nd phenytoin dose

Sponsor's Conclusions

- The major pathway of phenytoin metabolism is 2C9, however, at therapeutic concentrations, 2C9 is saturated, and 2C19 is becomes more relevant. Since BRV is a weak reversible inhibitor of CYP2C19, an inhibition of phenytoin metabolism by BRV can thus not be ruled out.
- BRV does not inhibit phenytoin metabolism (rather, phenytoin C_{max} decreases 15% and AUC_{0-t} decreased 13%, respectively). HPPH formation CL increased, suggesting induction of phenytoin metabolism.
- Comparison of the (S)/(R)-p-HPPH ratios found in this study with those reported in the literature cannot ensure that the study conditions are relevant for chronically-treated and often polymedicated patient population.

	<ul style="list-style-type: none">• More subjects reported AEs after the 2nd phenytoin dose.• Safety profile is in agreement with prior BRV studies.
<i>Reviewer Comment</i>	<ul style="list-style-type: none">• <i>Sponsor conducted this study because BRV is a weak 2C19 inhibitor and thus may inhibit phenytoin metabolism.</i>• <i>While BRV is known to inhibit 2C19, an enzyme responsible for phenytoin metabolism, the phenytoin exposures actually decrease when co-administered with BRV. Sponsor concludes that this may be due to an induction of phenytoin metabolism. However, based on the results from study N01067, as well as in-vitro induction studies, brivaracetam does not appear to significantly induce 2C19. The mechanism by which phenytoin exposures decrease with concomitant brivaracetam use is not clear.</i>• <i>However, Sponsor indicates that the study conditions may not be relevant for chronically-treated and often polymedicated patient population. Sponsor has also conducted a trial (N01172) where phenytoin and brivaracetam were co-administered and both drugs had reached steady-state (whereas the current study administered single phenytoin doses).</i>• <i>When phenytoin and BRV are coadministered and both reach steady state, the phenytoin C_{max} increases 20% and phenytoin AUC_{tau} increases 20% (see ISR for study N01172). According to the phenytoin label, phenytoin concentrations should be monitored when changing from one dosage form to another, during a loading dose, or during enteral feeding. Thus, due to the increase of up to 20% in phenytoin exposures with BRV, and due to the practice of monitoring phenytoin concentrations during dose adjustments or changing dosage forms, phenytoin levels should be monitored when initiating brivaracetam with existing phenytoin or initiating phenytoin with existing brivaracetam.</i>

4.4.8 N01109: Renal Impairment Study (Phase 1)

Study Report#	N01109 (protocol number RPCE02G0312)				
Title	Monocenter, open-label, parallel group, not randomized, pharmacokinetic study of a single oral administration of 200 mg capsule of UCB 34714, in subjects with normal renal function and with renal function impairment				
Objectives	<p><u>Primary:</u> Assess plasma pharmacokinetics and urinary excretion of UCB 34714 (brivaracetam) and metabolites in subjects with renal impairment compared to healthy subjects.</p> <p><u>Secondary:</u> Assess the safety in subjects with renal impairment</p>				
Study Design	Phase 1, open-label, parallel group, not randomized, single-dose trial				
Dosage and Administration	Subjects received a single dose of 200 mg brivaracetam as an oral capsule				
PK Assessment	<p><u>Blood Samples:</u> dose, 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 9h, 12h, 24h, 36h, 48h, and 72h post-dose.</p> <p><u>Urine Samples:</u> Day 1, Day 2, Day 3 and Day 4 at 12h intervals until 48 hrs post-dose and at 24h interval until 72h post-dose</p> <p><u>Analyses:</u> <i>Ucb 34714 (brivaracetam):</i> C_{max}, t_{max}, AUC_(0-t), AUC, λ_z, t_{1/2}, CL/F, V_z/F, A_e, f_e, CL_R <i>ucb 42145, ucb-100406-1 and ucb-107092-1 (metabolites):</i> C_{max}, t_{max}, AUC_(0-t), AUC, λ_z, t_{1/2}, A_e, f_e, CL_R</p>				
Bioanalytical Methods	HPLC-MS/MS Analytical Methods for Plasma Concentrations				
	Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
	Internal Standard (IS)	(b) (4)	(b) (4)		
	Standard curve concentrations	50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL	1.99, 4.98, 19.9, 49.8, 99.5, 498, 995, 1991 ng/mL*	1.87, 4.68, 18.7, 46.8, 93.5, 468, 935, 1871 ng/mL*	1.87, 4.67, 18.7, 46.7, 93.3, 467, 933, 1867 ng/mL*
	Standards accuracy	-6.7 to 7.6%	-7.0 to 3.0%	-3.3 to 3.1%	-4.2 to 6.9%
	Standards precision	4.3 to 8.9%	2.1 to 8.4%	1.1 to 3.5%	1.3 to 5.7%
	QC concentrations	151, 602, 1757 ng/mL	10.1, 75.4, 1810*	9.37, 70.3, 1687 ng/mL*	9.26, 69.4, 1667 ng/mL*
	QC Accuracy	5.1 to 6.8%	-11.1 to -0.9	-3.2 to -9.7%	-4.8 to 5.5%
	QC Precision	9.4 to 18%	7.1 to 13.1%	6.2 to 9.7%	4.0 to 6.3%
	LLOQ	0.05 µg/mL	0.002 µg/mL	0.002 µg/mL	0.002 µg/mL
<p>*The metabolites are presented as “effective concentrations” (ng eq ucb 34714/mL).</p> <p>IS (b) (4).</p> <p>IS (b) (4).</p>					
[Reviewer comment: The plasma assays are acceptable.]					

HPLC-MS/MS Analytical Methods for Urine Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Standard curve concentrations	0.251 to 10.0 µg/mL	0.25 to 9.99 µg/mL	0.235 to 9.35 µg/mL	1.87 to 1870 ng/mL
Standards accuracy	-6.0 to 6.3%	-2.6 to 1.1%	-3.1 to 3.8%	-14.3 to 6.1%
Standards precision	0.5 to 6.7%	0.4 to 7.2%	0.6 to 8.5%	4.0 to 8.1%
QC concentrations	0.765, 3.06, 8.93 µg/mL	0.758, 3.03, 8.85 µg*	0.703, 2.81, 8.20 µg/mL*	9.26, 69.4, 1667 ng/mL*
QC Accuracy	-1.9 to -0.3%	-6.8 to -2.4%	-6.2 to -3.6%	-4.2 to 10.4 %
QC Precision	3.2 to 7.6%	1.4 to 3.0%	2.4 to 3.6%	2.0 to 8.1%
LLOQ	0.25 µg/mL	0.25 µg/mL	0.25 µg/mL	0.02 µg/mL

*The metabolites are presented as “effective concentrations” (ng eq ucb 34714/mL)

IS (b) (4)
 IS (b) (4)
 IS (b) (4)

[Reviewer comment: The metabolite assays are acceptable.]

Population/ Demographics

N=18 subjects (n=9 with severe renal impairment, n=9 healthy). Sponsor recruited male and female subjects age 18 to 65 years, BMI 19 to 31 kg/m².

Group A (9 subjects): Normal renal function, CRCL > 80 mL/min/1.73 m²
Group D (9 subjects): Severe renal impairment, CRCL < 30 mL/min/1.73 m² and not requiring dialysis

Groups A and D were included in the first step. Groups B and C were to be included if Sponsor determined that a dose adjustment was warranted based on Groups A and D.

Group B (6 subjects): Mild renal impairment (50 ≤ CRCL ≤ 80 mL/min/1.73 m²).
Group C (6 subjects): Moderate renal impairment (30 ≤ CRCL < 50 mL/min/1.73²)

Inclusion Criteria (General):

1. Male and female subjects age 18 to 65 years
2. Females of childbearing potential must use adequate birth control
3. ECG is normal or abnormal but not clinically significant
4. Non-smoker or mild smoker (≤ 10 cigarettes per day)

Inclusion Criteria (Healthy Subject Group):

5. Good physical and mental health
6. Normal vital signs

7. ECG is normal or abnormal but not clinically significant
8. Clinical laboratory tests within reference range of laboratory
9. CRCL > 80 mL/min/1.73 m²

Inclusion Criteria (Renal Impairment Group):

10. Medical history and physical examination (within 2 weeks of treatment start) are consistent with clinical criteria for renal insufficiency)
11. Results of clinical tests within references range, except parameters usually found in subjects with renal insufficiency.
12. *Group B:* Mild impairment ($50 \leq \text{CLCR} < 80 \text{ mL/min/1.73 m}^2$; $50 \leq \text{CLCR} < 70 \text{ mL/min/1.73 m}^2$ considered for recruitment),
Group C: Moderate impairment ($30 \leq \text{CLCR} < 50 \text{ mL/min/1.73 m}^2$),
Group D: Severe impairment ($\text{CLCR} < 30 \text{ mL/min/1.73 m}^2$ and not requiring dialysis).

Exclusion Criteria (General):

1. Pregnant or lactating women
2. Gastrointestinal disease with potential to influence the absorption, including motility disorders.
3. Use of drugs known to affect tubular secretion within 2 weeks of study drug administration
4. Unstable renal function

Exclusion Criteria (Health Subject Group):

5. Systemic disease, e.g. urinary infection, hepatic impairment, on basis of hi story and clinical tests
6. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] $\leq 2 \text{ g/day}$, hormonal contraceptives for post-menopausal hormonal replacement therapy). Use of drugs during clinical trial

Exclusion Criteria (Renal Impairment Group):

6. Other clinical important systemic disease (aside from renal impairment)
7. Acute renal failure
8. Dialysis
9. Use of drugs for care of renal impairment, unless established in dose and scheduled or at least 7 days prior to administration of study drug

PK Results

Table N01109-1: Geometric Mean ± SD PK Parameters and 90% CI of GMR for BRV (ucb 34714) after a single 200 mg administration to health (Group A) and Severe RI (Group D) (PP population)

Parameter	Healthy Subjects (group A) n=9	Severe Renally Impaired Subjects (group D) n=9	Ratio ^(a) (90% CI)
C _{max} (µg/mL)	6.42 (5.21 – 7.90)	6.40 (5.31 – 7.71)	99.72% (84.78 - 117.29)
t _{max} (h) ^(b)	0.50 (0.5 – 1.5)	1.50 (0.5 – 4.0)	
AUC(0-t) (µg.h/mL)	61.8 (52.7-72.5)	75.2 (57.5-98.3)	
AUC (µg.h/mL)	63.1 (54.0 – 73.7)	76.5 (58.5 – 100.1)	121.25% (101.19 - 145.29)
λ _z (h ⁻¹)	0.083 (0.068-0.101)	0.071 (0.058-0.087)	
t _{1/2}	8.35 (6.86 – 10.17)	9.78 (7.94 – 12.0 3)	
CL/F (mL/min/1.73 m ²)	51.8 (43.7-61.3)	42.3 (34.4-51.9)	81.60% (69.84-95.33)
V _z /F (L/kg)	0.55 (0.44-0.69)	0.52 (0.44-0.60)	
Ae (mg)	17.3 (12.3 – 24.3)	7.84 (6.31 – 9.74)	
f _e (% dose)	8.66 (6.17 – 12.15)	3.92 (3.15 – 4.87)	
CL _R (mL/min/1.73 m ²)	4.48 (3.32-6.06)	1.66 (1.21-2.27)	

^(a) Ratio of severe renally impaired subjects (group D) divided by healthy subjects (group A), in %.

^(b) Median and range are given for t_{max}....

Table N01109-2: Geometric Mean ± SD PK Parameters and 90% CI of GMR for Metabolites after a single 200 mg administration to health (Group A) and Severe RI (Group D) (PP population)

Parameter	Healthy Subjects (group A) n=9	Severe Renally Impaired Subjects (group D) n=9	Ratio ^(a) (90% CI)
ucb 42145			
C _{max} (µg eq/mL)	0.270 (0.211 – 0.345)	0.646 (0.514 – 0.813)	239.5% (196.9 – 291.3)
t _{max} (h) ^(b)	4.00 (2.0 – 6.0)	4.00 (2.0 – 9.0)	
AUC(0-t) (µg eq.h/mL)	3.44 (2.65 - 4.46)	11.3 (7.91 - 16.0)	
AUC (µg eq.h/mL)	3.51 (2.71 – 4.55)	11.4 (7.97 – 16.3)	324.0% (250.7 – 418.5)
λ _z (h ⁻¹)	0.087 (0.075 – 0.101)	0.069 (0.056 – 0.086)	
t _{1/2} (h)	7.96 (6.89 – 9.21)	10.03 (8.05 – 12.49)	
Ae (mg eq)	44.23 (37.73 – 51.85)	16.31 (12.17 – 21.87)	
f _e (% eq dose)	22.12 (18.86 – 25.93)	8.16 (6.09 – 10.93)	
CL _R (mL/min/1.73 m ²)	205.6 (169.2 - 249.9)	23.2 (16.6 - 32.2)	
ucb-100406-1			
C _{max} (µg eq/mL)	0.498 (0.296 – 0.838)	0.978 (0.662 – 1.445)	196.5% (134.6 – 286.8)
t _{max} (h) ^(b)	12.0 (9.0 – 12.0)	24.0 (12.0 – 24.0)	
AUC(0-t) (µg eq.h/mL)	14.0 (8.66 - 22.5)	47.2 (32.0 - 69.5)	
AUC (µg eq.h/mL)	14.1 (8.78 – 22.7)	57.5 (39.1 – 84.8)	407.7% (285.3 – 582.0)
λ _z (h ⁻¹)	0.074 (0.065-0.085)	0.029 (0.024-0.035)	
t _{1/2} (h)	9.38 (8.19 – 10.75)	23.8 (19.7 – 28.8)	
Ae (mg eq)	52.5 (37.8 – 73.0)	17.8 (11.2 – 28.1)	
f _e (% eq dose)	26.2 (18.9 – 36.5)	8.88 (5.62 – 14.05)	
CL _R (mL/min/1.73 m ²)	61.4 (49.5 - 76.0)	6.09 (4.26 - 8.69)	
ucb-107092-1			
C _{max} (µg eq/mL)	0.074 (0.061 – 0.090)	0.868 (0.690-1.092)	1165% (978 – 1388)
t _{max} (h) ^(b)	6.0 (6.0 – 9.0)	12.0 (9.0 – 24.0)	
AUC(0-t) (µg eq.h/mL)	1.57 (1.23 - 2.01)	31.2 (21.0 - 46.3)	
AUC (µg eq.h/mL)	1.67 (1.31 – 2.13)	35.8 (23.8 – 54.0)	2148% (1627 – 2836)
λ _z (h ⁻¹)	0.041 (0.029-0.059)	0.030 (0.026-0.036)	
t _{1/2} (h)	16.8 (11.7 – 24.0)	22.7 (19.2 – 27.0)	
Ae (mg eq)	35.1 (30.2 - 40.8)	68.7 (56.4 - 83.8)	
f _e (% eq dose)	17.6 (15.1 – 20.4)	34.4 (28.2 – 41.9)	
CL _R (mL/min/1.73 m ²)	364.7 (290.5-457.9)	35.6 (24.6-51.7)	

^(a) Ratio of severe renally impaired subjects (group D) divided by healthy subjects (group A), in %.

^(b) Median and range are given for t_{max}....

Proposed label language

- Dose adjustments are not required for patients with impaired renal function.
- [REDACTED] (b) (4)
- Brivaracetam is not recommended in patients with end-stage renal disease that are undergoing dialysis due to a lack of data.

[Reviewer comment: [REDACTED] (b) (4)]

[REDACTED]

Comments on labeling for renal impairment can be found at the end of this ISR.]

Reviewer Comment

The following table summarizes BRV and metabolite exposures in subjects with severe RI relative to healthy subjects.

Table N01109-2: Effect of Severe Renal Impairment on PK of BRV and Metabolites Compared to Healthy Subjects

	C_{max} Geometric Mean Ratio (90% Confidence Interval)	AUC Geometric Mean Ratio (90% Confidence Interval)
Brivaracetam (ucb 34714)	99.72% (84.78 - 117.29)	121.25% (101.19 - 145.29)
carboxylic acid metabolite (ucb 42145)	239.5% (196.9 - 291.3)	324.0% (250.7 - 418.5)
hydroxy metabolite (ucb-100406-1)	196.5% (134.6 - 286.8)	407.7% (285.3 - 582.6)
hydroxyacid metabolite (ucb-107092-1)	1165% (978 - 1388)	2148% (1627 - 2836)

**Geometric mean ratio is expressed as the geometric mean of the PK parameter for subjects with severe renal impairment divided by the geometric mean of the PK parameter for healthy subjects.*

As there are no significant safety issues identified by the safety officer that may warrant a dose adjustment, then no dose adjustment is required based on 21% increase in BRV exposures observed in patients with severe RI.

The metabolite exposures increased between 324% - 2148% in patients with severe RI compared to healthy volunteers. None of the three metabolites are pharmacologically active at the target site(s). While the Safety Reviewer did not raise any concerns regarding the safety profile for BRV use in this severe RI single-dose study, this study does not provide safety data on the long-term use of BRV in patients with severe RI. In addition to a lack of long-term safety data in patients with severe RI, one particular safety concern regarding the metabolite exposures in patients with impaired renal function is that the results of the TQT study may not be representative of patients with severe renal impairment. A comparison of exposures in the TQT study (N01233) demonstrated that BRV

exposures after repeated 400 mg bid for 6.5 days to healthy volunteers were lower than exposures to the single 200 mg BRV oral dose to patients with severe RI in study N01109. As such, the TQT study does not appear to be representative of the metabolite exposures experienced in patients with severe renal impairment.

To help assess risk of metabolites exposures such as those observed in severe RI patients, the human BRV PK in study N01109 was compared with non-clinical PK. The $AUC_{0-\infty}$ after a single dose was used as an estimate of $AUC_{\tau,SS}$ for each metabolite. However, as the non-clinical toxicology studies reported $AUC_{0-24\text{hour}}$ at steady state the $AUC_{\tau,SS}$ for metabolites in humans was multiplied by 2 (as the tau is 12 hours) before comparison with the non-clinical $AUC_{0-24\text{hour}}$.

Though metabolite exposures in severe RI patients were over 3-, 4-, and 21-fold greater than in healthy volunteers, the Sponsor has conducted in-vivo non-clinical studies 4 to 13 weeks in duration which achieved metabolite exposures in 8.5-, 10.7-, and 25-fold excess of predicted SS metabolite exposures in patients with severe renal impairment (see the table below).

Table N01109-3: Comparison of Metabolite Exposures in Patients with Severe RI, Healthy Patients in TQT Study, and Animals:

Study	TQT (N01233)	Renal Impairment (N01109)			Animal Studies	Safety Margin
Name	$AUC_{\tau,SS}$ in healthy Volunteers receiving 6.5 days 400 mg BID	$AUC_{0-\infty}$ in Healthy Volunteer after <u>single</u> oral 200 mg dose	$AUC_{0-\infty}$ in severe RI after <u>single</u> oral 200 mg dose	<u>Predicted AUC_{0-24h} at SS in Severe RI Patients</u> ($AUC_{\tau,SS} = AUC_{0-\infty, \text{single dose}}$; $AUC_{0-24h,SS} = 2 \times AUC_{\tau,SS}$)	AUC_{0-24h} at SS in animal studies	Fold-Increase in animal AUC_{0-24h} at SS compared to severe RI predicted AUC_{0-24h} at SS
BRV (Ucb 34714)	123 $\mu\text{g}^*\text{h}/\text{mL}$	63.1 $\mu\text{g}^*\text{hr}/\text{mL}$	76.5 $\mu\text{g}^*\text{hr}/\text{mL}$	153 $\mu\text{g}^*\text{hr}/\text{mL}$	6795 $\mu\text{g}^*\text{hr}/\text{mL}$ (4-week rat study)	44-fold
carboxylic acid metabolite (ucb 42145)	7.52 $\mu\text{g}^*\text{hr}/\text{mL}$	3.51 $\mu\text{g}^*\text{hr}/\text{mL}$	11.4 $\mu\text{g}^*\text{hr}/\text{mL}$	22.8 $\mu\text{g}^*\text{hr}/\text{mL}$	195 $\mu\text{g}^*\text{hr}/\text{mL}$ (4-week rat study)	8.5-fold
hydroxy metabolite (ucb-100406-1)	10.8 $\mu\text{g}^*\text{hr}/\text{mL}$	14.1 $\mu\text{g}^*\text{hr}/\text{mL}$	57.5 $\mu\text{g}^*\text{h}/\text{mL}$	115 $\mu\text{g}^*\text{hr}/\text{mL}$	1231 $\mu\text{g}^*\text{hr}/\text{mL}$ (4-week monkey study)	10.7-fold
Hydroxy-acid metabolite (ucb-107092-1)	2.54 $\mu\text{g}^*\text{hr}/\text{mL}$	1.67 $\mu\text{g}^*\text{hr}/\text{mL}$	35.8 $\mu\text{g}^*\text{h}/\text{mL}$	71.6 $\mu\text{g}^*\text{hr}/\text{mL}$	1818 $\mu\text{g}^*\text{hr}/\text{mL}$ (13-week rat study)	25-fold

*These animal exposures exceed predicted SS exposure in severe RI patients, the actual clinical dose (100 mg bid, or 200 mg/day) will be half of the single 200 mg dose administered in this study, there were no significant safety signals identified in these non-clinical studies (please refer to the pharmacology/toxicology review of Dr. Edward Fisher for details) and the metabolites are not pharmacology active at the intended target site(s). Though altered blood pressure, heart rate, and so-called “minor” QT modifications were reported by the Sponsor, the safety reviewer indicates that the main safety signals of BRV are neurologic disorders (dizziness, fatigue/somnolence), psychiatric disorders (aggression/irritability, suicidality), and falls/injuries. **Overall, the use of BRV with no dose adjustment in patients with severe RI is acceptable.***

4.4.9 N01111: Hepatic Impairment Study (Phase 1)

Study Report#	RPCE03L0501 / N01111																																						
Title	Open-label, parallel group, not randomized, pharmacokinetics study of a single oral administration of 100 mg ucb 34714 (50 mg capsules) in health subjects and patients with impaired liver function (Child-Pugh classes A, B, and C)																																						
Objectives	<p><u>Primary</u>: Assess the effect of hepatic impairment on BRV PK</p> <p><u>Secondary</u>: Assess safety and tolerability of BRV use in patients with hepatic impairment</p>																																						
Study Design	Open-label, monocenter, parallel group, single dose administration study																																						
Duration	4 weeks maximum (3 weeks screening, 4-day treatment period)																																						
Dosage and Administration	Subjects received a single 100 mg oral BRV dose (2 x 50 mg capsule)																																						
PK Assessment	<p><u>Plasma PK samples</u>: pre-dose and 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 9h, 12 h, 24 h, 36 h, 48 h, 60 h, 72 h, 84 h and 96 h post-dose.</p> <p><u>Urine PK samples</u>: Days 1, 2, 3, 4 and 5 after the study drug administration (collection intervals were in 12-hour intervals until 96 hours post-dose).</p> <p><u>PK Analyses (all species)</u>: Cmax, tmax, λz, t1/2, AUC(0-t), AUC, Ae, fe, and CLR</p> <p><u>PK Analyses (BRV only)</u>: CL/F, CLu/F, CLNR, CLRu, CLNRu, Vz/F, Vz/F, and MRT</p> <p><u>PK Analyses (metabolites only)</u>: CLfm/F.</p> <p>Ninety percent (90%) confidence intervals around Cmax, and AUC ratios (each Child-Pugh class and healthy subjects) were computed. No effect of hepatic impairment on the pharmacokinetics of ucb 34714 would be concluded if the confidence interval for AUC and Cmax was lying entirely within 80.0-125.0% of reference boundaries.</p> <p>Protein binding was measured in plasma one hour post-dose.</p>																																						
Bioanalytical Methods	<p>The parent drug ucb 34714 and metabolites ucb 42145, ucb-100406-1 and ucb-107092-1 were measured in urine samples using the same LC-ESI/MS/MS assay after 10-fold dilution with blank plasma. The results are presented together.</p> <p>HPLC-MS/MS Analytical Methods for Plasma and Urine Concentrations</p> <table border="1"> <thead> <tr> <th>Analyte Name</th> <th>Brivaracetam</th> <th>Carboxylic Acid Metabolite</th> <th>Hydroxy Metabolite</th> <th>Hydroxy Acid Metabolite</th> </tr> </thead> <tbody> <tr> <td>Analyte ID</td> <td>ucb 34714</td> <td>ucb 42145</td> <td>ucb-100406-1</td> <td>ucb-107092-1</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> <td>(b) (4)</td> <td>(b) (4)</td> <td>(b) (4)</td> </tr> <tr> <td colspan="5" style="text-align: center;"><i>Plasma</i></td> </tr> <tr> <td>Standard curve concentrations</td> <td>10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL</td> <td>10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*</td> <td>10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*</td> <td>10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*</td> </tr> <tr> <td>Standards accuracy</td> <td>-1.6 to 1.6%</td> <td>-1.6 to 4.2%</td> <td>-3.3 to 4.3%</td> <td>-3.2 to 6.6%</td> </tr> <tr> <td>Standards</td> <td>1.9 to 4.0%</td> <td>1.7 to 5.0%</td> <td>1.4 to 4.3%</td> <td>2.2 to 7.4%</td> </tr> </tbody> </table>				Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1	Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	<i>Plasma</i>					Standard curve concentrations	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*	Standards accuracy	-1.6 to 1.6%	-1.6 to 4.2%	-3.3 to 4.3%	-3.2 to 6.6%	Standards	1.9 to 4.0%	1.7 to 5.0%	1.4 to 4.3%	2.2 to 7.4%
Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite																																			
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1																																			
Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)	(b) (4)																																			
<i>Plasma</i>																																							
Standard curve concentrations	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL*																																			
Standards accuracy	-1.6 to 1.6%	-1.6 to 4.2%	-3.3 to 4.3%	-3.2 to 6.6%																																			
Standards	1.9 to 4.0%	1.7 to 5.0%	1.4 to 4.3%	2.2 to 7.4%																																			

	precision				
	<i>Plasma and Urine (Results Averaged Over All Runs)</i>				
	QC concentrations	35, 150, 1800 ng/mL	9.95, 74.7, 1792 ng/mL*	9.34, 70, 1681 ng/mL*	9.5, 71.3, 1710 ng/mL*
	QC Accuracy	-0.9 to 1.3%	-4.9 to 2.6%	-2.3 to 10.3%	-6.4 to 2.4%
	QC Precision	7.2 to 9.0%	8.9 to 12.9%	3.3 to 5.4%	8.4 to 12.3%
	<i>Storage Conditions at Investigator's Sites (-20 degrees C)</i>				
	Plasma QC Concentrations	35.2, 151 and 1811 ng/mL	---	---	---
	Plasma QC Accuracy	2.1 to 12.8%	---	---	---
	Urine QC Concentrations	352, 1509 and 18108 ng/mL	---	---	---
	Urine QC Accuracy	-4.8 to -10.3%	---	---	---
	<i>LLOQ's</i>				
	Plasma LLOQ	10 ng/mL	1.99 µg/mL*	1.86 µg/mL*	1.85 µg/mL*
	Urine LLOQ	100 ng/mL	19.9 µg/mL*	18.6 µg/mL*	18.5 µg/mL*
	*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).				
	IS (b) (4)				
	IS (b) (4)				
	[Reviewer comment: The assay validation is acceptable.]				
Population/ Demographics	<p>N=26 male or female subjects age 18 to 65 years that were healthy or suffered from chronic liver disease (Child-Pugh A, B, or C). Creatinine clearance was ≥ 80 mL/min in Healthy subjects (Group D) and subjects with Child-Pugh score A or B. Subjects with Child-Pugh score C (Group C) had creatinine clearance ≥ 70 mL/min. Severity of the hepatic impairment was assessed according to the classification of Child-Pugh i.e., a score from 5 to 6 for group A, from 7 to 9 for group B and from 10 to 15 for group C.</p> <p><u>Inclusion Criteria (general):</u></p> <ol style="list-style-type: none"> 1. Male or female age between 18 and 65 years inclusive. 2. Non smokers or smokers less than 20 cigarettes per day. 3. Females of childbearing potential must use adequate birth control <p><u>Inclusion Criteria (healthy group, Group D):</u></p> <ol style="list-style-type: none"> 4. Good physical and metnal health 5. Normal vital signs 6. ECG is normal or abnormal but not clinically significant 7. Results of clinical laboratory tests within the reference ranges. 8. Estimated CRCL (Cockroft Gault method) above 80 mL/min <p><u>Inclusion Criteria (Hepatic Impairment Groups: A,B,C):</u></p> <ol style="list-style-type: none"> 9. Subjects with clinical criteria usually found in patients with chronic hepatic insufficiency using Child-Pugh classification (a score from 5 to 6 for group A, 				

- 7 to 9 for group B and from 10 to 15 for group C.)
10. Results of laboratory tests within the reference ranges except those usually found abnormal in subjects with chronic hepatic insufficiency.
 11. ECG is normal or abnormal but not clinically significant
 12. Estimated CRCL > 80 mL/min (Cockcroft Gault method) for groups A and B, > 70 mL/min for group C

Exclusion Criteria (general):

1. Pregnant or lactating women
2. Use of proton pump inhibitors

Exclusion Criteria (healthy group, Group D):

3. gastrointestinal disease that could potentially influence absorption, including motility disorders.
4. With any clinically important systemic disease
5. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day, hormonal contraceptives for post-menopausal hormonal replacement therapy). Use of drugs during clinical trial
6. Use of drugs within past 2 months that induce or inhibit metabolizing enzymes

Exclusion Criteria (Hepatic Impairment Groups, A,B,C):

7. Clinically important systemic disease, other than hepatic insufficiency
8. Acute liver failure
9. Biliary cirrhosis
10. Drugs indicated for hepatic impairment, unless on stable dose for at least 14 days prior to first dose
11. Drugs known to affect hepatic metabolism within the 2 months prior to the first liver function test

PK Results

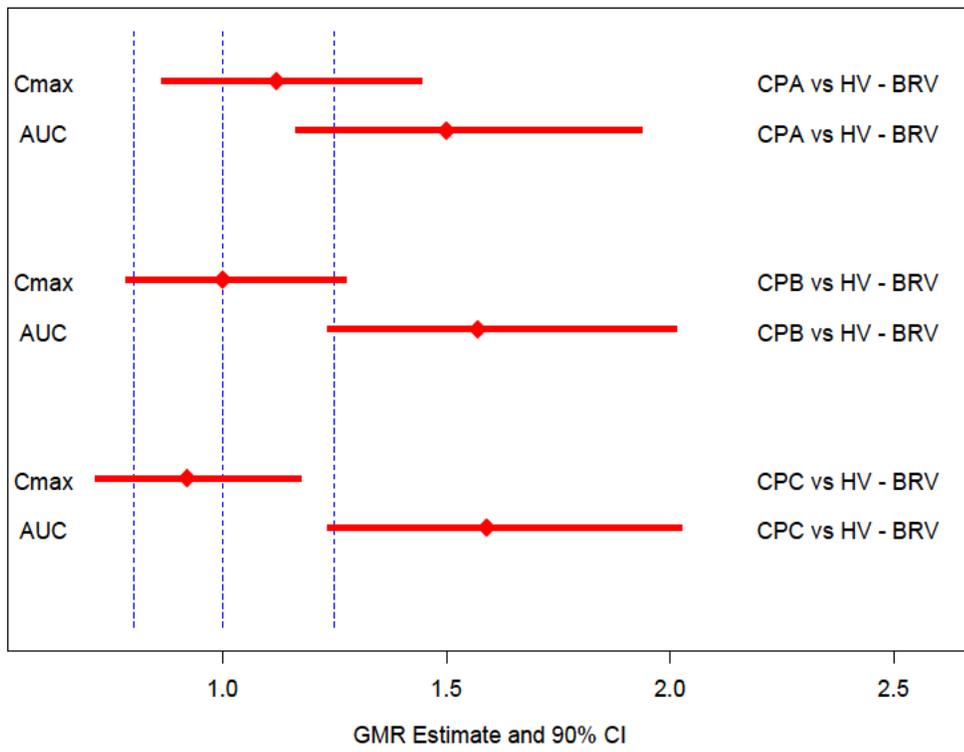
Table N01111-1: BRV PK Parameters (Geometric Mean, %CV) By Arm

Pharmacokinetic Parameters of Brivaracetam (Geometric Mean (CV%)) (ITT Population)

	Healthy (N=6)	Child-Pugh A (N=6)	Child-Pugh B (N=7)	Child-Pugh C (N=7)
AUC (0-t) (µg.h/mL)	29.5 (25.2)	44.2 (41.0)	46.1 (16.8)	46.4 (16.1)
AUC (µg.h/mL)	29.7 (25.2)	44.6 (41.1)	46.7 (17.4)	47.1 (16.2)
C _{max} (µg/mL)	2.86 (39.3)	3.21 (17.4)	2.86 (14.3)	2.62 (26.6)
t _{max} ^(a) (h)	1.00 (0.47-1.5)	0.50 (0.50-2.00)	0.50 (0.50-1.00)	0.53 (0.50-1.5)
t _{1/2} (h)	9.79 (30.0)	14.2 (24.5)	16.4 (10.4)	17.4 (10.8)
CL/F (mL/min/kg)	0.711 (26.4)	0.537 (26.2)	0.481 (14.5)	0.464 (13.7)
V _F /F (L/kg)	0.60 (17.6)	0.66 (12.5)	0.68 (9.35)	0.70 (13.1)
Ae (mg)	7.47 (61.0)	8.23 (45.7)	6.42 (63.8)	8.41 (35.6)
fe (%)	7.47 (61.0)	8.23 (45.7)	6.42 (63.8)	8.41 (35.6)
CL _R (mL/min/kg)	0.0531 (51.5)	0.0442 (53.0)	0.0309 (74.7)	0.0390 (42.7)
CL _{NR} (mL/min/kg)	0.651 (29.2)	0.489 (27.1)	0.444 (13.4)	0.423 (12.8)
CL _{NR} / CL/F (%)	91.6	91.1	92.3	91.2
MRT (h)	12.0 (21.6)	16.5 (18.3)	20.5 (13.1)	20.5 (9.6)
CL _u /F (mL/min/kg)	0.893 (30.9)	0.676 (28.5)	0.575 (18.6)	0.558 (15.8)
V _{zu} /F (L/kg)	0.76 (14.7)	0.83 (12.0)	0.82 (12.5)	0.84 (13.5)
CL _{RU} (mL/min/kg)	0.0666 (53.0)	0.0556 (55.2)	0.0369 (75.6)	0.0468 (44.8)
CL _{NRu} (mL/min/kg)	0.817 (33.7)	0.616 (29.1)	0.532 (18.1)	0.509 (14.7)

^(a) Median (range)

Figure N01111-1: BRV Exposure by HI Status

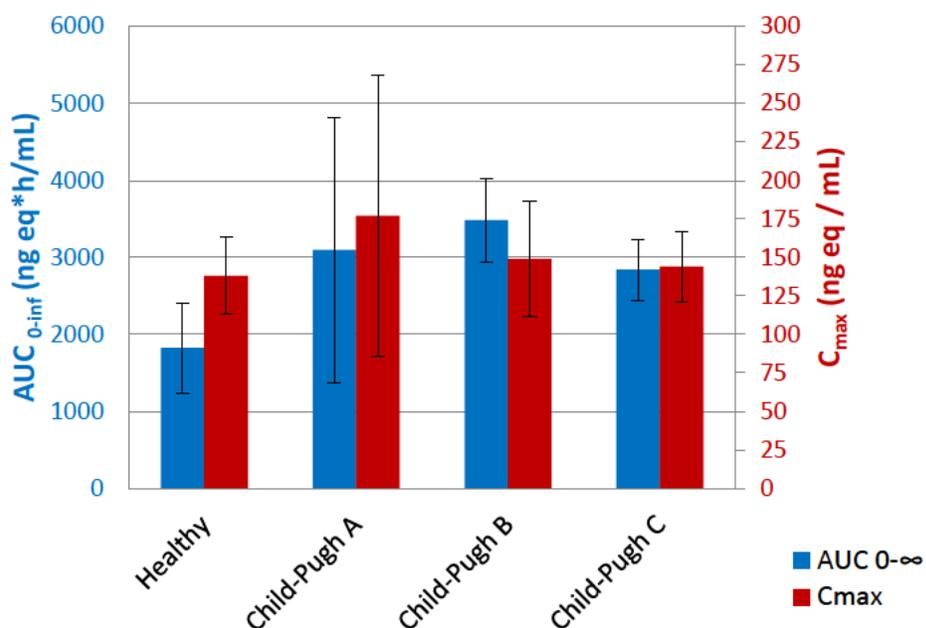


This plot shows $AUC_{0-\infty}$

Table N01111-2: Carboxylic Acid Metabolite Exposure By HI Status

	Healthy	Child-Pugh A	Child-Pugh B	Child-Pugh C
n	6	6	7	7
AUC ∞ geometric mean	1823	3098	3485	2839
AUC ∞ %CV	32.1	55.8	15.5	13.9
Cmax geometric mean	138	177	149	144
Cmax % CV	18.1	51.5	25.4	15.7

Figure N01111-2: HI Effect on Carboxylic Acid Metabolite (ucb 42145) PK

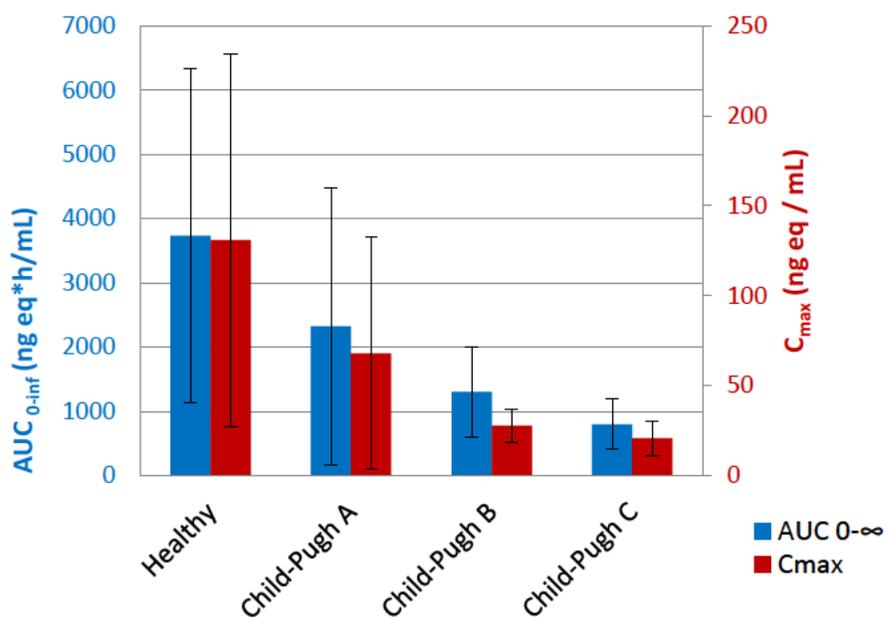


Results are expressed as mean ± SD

Table N01111-3: Hydroxy Metabolite Exposure By HI Status

	Healthy	Child-Pugh A	Child-Pugh B	Child-Pugh C
n	6	6	7	7
AUC ∞ geometric mean	3734	2323	1302	797
AUC ∞ %CV	69.7	93	53.9	48.9
Cmax geometric mean	131	67.9	27.8	20.6
Cmax % CV	79.2	95.1	32.6	45.7

Figure N01111-3: HI Effect on Hydroxy Metabolite (ucb-100406-1) PK

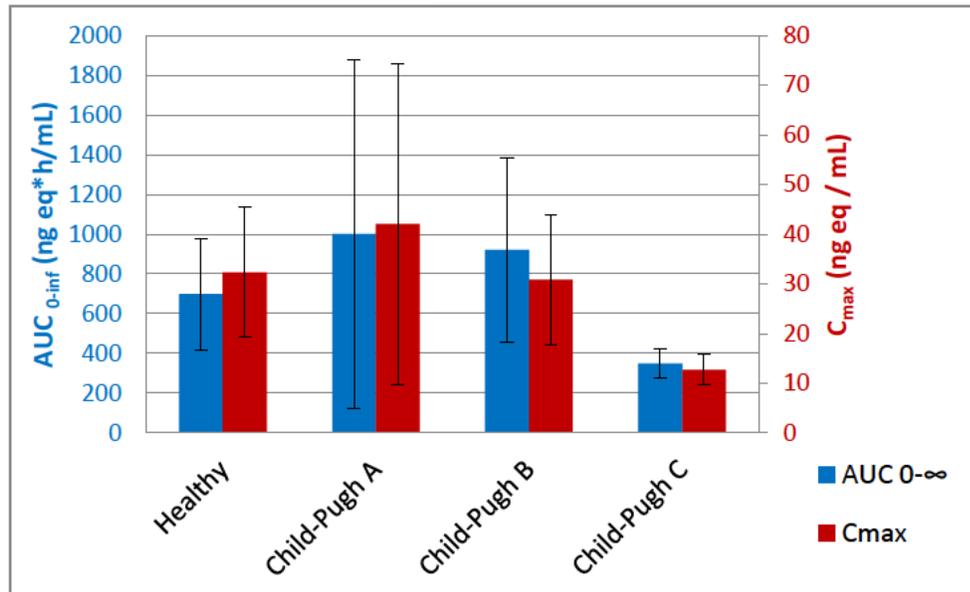


Results are expressed as mean ± SD

Table N01111-4: Hydroxyacid Metabolite Exposure By HI Status

	Healthy	Child-Pugh A	Child-Pugh B	Child-Pugh C
n	6	6	7	7
AUC ∞ geometric mean	699	1001	921	350
AUC ∞ %CV	40.3	87.7	50.3	21.3
Cmax geometric mean	32.3	42	30.8	12.7
Cmax % CV	40.5	76.7	42.1	24.4

Figure: N01111-4: HI Effect on Hydroxy Acid metabolite (ucb-107092-1) PK



Results are expressed as mean ± SD

Safety

The most frequent TEAEs were somnolence (42.3%), orthostatic hypotension (26.9%), vertigo (23.1%) and hypotension (11.5%). All TEAEs were mild or moderate. No SAEs were reported. The incidence of TEAEs was comparable in each of the 4 arms (healthy versus CPA, B, and C).

Table N01111-2: Overall TEAE Rate By Treatment Arm

	Healthy (N = 6) n (%)	Group A (N = 6) n (%)	Group B (N = 7) n (%)	Group C (N = 7) n (%)
Total number of TEAEs	20	13	9	9
Subjects with at least one TEAE	5 (83.3%)	4 (66.7%)	5 (71.4%)	5 (71.4%)
Subjects with drug-related TEAEs	5 (83.3%)	3 (50.0%)	5 (71.4%)	3 (42.9%)
Subjects with severe TEAEs	0	0	0	0
Subjects with Serious AEs	0	0	0	0
Number of deaths	0	0	0	0

Table N01111-3: Detailed TEAE Rate By Treatment Arm

Primary SOC Preferred Term	Healthy (N = 6) n (%)	Group A (N = 6) n (%)	Group B (N = 7) n (%)	Group C (N = 7) n (%)
Cardiac Disorders	2 (33.3)	0	1 (14.3)	0
Sinus bradycardia	1 (16.7)	0	0	0
Sinus tachycardia	1 (16.7)	0	1 (14.3)	0
Ear and Labyrinth Disorders	2 (33.3)	1 (16.7)	1 (14.3)	2 (28.6)
Vertigo	2 (33.3)	1 (16.7)	1 (14.3)	2 (28.6)
Gastrointestinal Disorders	1 (16.7)	2 (33.3)	0	1 (14.3)
Diarrhoea	1 (16.7)	0	0	0
Nausea	0	1 (16.7)	0	0
Saliva altered	0	0	0	1 (14.3)
Toothache	0	1 (16.7)	0	0
Nervous System Disorders	5 (83.3)	3 (50.0)	4 (57.1)	0
Dizziness	1 (16.7)	0	0	0
Headache	1 (16.7)	0	0	0
Somnolence	4 (66.7)	3 (50.0)	4 (57.1)	0
Vascular Disorders	4 (66.7)	1 (16.7)	1 (14.3)	4 (57.1)
Diastolic hypertension	1 (16.7)	0	0	0
Hypertension	1 (16.7)	0	0	0
Hypotension	1 (16.7)	1 (16.7)	0	1 (14.3)
Orthostatic hypotension	3 (50.0)	0	1 (14.3)	3 (42.9)

[Reviewer comment: Overall, the TEAE rates are comparable or lower in the hepatic impairment arms compared to the healthy subject arm.]

Sponsor's Conclusions

- BRV CL_{NR} represented 92% of the apparent total body CL in healthy subjects.
- Cumulative renal urinary excretion of brivaracetam was comparable between the 4 arms (6.4% to 8.4%).
- BRV was safety and well-tolerated in the present study
- BRV exposure increased 50% - 58% in subjects with hepatic impairment.

(b) (4)

[Reviewer comment:

(b) (4)

the current submission recommended a reduced starting dose and a reduced maximum dose. See the Reviewer Comments below for details.]

Reviewer Comment

A 50%-58% increase in BRV AUC_{0-∞} was observed in subjects with Child-Pugh A, B, as well as C compared to healthy controls. The exposure-efficacy relationship for BRV indicates a "plateau" of efficacy change at the exposures achieved from the clinical doses. However, relatively flat dose/exposure-safety relationships for BRV were observed for the most common adverse events (somnolence, dizziness, and fatigue are common adverse events).

As the three metabolites are not pharmacology active at the intended target site(s), the decreases of hydroxy metabolite (ucb-100406-1) exposure in Child-Pugh A, B, C as well as decreases of hydroxy-acid metabolite (ucb-107092-1) in Child-Pugh C are not expected to result in a loss of efficacy.

Both the increased carboxylic acid metabolite (ucb 42145) exposures in Child-Pugh A, B, and C as well as the increased hydroxy-acid exposures in Child-Pugh A and B were increased in comparison to healthy subjects. However, these metabolite exposure increases are not expected to result in safety or tolerability issues. This conclusion is based on non-clinical studies which rats and monkeys experienced metabolite exposures in excess of those observed in hepatic impairment subjects for several weeks (see the ISR for study N01109 for details).

(b) (4)
in the current submission proposes a dose reduction. The Sponsor's proposed dosing for patients with hepatic impairment of any severity is 50 mg/day (25 mg twice/day) as the starting dose, and a maximum dose of 150 mg/day (75 mg twice/day).

*However, due to the flat BRV exposure-safety relationship for the common adverse events (e.g. somnolence, dizziness, and fatigue are common adverse events), as well as the safety profile reported in the current study, and the non-clinical support of the metabolite exposures, the Sponsor's upper dose limit of 150 mg bid seems unnecessary. For the same reasons, the reduced starting dose is unnecessary. Overall, **no dose adjustment is required for hepatic impairment.***

Please refer to section 3.0 for detailed labeling recommendations.

4.4.10 N01114: Dose-Ranging, 50 and 150 mg/day oral capsules (Phase 2)

Study Report#	RPCE02K0301 / N01114							
Title	A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 used as adjunctive treatment at doses of 50 and 150 mg/day in b.i.d. administration (oral capsules of 25 mg) for a maximum of 12 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized							
Objectives	<p><u>Primary</u>: Assess efficacy 50 mg/day bid and 150 mg/day bid</p> <p><u>Secondary</u>: Assess dose/response, safety and tolerability, seizure-free days</p> <p><u>Exploratory</u>: Assess population PK (identify covariates and impact of BRV on concomitant AED plasma levels), quality of life measures</p>							
Study Design	International, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study							
Duration	18 weeks, 12 weeks exposure to BRV (4-week baseline period, 10 week treatment period [3-week up-titration, and 7-week maintenance period], 2-week down titration or conversion period, 2-week study-drug-free period [for down-titrated subjects])							
Dosage and Administration	<p>After baseline period, patients were randomized 1:1:1 to placebo, BRV 50, or 150 mg/day as oral capsules administered BID (2 equal intakes, morning and evening). Subjects were titrated over a period of 3 weeks, and underwent a 7-week maintenance period (for a total of 10 weeks as the Treatment Period). Patients were down-titrated over a period of 2-weeks and then underwent a 2-week study-drug-free period.</p> <p>The diagram illustrates the dosing schedule. It starts with a 4-week baseline (Weeks -4 to 0) at 0 mg/day. At Week 0, patients are randomized to three groups: 25 mg/day, 50 mg/day, or 150 mg/day. Over the next 3 weeks (Weeks 0 to 3), the dosage is increased in 25 mg increments. From Week 3 to Week 10, patients remain on their assigned dosage (25, 50, or 150 mg/day). At Week 10, patients are down-titrated over 2 weeks (Weeks 10 to 12) to 0 mg/day. A 'DOUBLE BLIND' period is indicated from Week 3 to Week 12. Dashed lines represent fallback paths: from 150 mg/day to 100 mg/day and from 50 mg/day to 25 mg/day. Sampling points are marked as V1-V11 and W-4 to W14.</p>							
PK Assessment	Trough BRV (parent only) plasma level was determined at Week 0 (randomization), Weeks, 3, 4, 7, 10, 13 (or early discontinuation).							
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> </table>		Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)
Analyte Name	Brivaracetam							
Analyte ID	ucb 34714							
Internal Standard (IS)	(b) (4)							

	<table border="1"> <tr> <td>Standard curve concentrations</td> <td>10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.0 to 3.9%</td> </tr> <tr> <td>Standards precision</td> <td>2.8 to 6.2%</td> </tr> <tr> <td>QC concentrations</td> <td>30, 300, 900, 3600 µg/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-4.6 to 4.4%</td> </tr> <tr> <td>QC Precision</td> <td>9.2 to 11.7%</td> </tr> <tr> <td>LLOQ</td> <td>10 ng/mL</td> </tr> </table> <p>[Reviewer comment: The assay is acceptable.]</p>	Standard curve concentrations	10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL	Standards accuracy	-4.0 to 3.9%	Standards precision	2.8 to 6.2%	QC concentrations	30, 300, 900, 3600 µg/mL	QC Accuracy	-4.6 to 4.4%	QC Precision	9.2 to 11.7%	LLOQ	10 ng/mL														
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QC Precision	9.2 to 11.7%																												
LLOQ	10 ng/mL																												
Population/ Demographics	<p>N=157</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female patients with epilepsy age 16 to 65 years 2. Focal epilepsy or epileptic syndrome, history of partial onset seizures 3. Refractory while receiving 1 or 2 co-AEDs (Vagal nerve stimulation allowed, but not counted as a co-AED). 4. Females of childbearing potential must use acceptable birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Use of felbamate or vigabatrine 2. Use of drugs with possible CNS effects unless stable for 1 month prior to Visit 1 and for whole study period. Benzodiazepines taken more than once/week (for any indication) is considered as a concomitant AED. 3. Use of drugs that influence BRV metabolism (2C or 3A potent inhibitors) unless stable for 1 more before visit 1 and for entire study duration. 4. Impaired hepatic function (ALAT/SGPT, ASAT/SGOT, ALP, GGT > 3 x ULN) 5. Creatinine CL < 50 mL/min 6. Clinically significant ECG abnormalities 7. Pregnant/lactating women <p>[Reviewer comment: Use of <u>levetiracetam</u> was permitted in this study.]</p>																												
PK Results	<p>The population pharmacokinetics (PK) of brivaracetam (BRV) in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358)</p> <p>PK results from these studies are pooled and provided in the ISR for N01358.</p>																												
Efficacy	<p>Table N01114-1: Percent Reduction Compared to Placebo in POS Per Week Throughout Maintenance Period</p> <table border="1"> <thead> <tr> <th>Partial onset seizure frequency per week (type I) (Maintenance period)</th> <th>PBO N=52</th> <th>BRV 50 N=53</th> <th>BRV 150 N=52</th> </tr> </thead> <tbody> <tr> <td>LS means (log transformed)</td> <td>1.278</td> <td>1.119</td> <td>1.132</td> </tr> <tr> <td>LS means (back-transformed)</td> <td>2.590</td> <td>2.062</td> <td>2.103</td> </tr> <tr> <td colspan="4">Difference vs. Placebo</td> </tr> <tr> <td>% reduction over Placebo</td> <td></td> <td>14.7%</td> <td>13.6%</td> </tr> <tr> <td>2-sided 95% confidence interval</td> <td></td> <td>(-2.7%, 29.2%)</td> <td>(-4.1%, 28.3%)</td> </tr> <tr> <td>p-value</td> <td></td> <td>0.093</td> <td>0.124</td> </tr> </tbody> </table> <p>The estimated percent reductions over placebo in the partial onset seizure</p>	Partial onset seizure frequency per week (type I) (Maintenance period)	PBO N=52	BRV 50 N=53	BRV 150 N=52	LS means (log transformed)	1.278	1.119	1.132	LS means (back-transformed)	2.590	2.062	2.103	Difference vs. Placebo				% reduction over Placebo		14.7%	13.6%	2-sided 95% confidence interval		(-2.7%, 29.2%)	(-4.1%, 28.3%)	p-value		0.093	0.124
Partial onset seizure frequency per week (type I) (Maintenance period)	PBO N=52	BRV 50 N=53	BRV 150 N=52																										
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p-value		0.093	0.124																										

	frequency per week (type I) over the Maintenance period were 14.7% and 13.6% in respectively the BRV 50 and BRV 150 groups. Those reductions over placebo were <u>not</u> statistically significant at the 5% significance level (see table below).
Safety	<ol style="list-style-type: none"> 1. TEAEs were experienced by 76.9%, 73.6%, and 67.3% of subjects in the placebo, BRV 50 mg bid, and BRV 150 mg bid group, respectively. The most frequent TEAEs were headache (10.2%), fatigue and nausea (8.9%), nasopharyngitis (7.6%), somnolence (7.0%), and dizziness (6.4%). 2. There were no medically relevant differences between the three treatment groups. 3. 5 SAEs occurred in PBO group, 1 SAE in the BRV 50 mg bid group, 3 in BRV 150 mg bid group
Sponsor's Conclusions	<ul style="list-style-type: none"> • Though BRV did <u>not</u> present a statistically significant improvement over placebo, the 14.7% and 13.6% improvement compared to placebo 50 mg/day bid and 150 mg/day bid demonstrate a clear differentiation from placebo on secondary analyses. • There was no evidence of additional benefit after brv 150 mg/day • BRV 50 mg/day and 150 mg/day as bid were well-tolerated
Reviewer Comment	<ul style="list-style-type: none"> • <i>The study did not appear to present any new safety signals due to BRV.</i> • <i>The efficacy results from this study and study N01252 are not consistent with the results from study N01193 or N01253. While the 50 mg dose in this study did not provide a statistically significant reduction in seizure frequency over placebo (13.6% reduction compared to placebo, p=0.093) in this study or study N01252, in study N01193 and N0125 showed that the 50 mg dose <u>did</u> provide a statistically significant improvement compared to placebo. The reason for the difference in the efficacy of the 50 mg dose across the studies is not clear.</i> • <i>Please refer to the medical officer's review for more information about the acceptability of the 50 mg/day bid (25 mg twice per day) dose level.</i> • <i>For insight into the population pharmacokinetic analyses and exposure-efficacy analyses, please refer to the pharmacometric portion of this review.</i>

4.4.11 N01118: Elderly PK Study (Phase 1)

Study Report#	RPCE02L0401 / N01118
Title	Multicenter, open-label, pharmacokinetic, safety and tolerability study of a single dose followed by a 10 day b.i.d. dosing regimen of ucb 34714 administered twice a day orally as 200 mg capsules in healthy elderly volunteers.
Objectives	<u>Primary:</u> Assess oral BRV PK in elderly volunteers <u>Secondary:</u> Gain information on BRV safety in volunteers
Study Design	Multicenter, open-label study
Duration	7 weeks from screening to discharge (10 days BRV treatment)
Dosage and Administration	N=16 subjects received a single oral dose of ucb 34714 (200 mg, oral capsule) on Day 1 followed by a twice daily oral dose from Day 3 to Day 11 (400 mg/day). A single oral dose was administered on the last treatment day (Day 12).
PK Assessment	<p><u>Plasma Samples:</u> Day 1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours post single dose; Day 2: 24 and 36 hours post single dose; Day 3: 48 hours post single dose; Days 6, 8 and 10: pre-morning dose; Day 12: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours post-dose.</p> <p><u>Urine Samples:</u> Day 1 : pre-dose and fraction 0-12 h; Day 2 : fractions 12-24 h and 24-36 h; Day 3 : fraction 36-48 h; Day 12: fraction 0-12 h.</p> <p><u>PK Analyses:</u></p> <p>For <u>ucb 34714:</u> Day 1: AUC(0-t), AUC, Cmax, tmax, t½, CL/F, Ae, fe, CLR. Day 12: AUCtau, Cmax, tmax, CLSS/F, Ae,tau, fe, CLR, LF, R.</p> <p>For <u>ucb-100406-1</u>, <u>ucb 42145</u> and <u>ucb-107092-1:</u> Day 1: AUC(0-t), AUC, Cmax, tmax, t½, Ae, fe, CLR Day 12: AUCtau, Cmax, tmax, Ae,tau, fe, CLR.</p>

Bioanalytical Methods

The parent drug ucb 34714 and metabolites ucb 42145, ucb-100406-1 and ucb-107092-1 were measured in urine samples using the same LC-ESI/MS/MS assay after 10-fold dilution with blank plasma. The results are presented together.

HPLC-MS/MS Analytical Methods for Plasma Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
Internal Standard (IS)	(b) (4)	(b) (4)		
Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL	0.002 to 2 µg eq/mL		
Standards accuracy	-5.1 to 4.2%	-4.8 to 3.0%	-3.3 to 3%	-4.8 to 3.9%
Standards precision	3.4 to 9.8%	1.8 to 6.1%	1.2 to 3.1%	1.7 to 5.4%
QC concentrations	0.150, 0.600 1.75 µg/mL	0.010, 0.075 and 1.75 µg/mL*		
QC Accuracy	-0.4 to 5.8%	-9.2 to 3.5%	-2.8 to 2.7%	-1.3 to 9.7%
QC Precision	5.9, 8.9, 18.2%	6.6 to 10.5%	4.4 to 6.4%	5.2 to 6.8%
LLOQ	0.05 µg/mL	0.002 µg eq/mL		

*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).

IS (b) (4)

IS (b) (4)

HPLC-MS/MS Analytical Methods for Urine Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Standard curve concentrations	0.25 to 10 µg/mL	0.25 to 10 µg/mL*	0.25 to 10 µg/mL*	1.85 4.63 18.5 46.3 92.6 463 926 1852 ng/mL
Standards accuracy	-1.2 to 1.7%	-1.2 to 1.7%	-3.1 to 2.9%	-6.1 to 6.9%
Standards precision	1.0 to 5.5%	1.2 to 4.6%	0.4 to 4.4%	1.5 to 6.4%
QC concentrations	0.750, 3.00 and 8.80 µg/mL	0.750, 3.00 and 8.80 µg/mL*	0.750, 3.00 and 8.80 µg/mL*	9.26, 69.4 and 1667 µg/mL
QC Accuracy	-3.3 to -0.9%	-3.2 to -1.5%	-4.5 to 0.1%	-2.1 to 7.5%
QC Precision	3.5 to 4.1%	2.6 to 4.6%	2.4 to 3.7%	2.1 to 6.7%
Urine LLOQ	0.25 µg/mL	0.25 µg/mL*		0.02 µg/mL*

	<p>[Reviewer comment: The assays are acceptable.]</p>																																				
Population/ Demographics	<p>N=16 health male and postmenopausal female subjects age ≥ 65 years. There was 10 subjects age 65-75 years who finished the study and 5 subjects age > 75 years who finished the study.</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none">1. Healthy male or postmenopausal female age ≥ 65 years2. Good physical and mental health (according to age group)3. Renal function within normal for age and gender<ol style="list-style-type: none">a. For males from 65 to 75 years old inclusive: ≥ 55 mL/min.b. For females from 65 to 75 years old inclusive: ≥ 50 mL/min.c. For males > 75 years old: ≥ 45 mL/min.d. For females > 75 years old: ≥ 40 mL/min.4. Normal liver function tests, absence of hepatic disease or impaired liver function5. ECG is normal or abnormal but not clinically significant (for age of subject)6. Results of clinical laboratory tests within reference range from the laboratory <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none">1. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug2. Gastrointestinal disease with potential to influence the absorption, including motility disorders.3. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day, hormonal contraceptives for post-menopausal hormonal replacement therapy). Use of drugs during clinical trial4. currently smoking and not able to stop during the clinical phase of the study																																				
PK Results	<p>Figure N01118-1: Mean \pm SD BRV (ucb 34714) PK Profile</p> <table border="1"><caption>Approximate data points from Figure N01118-1</caption><thead><tr><th>Time from first dose (h)</th><th>Mean plasma concentration (µg/mL)</th></tr></thead><tbody><tr><td>0</td><td>5.5</td></tr><tr><td>1</td><td>5.0</td></tr><tr><td>2</td><td>4.5</td></tr><tr><td>3</td><td>4.0</td></tr><tr><td>4</td><td>3.8</td></tr><tr><td>6</td><td>3.5</td></tr><tr><td>12</td><td>2.5</td></tr><tr><td>24</td><td>1.0</td></tr><tr><td>36</td><td>0.5</td></tr><tr><td>48</td><td>0.2</td></tr><tr><td>264</td><td>8.5</td></tr><tr><td>266</td><td>8.0</td></tr><tr><td>268</td><td>7.5</td></tr><tr><td>270</td><td>6.5</td></tr><tr><td>272</td><td>5.5</td></tr><tr><td>274</td><td>4.0</td></tr><tr><td>276</td><td>2.8</td></tr></tbody></table>	Time from first dose (h)	Mean plasma concentration (µg/mL)	0	5.5	1	5.0	2	4.5	3	4.0	4	3.8	6	3.5	12	2.5	24	1.0	36	0.5	48	0.2	264	8.5	266	8.0	268	7.5	270	6.5	272	5.5	274	4.0	276	2.8
Time from first dose (h)	Mean plasma concentration (µg/mL)																																				
0	5.5																																				
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3	4.0																																				
4	3.8																																				
6	3.5																																				
12	2.5																																				
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272	5.5																																				
274	4.0																																				
276	2.8																																				

Figure N01118-2: Mean \pm SD Carboxylic Acid Metabolite (ucb 42145) PK Profile

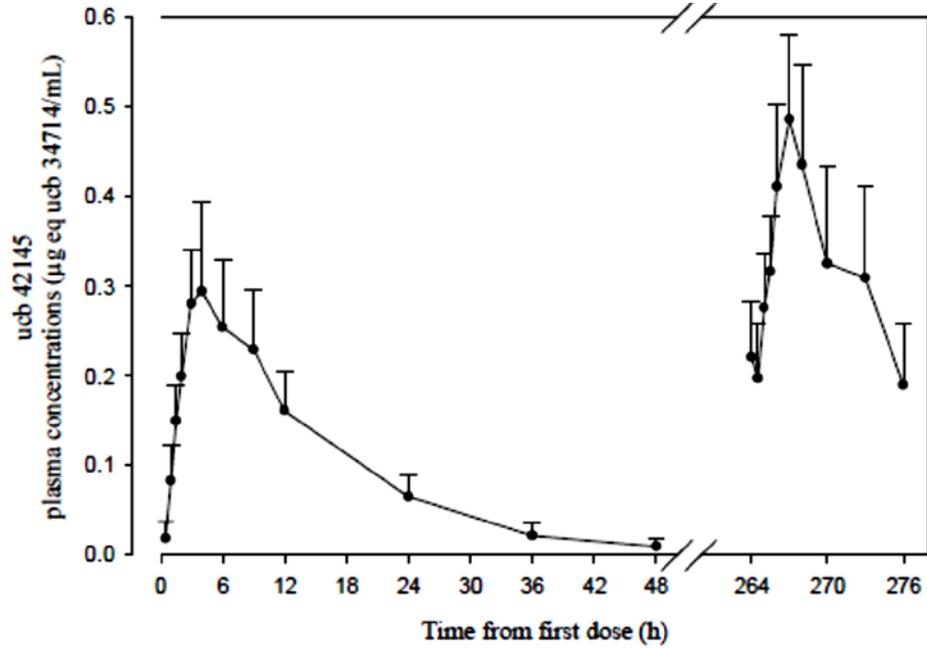


Figure N01118-3: Mean \pm SD Hydroxy Metabolite (ucb 100406-1) PK Profile

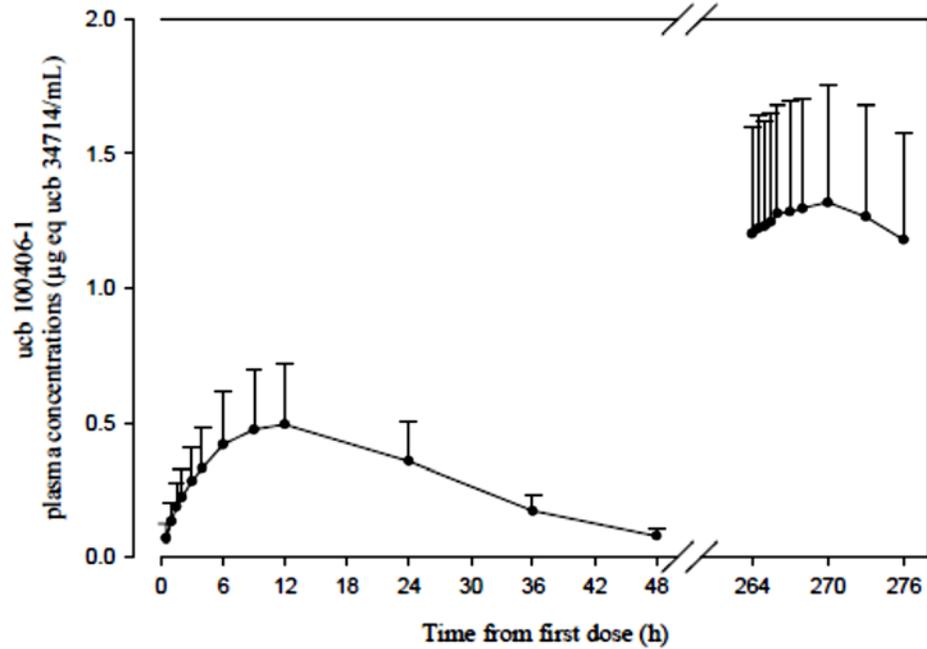


Figure N01118-4: Mean ± SD Hydroxy-Acid Metabolite (ucb-107092-1) PK Profile

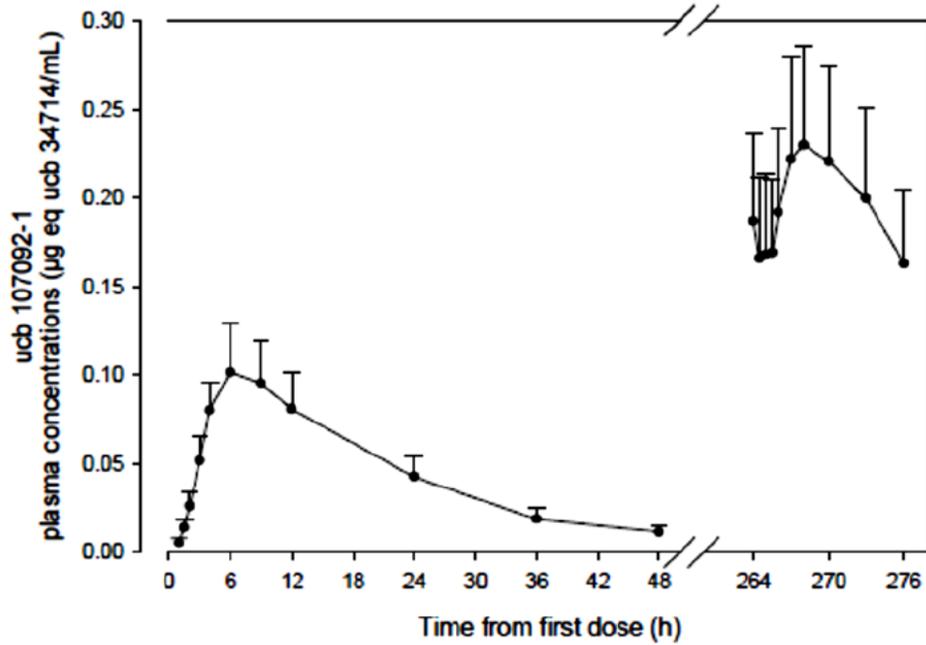


Table N01118-1: Geometric Mean (CV%) PK Parameters and Urinary Excretion of BRV and Metabolites

Parameters	ucb 34714		ucb-100406-1		ucb 42145		ucb-107092-1	
	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12
C_{max} (µg/mL)	5.935 (24.4%)	8.751 (19.9%)	0.4315 (45.8%)	1.253 (33.0%)	0.3084 (28.0%)	0.5016 (19.0%)	0.1003 (26.1%)	0.2285 (24.2%)
$t_{max}^{(a)}$ (h)	1.50 (0.5-3.0)	1.50 (0.5-4.0)	12.00 (9.0-12.1)	4.00 (0.5-6.0)	4.00 (3.0-9.0)	3.00 (2.0-6.0)	6.00 (6.0-9.0)	4.00 (3.0-6.0)
AUC ^(b) (µg.h/mL)	72.94 (18.2%)	63.59 (15.0%)	13.89 (39.3%)	14.19 (32.7%)	4.625 (27.4%)	3.822 (24.8%)	2.281 (25.1%)	2.332 (24.5%)
$t_{1/2}$ (h)	8.316 (16.1)	-- ^(c)	11.34 (18.7%)	-- ^(c)	8.215 (23.1%)	-- ^(c)	12.29 (6.1%)	-- ^(c)
CL/F ^(b) (mL/min/kg)	0.6624 (15.0%)	0.7598 (15.6%)	-- ^(c)	-- ^(c)	-- ^(c)	-- ^(c)	-- ^(c)	-- ^(c)
Ae ^(b) (mg)	17.83 (30.6%)	25.80 (21.3%)	44.28 (40.0%)	72.01 (31.3%)	37.52 (32.5%)	40.87 (22.9%)	27.40 (34.6%)	37.86 (22.5%)
f_e (%)	8.914 (30.6%)	12.90 (21.3%)	22.14 (40.0%)	36.00 (31.3%)	18.76 (32.5%)	20.44 (22.9%)	13.70 (34.6%)	18.93 (22.5%)
CL _R (mL/min/kg)	0.0588 (30.1%)	0.0980 (26.2%)	0.8532 (32.4%)	1.226 (23.1%)	1.972 (30.7%)	2.583 (21.2%)	3.099 (34.6%)	3.922 (27.0%)

^(a) Median (min-max)

^(b) AUC, CL/F, Ae on Day 1 and AUC_τ, CL_{SS}/F, Ae_τ on Day 12, respectively.

^(c) Not determined

[Reviewer comment: The C_{max} values of BRV as well as all metabolites increase on Day 12 compared to Day 1.

In the table above, the Sponsor is comparing AUC_{0-∞, Day 1} to AUC_{τ, Day 12} (SS). In theory, the AUC during one dosing interval at steady state is the same as the AUC from zero to infinity after the first dose. However, the BRV AUC_{τ, Day 12} is about 13% less than the AUC_{0-∞, Day 1}. Please refer to the comments at the end of the review for discussion.

In terms of accumulation, Sponsor indicates that the mean BRV AUC_{τ, Day 1} is 43.27 µg·h/mL and on Day 12 is 63.59 µg·h/mL. The Sponsor computes an accumulation ratio of 1.47 based on AUC_{τ, Day 12} compared to Day 1.

	<p>Table N01118-2: AUC_{tau} Comparison on Day 1 and Day 12</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="2">BRV (ucb 34714)</th> <th rowspan="2">Ratio</th> </tr> <tr> <th>Day 1</th> <th>Day 12</th> </tr> </thead> <tbody> <tr> <td>AUC_{tau} Mean (%CV)</td> <td>43.27 (19.1%)</td> <td>63.59 (15%)</td> <td>1.47</td> </tr> </tbody> </table> <p><i>This reviewer concurs with the accumulation ratio estimate based on AUC_{tau}. Such accumulation is comparable with that observed in non-elderly adults.]</i></p>	Parameter	BRV (ucb 34714)		Ratio	Day 1	Day 12	AUC _{tau} Mean (%CV)	43.27 (19.1%)	63.59 (15%)	1.47																																																																				
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<p>Safety</p>	<p>Table N01118-3: Summary of Treatment Emergent Adverse Events</p> <table border="1"> <thead> <tr> <th>Treatment-emergent AEs</th> <th>65-75 years n= 10</th> <th>> 75 years n= 6</th> <th>Male n= 8</th> <th>Female n= 8</th> <th>Overall n= 16</th> </tr> </thead> <tbody> <tr> <td>n (%) with ≥ 1 treatment-emergent AE</td> <td>9 (90.0%)</td> <td>5 (83.3%)</td> <td>6 (75.0%)</td> <td>8 (100%)</td> <td>14 (87.5%)</td> </tr> <tr> <td>n (%) discontinued due to an AE</td> <td>0</td> <td>1 (16.7%)</td> <td>1 (12.5%)</td> <td>0</td> <td>1 (6.3%)</td> </tr> <tr> <td>n (%) with ≥ 1 drug-related AE</td> <td>9 (90.0%)</td> <td>5 (83.3%)</td> <td>6 (75.0%)</td> <td>8 (100%)</td> <td>14 (87.5%)</td> </tr> <tr> <td>n (%) with ≥ 1 severe AEs</td> <td>0</td> <td>1 (16.7%)</td> <td>1 (12.5%)</td> <td>0</td> <td>1 (6.3%)</td> </tr> <tr> <td>n (%) with ≥ 1 SAE</td> <td>0</td> <td>1 (16.7%)</td> <td>1 (12.5%)</td> <td>0</td> <td>1 (6.3%)</td> </tr> <tr> <td>General disorders</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Fatigue</td> <td>4 (40.0%)</td> <td>0</td> <td>2 (25.0%)</td> <td>2 (25.0%)</td> <td>4 (25.0%)</td> </tr> <tr> <td>Feeling drunk</td> <td>2 (20.0%)</td> <td>2 (33.3%)</td> <td>3 (37.5%)</td> <td>1 (12.5%)</td> <td>4 (25.0%)</td> </tr> <tr> <td>Nervous system disorders</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Dizziness</td> <td>4 (40.0%)</td> <td>3 (50.0%)</td> <td>2 (25.0%)</td> <td>5 (62.5%)</td> <td>7 (43.7%)</td> </tr> <tr> <td>Headache</td> <td>4 (40.0%)</td> <td>2 (33.3%)</td> <td>3 (37.5%)</td> <td>3 (37.5%)</td> <td>6 (37.5%)</td> </tr> <tr> <td>Somnolence</td> <td>4 (40.0%)</td> <td>5 (83.3%)</td> <td>3 (37.5%)</td> <td>6 (75.0%)</td> <td>9 (56.2%)</td> </tr> </tbody> </table> <ul style="list-style-type: none"> • All AEs related to study medications were mild • The most frequent AEs were fatigue, feeling drunk, somnolence, dizziness, and headache. • Incidence of AEs was similar among age groups • Cardiovascular findings (SBP, DBP, HR, and RF) were consistent with previous observations in health subjects. • The observed QTc prolongation was considered not clinically significant by investigator • One subject discontinued due to a SAE (spontaneous paroxysmal atrial fibrillation) that was considered unlikely to be related to study medication 	Treatment-emergent AEs	65-75 years n= 10	> 75 years n= 6	Male n= 8	Female n= 8	Overall n= 16	n (%) with ≥ 1 treatment-emergent AE	9 (90.0%)	5 (83.3%)	6 (75.0%)	8 (100%)	14 (87.5%)	n (%) discontinued due to an AE	0	1 (16.7%)	1 (12.5%)	0	1 (6.3%)	n (%) with ≥ 1 drug-related AE	9 (90.0%)	5 (83.3%)	6 (75.0%)	8 (100%)	14 (87.5%)	n (%) with ≥ 1 severe AEs	0	1 (16.7%)	1 (12.5%)	0	1 (6.3%)	n (%) with ≥ 1 SAE	0	1 (16.7%)	1 (12.5%)	0	1 (6.3%)	General disorders						Fatigue	4 (40.0%)	0	2 (25.0%)	2 (25.0%)	4 (25.0%)	Feeling drunk	2 (20.0%)	2 (33.3%)	3 (37.5%)	1 (12.5%)	4 (25.0%)	Nervous system disorders						Dizziness	4 (40.0%)	3 (50.0%)	2 (25.0%)	5 (62.5%)	7 (43.7%)	Headache	4 (40.0%)	2 (33.3%)	3 (37.5%)	3 (37.5%)	6 (37.5%)	Somnolence	4 (40.0%)	5 (83.3%)	3 (37.5%)	6 (75.0%)	9 (56.2%)
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<p>Sponsor's Conclusions</p>	<ul style="list-style-type: none"> • On Day 12, C_{max} and AUC were slightly lower than expected on the basis of single administration, indicating an auto-induction of the metabolism • T_{1/2} was 8.3 hours overall, and 9.1 hours in male subjects. T_{1/2} in elderly male subjects is 25% longer than observed in healthy younger male subjects (7.3 hours). This suggests a decrease in BRV metabolism in elderly subjects compared to non-elderly subjects. • The % of ucb 34714 (BRV), ucb-100406-1 (hydroxy metabolite), ucb 42145 (carboxylic acid metabolite) and ucb-107092-1 (hydroxy-acid metabolite), excreted in urine were higher in the elderly population (9%, 22%, 18% and 14% in N01118) than in the non-elderly adult population (5.4%, 11.4% and 21.7% in N01067) • BRV Accumulation from Day 12 to Day 1 based on AUC_{tau} was 1.47 • The point estimate (90% CI) of AUC_{0-∞, Day 1} / AUC_{tau, Day 12} GMR is 87.19% (84.24 – 90.23%). The decrease in BRV Day 1 to Day 12 is likely due to an auto-induction phenomenon. • On the basis of these pharmacokinetic results and in the conditions of this study, no dose adjustment would be necessary in healthy elderly male or female subjects. 																																																																														

Reviewer Comment	<ul style="list-style-type: none">• <i>Although the BRV C_{max} values increased by about 50% over 2 weeks, BRV appeared to be reasonably well-tolerated in elderly subjects (e.g. only one subject discontinued, and it was due to a SAE that was considered not likely related to the study medication). Overall, the safety profile for 200 mg bid BRV use in elderly subjects is comparable to non-elderly adults.</i>• <i>AUC_{tau} accumulation was comparable in elderly adults ($R_{AUC,tau} = 1.47$ in current study) and non-elderly adults ($R_{AUC,tau} = 1.5$ in N01067)</i>• <i>C_{max} was 14% greater after multiple 200 mg bid doses to elderly subjects (Day 12 mean C_{max} 8.751 [19.9%] $\mu\text{g/mL}$) compared to multiple 200 mg bid doses to healthy non-elderly subjects (Day 14 mean C_{max} 7.65 [26.2%] $\mu\text{g/mL}$ in study N01067).</i>• <i>AUC_{tau} was 15% greater after multiple 200 mg bid doses to elderly subjects (Day 12 mean AUC_{tau} 63.59 [15.0%] $\mu\text{g}\cdot\text{h/mL}$) compared to multiple 200 mg bid doses to healthy non-elderly subjects (Day 14 mean AUC_{tau} 55.38 [18.3%] $\mu\text{g/mL}$ in study N01067).</i>• <i>Considering the safety profile in the current study, and that the current study administered 200 mg bid (double the maximum proposed dose for the label), no dose reduction is required based on the observed C_{max} and AUC elevations in elderly subjects.</i>• Overall, no dose adjustment is necessary in elderly subjects• <i>In theory, the AUC during one dosing interval at steady state is the same as the $AUC_{0-\infty}$ after the first dose (if PK parameters do not change with time). However, $AUC_{tau, Day 12}$ is ~13% lower than $AUC_{0-\infty, Day 1}$. This is likely due to the increase in BRV CL_{NR} as well as BRV CL_R on Day 12 compared to Day 1</i>• <i>It is not clear why non-renal BRV CL_{NR} increases over time (0.6036 mL/min/kg versus 0.6618 mL/min/kg on Days 1 and 12, respectively; 9.6% increase over 12 days).</i>• <i>It is not clear why renal CL increases over time for BRV (66% increase) and for all metabolites. However, the renal CL of BRV is a minor route of elimination (10-15%) and the change is not likely to result in a clinically significant reduction of efficacy or increase in AE risk. As the metabolites are not active, an increase in metabolite renal CL over time is not expected to result in a reduction of efficacy.</i>
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4.4.12 N01133: DDI – Carbamazepine (Phase 1)

Study Report#	RPCE03D1101 / N01133				
Title	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.				
Objectives	<p><u>Primary:</u> to evaluate the effect of <i>steady-state</i> ucb 34714 (brivaracetam) administration on the <i>steady-state</i> plasma levels of CBZ, CBZ-E, and CBZ-diol</p> <p><u>Secondary:</u> to gain information on the safety of concomitant ucb 34714 + CBZ.</p>				
Study Design	open-label, unilateral interaction trial				
Duration	9 weeks				
Dosage and Administration	<p>Subjects received BRV + CBZ extended release (≥600 mg daily):</p> <p>a) 1x50 mg capsule BRV twice daily from Days 1 to 7 (50 mg bid, up-titration, Period A)</p> <p>b) 2x50 mg capsules BRV twice daily from Days 8 to 14 (100 mg bid, up-titration, Period B)</p> <p>c) 1x200 mg capsule BRV twice daily from Days 15 to 21 (200 mg bid, <i>maintenance</i>, Period C)</p> <p>d) 2x50 mg capsules BRV twice daily from Days 22 to 28 (100 mg bid, down-titration, Period D)</p>				
PK Assessment	<p>Sponsor assessed PK of BRV, CBZ, CBZ-E (carbamazepine-10,11 epoxide), and CBZ-diol (carbamazepine-diol)</p> <p><u>Plasma Samples:</u> Plasma samples were obtained before the morning dose of 50 mg (Day 1), 100 mg (Day 8), 200 mg (Day 15), 100 mg (Day 22) and at the end of the treatment (Day 29).</p> <p><u>PK analyses:</u> Sponsor conducted pairwise comparison of CBZ, CBZ-E, and CBZ-diol exposures on Day 1 (without BRV) compared to Days 8, 15, 22, and 29 (with BRV) and on discharge (without BRV).</p>				
Bioanalytical Methods	HPLC-MS/MS Analytical Methods for BRV Concentrations				
	Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
	Internal Standard (IS)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Standard curve concentrations	10.0 20.0 45.1 100 200 451 1002 2004 ng/mL	2.00 5.00 20.0 50.0 99.9 500 999 1999 ng/mL	1.88 4.71 18.8 47.1 94.1 471 941 1882 ng/mL	1.87 4.67 18.7 46.7 93.3 467 933 1867 ng/mL
	Standards accuracy	-9.0 to 8.0%	-7.3 to 5.1%	-5.5 to 8.0%	-5.1 to 3.7%
	QC concentrations	0.036, 0.154 and 1.82 µg/mL	10.0, 74.2 and 1806 ng/mL*	9.54, 70.6 and 1717 ng/mL*	9.50, 70.3 and 1710 ng/mL*
	QC Accuracy	-5.6 to -0.3%	-5.9 to 6.4%	0.7 to 9.7%	-6.6 to 9.7%
	LLOQ	0.01 µg/mL	0.002 µg/mL*	0.002 µg/mL*	0.002 µg/mL*
*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).					

	<p>IS (b) (4) IS (b) (4)</p> <p>HPLC-MS/MS Analytical Methods for CBZ and CBZ-E Concentrations</p> <table border="1"> <thead> <tr> <th>Analyte Name</th> <th>Carbamazepine</th> <th>Carbamazepine-Epoxyde</th> <th>Carbamazepine-diol</th> </tr> </thead> <tbody> <tr> <td>Analyte ID</td> <td>CBZ</td> <td>CBZ-E</td> <td>CBZ-D</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> <td colspan="2">(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>2.5, 5.0, 10, 15, 20 µg/mL</td> <td>1, 2.5, 5, 7.5, 10 µg/mL</td> <td>1.25, 2.5, 5, 7.5, 10 µg/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.2 to 11.5%</td> <td>-12.5 to 12.9%</td> <td>-4.6 to 7.1%</td> </tr> <tr> <td>QC concentrations</td> <td>3, 12 18 µg/mL</td> <td>1.5, 6, 9 µg/mL</td> <td>1.5, 6, 9 µg/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>1.2 to 3.3%</td> <td>6.7 to 16%</td> <td>4.2 to 10.7%</td> </tr> <tr> <td>QC Precision</td> <td>4.0 to 6.8%</td> <td>6.9 to 9.8%</td> <td>4.1 to 4.7%</td> </tr> <tr> <td>LLOQ</td> <td>2.5 µg/mL</td> <td>1.25 µg/mL</td> <td>1.25 µg/mL</td> </tr> </tbody> </table> <p><i>*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).</i></p> <p>IS (b) (4) IS (b) (4)</p> <p>[Reviewer comment: The assays for BRV, BRV metabolites, CBZ, and CBZ metabolites are acceptable.]</p>	Analyte Name	Carbamazepine	Carbamazepine-Epoxyde	Carbamazepine-diol	Analyte ID	CBZ	CBZ-E	CBZ-D	Internal Standard (IS)	(b) (4)	(b) (4)		Standard curve concentrations	2.5, 5.0, 10, 15, 20 µg/mL	1, 2.5, 5, 7.5, 10 µg/mL	1.25, 2.5, 5, 7.5, 10 µg/mL	Standards accuracy	-4.2 to 11.5%	-12.5 to 12.9%	-4.6 to 7.1%	QC concentrations	3, 12 18 µg/mL	1.5, 6, 9 µg/mL	1.5, 6, 9 µg/mL	QC Accuracy	1.2 to 3.3%	6.7 to 16%	4.2 to 10.7%	QC Precision	4.0 to 6.8%	6.9 to 9.8%	4.1 to 4.7%	LLOQ	2.5 µg/mL	1.25 µg/mL	1.25 µg/mL
Analyte Name	Carbamazepine	Carbamazepine-Epoxyde	Carbamazepine-diol																																		
Analyte ID	CBZ	CBZ-E	CBZ-D																																		
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Standards accuracy	-4.2 to 11.5%	-12.5 to 12.9%	-4.6 to 7.1%																																		
QC concentrations	3, 12 18 µg/mL	1.5, 6, 9 µg/mL	1.5, 6, 9 µg/mL																																		
QC Accuracy	1.2 to 3.3%	6.7 to 16%	4.2 to 10.7%																																		
QC Precision	4.0 to 6.8%	6.9 to 9.8%	4.1 to 4.7%																																		
LLOQ	2.5 µg/mL	1.25 µg/mL	1.25 µg/mL																																		
<p>Population/ Demographics</p>	<p>N=9 male subjects with epilepsy receiving steady-state carbamazepine</p> <p>Inclusion:</p> <ol style="list-style-type: none"> 1. Male patients with epilepsy age 18 to 65 years 2. Receiving CBZ extended release therapy (≥ 600 mg bid), on stable dose for 3 months before and during trial, CBZ plasma levels 4-12 µg/mL <p>Exclusion:</p> <ol style="list-style-type: none"> 5 Use of other drugs with CNS effects 6 Drugs which may affect BRV metabolism (2C or 3A potent inducers inhibitors) unless dose is stable or 3 months before and during trial 7 Clinically significant laboratory parameter deviations (ALT/SGPT, AST/SGOT, GGT > 3 x ULN). Non-significant deviations must be stable for at least 6 months. 8 Clinically significant EGE abnormalities 																																				

PK Results

Figure N01133-1: Mean (\pm SD on In-data) SS BRV Plasma PK Profile over 4 weeks of BRV Administration

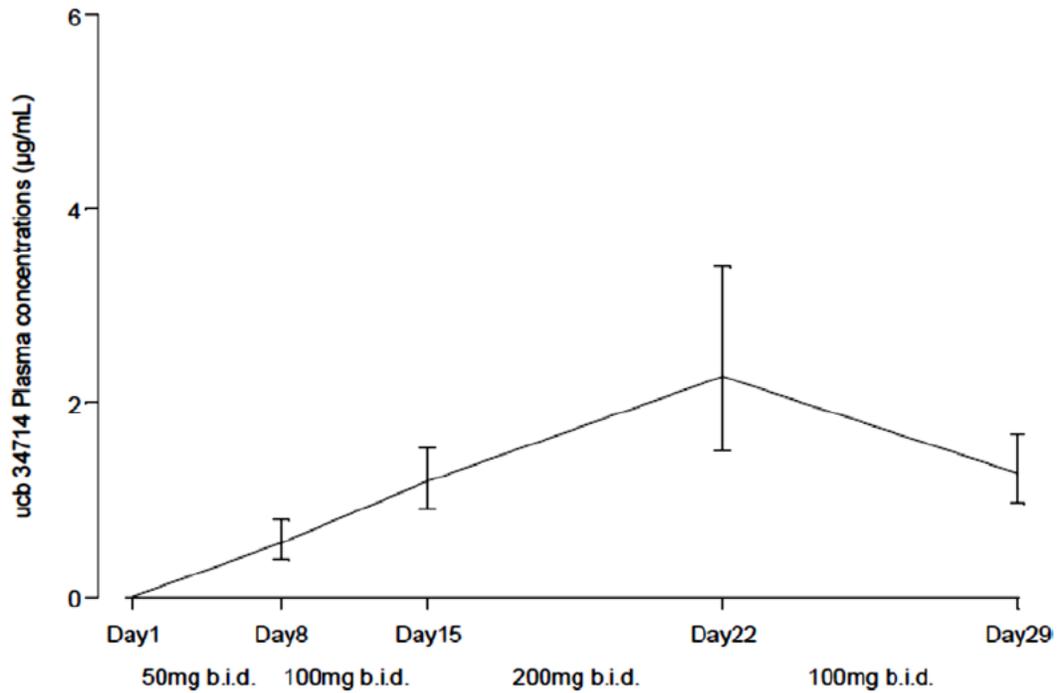


Figure N01133-2: Mean (\pm SD on In-data) SS CBZ Plasma PK Profile Before, During, and After 4 weeks of BRV Administration

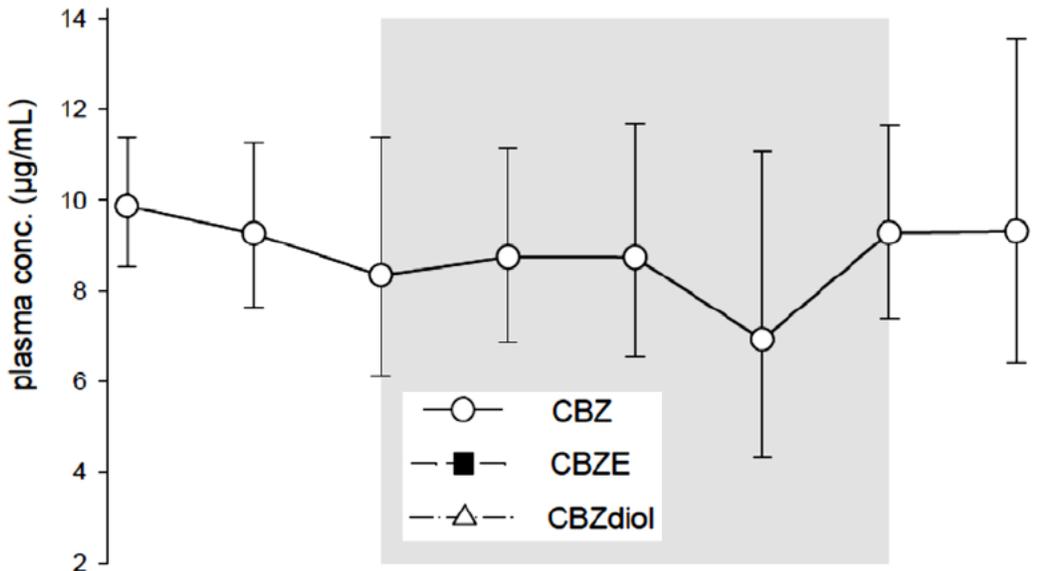
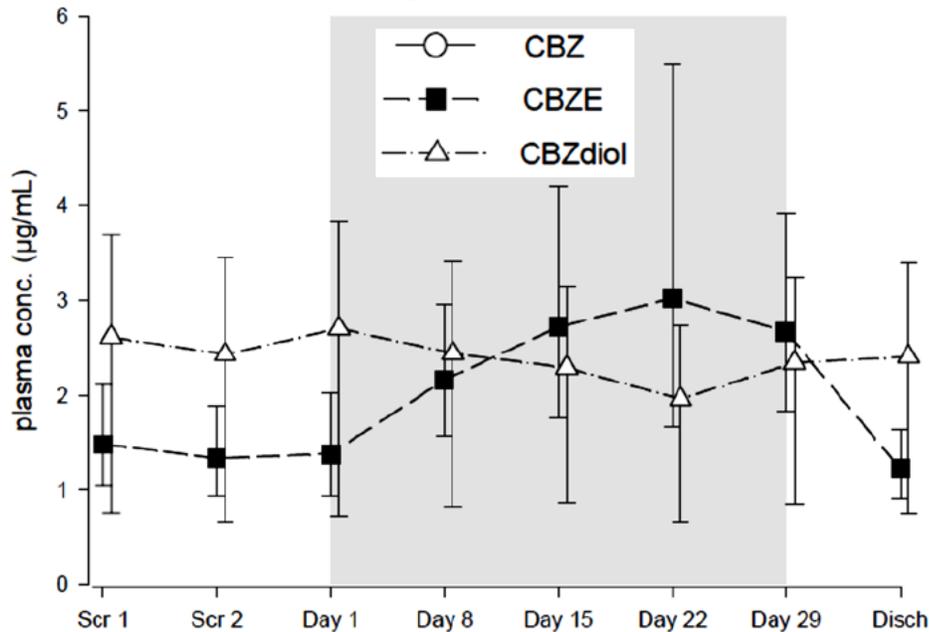


Figure N01133-3: Geometric Mean (\pm SD on In-data) SS **CBZ-E and **CBZ-Diol** Plasma PK Profile Before, During, and After 4 weeks of **BRV** Administration**



[Reviewer comment: The plot above displays the geometric mean. Sponsor reports the following CBZ-E concentrations over time (arithmetic mean \pm SD) as: 1.48 (0.65), 2.26 (0.74), 2.96 (1.26), 3.46 (1.67), 2.84 (1.01) 1.27 (0.42) on Day 1 (pre-dose), Day 8, Day 15, Day 22, Follow-up, discharge]

Table N01133-1: Statistical Comparison of SS **CBZ, **CBZ-E**, and **CBZ-Diol** Plasma PK Parameters Before, During, and After 4 weeks of **BRV** Administration**

Day pre-dose	CBZ ($\mu\text{g/mL}$)		CBZE ($\mu\text{g/mL}$)		CBZ-diol ($\mu\text{g/mL}$)	
	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

[Reviewer comment: The increase in CBZ-E trough concentration on Day 22 is comparable to the CBZ-E trough increase observed in study N01135 (223%).]

Safety

- TEAEs occurred in 89% (8 of 9) subjects. Of these 6, were considered drug related
- 1 subject had 2 severe TEAEs (post ictal state, and aggression) which required hospitalization. These occurred 2-days after the last study drug intake (during the down-titration).
- The most frequent TEAEs were fatigue (2 subjects) and nasopharyngitis (2 subjects). Convulsion, dizziness, and "post-ictal state" were experienced by 1 subject each. Aside from the 2 SAEs, other TEAEs were mild.
- subjects exhibited borderline increases (from 430 to 450 ms), and 2 subjects

	<p>showed a prolongation (>450 ms) of QTc, one at 100 mg up-titration Day 8 and one at 100 mg down-titration Day 22. Sponsor did not consider ECG parameter modifications in this study to be clinically significant.</p>
<p>Sponsor's Conclusions</p>	<ol style="list-style-type: none"> 1. BRV and metabolites increased dose-proportionally across 50, 100, and 200 mg bid BRV administration (when administered concomitantly with CBZ). 2. BRV 200 mg bid administration resulted in higher BRV in this study compared to study N01081. This may be due to the fact that N01081 was conducted in healthy subjects and this study in epilepsy patients). Also, this study utilized XR CBZ while N01081 utilized IR CBZ. 3. BRV dose-dependently increases CBZ-E trough levels, whereas CBZ trough levels were unaffected at the lower two doses (50 and 100 mg bid BRV) and reduced CBZ trough 17% after 200 mg bid BRV. 4. CBZ-E plasma concentration remained within the limits of "normal range" for adults taking other AEDs (increase from 1.4 to 3.0, normal range 1.4 to 4.2 µg/mL), citing a 1998 article by Potter et al. (PMID: 9853982). 5. The increase in CBZ-E / CBZ ratio is comparable to the previous CBZ interaction study (N01081). 6. CBZ-diol concentrations tended to decrease with increasing BRV exposure 7. The SAEs were likely related to epileptic pathology or treatment. The ECG findings do not suggest the need for specific precaution for concomitant BRV + CBZ.
<p>Reviewer Comment</p>	<ol style="list-style-type: none"> 1. <i>BRV was administered up to 200 mg bid, whereas the current label is proposing a maximum dose of 100 mg bid.</i> 2. <i>BRV exposure change does not warrant a BRV dose adjustment</i> 3. <i>CBZ exposure change was not consistent across the 4 weeks of concomitant BRV treatment (e.g. +4.8% on Day 8, -17% on Day 22, and +11.1% on Day 29, +11.6% at discharge).</i> 4. <i>CBZ-E exposure increased 56.6% to 119.6% across Day 8 to 29. At discharge, the CBZ-E exposure decreased to 11% below Day 1 levels. The accumulation of the CBZ-E metabolite is likely due to the inhibition of epoxide hydrolase by BRV.</i> 5. <i>Sponsor states that the increase in CBZ-E lead to CBZ-E levels that are "normally" seen in patients receiving CBZ therapy (Sponsor reports normal range to be 1.4 to - 4.2 µg/mL for CBZ-E).</i> 6. <i>No new safety findings are apparent from this study report. While the lack of a safety signal can be viewed as supportive of concomitant CBZ-E and BRV, the 4-weeks of concomitant use may not provide adequate safety information to assess concomitant BRV and CBZ use. However, patients were receiving 600 mg CBZ bid (1200 mg/day), and patients with greater CBZ doses (e.g. 2000 mg/day) may experience tolerability issues with concomitant BRV due to increased CBZ-E levels.</i> 7. <i>While the potential for increased toxicity is possible with increased carbamazepine-epoxide, it may also result in increased efficacy. A carbamazepine dose reduction should be considered if tolerability issues arise.</i>

4.4.13 N01135: DDI – Carbamazepine (+ VPA) (Phase 1)

Study Report#	RPCE03E1603 / N01135																
Title	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).																
Objectives	<u>Primary:</u> Assess the effect of steady state BRV on SS plasma levels of CBZ and metabolites <u>Secondary:</u> 1. To gain information on the safety BRV use with CBZ + VPA 2. To confirm that BRV does not modify VPA trough levels.																
Study Design	Two-center, open-label, unilateral interaction trial																
Duration	4 weeks exposure for each subject (9 weeks total)																
Dosage and Administration	Subjects were already receiving CBZ (≥600 mg daily) and VPA (≥500 mg daily). BRV was introduced with the background CBZ and VPA as follows: <ul style="list-style-type: none"> • Baseline period (3 weeks) : screening. • Evaluation period (3 weeks) : <ul style="list-style-type: none"> ○ Up-titration period (1 week) : 50 mg of ucb 34714 bid. ○ Up-titration period (1 week) : 100 mg of ucb 34714 bid. ○ Maintenance period (1 week) : 200 mg of ucb 34714 bid. • Down-titration (1 week) : 100 mg of ucb 34714 bid. • Follow-up : 2 weeks without study treatment. 																
PK Assessment	Sponsor assessed the trough concentrations of brivaracetam and CBZ, CBZE and CBZD and VPA. All PK samples were collected before the morning dose. <u>Plasma PK samples – BRV:</u> Days 1, 8, 15, 22 and 29 <u>Plasma PK samples – CBZ and VPA:</u> Screening (two samples separated by 3-8 days), Days 1, 8, 15, 22, 29, and discharge. <u>PK Analyses:</u> Sponsor conducted pairwise comparison of CBZ, CBZ-E, and CBZ-diol exposures on Day 1 (without BRV) compared to Days 8, 15, 22, and 29 (with BRV) and on discharge (without BRV).																
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>40, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.4 to 5.9%</td> </tr> <tr> <td>QC concentrations</td> <td>150, 600, 1750 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-3.3 to 0.7%</td> </tr> <tr> <td>LLOQ</td> <td>0.05 µg/mL</td> </tr> </table> <p>[Reviewer comment: The BRV assay has been previously validated. The performance of this assay is acceptable. Please refer to study N01133 ISR for details regarding the assay for CBZ, CBZ-E, and CBZ-D.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	40, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL	Standards accuracy	-4.4 to 5.9%	QC concentrations	150, 600, 1750 ng/mL	QC Accuracy	-3.3 to 0.7%	LLOQ	0.05 µg/mL
Analyte Name	Brivaracetam																
Analyte ID	ucb 34714																
Internal Standard (IS)	(b) (4)																
Standard curve concentrations	40, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL																
Standards accuracy	-4.4 to 5.9%																
QC concentrations	150, 600, 1750 ng/mL																
QC Accuracy	-3.3 to 0.7%																
LLOQ	0.05 µg/mL																

<p>Population/ Demographics</p>	<p>N=9</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female epilepsy patients age 18 to 65 years 2. Receiving CBZ (≥ 600 mg/day) for at least 3 months and on a stable valproic acid (VPA) dose for at least 3 months (≥ 500 mg/day), 3. CBZ concentration 4 to 12 $\mu\text{g/mL}$ 4. VPA concentration 40 to 100 $\mu\text{g/mL}$ (280 to 700 $\mu\text{mole/L}$) 5. Women of childbearing potential were to use an acceptable birth control method <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Pregnant or nursing 2. Use of other drugs with CNS effects 3. Drugs which may affect BRV metabolism (2C or 3A potent inducers/inhibitors) unless dose is stable or 3 months before and during trial 4. CRCL < 80 ml/min 5. Impaired hepatic function, clinically significant laboratory parameter deviations (SGPT/SGPT, SGOT/SGOT, alkaline phosphatase, GGT $> 3 \times$ ULN). Non-significant deviations must be stable for at least 3-weeks (and attributable to hepatic enzyme induction, due to CBZ or VPA). 6. Clinically significant EGE abnormalities 																		
<p>PK Results</p>	<p>BRV trough concentrations were approximately proportional between 50 and 200 mg bid.</p> <p>Figure N01135-1: Geometric Mean (\pm SD on In-data) <u>BRV</u> Trough Concentration Profiles</p> <table border="1"> <caption>Data for Figure N01135-1: Geometric Mean (\pm SD on In-data) <u>BRV</u> Trough Concentration Profiles</caption> <thead> <tr> <th>Day</th> <th>Dose</th> <th>Geometric Mean Plasma Concentration ($\mu\text{g/mL}$)</th> </tr> </thead> <tbody> <tr> <td>D1</td> <td>0 mg</td> <td>0.0</td> </tr> <tr> <td>D8</td> <td>50 mg bid</td> <td>~0.45</td> </tr> <tr> <td>D15</td> <td>100 mg bid</td> <td>~0.95</td> </tr> <tr> <td>D22</td> <td>200 mg bid</td> <td>~1.55</td> </tr> <tr> <td>D29</td> <td>100 mg bid</td> <td>~0.8</td> </tr> </tbody> </table> <p>[Reviewer comment: The Day 22 BRV gmean concentration in the current study is 1.41 $\mu\text{g/mL}$ and the Day 22 BRV gmean concentration is 2.26 $\mu\text{g/mL}$ in study N01133 (37% lower BRV concentration). Please refer to the comments at the end of this ISR for details.]</p>	Day	Dose	Geometric Mean Plasma Concentration ($\mu\text{g/mL}$)	D1	0 mg	0.0	D8	50 mg bid	~0.45	D15	100 mg bid	~0.95	D22	200 mg bid	~1.55	D29	100 mg bid	~0.8
Day	Dose	Geometric Mean Plasma Concentration ($\mu\text{g/mL}$)																	
D1	0 mg	0.0																	
D8	50 mg bid	~0.45																	
D15	100 mg bid	~0.95																	
D22	200 mg bid	~1.55																	
D29	100 mg bid	~0.8																	

Figure N01135-2: Geometric Mean (\pm SD on In-data) CBZ Trough Concentration Profiles (Grey Box is BRV Dosing Period)

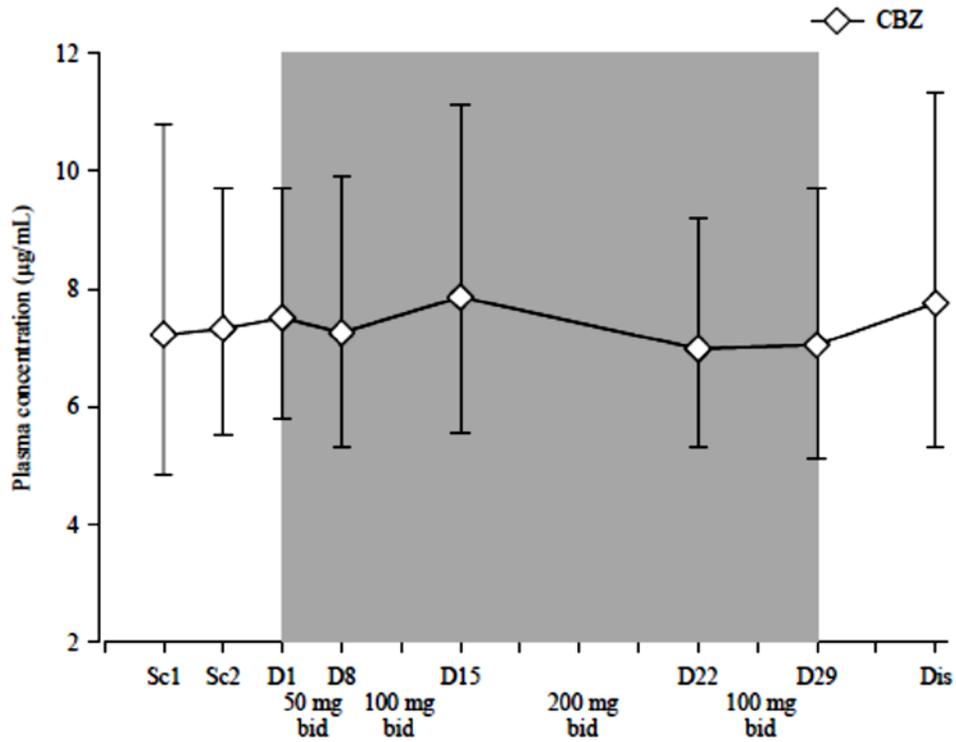


Figure N01135-3: Geometric Mean (\pm SD on In-data) CBZ-D and CBZ-E Trough Concentration Profiles (Grey Box is BRV Dosing Period)

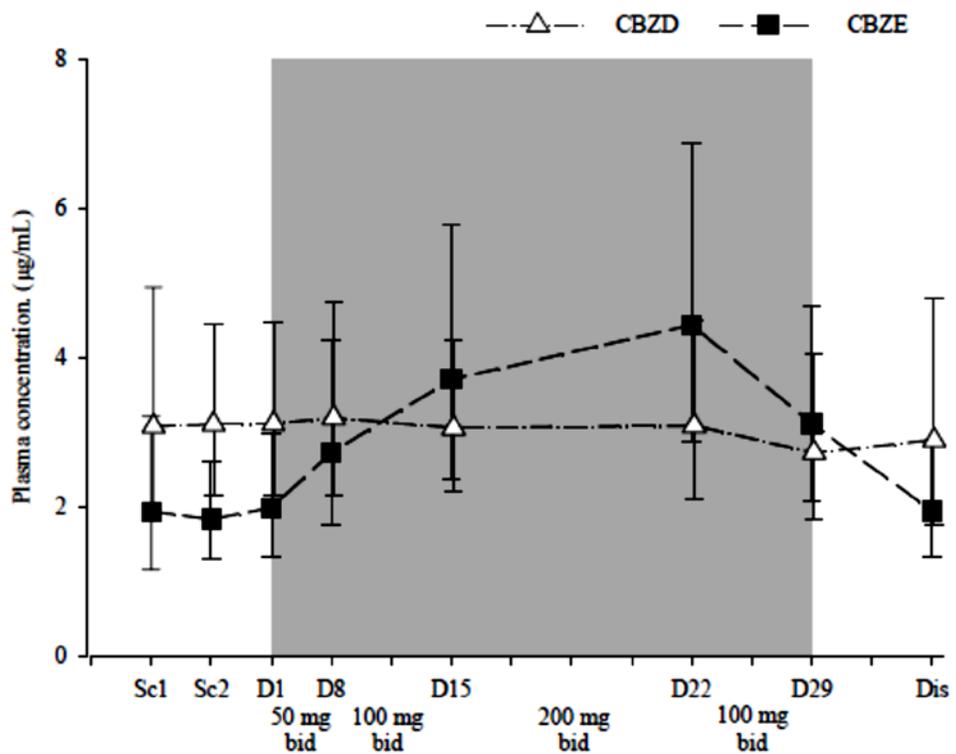


Figure N01135-4: Geometric Mean (± SD on In-data) VPA Trough Concentration Profiles (Grey Box is BRV Dosing Period)

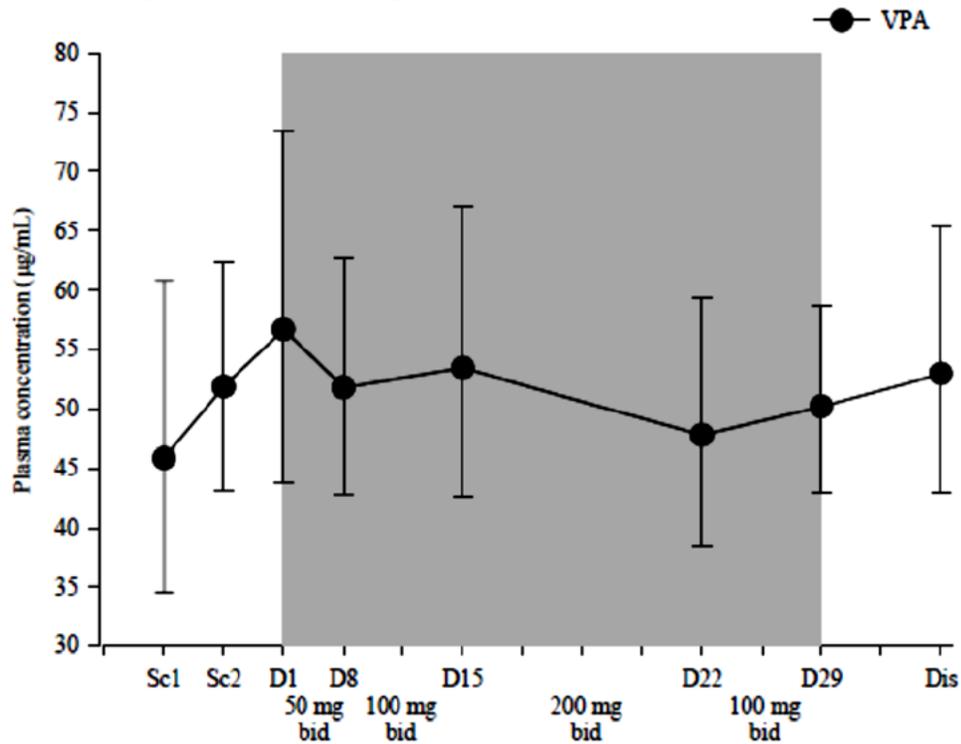


Table N01135-1: Statistical Comparison of SS CBZ, CBZ-E, and CBZ-Diol Plasma PK Parameters Before, During, and After 4 weeks of BRV Administration

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

[Reviewer comment: The increase in CBZ-E trough concentration on Day 22 is comparable to the CBZ-E trough increase observed in study N01133 (219%).]

Safety	TEAEs were observed in 78% (n=7) of subjects, 33% (n=3) of subjects experienced TEAEs that were considered drug related. 2 subjects experienced SAEs (“feeling abnormal” and “epilepsy”) and required hospitalization. A limited increase of SGOT, GGT, and to a lesser extent SGPT increase was observed (but determined to be clinically insignificant). No QTc values were > 500 ms. A limited SBP decrease was observed which was not-dose-related was attenuated with repeat administration
Sponsor’s Conclusions	<ul style="list-style-type: none"> • CBZ trough levels did not vary significantly after the BRV regimen (compared to before the BRV regimen) • A dose-related increase of mean trough CBZ-E was observed. • VPA levels were not significantly altered after the BRV regimen (compared to before the BRV regimen)

	<ul style="list-style-type: none">• BRV has a limited tendency to decrease SBP (no effect on DBP or heart rate)• ECG changes do not warrant any special warning for BRV+CBZ+VPA.• This study does not suggest the need for any specific warnings for BRV+CBZ+ VPA.
<i>Reviewer Comment</i>	<ul style="list-style-type: none">• <i>The Day 22 BRV mean concentration in the current study is 1.41 µg/mL and the Day 22 BRV mean concentration was 2.26 µg/mL in study N01133 (37% lower BRV concentration). Concomitant VPA use, in combination with CBZ use, may be causing a BRV decrease (as VPA is not permitted in study N01133). However, considering the shallow exposure-response relationship at the 200 mg/day dose level, the 37% BRV decrease from 2.26 to 1.41 µg/mL is not expected to result in a clinically significant reduction in efficacy. Please refer to the pharmacometrics section of this review for additional details.</i>• <i>CBZ and CBZ-Diol did not appear to be altered by BRV in the current study.</i>• <i>CBZ-E increased up to 123.7% in the current study. Please refer to the ISR for study N01133 for labeling recommendations regarding CBZ-E increases when CBZ is used concomitantly with BRV.</i>• <i>VPA concentrations showed a decreasing trend throughout the concomitant BRV treatment. However, in comparison to the changes in VPA PK profile prior to BRV administration, there is no consistent effect of BRV on VPA.</i>

4.4.14 N01170: DDI – Topiramate (Phase 1)

Study Report#	RPCE04K1904 / N01170																																									
Title	Monocenter, open label, unilateral interaction study of brivaracetam at steady-state (200 mg twice daily) on topiramate (200 mg single dose) in 14 healthy volunteers.																																									
Objectives	<u>Primary:</u> Assess the effect of steady-state BRV affects single-dose topiramate PK <u>Secondary:</u> Gain information on tolerability of TPM + BRV																																									
Study Design	monocenter, open label interaction study.																																									
Duration	17 days																																									
Dosage and Administration	Brivaracetam (200 mg capsules twice daily) was taken morning and evening from Day 5 to Day 16 and once the morning of Day 17. Topiramate (TPM, 100 mg tablet) was taken on the morning of Day 1 and Day 14.																																									
PK Assessment	<p>PK samples were acquired pre-morning dose.</p> <p><u>Plasma PK Samples - BRV:</u> Days 7, 10, 13, 14, and 16 <u>Plasma PK Samples – TPM:</u> Day 1 and 14 at pre-dose, 0.5h, 1h, 1.5h, 2h, 3h, 6h, 9h, 12h, 24h, 48h, 72h and 96 hours after the morning dose</p> <p><u>PK Analyses:</u> Cmax, tmax, AUC(0-t), AUC, λz , t½, CL/F and Vz/F.</p>																																									
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1"> <tr><td>Analyte Name</td><td>Brivaracetam</td></tr> <tr><td>Analyte ID</td><td>ucb 34714</td></tr> <tr><td>Internal Standard (IS)</td><td>(b) (4)</td></tr> <tr><td>Standard curve concentrations</td><td>50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL</td></tr> <tr><td>Standards accuracy</td><td>-3.6 to 4.0%</td></tr> <tr><td>QC concentrations</td><td>150, 600, 1750 ng/mL</td></tr> <tr><td>QC Accuracy</td><td>-4.7 to 1.3%</td></tr> <tr><td>QC Precision</td><td>1.9 to 6.5%</td></tr> <tr><td>LLOQ</td><td>0.05 µg/mL</td></tr> </table> <p>HPLC-MS/MS Analytical Methods for TPM Plasma Concentrations</p> <table border="1"> <tr><td>Analyte Name</td><td>Topiramate</td></tr> <tr><td>Analyte ID</td><td>TPM</td></tr> <tr><td>Internal Standard (IS)</td><td>(b) (4)</td></tr> <tr><td>Recovery</td><td>99.4 to 105%</td></tr> <tr><td>Standard curve concentrations</td><td>1.25, 2.50, 6.25, 12.5, 25.0, 62.5, 125 µg/mL</td></tr> <tr><td>Standards accuracy</td><td>97 to 102%</td></tr> <tr><td>Standards Precision</td><td>1.3 to 5.0%</td></tr> <tr><td>QC concentrations</td><td>3.75, 37.5, 112.5 µg/mL</td></tr> <tr><td>QC Accuracy</td><td>105 to 113%</td></tr> <tr><td>QC Precision</td><td>2.6 to 7.1%</td></tr> <tr><td>LLOQ</td><td>1 .25 µg/mL</td></tr> </table>		Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50, 100, 250, 500, 750, 1000, 1500, 2000 ng/mL	Standards accuracy	-3.6 to 4.0%	QC concentrations	150, 600, 1750 ng/mL	QC Accuracy	-4.7 to 1.3%	QC Precision	1.9 to 6.5%	LLOQ	0.05 µg/mL	Analyte Name	Topiramate	Analyte ID	TPM	Internal Standard (IS)	(b) (4)	Recovery	99.4 to 105%	Standard curve concentrations	1.25, 2.50, 6.25, 12.5, 25.0, 62.5, 125 µg/mL	Standards accuracy	97 to 102%	Standards Precision	1.3 to 5.0%	QC concentrations	3.75, 37.5, 112.5 µg/mL	QC Accuracy	105 to 113%	QC Precision	2.6 to 7.1%	LLOQ	1 .25 µg/mL
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LLOQ	1 .25 µg/mL																																									

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	<p>[Reviewer comment: The assays are acceptable.]</p>																											
Population/ Demographics	<p>N=14</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none">1. healthy male and female subjects age 18-55 years.2. Good physical and mental health, normal ECG or abnormal but not clinically significant, laboratory test results within reference range. <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none">1. Hepatic, renal, gastrointestinal or other disorder that may affect drug ADME2. Heavy caffeine drinkers3. Current smokers (or smokers within 6 months)4. Any concomitant treatment (prescription or non-prescription) within 14 days of first drug administration (paracetamol 2 g/day and hormonal contraceptives 10 g / 14 days are permitted)5. Hepatic enzyme inducing drugs6. Women of childbearing potential unless using acceptable birth control																											
PK Results	<p>Figure N01170-1: Mean ± SD Plasma Concentration Profile for Topiramate</p> <table border="1"><caption>Estimated data from Figure N01170-1</caption><thead><tr><th>Time (hour)</th><th>Topiramate (µg/mL)</th><th>Topiramate + ucb34714 (µg/mL)</th></tr></thead><tbody><tr><td>0</td><td>0</td><td>0</td></tr><tr><td>1</td><td>1.2</td><td>1.0</td></tr><tr><td>2</td><td>2.5</td><td>2.0</td></tr><tr><td>3</td><td>3.2</td><td>2.8</td></tr><tr><td>4</td><td>3.6</td><td>3.4</td></tr><tr><td>8</td><td>3.3</td><td>3.2</td></tr><tr><td>12</td><td>2.9</td><td>2.7</td></tr><tr><td>24</td><td>2.0</td><td>1.9</td></tr></tbody></table>	Time (hour)	Topiramate (µg/mL)	Topiramate + ucb34714 (µg/mL)	0	0	0	1	1.2	1.0	2	2.5	2.0	3	3.2	2.8	4	3.6	3.4	8	3.3	3.2	12	2.9	2.7	24	2.0	1.9
Time (hour)	Topiramate (µg/mL)	Topiramate + ucb34714 (µg/mL)																										
0	0	0																										
1	1.2	1.0																										
2	2.5	2.0																										
3	3.2	2.8																										
4	3.6	3.4																										
8	3.3	3.2																										
12	2.9	2.7																										
24	2.0	1.9																										

Table N01170-2: Geometric Mean (CV%) Topiramate Single Dose PK With BRV Versus Without BRV

Parameters	Topiramate 200 mg alone ^(a)	Topiramate 200 mg with brivaracetam 200 mg <i>bid</i> ^(a)
C _{max} (µg/mL)	3.817 (10.4)	3.735 (12.9)
t _{max} (h)	3.00 (1.50-9.00)	3.00 (0.50-6.00)
AUC _(0-t) (µg*h/mL)	126.5 (17.6)	120.2 (18.1)
AUC (µg*h/mL)	142.9 (18.4)	133.8 (17.6)
t _{1/2} (h)	29.27 (17.4)	26.46 (16.5)
CL/F (mL/min/kg)	0.335 (16.9)	0.357 (19.2)
V _z /F (L/kg)	0.848 (10.9)	0.819 (9.36)

^(a) Values are geometric means (CV%), t_{max} values are median (minimum-maximum).

Source: Table 14.2.1:3

Table N01170-2: Statistical Comparison of Topiramate Single Dose PK With BRV Versus Without BRV

Parameters	Reference ^(a) : topiramate 200 mg	Test ^(a) : topiramate 200 mg and brivaracetam 200 mg <i>bid</i>	CV ^(b) (%)	Test versus reference ^(c)	
				Point estimate	90% CI
AUC (µg*h/mL)	142.9 (129.1 - 158.1)	133.8 (120.9 - 148.1)	8.59	93.66	88.43 - 99.19
AUC _(0-t) (µg*h/mL)	126.5 (114.4 - 139.8)	120.2 (108.8 - 132.8)	9.04	95.05	89.48 - 101.0
C _{max} (µg/mL)	3.817 (3.576 - 4.074)	3.735 (3.500 - 3.987)	7.12	97.86	93.31 - 102.6
t _{max} (h)	3.00 (1.50 - 9.00)	3.00 (0.50 - 6.00)	-	-0.52	-3.50 - 0.23

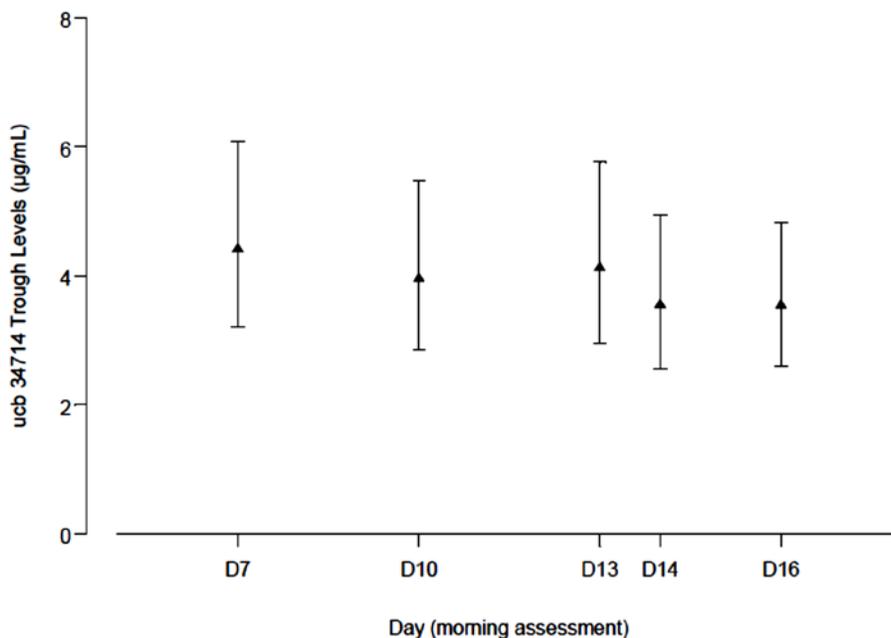
^(a) Values are geometric lsmeans (95% confidence interval), t_{max} values are median (minimum-maximum)

^(b) Intra-individual coefficient of variation (%)

^(c) Point estimate (90% confidence interval) for the Test/Reference geometric lsmeans ratio (%) derived from ANOVA; for t_{max}: median point estimate (90% non-parametric confidence interval) of the Test-Reference difference

The steady-state of brivaracetam was achieved by Day 14 when TPM 200 mg was administered. The mean trough levels were higher than those previously reported possibly due to the inclusion of female subjects in the study.

Figure N01170-2: Geometric Mean ± SD Plasma Concentration Profile for Brivaracetam



Safety	TEAEs were reported by 100% of subjects. The most common TEAEs were dizziness (n=14), fatigue (n=9), euphoric mood (n=5), headache and somnolence (n=4 each). One SAE was reported (anxiety). All other AEs were mild. The treatments were well-tolerated
Sponsor's Conclusions	<ul style="list-style-type: none">• BRV does not significantly alter the pharmacokinetics of TPM• The overall safety profile is in agreement with previous BRV studies
Reviewer Comment	<ul style="list-style-type: none">• <i>Sponsor states that presence of females in the study may be responsible for the increased exposures compared to previous trials. According to the population PK report (CL0028), females have approximately 13% greater C_{ss} than men.</i>• <i>Though the BRV may be elevated in this trial compared to others, the population PK analysis demonstrates that TPM decreases BRV C_{ss} by 8%. Please refer to the Extrinsic Factors portion of this review for more details regarding drug interactions.</i>• <i>The data support the Sponsor's claims that a) BRV does not significantly alter the pharmacokinetics of TPM and b) that the overall safety profile is in agreement with previous BRV studies.</i>

4.4.15 N01171: DDI – Lamotrigine (Phase 1)

Study Report#	RPCE04C0101 / N01171																																							
Title	Monocenter, open label, unilateral interaction study of ucb 34714 at steady-state (200 mg twice daily) on lamotrigine (25 mg single dose) in 14 healthy male volunteers.																																							
Objectives	<p><u>Primary</u>: Assess whether steady state BRV alters single dose PK of lamotrigine (LTG)</p> <p><u>Secondary</u>: Gain info on safety and tolerability of concomitant BRV + LTG</p>																																							
Study Design	monocenter, open label interaction																																							
Duration	7 weeks per subject																																							
Dosage and Administration	<p>BRV capsules (200 mg bid) were administered for 12 days (from D5 to D16 and once on the morning D17)</p> <p>A single oral LTG tablet (25 mg) was administered on D1 and D14</p>																																							
PK Assessment	<p><u>Plasma PK Samples – BRV</u>: in the morning of Days 7, 10, 13, 14 and 16 (before the breakfast and before the new administration of ucb 34714).</p> <p><u>Plasma PK Samples – LTG</u>: Day 1 and Day 14 (before breakfast) at pre-dose, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 6 h, 9 h, 12 h, 24 h, 48 h, 72 h and 96 h after the morning dose.</p> <p><u>PK Analyses</u>: Cmax, tmax, AUC(0-t), λz, t1/2, AUC, Vz/F and CL/F.</p>																																							
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1"> <tr><td>Analyte Name</td><td>Brivaracetam</td></tr> <tr><td>Analyte ID</td><td>ucb 34714</td></tr> <tr><td>Internal Standard (IS)</td><td>(b) (4)</td></tr> <tr><td>Standard curve concentrations</td><td>50.0 100 250 500 750 1000 1500 2000 ng/mL</td></tr> <tr><td>Standards accuracy</td><td>-1.9 to 2.2%</td></tr> <tr><td>Standards precision</td><td>1.4 to 5.0%</td></tr> <tr><td>QC concentrations</td><td>151, 604, 1761 ng/mL</td></tr> <tr><td>QC Accuracy</td><td>0.8 to 4.4%</td></tr> <tr><td>QC Precision</td><td>2.7 to 5.1%</td></tr> <tr><td>LLOQ</td><td>0.05 µg/mL</td></tr> </table> <p>HPLC-MS/MS Analytical Methods for LTG Plasma Concentrations</p> <table border="1"> <tr><td>Analyte Name</td><td>Lamotrigine</td></tr> <tr><td>Analyte ID</td><td>LTG</td></tr> <tr><td>Internal Standard (IS)</td><td>(b) (4)</td></tr> <tr><td>Standard curve concentrations</td><td>9.39, 2.98, 57.7, 7.13, 13.6, 23.4, 11.8 and 8.11 µg/mL</td></tr> <tr><td>Standards accuracy</td><td>-4.5 to 8.4%</td></tr> <tr><td>QC concentrations</td><td>1.47, 4.94, 10.0</td></tr> <tr><td>QC Accuracy</td><td>-6.8 to -3.0%</td></tr> <tr><td>QC Precision</td><td>3.2 to 4.0%</td></tr> <tr><td>LLOQ</td><td>0.5 µg/mL</td></tr> </table>		Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL	Standards accuracy	-1.9 to 2.2%	Standards precision	1.4 to 5.0%	QC concentrations	151, 604, 1761 ng/mL	QC Accuracy	0.8 to 4.4%	QC Precision	2.7 to 5.1%	LLOQ	0.05 µg/mL	Analyte Name	Lamotrigine	Analyte ID	LTG	Internal Standard (IS)	(b) (4)	Standard curve concentrations	9.39, 2.98, 57.7, 7.13, 13.6, 23.4, 11.8 and 8.11 µg/mL	Standards accuracy	-4.5 to 8.4%	QC concentrations	1.47, 4.94, 10.0	QC Accuracy	-6.8 to -3.0%	QC Precision	3.2 to 4.0%	LLOQ	0.5 µg/mL
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[Reviewer comment: The assays are validated.]

Population/ Demographics
 N=14
Inclusion Criteria:
 1. healthy male subjects age 18-55 years.
 2. Good physical and mental health, normal ECG or abnormal but not clinically significant, laboratory test results within reference range.
Exclusion Criteria:
 1. Hepatic, renal, gastrointestinal or other disorder that may affect drug ADME
 2. Heavy caffeine drinkers
 3. Current smokers (or smokers within 6 months)
 4. Any concomitant treatment (prescription or non-prescription) within 14 days of first drug administration (paracetamol 2 g/day is permitted)
 5. Hepatic enzyme inducing drugs

PK Results
Figure N01171-1: Geometric Mean (± SD) LTG Plasma Concentration after a Single oral Dose Alone and With BRV 200 mg bid

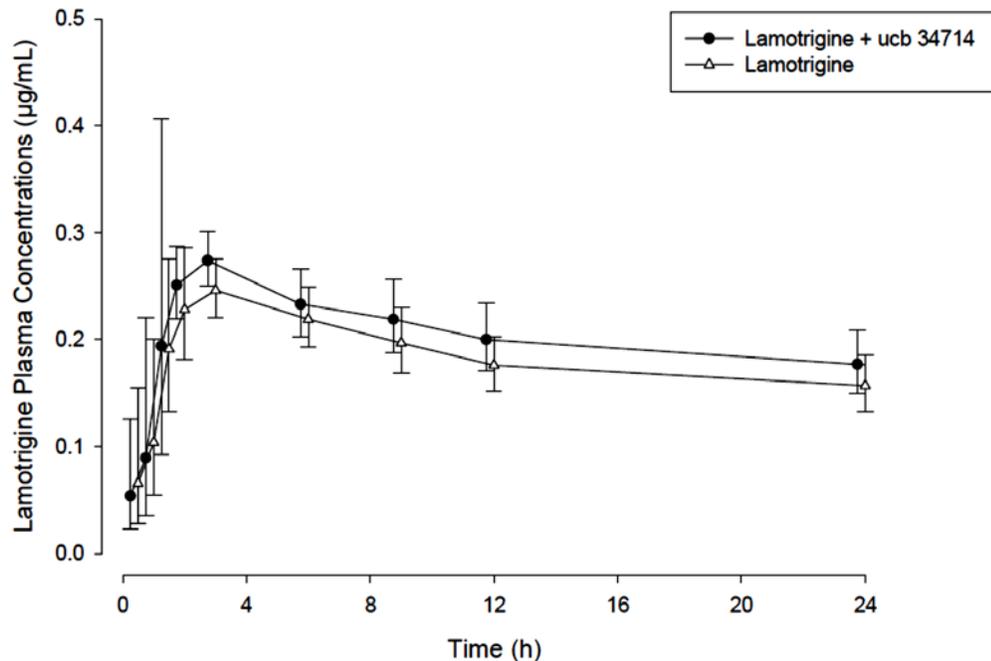
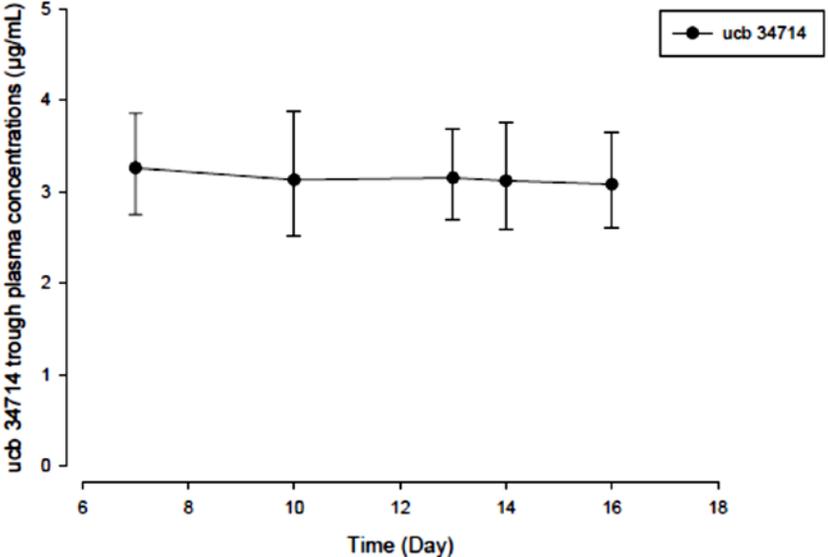


Table N01171-1: Statistical Comparison of LTG Plasma PK after a Single oral Dose Alone and With BRV 200 mg bid

Parameters	Reference: Lamotrigine 25 mg alone ^(a)	Test: Lamotrigine 25 mg with ucb 34714 200 mg bid ^(a)	Test versus Reference ^(b)		CV (%) ^(c)
			Point estimate	90% CI	
AUC _(0-t) (µg.h/mL)	10.78 (19.8)	12.57 (16.8)	116.6	108.8; 125.0	9.97
C _{max} (µg/mL)	0.261 (12.2)	0.288 (8.53)	110.0	103.1; 117.4	9.28
t _{max} (h)	3.00 (0.50; 6.00)	3.00 (1.50; 3.00)	-0.500	-1.750; 0.750	NA

^(a) Values are geometric mean: (Exp(mean, ln data)) and, between brackets, GeoCV(%): (100 x sqrt[exp(SD²)-1]), with SD of ln data. t_{max} values are median (min-max).
^(b) Point estimate (90% confidence interval) for the Test/Reference geometric lsmmeans ratio (%) derived from ANOVA; for t_{max}: median point estimate (90% non-parametric confidence interval) of the difference Test-Reference
^(c) Intra-subject coefficient of variation (%)
 NA: Not Applicable

	<p>Figure N01171-1: Geometric Mean (\pm SD) BRV Plasma Concentration During 200 mg bid Administration From Days 5 to 16</p>  <table border="1"> <caption>Data for Figure N01171-1</caption> <thead> <tr> <th>Time (Day)</th> <th>Geometric Mean (µg/mL)</th> </tr> </thead> <tbody> <tr> <td>7</td> <td>3.3</td> </tr> <tr> <td>10</td> <td>3.1</td> </tr> <tr> <td>13</td> <td>3.1</td> </tr> <tr> <td>14</td> <td>3.1</td> </tr> <tr> <td>16</td> <td>3.1</td> </tr> </tbody> </table>	Time (Day)	Geometric Mean (µg/mL)	7	3.3	10	3.1	13	3.1	14	3.1	16	3.1
Time (Day)	Geometric Mean (µg/mL)												
7	3.3												
10	3.1												
13	3.1												
14	3.1												
16	3.1												
<p>Safety</p>	<p>TEAEs occurred in 100% of subjects. The most common AEs were feeling drunk (n=12) and asthenia (n=4). All AEs were mild. Almost all AEs occurred after the first BRV administration.</p>												
<p>Sponsor's Conclusions</p>	<ul style="list-style-type: none"> • Concomitant BRV use was associated with a 17% and 10% increase in lamotrigine AUC and C_{max}. The 95% CI were contained within the no-effect boundaries. • LTG T_{max} was not significantly modified • BRV does not significantly affect the PK of LTG • The treatments were safe and well-tolerated 												
<p>Reviewer Comment</p>	<p><i>This reviewer concurs with the Sponsor's conclusions.</i> No dose adjustment of LTG is required when used concomitantly with BRV.</p>												

4.4.16 N01172: DDI – Phenytoin (Phase 1)

Study Report#	RPCE04B1113 / N01172	
Title	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	
Objectives	<u>Primary:</u> Assess the effect of steady state BRV on steady state PHT PK <u>Secondary:</u> Gain information on the tolerability and safety of concomitant BRV + PHT administration	
Study Design	Multi-center, open-label, unilateral interaction study	
Duration	45 days days	
Dosage and Administration	Subjects receiving stable daily PHT doses received the following BRV regimen over a 45-day period: <ul style="list-style-type: none"> • up-titration period (3 days) : 100 mg bid • maintenance period (21 days) : 200 mg bid • down-titration period (21 days) : down titration every week to the next lower dose; 150 mg bid for 7 days, 100 mg bid for 7 days and 50 mg bid for 7 days. 	
PK Assessment	<u>Plasma PK Samples – BRV:</u> Trough concentrations obtained Days 4, 5, 6, 8, and 11. <u>Plasma PK Samples – PHT:</u> pre-dose and 1, 2, 4, 6, 8, and 12 hours after the morning dose of PHT on Day -1 and Day 24. Trough concentration obtained on Days 3, 4, 5, 6, 8, and 11.	
Bioanalytical Methods	HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations	
	Analyte Name	Brivaracetam
	Analyte ID	ucb 34714
	Internal Standard (IS)	(b) (4)
	Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL
	Standards accuracy	-2.4 to 2.7%
	Standards precision	0.9 to 4.7%
	QC concentrations	150, 600, 1750 ng/mL
	QC Accuracy	-4.5 to -1.0%
	QC Precision	3.3 to 3.7%
	LLOQ	0.05 µg/mL
	HPLC-MS/MS Analytical Methods for PHT Plasma Concentrations	
	Analyte Name	Phenytoin
	Analyte ID	PHT
	Internal Standard (IS)	(b) (4)
	Standard curve concentrations	2.98 to 57.7 µg/mL
	Standards accuracy	-3.4 to 2.5%
	QC concentrations	4.86, 19.2, 29.0 µg/mL
	QC Accuracy	-4.0 to -2.5%
	QC Precision	2.3 to 3.3%
	LLOQ	0.5 µg/mL

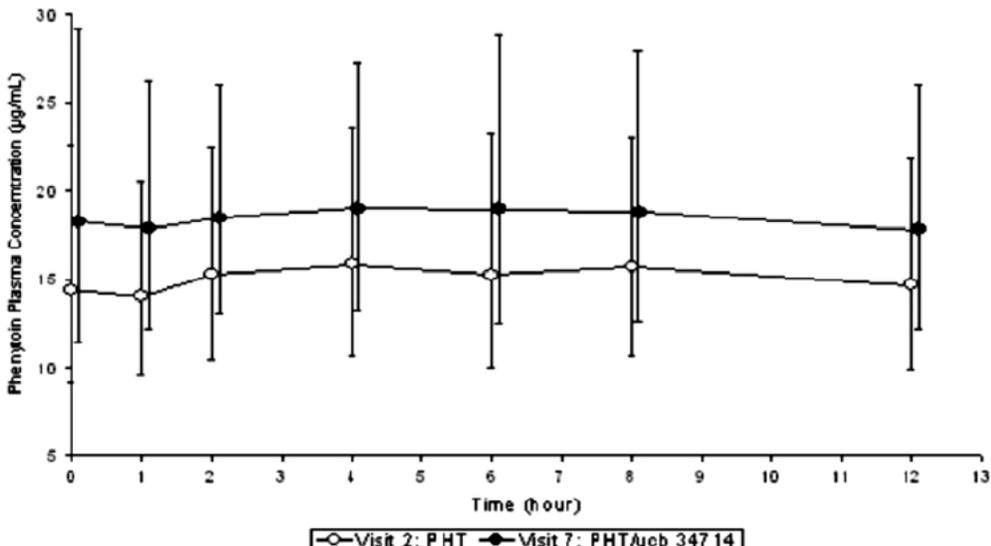
<p>Population/ Demographic s</p>	<p>[Reviewer comment: The assays are validated.]</p> <p>N=19</p> <p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female epilepsy patients age 18-65 years 2. Receiving PHT, stable for 3 months, in range of 7-23 µg/mL 3. Females of childbearing potential must utilize 2 acceptable birth control methods. <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Taking any known CYP inducer 2. Use of other drugs with CNS effects 3. Drugs which may affect BRV metabolism (2C or 3A potent inducers/inhibitors) unless dose is stable or 3 months before and during trial 4. Severe hepatic disease 5. Creatinine CL ≤ 50 mL/min 6. Clinically significant deviations from reference laboratory parameters 7. ECG abnormalities 8. Use of warfarin 																					
<p>PK Results</p>	<p>Figure N01172-1: Geometric Mean (± SD) PHT Plasma Concentration Before BRV and After Repeated BRV</p>  <p>Table N01172-1: Geometric Mean (%CV) PHT Plasma PK Parameters Before BRV and After Repeated BRV</p> <table border="1" data-bbox="373 1512 1461 1659"> <thead> <tr> <th></th> <th>Treatment</th> <th>C_{max}</th> <th>t_{max}^(a)</th> <th>AUC_τ</th> <th>C_{av}</th> <th>CL_{ss}/F</th> </tr> </thead> <tbody> <tr> <td>Visit 2 (Day -1)</td> <td>PHT</td> <td>16.92 (37.5)</td> <td>4.0 (1.0-12.0)</td> <td>252.2 (54.8)</td> <td>14.86 (43.3)</td> <td>1.063 (51.2)</td> </tr> <tr> <td>Visit 7 (Day 24)</td> <td>PHT/BRV</td> <td>20.66 (38.1)</td> <td>4.0 (1.0- 24.0)</td> <td>305.8 (42.6)</td> <td>18.39 (39.8)</td> <td>0.8564 (42.1)</td> </tr> </tbody> </table>		Treatment	C _{max}	t _{max} ^(a)	AUC _τ	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)
	Treatment	C _{max}	t _{max} ^(a)	AUC _τ	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)																

Table N01172-2: Statistical Comparison of PHT Plasma PK Parameters Before BRV and After Repeated BRV				
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.

Cmax and AUCtau of PHT increase by about 20% after concomitant BRV administration. Seizure frequency was 0.3 ± 1.2 seizures/week during baseline and 0.3 ± 1.0 seizures/week during treatment and 0.4 ± 1.1 seizures/week during follow-up.

Safety	TEAEs were reported by 94.7% of subjects, 89.5% were considered drug-related. Most AEs occurred during the up-titration (10 subjects) and maintenance (16 subjects). 3 TEAEs were reported by 3 (15.8%) of subjects during down-titration. One TEAE was severe (toothache) but was not considered drug-related. The most common TEAEs were dizziness (14 subjects) and fatigue (9 subjects). Headache and somnolence were reported by 2 subjects each.
Sponsor's Conclusions	<ul style="list-style-type: none"> A statistically significant increase in PHT exposure was observed. Results should be interpreted with caution as patients were receiving different PHT doses (200 to 700 mg/day). TEAEs observed in this study were consistent with previous BRV studies. Concomitant BRV and PHT were well-tolerated.
Reviewer Comment	<ul style="list-style-type: none"> The study demonstrated no apparent safety signals associated with concomitant BRV and PHT administration. The mean seizure rate appears comparable before, during and after introduction of BRV to existing steady state PHT. However, due to the increase of up to 20% in phenytoin exposures with BRV, and due to the practice of monitoring phenytoin concentrations during dose adjustments or changing dosage forms, phenytoin concentrations should be monitored when used concomitantly with BRV. Please refer to section 3.0 for details.

4.4.17 N01185: Intestinal Absorption Study (Phase 1)

Study Report#	RPCE04G2605 / N01185																				
Title	<i>Pharmacoscintigraphic investigation of the regional drug absorption of ucb 34714 (200 mg) delivered using the Enterion™ capsule in 3 different sites of the GI tract in comparison with the 200 mg immediate release oral capsule: open-label, randomized, four-way cross-over, single dose study, in 9 healthy adult male volunteers.</i>																				
Objectives	<i>Primary:</i> Assess regional absorption profile for BRV (200 mg) from 3 different regions of the gastrointestinal tract (proximal small bowel, distal small bowel, and ascending colon) using the Enterion™ capsule drug delivery system as compared to the 200 mg capsule absorption profile. <i>Secondary:</i> Assess safety																				
Study Design	Randomized, open-label, four-way cross-over, single-dose study																				
Duration	7 weeks for each subject																				
Dosage and Administration	Each subject received a single 200 mg BRV dose according to one of four regimens: A: immediate release oral capsule B: Enterion™ capsule delivered to the <i>proximal</i> small bowel C: Enterion™ capsule delivered to the <i>distal</i> small bowel D: Enterion™ capsule administered to the ascending colon There was a 7-day washout between treatment periods.																				
PK Assessment	BRV plasma samples: pre-dose, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 6 h, 9 h, 12 h, 16 h, 20 h, 24 h, 30 h and 36 h post-dose or post-activation PK measures: C _{max} , t _{max} , AUC _{0-t} , AUC, t _{1/2} , CL/F, V _z /F and F _{rel} were assessed for BRV. Scintigraphy: gastric emptying time, small intestinal transit time, ileo-caecal junction arrival time (ICJ), residence time in ICJ, colon arrival time, colon transit time, total transit time, anatomical location and time of successful activation of Enterion™ capsules																				
Statistical Analysis	A mixed effects ANOVA was used and the 95% CI was estimated for test/reference geometric mean ratios for C _{max} , AUC _{0-t} , and AUC. For T _{max} , a “distribution-free” 95% CI was computed for the median difference between test and reference. The “test” formulation was the Enterion™ capsule and the “reference” formulation was the immediate release capsule.																				
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>50.5, 101, 253, 505, 758, 1010, 1515, 2020 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-2.0 to 3.0%</td> </tr> <tr> <td>Standards precision</td> <td>1.4 to 3.2%</td> </tr> <tr> <td>QC concentrations</td> <td>152, 607, 1771 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-2.0 to 1.2%</td> </tr> <tr> <td>QC Precision</td> <td>2.3 to 3.5%</td> </tr> <tr> <td>LLOQ</td> <td>0.05 µg/mL</td> </tr> </table>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	50.5, 101, 253, 505, 758, 1010, 1515, 2020 ng/mL	Standards accuracy	-2.0 to 3.0%	Standards precision	1.4 to 3.2%	QC concentrations	152, 607, 1771 ng/mL	QC Accuracy	-2.0 to 1.2%	QC Precision	2.3 to 3.5%	LLOQ	0.05 µg/mL
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	<p>The internal standard, (b) (4) [Reviewer comment: The assay is validated.]</p>																					
<p>Population/ Demographics</p>	<p>N=7 healthy adult male volunteers</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male subjects age 18 to 65 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 5. Must agree to minimize risk of impregnating females partners <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Female subjects 2. Hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness 4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical trial 5. Heavy caffeine drinker (> 5 cups of coffee, tea, etc. per day) 6. Current smoker or had given up smoking in the last 6 months 7. Use of hepatic enzymes inducing drugs within 2 months of first administration 8. Gastrointestinal disorders (unless, irritable bowel syndrome, etc.) 																					
<p>PK Results</p>	<p>Subjects 0004 and 0008 were not included in the per-protocol (PP) population due to incorrect site of activation (Subject 0004) and withdrawal of consent (0008).</p> <p>Table N01185-1: Geometric Mean (%CV) of PK Parameters After a Single Dose of Each of the 4 BRV Regimens (PP Population) (n=6)</p> <table border="1" data-bbox="370 1119 1429 1396"> <thead> <tr> <th>Treatment</th> <th>C_{max} (µg/mL)</th> <th>t_{max}^(a) (h)</th> <th>AUC(0-t) (µg.h/mL)</th> <th>AUC (µg.h/mL)</th> <th>t_{1/2} (h)</th> <th>CL/F (L/h)</th> <th>V_z/F (L)</th> <th>F_{rel}</th> </tr> </thead> <tbody> <tr> <td>IR capsule</td> <td colspan="8" rowspan="4" style="background-color: #cccccc;">(b) (4)</td> </tr> <tr> <td>Proximal small bowel</td> </tr> <tr> <td>Distal small bowel</td> </tr> <tr> <td>Ascending colon</td> </tr> </tbody> </table> <p>^(a) median (min-max) Time scale is time after intake of the IR capsule and after activation of the Enterion™ capsule in the proximal small bowel, in the distal small bowel, and in the ascending colon ^(b) Subject 0007</p> <p>Sponsor noted that subject 0005 had lower exposures for all treatments compared to other subjects (particularly for AUC). The individual exposures are presented in the figure below.</p>	Treatment	C _{max} (µg/mL)	t _{max} ^(a) (h)	AUC(0-t) (µg.h/mL)	AUC (µg.h/mL)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)	F _{rel}	IR capsule	(b) (4)								Proximal small bowel	Distal small bowel	Ascending colon
Treatment	C _{max} (µg/mL)	t _{max} ^(a) (h)	AUC(0-t) (µg.h/mL)	AUC (µg.h/mL)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)	F _{rel}														
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Figure N01185-1: Individual BRV AUC Values After administration of IR 200 mg Oral Capsule (A), 200 mg delivery in Proximal Small Bowel (B), Distal Small Bowel (C), and Ascending Colon (D) via Enterion™ Capsule (PP population)

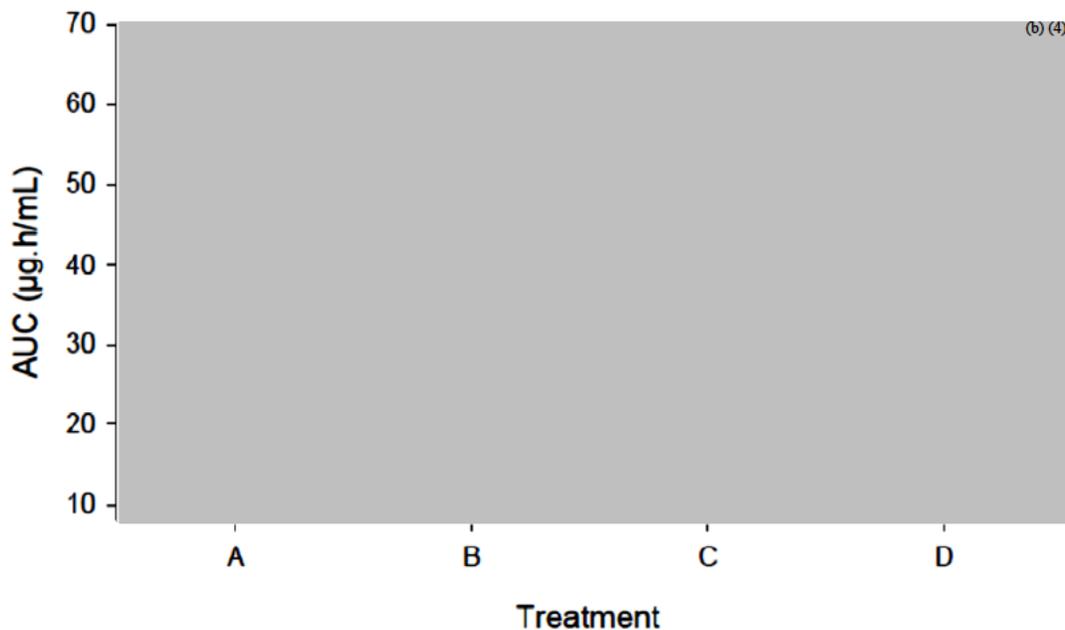
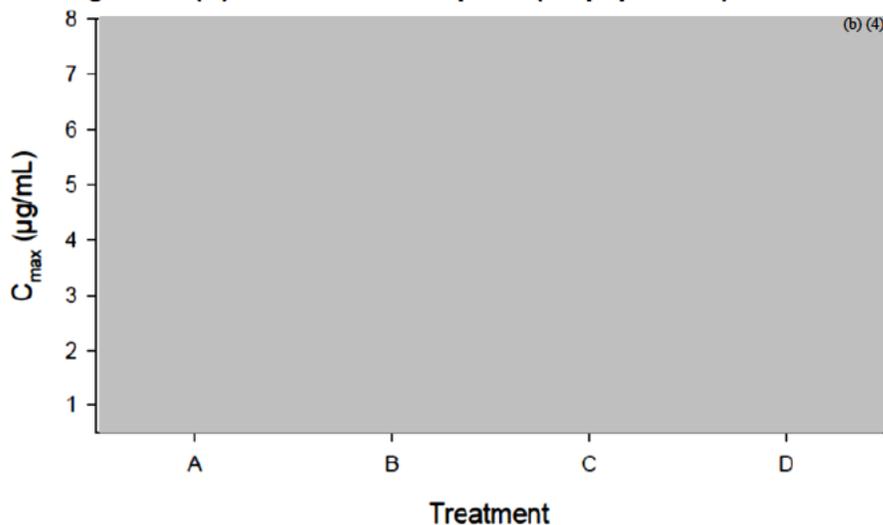
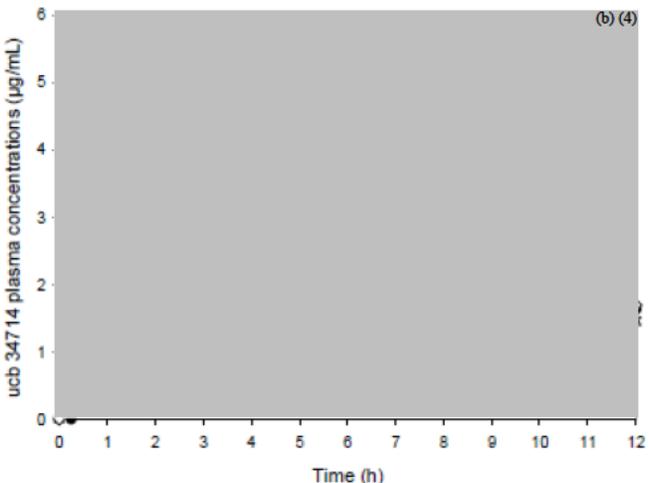
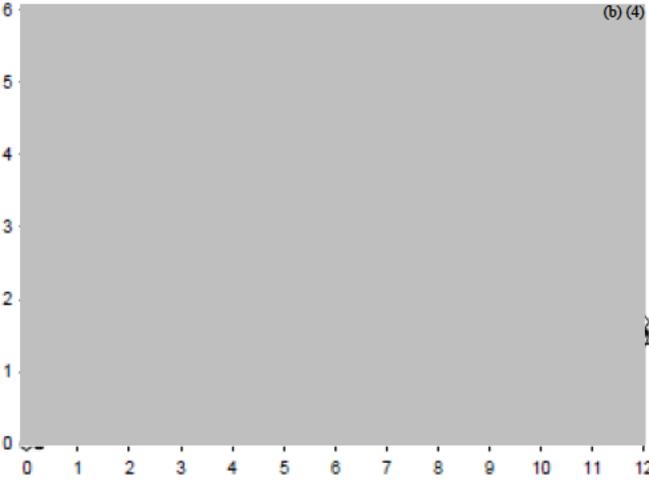


Figure N01185-2: Individual BRV C_{max} Values After administration of IR 200 mg Oral Capsule (A), 200 mg delivery in Proximal Small Bowel (B), Distal Small Bowel (C), and Ascending Colon (D) via Enterion™ Capsule (PP population)



	<p>Figure N01185-3: Geometric Mean BRV Plasma Concentration Profile for IR 200 mg Oral Capsule (Including Subject 5, with)</p>  <p>Figure N01185-4: Geometric Mean BRV Plasma Concentration Profile for IR 200 mg Oral Capsule (Excluding Subject 0005)</p> 
<p>Safety Results</p>	<p>All 7 subjects experienced at least one TEAE. All AEs were mild or moderate and the most frequently reported AEs were dizziness (7 subjects) and balance disorder (2 subjects). All TEAE were resolved during the study and none led to discontinuation.</p>
<p>Sponsor's Conclusions</p>	<p>(b) (4)</p> <ul style="list-style-type: none"> 200 mg BRV administered as IR capsule, Enterion™ capsule in 3 different sites of the GI tract appeared generally safe and was well tolerated in healthy subjects.

Reviewer Comment	(b) (4)

4.4.18 N01193: Dose Ranging, 5, 20, and 50 mg/day Oral Tablets (Phase 2)

Study Report#	RPCE05C2201 / N01193
Title	A multicenter, double-blind, randomized, placebo-controlled, 4 parallel groups, dose-ranging trial evaluating the efficacy and safety of brivaracetam used as adjunctive treatment at doses of 5, 20 and 50 mg/day in b.i.d. administration (oral tablets of 2.5 or 10 mg) for a maximum of 7 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized.
Objectives	<u>Primary:</u> Assess BRV efficacy <u>Secondary:</u> Assess dose/response, narrow down dose range, explore tolerability, assess seizure-free and days an seizure-free subjects, bridge efficacy and safety results to study N01114 <u>Exploratory:</u> Asses population PK of BRV and drug interactions
Study Design	Double-blind, randomized, placebo-controlled, multicenter, 4-parallel groups, dose ranging study
Duration	13 weeks total, 7 weeks BRV exposure, (4 week baseline, 7-week treatment period, 2 week study –drug-free period)
Dosage and Administration	<ul style="list-style-type: none"> After a 4-week Baseline Period (screening visit V1), subjects who entered the Treatment Period were randomized (visit V2) to one treatment group: <ul style="list-style-type: none"> 5 mg/day, 20 mg/day, and 50 mg/day of Brivaracetam or placebo. Oral tablets were used, and all treatment were administered BID The Treatment Period at stable dose lasted 7 weeks and at the end of this Treatment Period (evaluation visit V4), a decision was made on whether the subject continued with Brivaracetam (i.e. entering LTFU trial N01199) or not. Subjects that did not continue with Brivaracetam treatment entered a Trial Drug-free Period for a minimum of two weeks. A Safety Visit (V5) was performed by all subjects that were not entered in LTFU trial N01199. This procedure was also applied in case of early discontinuation (visit EDV). <p>The diagram illustrates the study timeline. It is divided into three main phases: a Baseline Period (4 weeks) from V1 (W-4) to V2 (W0), a Double Blind Period (7-week treatment) from V2 (W0) to V4/EDV (W7), and a Trial Drug-Free Period (2 weeks) from V4/EDV (W7) to V5 (W9). Four treatment groups are shown: 50 mg/d, 20 mg/d, 5 mg/d, and Placebo. All groups start at V2 (W0) and continue through V4/EDV (W7). The 50 mg/d group is represented by the top horizontal line, 20 mg/d by the second, 5 mg/d by the third, and Placebo by the bottom line. Vertical dashed lines indicate the start and end of each phase and the timing of visits V1, V2, V3, V4/EDV, and V5.</p>

<p>PK Assessment</p>	<p><u>Plasma Samples – BRV</u>: One blood sample at visit V02, at EDV (early discontinuation visit) and by collecting two blood samples - with at least 15 minutes time interval between collections - at visit 3 and 4 (V03-0, V03-15, V04-0 and V04-15)</p> <p><u>Plasma Samples – AEDs</u>: one blood sample at visit V01, V02, V03-0, V04-0, EDV and visit V05.</p>																				
<p>Bioanalytical Methods</p>	<p>HPLC-MS/MS Analytical Methods for <i>BRV Plasma Concentrations</i></p> <table border="1" data-bbox="469 472 1313 934"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-3.5 to 4.8%</td> </tr> <tr> <td>Standards precision</td> <td>2.6 to 5.7%</td> </tr> <tr> <td>QC concentrations</td> <td>30, 300, 900, 3600 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-1.6 to 5.0%</td> </tr> <tr> <td>QC Precision</td> <td>6.3 to 7.7%</td> </tr> <tr> <td>LLOQ</td> <td>10 ng/mL</td> </tr> </table> <p>[Reviewer Comment: The assay is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL	Standards accuracy	-3.5 to 4.8%	Standards precision	2.6 to 5.7%	QC concentrations	30, 300, 900, 3600 ng/mL	QC Accuracy	-1.6 to 5.0%	QC Precision	6.3 to 7.7%	LLOQ	10 ng/mL
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LLOQ	10 ng/mL																				
<p>Population/ Demographics</p>	<p>N=210</p> <p><u>Inclusion Criteria</u>:</p> <ol style="list-style-type: none"> 1. Male and female patients with epilepsy age 16 to 65 years 2. Focal epilepsy or epileptic syndrome with history on partial onset seizures 3. Receiving 1 or concomitant AEDs (vagal nerve stimulation was allowed but did not count as a concomitant AED) that are stable for at least 1 month before visit 1. 4. Females of childbearing potential must use adequate birth control <p><u>Exclusion Criteria</u>:</p> <ol style="list-style-type: none"> 1. Use of felbamate in last year 2. Use of phenobarbital in last 6 months 3. Current use of vigabatrine 4. Use of drugs with possible CNS effects unless stable for 1 month prior to Visit 1 and for whole study period. Benzodiazepines taken more than once/week (for any indication) is considered as a concomitant AED. 5. Use of drugs that influence BRV metabolism (2C or 3A potent inhibitors) unless stable for 1 more before visit 1 and for entire study duration. 6. Impaired hepatic function (ALAT/SGPT, ASAT/SGOT, ALP, GGT > 3 x ULN) 7. Creatinine CL < 50 mL/min 8. Clinically significant ECG abnormalities 9. Pregnant/lactating women <p>[Reviewer comment: Use of <u>levetiracetam</u> was <u>permitted</u> in this study.]</p>																				
<p>PK Results</p>	<p>The population pharmacokinetics (PK) of brivaracetam (BRV) in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358)</p>																				

	PK results from these studies are pooled and provided in the ISR for N01358.																														
Efficacy	<p>Table N01193-1: Primary Efficacy Analysis on the Partial Onset Seizure Frequency Per Week over the Treatment Period</p> <table border="1"> <thead> <tr> <th></th> <th>PBO N=54</th> <th>BRV 5 mg N=50</th> <th>BRV 20 mg N=52</th> <th>BRV 50 mg N=52</th> </tr> </thead> <tbody> <tr> <td>LS means (log-transformed)</td> <td>1.296</td> <td>1.194</td> <td>1.135</td> <td>1.047</td> </tr> <tr> <td>LS means (back-transformed)</td> <td>2.656</td> <td>2.299</td> <td>2.110</td> <td>1.848</td> </tr> <tr> <td>Percent reduction over Placebo</td> <td>-</td> <td>9.8%</td> <td>14.9%</td> <td>22.1%</td> </tr> <tr> <td>95% CI</td> <td>-</td> <td>(-7.2% , 24.0%)</td> <td>(-0.8% , 28.2%)</td> <td>(7.6% , 34.3%)</td> </tr> <tr> <td>p-value</td> <td>-</td> <td>0.240</td> <td>0.062</td> <td>0.004</td> </tr> </tbody> </table> <p>Only the 50 mg/day dose group (25 mg twice daily) demonstrated a statistically significant improvement over placebo.</p>		PBO N=54	BRV 5 mg N=50	BRV 20 mg N=52	BRV 50 mg N=52	LS means (log-transformed)	1.296	1.194	1.135	1.047	LS means (back-transformed)	2.656	2.299	2.110	1.848	Percent reduction over Placebo	-	9.8%	14.9%	22.1%	95% CI	-	(-7.2% , 24.0%)	(-0.8% , 28.2%)	(7.6% , 34.3%)	p-value	-	0.240	0.062	0.004
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p-value	-	0.240	0.062	0.004																											
Safety	<ul style="list-style-type: none"> TEAEs occurred in 53.7%, 52%, 55.8%, and 53.8% in the placebo, 5 mg/day, 20 mg/day, 50 mg/day groups, respectively. TEAEs include: headache in 5.3%, somnolence in 5.2%, influenza reported in 4.3%, dizziness in 3.8%, neutropenia in 3.4%, and fatigue in 3.4% TEAEs leading to permanent study drug discontinuation were reported in: <ul style="list-style-type: none"> 2 in the PBO group, 3 in the BRV 5 mg/day group, 1 in the BRV 20 mg/day group and none in the BRV 50 mg/day group. One treatment-emergent SAE (Neurotoxicity) was reported in the BRV 20 mg/day group and was considered highly probably drug-related by the Investigator. 																														
Sponsor's Conclusions	<ul style="list-style-type: none"> Statistically significant efficacy was demonstrated in the 50 mg/day group. Evaluation of TEAEs of special interest (blood and lymphatic disorders, cardiac disorders, eye disorders, gastrointestinal disorders, hepatobiliary disorders, infections and infestations, nervous system disorders, psychiatric disorders, skin and subcutaneous disorders, and vascular disorders) did not reveal any clinically significant differences between the treatment groups. BRV at a dose of 5, 20, or 50 mg/day bid was safe and well-tolerated in this population in this study. 																														
Reviewer Comment	<ul style="list-style-type: none"> <i>This study did not appear to present any new safety signals.</i> <i>The 50 mg/day bid dose was statistically-significantly better than placebo in the current study as well as N01253, but this dose level was not statistically significantly better than placebo in study N01114 or N01252 regarding efficacy.</i> <i>Please refer to the review of the medical officer regarding the acceptability of the 50 mg/day bid dose level.</i> <i>For insight into the population pharmacokinetic analyses and exposure-efficacy analyses, please refer to the pharmacometric portion of this review.</i> 																														

4.4.19 N01209a: Single-Dose PK in Japanese Subjects (Phase 1)

Study Report#	RPCE07F1104 / N01209
Title	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects
Objectives	<u>Primary:</u> Assess safety and tolerability of <i>single</i> BRV doses <u>Secondary:</u> Assess PK of BRV and metabolites after <i>single</i> BRV doses <u>Genotype Analyses:</u> Identify genotypic variation in BRV PK after <i>single</i> BRV doses
Study Design	monocenter, randomized, parallel, double-blind, placebo-controlled, single rising oral dose study
Duration	6 weeks maximum (4 weeks screening, 5 days confinement to CRU, follow-up 1 week after administration)
Dosage and Administration	N=50 subjects were randomized to a group to receive a single oral dose of BRV 2.5mg, 10mg, 25mg, 50mg, 100mg or placebo. The dose in the group was increased stepwise based on the results of the safety variables in the previous dose. <i>Step1:</i> 2.5 mg BRV or placebo (1 tablet) <i>Step2:</i> 10 mg BRV or placebo (1 tablet) <i>Step3:</i> 25 mg BRV or placebo (1 tablet) <i>Step4:</i> 50 mg BRV or placebo (1 tablet) <i>Step5:</i> 100 mg BRV or placebo, (2 tablets) In each step (or group), n=8 subjects received BRV and n=2 subjects received placebo. N=43 subjects completed the genotype analysis.
PK Assessment	<u>Plasma Samples:</u> pre-dose, 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 9 h, 12 h, 16 h, 24 h, 36 h and 48 h post-dose. In 100 mg group only, plasma sample was taken 72 h after administration. <u>Urine samples:</u> pre-dose, 0-6 h, 6-12 h, 12-24 h, 24-36 h, 36-48 h post-dose. In 100 mg group <i>only</i> , urine samples were collected at 48-72 h post-dose. <u>PK Analyses:</u> <i>Plasma:</i> C _{max} , t _{max} , AUC _{0-t} , AUC, t _{1/2} for BRV and its metabolites, MRT, CL/F, V _z /F for BRV, CL _{fm} /F for ucb 42145 and ucb-100406-1 and AUC Ratio <i>Urine:</i> Ae, fe, and CLR, for BRV and its metabolites
Bioanalytical Methods	The parent drug ucb 34714 and metabolites ucb 42145, ucb-100406-1 and ucb-107092-1 were measured in urine samples using the same LC-ESI/MS/MS assay after 10-fold dilution with blank plasma. The results are presented together.

HPLC-MS/MS Analytical Methods for Plasma and Urine Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
Internal Standard (IS)	(b) (4)	(b) (4)		
Standard curve concentrations	2, 5, 50, 200, 600, 1200, 1800, 2000 ng/mL	1.86, 4.65, 18.6, 46.5, 93, 232, 418, 465 ng/mL*	1.99, 4.98, 19.9, 49.8, 99.5, 249, 448, 498 ng/mL*	1.85, 4.63, 46.3, 185, 556, 1111, 1667, 1852 ng/mL*
Standards accuracy	-3 to 4.2%	-1.3 to 1.4%	-1.6 to 1.8%	-1.4 to 4.1%
Standards precision	2.3 to 5.8%	2.2 to 5.1%	2.2 to 6.2%	2.0 to 6.0%
QC concentrations	6, 75, 1600 ng/mL	5.58, 27.9, 372 ng/mL*	5.97, 29.9, 398 ng/mL*	5.56, 69.4, 1481 ng/mL*
QC Accuracy	-4.4 to 1.6%	1.1 to 1.8%	1.0 to 2.5%	-5 to 2.2%
QC Precision	7.4 to 11.7%	9.3 to 10.5%	8.4 to 9.2%	7.8 to 9.5%
<i>QC for Dilution of Urine Samples using Citrated Human Plasma</i>				
Dilution Factor	5x dilution and 10x dilution of 1600 ng/mL	5x dilution and 10x dilution of 398 ng/mL*	5x dilution and 10x dilution of 372 ng/mL*	5x dilution and 10x dilution of 1481 ng/mL*
QC Accuracy for dilution	-2.4 to 0.8 ng/mL	-7.2 to 1.5%	-10.5 to -1.6%	-4.1 to -2.1%
QC Precision for Dilution	2.4 to 10.8%	3.1 to 11.9%	1.1 to 10%	2.7 to 9.1%
LLOQ	2.00 ng/mL	1.99 ng/mL*	1.86 ng/mL*	1.85 ng/mL*

*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).

IS (b) (4)

IS (b) (4)

[Reviewer comment: The assays are acceptable.]

Population / Demographics

N=50 Japanese healthy male adults age 20 to 40 years without clinically relevant cardiovascular abnormalities (e.g. S/DBP, HR, ECG parameters) or laboratory abnormalities.

Inclusion Criteria:

1. Japanese healthy men age 20 to 40 years
2. Physical and mental conditions judged to favorable by investigators
3. No clinically-relevant ECG abnormalities.
4. Clinical laboratory values within referene range at screening (or non-clinically significant deviations)

Key exclusion criteria:

1. Any condition which may affect BRV ADME
2. Subjects who used other drugs including OTC products (excluding topical products) within 14 days before administration of the investigational drug
3. Subjects who used hepatic enzyme-inducing drugs (e.g., glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin etc.) within 2 months before the first administration
4. Subjects who are heavy caffeine drinkers (drinking more than 10 cups per day)
5. Smoker more than 5 cigarettes per day
6. Subjects who took grapefruit (as beverage or fruit) within 1 week before administration of the investigational product.

PK Results

Figure N01209a-1: Geometric Mean \pm SD Plasma Concentration Profile for BRV After Single Oral Tablet Administration in Healthy Japanese Subjects

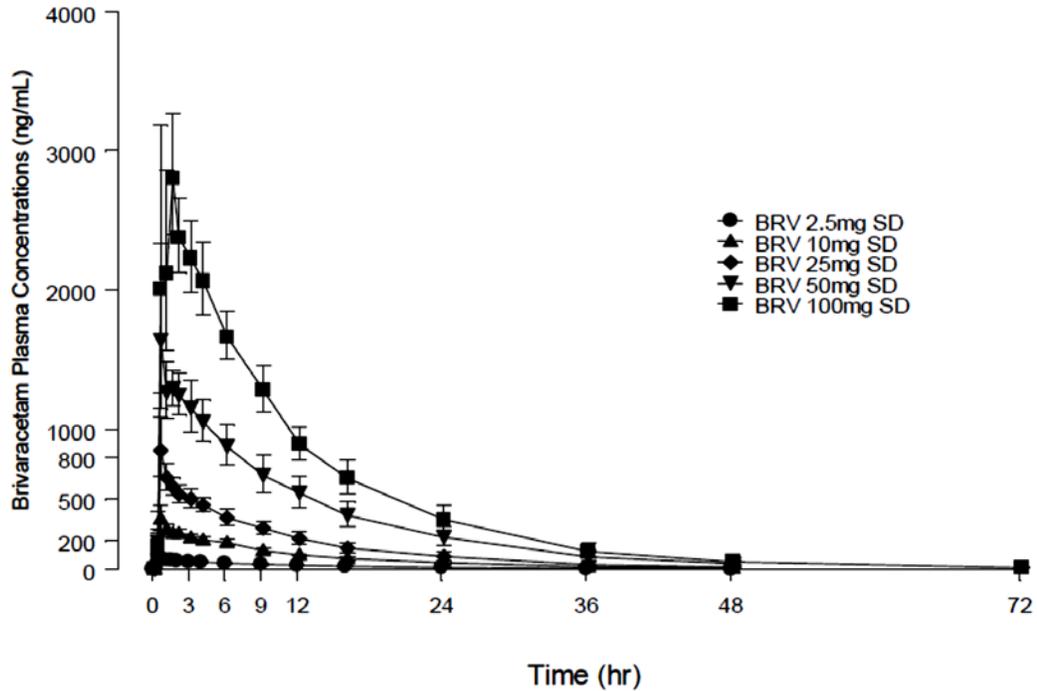


Table N01209a-1: Geometric Mean ± SD BRV Plasma PK Parameters for BRV After Single Oral Tablet Administration in Healthy Japanese Subjects

PK parameters (unit)	Geometric Mean (geo CV[%])				
	BRV 2.5mg (N=8)	BRV 10mg (N=8)	BRV 25mg (N=8)	BRV 50mg (N=8)	BRV 100mg (N=8)
C _{max} (ng/mL)	86.6 (17.8)	373 (18.0)	900 (18.8)	1921 (20.2)	3083 (17.3)
t _{max} (h) ^(a)	0.50 (0.25-0.50)	0.50 (0.50-1.00)	0.50 (0.50-1.50)	0.50 (0.50-2.00)	1.5 (0.50-1.50)
AUC _{0-t} (ng.h/mL)	827 (19.0)	3506 (12.4)	7456 (18.9)	17804 (17.2)	32037 (14.0)
AUC (ng.h/mL)	865 (18.9)	3606 (13.5)	7649 (20.5)	18358 (18.2)	32203 (14.1)
λ _z (1/h) ^(b)	0.0750 (0.0120)	0.0755 (0.00909)	0.0835 (0.0188)	0.0748 (0.0101)	0.0797 (0.0160)
t _{1/2} (h)	9.34 (15.5)	9.24 (11.9)	8.49 (22.4)	9.34 (12.9)	8.84 (19.2)
CL/F (L/h)	2.89 (18.9)	2.77 (13.5)	3.27 (20.5)	2.72 (18.2)	3.11 (14.1)
CL/F (mL/min/kg)	0.816 (16.8)	0.807 (18.0)	0.849 (18.2)	0.784 (13.1)	0.847 (19.2)
V _z /F (L)	38.9 (9.71)	37.0 (6.24)	40.0 (7.87)	36.7 (12.0)	39.6 (13.8)
V _z /F (L/kg)	0.660 (4.98)	0.645 (11.4)	0.623 (6.15)	0.634 (4.67)	0.648 (4.56)
MRT (h)	13.1 (14.4)	12.7 (12.3)	12.1 (22.4)	13.1 (14.1)	12.2 (18.0)
Ae (mg)	0.205 (25.5)	1.07 (20.6)	1.88 (27.2)	4.27 (29.3)	10.0 (24.4)
fe (%)	8.18 (25.5)	10.7 (20.6)	7.51 (27.2)	8.55 (29.3)	10.0 (24.4)
CL _R (L/h)	0.236 (13.8)	0.296 (17.8)	0.245 (22.8)	0.233 (25.6)	0.311 (24.4)
CL _R (mL/min/kg)	0.0668 (22.0)	0.0860 (24.0)	0.0637 (24.7)	0.0671 (25.7)	0.0849 (21.2)

CV=Coefficient of Variation, geo=geometric, N=number of subjects

(a) Median (range)

(b) Arithmetic mean (±SD)

Table N01209a-2: Geometric Mean ± SD Carboxylic Acid Metabolite (ucb 42145) Plasma PK Parameters for BRV After Single Oral Tablet Administration in Healthy Japanese Subjects

ucb 42145 PK parameters (units)	Geometric Mean (geo CV[%])				
	BRV 2.5mg (N=8)	BRV 10mg (N=8)	BRV 25mg (N=8)	BRV 50mg (N=8)	BRV 100mg (N=8)
C _{max} (ng/mL)	3.15 (22.1)	15.1 (19.9)	39.2 (19.5)	88.3 (11.2)	158 (13.9)
t _{max} (h) ^(a)	3.0 (1.5-4.0)	3.0 (2.0-4.0)	4.0 (2.0-4.0)	3.0 (3.0-4.0)	4.0 (3.0-4.0)
AUC _{0-t} (ng.h/mL)	12.8 (64.8)	185 (31.0)	473 (19.5)	1177 (13.2)	2171 (13.1)
AUC (ng.h/mL)	NC	NC	524 (17.4)	1248 (13.9)	2242 (13.7)
λ _z (1/h) ^(b)	NC	NC	0.0670 (0.0162)	0.0655 (0.0101)	0.0716 (0.0161)
t _{1/2} (h)	NC	NC	10.7 (26.9)	10.7 (15.0)	9.89 (22.4)
CL _{fm} /F (L/h)	0.938 (13.6)	0.985 (11.8)	0.985 (9.82)	0.871 (15.0)	1.06 (12.9)
Ae (mg)	0.812 (15.6)	3.55 (15.8)	7.54 (16.8)	16.0 (15.1)	34.3 (16.1)
fe (%)	32.5 (15.6)	35.5 (15.8)	30.1 (16.8)	32.0 (15.1)	34.3 (16.1)
CL _R (L/h)	NC	NC	14.4 (10.0)	12.8 (15.5)	15.3 (8.40)

CV=Coefficient of Variation, geo=geometric, N=number of subjects, NC=Not Calculated

(a) Median (range)

(b) Arithmetic mean (SD)

Table N01209a-3: Geometric Mean ± SD Hydroxy Metabolite (ucb-100406-1) Plasma PK Parameters for BRV After Single Oral Tablet Administration in Healthy Japanese Subjects

ucb-100406-1 PK parameters (units)	Geometric Mean (geo CV[%])				
	BRV 2.5mg (N=8)	BRV 10mg (N=8)	BRV 25mg (N=8)	BRV 50mg (N=8)	BRV 100mg (N=8)
C _{max} (ng/mL)	2.97 (53.1) ^(c)	10.5 (101)	25.1 (134)	23.0 (143)	53.6 (167)
t _{max} (h) ^(a)	7.5 (6.0-12.0) ^(c)	7.5 (6.0-9.0)	9.0 (6.0-9.0)	9.0 (6.0-9.0)	9.0 (6.0-9.0)
AUC _{0-t} (ng.h/mL)	24.8 (280) ^(c)	179 (188)	612 (145)	549 (154)	1383 (166)
AUC (ng.h/mL)	NC	322 (42.8) ^(d)	909 (48.4) ^(d)	657 (122)	1467 (153)
λ _z (1/h) ^(b)	NC	0.0601 (0.0117) ^(d)	0.0737 (0.0147) ^(d)	0.0626 (0.0159)	0.0679 (0.0145)
t _{1/2} (h)	NC	11.7 (19.6) ^(d)	9.56 (19.1) ^(d)	11.5 (33.2)	10.4 (20.5)
CL _{fm} /F (L/h)	0.193 (268)	0.282 (97.3)	0.378 (139)	0.130 (162)	0.203 (174)
Ae (mg)	0.167 (207)	1.02 (78.4)	2.89 (107)	2.40 (127)	6.55 (148)
fe (%)	6.69 (207)	10.2 (78.4)	11.6 (107)	4.79 (127)	6.55 (148)
CL _R (L/h)	NC	3.89 (15.4) ^(d)	4.14 (6.88) ^(d)	3.65 (22.2)	4.47 (19.0)

CV=Coefficient of Variation, geo=geometric, N=number of subjects, NC=Not Calculated

- (a) Median (range)
- (b) Arithmetic mean (SD)
- (c) N=6
- (d) N=7

Table N01209a-4: Geometric Mean ± SD Hydroxy-Acid Metabolite (ucb-107092-1) Plasma PK Parameters for BRV After Single Oral Tablet Administration in Healthy Japanese Subjects

ucb-107092-1 PK parameters (units)	Geometric Mean (geo CV[%])				
	BRV 2.5mg (N=8)	BRV 10mg (N=8)	BRV 25mg (N=8)	BRV 50mg (N=8)	BRV 100mg (N=8)
C _{max} (ng/mL)	NC	3.31 (17.6)	8.05 (17.2)	18.5 (13.2)	29.2 (12.8)
t _{max} (h) ^(a)	NC	4.0 (4.0-6.0)	6.0 (4.0-6.0)	6.0 (4.0-6.0)	6.0 (4.0-9.0)
AUC _{0-t} (ng.h/mL)	NC	23.1 (96.9)	115 (12.4)	297 (16.3)	515 (8.68)
AUC (ng.h/mL)	NC	65.0 (20.4) ^(c)	165 (9.94) ^(d)	354 (14.5)	558 (8.65)
λ _z (1/h) ^(b)	NC	0.0620 (0.0146) ^(c)	0.0571 (0.0108) ^(d)	0.0640 (0.0137)	0.0600 (0.00478)
t _{1/2} (h)	NC	11.5 (25.8) ^(c)	12.3 (20.5) ^(d)	11.1 (23.4)	11.6 (7.56)
Ae (mg)	0.305 (8.38)	1.43 (17.0)	3.45 (9.65)	6.67 (12.1)	13.1 (8.02)
fe (%)	12.2 (8.38)	14.3 (17.0)	13.8 (9.65)	13.3 (12.1)	13.1 (8.02)
CL _R (L/h)	NC	NC	20.4 (6.50) ^(d)	18.8 (16.8)	23.5 (8.91)

CV=Coefficient of Variation, geo=geometric, N=number of subjects, NC=Not Calculated

- (a) Median (range)
- (b) Arithmetic mean (SD)
- (c) N=6
- (d) N=7

Table N01209a-5: Dose-Proportionality Analysis Results

Parameter (unit)	Estimate Slope	90% CI
C _{max} (ng/mL)	0.984	(0.944, 1.02)
AUC _{0-t} (ng.h/mL)	0.994	(0.959, 1.03)
AUC (ng.h/mL)	0.986	(0.949, 1.02)

Table N01209a-6: Dose-Independence Analysis Results

Parameter (unit)	Estimate Slope	90% CI
CL/F (mL/min/kg)	0.00478	(-0.0297, 0.0392)
CL _R (mL/min/kg)	0.0248	(-0.0285, 0.0781)
V _z /F (L/kg)	-0.00764	(-0.0217, 0.00641)
t _{1/2} (h)	-0.0124	(-0.0464, 0.0216)
MRT (h)	-0.0133	(-0.0467, 0.0201)
fe (%)	0.0200	(-0.0368, 0.0768)

[Reviewer comment: The 90% CI of the slope contains zero, which supports the notion that the single-dose BRV PK parameters are dose-independent from 2.5 mg to 100 mg.]

Genotype analyses:

The BRV CL/F decreased by 30% in poor metabolizer (PM) group and by 18% in heterozygous extensive metabolizer (EM) group compared to homozygous EM group.
ucb-100406-1: the AUC_{0-t} and the urinary excretion significantly decreased in PM group and in heterozygous EM group compared to homozygous EM group
ucb 42145: the AUC_{0-t} increased in PM group and in heterozygous EM group compared to homozygous EM group
ucb-107092-1: The values of AUC_{0-t} and fe were similar among 3 groups.

Safety	<p>Out of a total of 50 subjects assessed, 4 AEs, all mild intensity, were reported by 4 subjects (1 pharyngolaryngeal pain AE in the BRV 10mg group, 1 asthenia AE in the BRV 50mg group, and 2 somnolence AEs in the BRV 100mg group). No new safety signals were apparent.</p> <p>Based on genotype analyses, 3 of the subjects that experienced an AE were not in the “poor metabolizer” group. The one AE in the “poor metabolizer” group was considered to have no causal relationship to the study drug.</p>
Sponsor’s Conclusions	<ul style="list-style-type: none"> • Single doses of BRV tablets up to 100 mg were safe and well-tolerated • 2C19 is the main enzyme involved in hydroxylation of BRV into ucb-100406-1 • The effect of 2C19 polymorphism on BRV PK is not clinically relevant in terms of safety and efficacy.
Reviewer Comment	<ul style="list-style-type: none"> • Please refer to the Appendix for the pharmacogenomics review of the genomic analyses conducted in this study. • Overall, the BRV PK increased proportionally with dose from 2.5 mg to 100 mg single doses for AUC and from 2.5 to 50 mg for C_{max}. C_{max} increased less than proportionally from 50 mg to 100 mg. • Weight-normalized CL/F, weight-normalized V_z/F, and t_{1/2} were comparable among the dose groups. • This study is supportive of the use of single BRV doses up to 100 mg in Japanese subjects.

4.4.20 N01209b: Multiple-Dose PK in Japanese Subjects (Phase 1)

Study Report#	RPCE07F1104 / N01209
Title	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single-oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects.
Objectives	<u>Primary:</u> Assess safety and tolerability of <i>multiple</i> BRV doses <u>Secondary:</u> Assess PK of BRV and metabolites after <i>multiple</i> BRV doses <u>Genotype Analyses:</u> Identify genotypic variation in BRV PK after <i>multiple</i> BRV doses
Study Design	Monocenter, randomized, parallel, double-blind, placebo-controlled, repeat oral dose study
Duration	6 weeks maximum (4 weeks screening, 5 days confinement to CRU, follow-up 1 week after administration)
Dosage and Administration	N=29 subjects were randomized to a group to receive repeat doses of BRV or placebo. Sponsor started with Group 6 (Step 6), and increased to the subsequent Group after examination of safety data collected up to and including Day 19 follow-up safety visit. <i>Step 6:</i> 2.5 mg BRV bid (5 mg/day) or placebo bid (1 tablet/time) <i>Step 7:</i> 10 mg BRV bid (20 mg/day) or placebo bid (1 tablet/time) <i>Step 8:</i> 50 mg BRV bid (100 mg/day) or placebo bid (1 tablet/time) For each Group (Step), n=8 subjects received BRV and n=2 received placebo. On Day 1 and Day 12, subjects received the morning dose of study drug after an overnight fast. Day 2 was a washout day. On Day 3 through Day 11, subjects received the study drug every 12 hours (1 hour after breakfast in the morning, and 2 hours after dinner in the evening).
PK Assessment	<u>Plasma Samples:</u> Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours post-1st-dose Day 2: 16, 24 and 36 hours after the 1st administration <i>Day 3:</i> just before morning (2nd) and evening (3rd) administration <i>Day 4 – 6:</i> just before morning (4th, 6th and 8th) administration <i>Day 7:</i> just before morning (10th) and evening (11th) administration <i>Day 8 - 10:</i> just before morning (12th, 14th and 16th) administration <i>Day 11:</i> just before morning (18th) and evening (19th) administration Day 12: just before the first administration, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours after the last administration. Day 13: 16, 24 and 36 hours after the last administration <i>Day 14:</i> 48 hours after the last administration <i>Day 15:</i> 72 hours after the last administration <u>Urine Samples:</u> <i>Day 1-2:</i> before the first administration, 0-12 and 12-24 hours after 1 st administration <i>Day 2-3:</i> 24-48 hours after the 1st administration <i>Day 3 to 11-12:</i> 0-24 hours after morning-administration <i>Day 12-13:</i> 0-12, 12-24 hours after the last administration <i>Day 13-14:</i> 24-48 hours after the last administration <i>Day 14-15:</i> 48-72 hours after the last administration

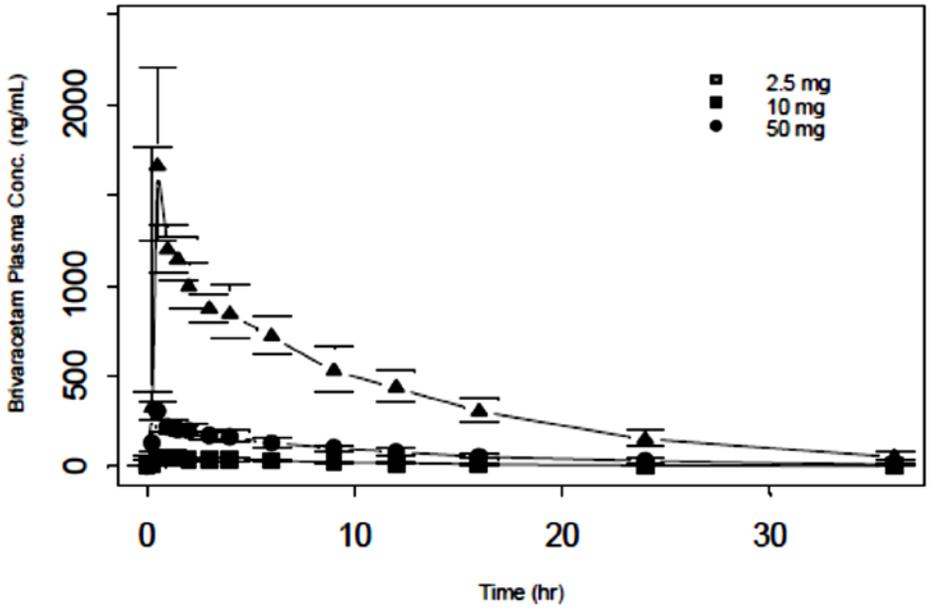
	<p>Pharmacokinetic Analyses: BRV:</p> <ul style="list-style-type: none"> On Day 1 (after single dose administration): C_{max}, t_{max}, AUC_{0-t}, AUC, AUC₀₋₁₂, λ_Z, t_{1/2}, CL/F, V_Z/F, MRT, Ae, fe, CLR On Day 12 (after repeated oral administration): C_{max}, C_{min}, t_{max}, AUC_T, Cav, PTF, λ_Z, t_{1/2}, CL_{ss}/F, V_Z/F, MRT, Ae, fe, CLR, R <p>Metabolites:</p> <ul style="list-style-type: none"> On Day 1 (after single dose administration): C_{max}, t_{max}, AUC_{0-t}, AUC, AUC₀₋₁₂, λ_Z, t_{1/2}, Ae, fe, CLR, CL_{fm}/F (CL_{fm}/F for ucb-100406-1 and ucb 42145 only) On Day 12 (after repeated oral administration): C_{max}, t_{max}, AUC_T, AUC_{0-t}, λ_Z, t_{1/2}, Ae, fe, CLR, CL_{fm}/F (CL_{fm}/F for ucb-100406-1 and ucb 42145 only)
<p>Bioanalytical Methods</p>	<p>Please refer to the bioanalytical methods presented in the ISR for N01209a, which are considered acceptable.</p>
<p>Population/ Demographics</p>	<p>N=29 subjects participated in the main portion of the study. The inclusion / exclusion criteria are identical to those described in the ISR for study N01209a. N=26 subjects participated in the genotype analysis</p>
<p>PK Results</p>	<p>Figure N01209b-1: Geometric Mean ± SD BRV Profile By Dose Group on Day 1</p>  <p>The graph displays the plasma concentration of Brivaracetam (BRV) over a 36-hour period for three different dose groups: 2.5 mg, 10 mg, and 50 mg. The y-axis represents the concentration in ng/mL, ranging from 0 to 2000. The x-axis represents time in hours, ranging from 0 to 36. The 50 mg group (represented by triangles) shows the highest peak concentration, reaching approximately 1800 ng/mL at 1 hour. The 10 mg group (represented by squares) peaks at about 400 ng/mL, and the 2.5 mg group (represented by circles) peaks at about 100 ng/mL. All groups show a rapid decline in concentration, with the 50 mg group still having a concentration of about 200 ng/mL at 36 hours, while the other groups are near zero.</p>

Figure N01209b-2: Geometric Mean ± SD BRV Profile By Dose Group on Day 12

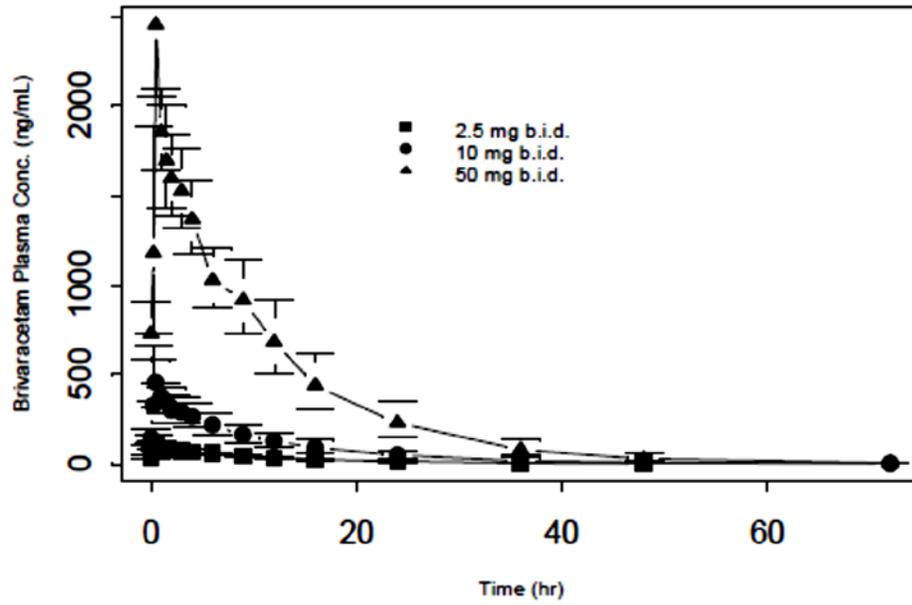


Figure N01209b-3: Geometric Mean ± SD Trough BRV Profile By Dose Group on Days 1 to 12

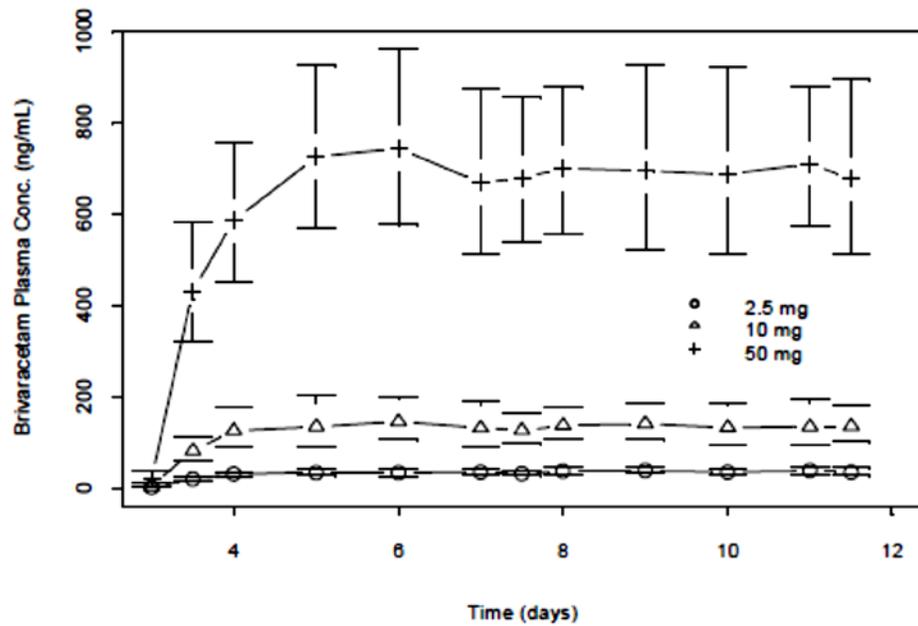


Table N01209b-1: Accumulation Analysis of BRV (AUC_{0-∞} on Day 1 and AUC_τ on Day 12)

Dose	Reference ^(a) AUC at Day 1	Test ^(a) AUC _τ at Day 12	Test ^(b) / Reference
BRV 2.5mg bid	673 (602, 753)	702 (628, 785)	104 (101, 108)
BRV 10mg bid	2830 (2260, 3545)	2939 (2346, 3682)	104 (98.9, 109)
BRV 50mg bid	14362 (12563, 16418)	14239 (12456, 16277)	99.1 (95.4, 103)

(a) Geometric lsmean (95% confidence interval).

(b) Point estimate (90% confidence interval) for the Test/Reference geometric lsmean ratio (%) derived from ANOVA.

Table N01209b-2: Geometric Mean (%CV) BRV PK Parameters By Dose Group on Days1 to 12

PK parameters (unit)	Geometric Mean (geo CV[%])					
	BRV 2.5mg bid (N=8)		BRV 10mg bid (N=8)		BRV 50mg bid (N=8)	
	Day 1	Day 12	Day 1	Day 12 ^(b)	Day 1	Day 12
C _{max} (ng/mL)	63.7 (20.9)	113 (14.5)	329 (23.3)	508 (35.7)	1842 (30.7)	2477 (16.5)
C _{min} (ng/mL)	-	35.0 (20.4)	-	125 (29.8)	-	670 (27.8)
t _{max} (h) ^(a)	0.50 (0.50-1.50)	0.50 (0.25-1.50)	0.50 (0.25-0.50)	0.50 (0.25-1.0)	0.50 (0.25-1.0)	0.50 (0.50-1.50)
AUC (ng.h/mL)	673 (14.3)	-	2830 (26.0)	-	14362 (16.6)	-
AUC _τ (ng.h/mL)	-	702 (12.8)	-	2785 (26.2)	-	14239 (16.1)
t _{1/2} (h)	9.36 (17.0)	9.42 (8.51)	9.34 (21.2)	8.73 (17.2)	8.39 (14.9)	8.59 (16.4)
CL/F (mL/min/kg)	0.964 (13.4)	-	0.989 (25.1)	-	0.959 (14.1)	-
CL _{ss} /F (mL/min/kg)	-	0.925 (10.0)	-	1.00 (26.2)	-	0.968 (11.7)
V _z /F (L)	50.1 (20.4)	28.5 (10.9)	47.6 (8.53)	28.1 (18.5)	42.1 (11.4)	27.7 (14.2)
PTF (%)	-	131 (32.3)	-	163 (29.5)	-	151 (24.6)
MRT (h)	13.3 (15.2)	13.3 (14.0)	12.7 (20.1)	12.1 (14.0)	11.8 (13.2)	11.7 (18.1)
fe (%)	6.87 (22.7)	13.4 (23.6)	7.75 (27.9)	12.5(31.2)	7.57 (28.5)	12.3 (30.0)
CL _R (mL/min/kg)	0.0662 (25.0)	0.0750 (29.2)	0.0766 (14.1)	0.0924 (18.4)	0.0727 (18.1)	0.0886 (14.4)

CV=Coefficient of Variation, geo=geometric, N=number of subjects

(a) Median (range)

(b) N=7

Figure N01209b-4: Geometric Mean ± SD Hydroxy Metabolite (ucb-100406-1) Profile By Dose Group on Day 1 and Day 12

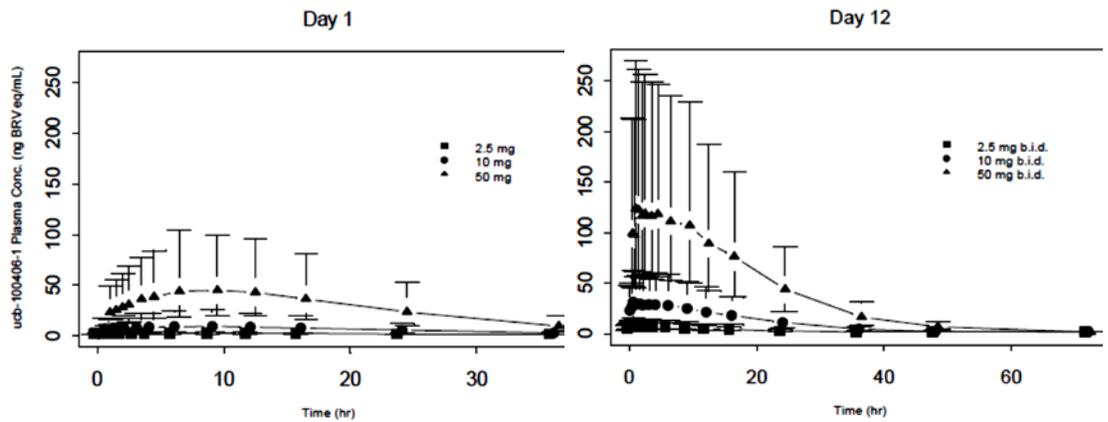


Table N01209b-3: Geometric Mean (%CV) Hydroxy Metabolite (ucb-100406-1) PK Parameters By Dose Group on Days 1 and 12

ucb-100406-1 PK parameters (units)	Geometric Mean (geo CV[%])					
	BRV 2.5mg bid (N=8)		BRV 10mg bid (N=8)		BRV 50mg bid (N=8)	
	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12
C_{max} (ng/mL)	3.06 (28.6) ^(b)	8.12 (46.5)	12.1 (99.0) ^(b)	32.1 (83.9) ^(b)	46.1 (95.9)	130 (90.5)
t_{max} (h) ^(a)	6.0 (4.0-9.0) ^(b)	1.0 (0.5-4.0)	9.0 (6.0-9.0) ^(b)	0.5 (0.5-1.0) ^(b)	9.0 (6.0-12.0)	0.5 (0.5-4.0)
AUC (ng.h/mL)	NC	-	432 (23.9) ^(c)	-	1218 (90.3)	-
AUC _t (ng.h/mL)	-	79.8 (44.0)	-	322 (84.5) ^(b)	-	1321 (87.4)
$t_{1/2}$ (h)	NC	15.2 (40.7)	10.4 (16.4) ^(c)	10.6 (26.5) ^(b)	9.80 (14.9)	9.29 (12.5)
CL _{fm} /F (mL/min/kg)	0.128 (40.5)	0.136 (45.4)	0.103 (156)	0.139 (110) ^(b)	0.0996 (111)	0.113 (106)
fe (%)	13.3 (30.4)	30.3 (34.5)	10.4 (113)	26.8 (73.6) ^(b)	10.4 (95.1)	23.4 (78.5)
CL _R (mL/min/kg)	NC	1.19 (10.1)	1.07 (16.6) ^(c)	1.20 (13.8) ^(b)	1.17 (11.6)	1.22 (26.0)

CV=Coefficient of Variation, geo=geometric, N=number of subjects, NC=Not calculated

- (a) Median (range)
- (b) N=7
- (c) N=6

Figure N01209b-5: Geometric Mean ± SD Carboxylic Acid Metabolite (ucb 42145) Profile By Dose Group on Day 1 and Day 12

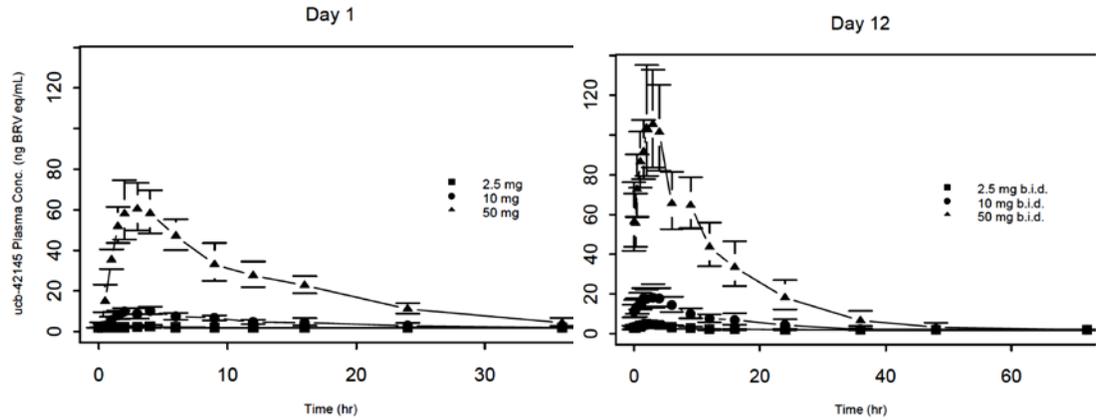


Table N01209b-4: Geometric Mean (%CV) Carboxylic Acid Metabolite (ucb 42145) PK Parameters By Dose Group on Days 1 and 12

ucb 42145 PK parameters (units)	Geometric Mean (geo CV[%])					
	BRV 2.5mg bid (N=8)		BRV 10mg bid (N=8)		BRV 50mg bid (N=8)	
	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12
C_{max} (ng/mL)	3.03 (17.6) ^(b)	5.28 (14.7)	10.8 (15.1)	19.6 (24.2) ^(c)	68.9 (17.3)	113 (23.7)
t_{max} (h) ^(a)	3.5 (3.0-4.0) ^(b)	2.0 (1.5-6.0)	4.0 (2.0-4.0)	3.0 (1.5-4.0) ^(c)	3.0 (1.5-4.0)	2.5 (1.0-4.0)
AUC (ng.h/mL)	NC	-	185 (34.0)	-	905 (15.5)	-
AUC_{τ} (ng.h/mL)	-	42.2 (17.2) ^(b)	-	162 (24.9) ^(c)	-	901 (18.7)
$t_{1/2}$ (h)	NC	NC	11.6 (30.2)	10.7 (15.8) ^(c)	8.71 (21.4)	9.23 (21.6)
CL _{fm} /F (mL/min/kg)	0.280 (13.7)	0.300 (6.52)	0.275 (21.4)	0.322 (17.7) ^(c)	0.293 (14.2)	0.337 (13.3)
fe (%)	29.0 (13.6)	59.4 (17.7)	27.8 (17.7)	52.5 (25.6) ^(c)	30.6 (14.1)	54.3 (26.6)
CL _R (mL/min/kg)	NC	5.10 (8.97) ^(b)	4.19 (38.8)	5.54 (24.5) ^(c)	4.66 (10.4)	5.32 (19.1)

CV=Coefficient of Variation, geo=geometric, N=number of subjects, NC=Not calculated

- (a) Median (range)
- (b) N=6
- (c) N=7

Figure N01209b-6: Geometric Mean ± SD Hydroxy-Acid Metabolite (ucb-107092-1) Profile By Dose Group on Day 1 and Day 12

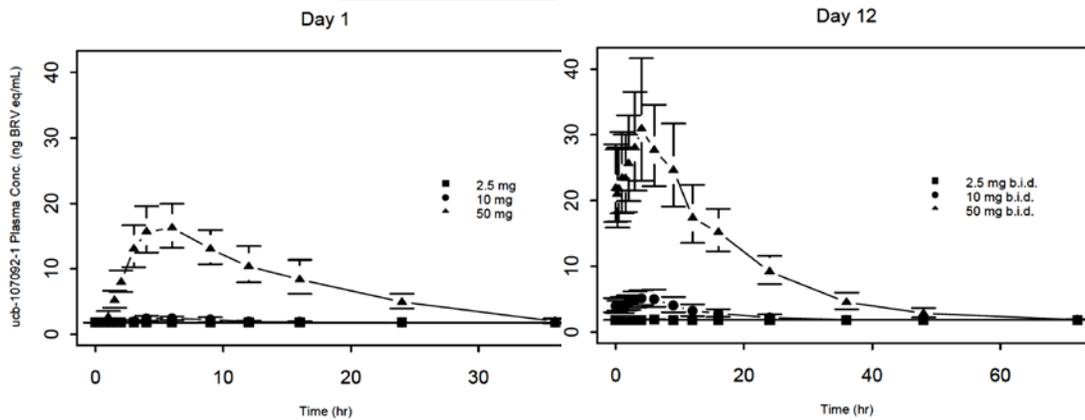


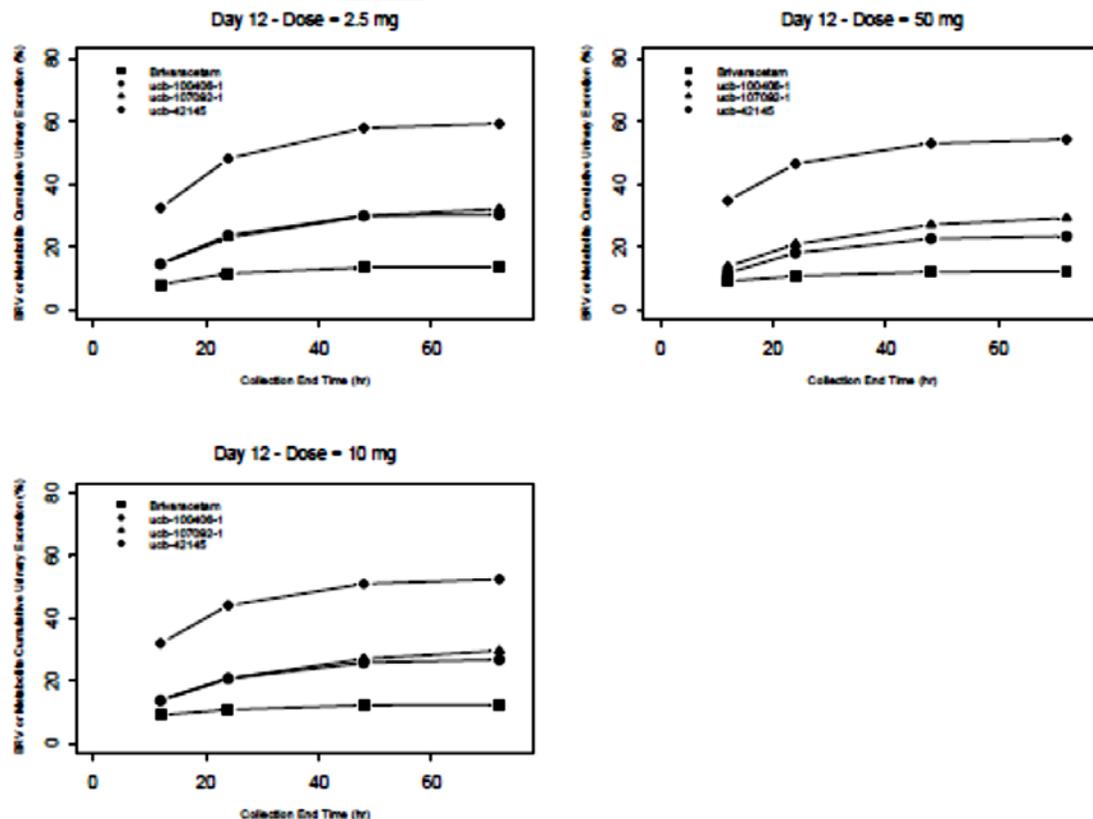
Table N01209b-5: Geometric Mean (%CV) Hydroxy-Acid Metabolite (ucb-107092-1) PK Parameters By Dose Group on Days 1 and 12

ucb 107092-1 PK parameters (units)	Geometric Mean (geo CV[%])					
	BRV 2.5mg bid (N=8)		BRV 10mg bid (N=8)		BRV 50mg bid (N=8)	
	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12
C_{max} (ng/mL)	NC	NC	2.50 (14.6)	5.35 (21.7) ^(b)	16.7 (19.6)	31.1 (30.1)
t_{max} (h) ^(a)	NC	NC	6.0 (4.0-9.0)	4.0 (4.0-6.0) ^(b)	6.0 (4.0-6.0)	4.0 (2.0-4.0)
AUC (ng.h/mL)	NC	-	NC	-	316 (20.9)	-
AUC _τ (ng.h/mL)	-	NC	-	56.9 (12.6) ^(c)	-	303 (25.1)
$t_{1/2}$ (h)	NC	NC	NC	16.2 (14.6) ^(c)	11.1 (22.0)	14.4 (20.2)
fe (%)	13.2 (13.3)	32.2 (14.0)	12.8 (13.9)	29.6 (14.9) ^(b)	14.3 (16.8)	29.3 (13.6)
CL _R (mL/min/kg)	NC	NC	NC	7.48 (16.7) ^(b)	6.23 (16.3)	6.29 (41.9)

CV=Coefficient of Variation, geo=geometric, N=number of subjects, NC=Not calculated

- (a) Median (range)
- (b) N=7
- (c) N=6

Figure N01209b-7: Geometric Mean Urinary Excretion of BRV, Hydroxy Metabolite (ucb-100406-1), Hydroxy-Acid Metabolite (ucb-107092-1), Carboxylic Acid Metabolite (ucb-42145) By Dose Group on Day 12



Safety

- 7 AEs, all mild, were reported by 5 subjects (1 rash in the BRV 10mg bid group, 3 diarrhea in the BRV 50mg bid and 1 diarrhea in placebo groups, 1 headache in the BRV 50mg bid group, and 1 dizziness in the BRV 50mg bid group). All of these AEs were considered related to the study drug.
- Subjects with 6 of the 7 AEs recovered spontaneously before the end of the study.
- The rash (10 mg BRV bid group) persisted for 8 days before recovery.
- No new safety signals were determined.

Sponsor's Conclusions

- BRV 2.5 mg bid, 10 mg bid, and 50 mg bid are safe and well-tolerated.
- The CYP2C19 genotype class may have no clinical relevant b/c the difference in BRV PK among homozygous EM, heterozygous EM and PM was not clinically significant on safety and this allelic variation predominantly affects the PK of ucb-100406-1 which is an inactive metabolite of BRV.
- 90% CI for $AUC_{tau, Day 12} / AUC_{0-\infty Day 1}$ was 99.1% to 104% (and thus, no unexpected accumulation was expected in 2.5 mg bid to 50 mg bid)
- BRV C_{max} and AUC increased proportionally with dose on Days 1 and 12. Other BRV PK parameters were independent of dose.
- All 3 metabolites had C_{max} and AUC increase proportionally with the dose.
- All 3 metabolites had comparable urinary excretion (e.g. f_e) and CL_{ren} across all dose groups.
- Urinary excretion of the 3 metabolites was nearly complete 48 hours after the final BRV dose on Day 12.

Reviewer Comment	<ul style="list-style-type: none">• Please refer to the Appendix for the pharmacogenomics review of the genomic analyses conducted in this study.• This reviewer concurs with the Sponsor that the observed 40% increase in ucb-100406-1 in the present study is not likely to result in safety or tolerability issues (as ucb-100406-1 is not active).• Within the dose range of 2.5 mg bid to 50 mg bid, the BRV $AUC_{0-\infty, Day 1}$ (AUC infinity after a single dose) is comparable to BRV $AUC_{\tau, Day 12}$ (AUC tau at steady state). This observation is consistent with the theory that these two AUC measures should be equal (provided there is no change to ADME over time).• This reviewer concurs that the f_e as well as CL_{ren} did not vary with dose for BRV or metabolites.• The fraction of the dose excreted in the urine increased between Day 1 and Day 12 for BRV (2-fold increase) as well as all metabolites (2-3-fold increase). In addition, urinary excretion of metabolites is greater on Day 12 compared to Day 1. The reason for this increase in renal CL is not clear. However, the safety of this study suggests that BRV 50 mg bid for up to 12 days is well-tolerated in Japanese patients.• This reviewer concurs that BRV and metabolite C_{max} and AUC increased approximately proportionally with dose from 2.5 mg bid to 50 mg bid. The other parameters did not appear to vary significantly with dose.
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4.4.21 N01233: TQT (Phase 1)

Study Report#	RPCE06A1207 / N01233
Title	Randomized, placebo- and moxifloxacin-controlled study of the effect of brivaracetam on cardiac repolarization in four parallel groups of healthy male and female subjects.
Objectives	<p><u>Primary:</u> Assess whether BRV has a threshold pharmacologic effect on cardiac repolarization as detected by QTc prolongation</p> <p><u>Secondary:</u></p> <ol style="list-style-type: none"> Assess the effect of BRV on: <ul style="list-style-type: none"> Time-matched baseline subtracted QT, QTcB, QTcF, RR, PR and QRS intervals Non-baseline adjusted QTcSS, QT, and RR at each post-dose time point Largest time-matched QTcSS and QTcF change from baseline: Δ_{max} Time-matched baseline subtracted QTcSS and QTcF at t_{max} Determine the incidence of new outliers with abnormal T-U waves, and/or QTc > 500 ms and/or QTc change from baseline > 60 ms Determine the plasma levels of BRV and metabolites Assess the safety of repeated oral 75-mg and 400-mg BRV bid during 6.5 days.
Study Design	Two centers, randomized, multiple-dose (single dose of moxifloxacin), 4 parallel groups study, of three double-blind treatments and one open-label treatment (moxifloxacin)
Duration	5 weeks
Dosage and Administration	<p>Four parallel groups were to be enrolled:</p> <ol style="list-style-type: none"> A group constituted of 52 subjects received placebo (8 x 50 mg placebo capsules), b.i.d., from Day 1 morning to Day 7 morning. A group constituted of 52 subjects received a 400 mg moxifloxacin oral tablet on Day 1. A group constituted of 39 subjects received 75 mg brivaracetam (1 x 25 mg, 1 x 50 mg BRV capsules and 6 x 50 mg placebo capsules), b.i.d., from Day 1 morning to Day 7 morning. A group constituted of 39 subjects received 400 mg brivaracetam (8 x 50 mg BRV capsules), b.i.d., from Day 1 morning to Day 7 morning. <p>Moxifloxacin was provided as Avelox® tablets (400 mg)</p>
PK Assessment	<p><u>Plasma Samples:</u> pre-dose, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 9 h and 12 h post-dose on Day 7. BRV and moxifloxacin were measured at the same time points.</p> <p><u>PK Analyses:</u> C_{max}, t_{max} and AUC_{0-12h} were computed for BRV and moxifloxacin</p>
ECG Assessments	<p><u>ECG Measurement Times:</u> Clinical cardiac safety pharmacology was assessed through central reading of ECGs on Day -1 (baseline) and Day 7 (Day 1 for group 2), registered at the same time points as the blood samples for pharmacokinetic assessments (pre-dose, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 9 h and 12 h post-dose). The following parameters were recorded or derived: QT, RR, PR, QRS, QTcB, QTcF, and QTcSS.</p> <p><u>Cardiac Safety Analyses:</u> The effect of BRV on the QT/QT_c interval was primarily analyzed using the largest time-matched mean difference between the drug and placebo (baseline-adjusted, $\Delta\Delta QT_{cSS}$) over the ECG collection period. The relationship between QTc (QTSS and QTcF) interval and pharmacokinetics was</p>

explored via scatter plots and regression models of QTc (raw values and change from baseline) versus BRV and moxifloxacin plasma levels.

Bioanalytical Methods

HPLC-MS/MS Analytical Methods for BRV and Metabolite Plasma Concentrations

Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
Internal Standard (IS)	(b) (4)	(b) (4)		
Standard curve concentrations	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL	1.99, 4.98, 19.9, 49.8, 99.5, 498, 995, 1991 ng/mL*	1.86, 4.65, 18.6, 46.5, 93, 465, 930, 1860 ng/mL*	1.85, 4.63, 18.5, 46.3, 92.6, 463, 926, 1852 ng/mL*
Standards accuracy	-3.1 to 3.3%	-6.6 to 3.5%	-3.9 to 2.2%	-7.6 to 7.9%
Standards precision	< 5.8%	< 7.3%	< 3.2%	< 4.2%
QC concentrations	25.0, 150 and 1800 ng/mL	5.97, 74.7 and 1792 ng/mL*	5.58, 69.7 and 1674 ng/mL*	5.56, 69.4 and 1667 ng/mL
QC Accuracy	-2.0 to 4.7%	-4.4 to 2.0%	-11.2 to -6.3%	-3.8 to 5.2%
QC Precision	< 7.8%	< 10.1%	< 5.3%	< 6.3%
LLOQ	10 ng/mL	1.99 ng/mL*	1.86 ng/mL*	1.85 ng/mL*

*The metabolites are presented as "effective concentrations" (ng eq ucb 34714/mL).

IS (b) (4)

IS (b) (4)

HPLC-MS/MS Analytical Methods for MOX Plasma Concentrations

Analyte Name	Moxifloxacin
Analyte ID	MOX
Internal Standard (IS)	
Standard curve concentrations	25, 50, 100, 200, 500, 1000, 2000, 4000, 5000 ng/mL
Standards accuracy	-4.2% to 3.2%
Standards precision	< 8.0%
QC concentrations	75, 750, 3500 ng/mL
QC Accuracy	1.2 to 2.3%
QC Precision	< 8.5%
LLOQ	25 ng/mL

[Reviewer comment: The assays are acceptable.]

<p>Population/ Demographics</p>	<p>N=292</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female subjects age 18 to 45 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 5. Females of childbearing potential must use adequate birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. QT_{CB} < 300 ms and/or > 450 ms for males, or > 470 ms for females 2. History of Torsade de Pointes, family history of arrhythmia, or any other cardiac condition 3. Hepatic/biliary, renal, gastrointestinal, or other disorder that would alter ADME of drugs or constitute a possible risk factor when taking the study medication 4. Concomitant chronic or acute illness 5. Drug treatment, including prescribed or OTC medications taken within 14 days (or 2 months for enzyme-inducing drugs) predicting first intake of study drug. Paracetamol (acetaminophen) is permitted up to 2 g/day, and up to 10 g / 2 weeks. Oral contraceptives and HRT are permitted. 6. Currently smoker or have quit within 6 months 7. Heavy caffeine intake 8. Quinine, caffeine containing foods, grapefruit, chocolate, coffee or tea within 48 hours of first drug administration 9. Abnormal blood pressure or heart rate at screening 																																																																																
<p>PK Results</p>	<p>Table N01233-1: Largest Time-Matched Difference Between Active Treatment and Placebo (Maximum $\Delta\Delta\text{QT}_{\text{CSS}}$)</p> <table border="1"> <thead> <tr> <th rowspan="2">Population</th> <th rowspan="2">Treatment</th> <th rowspan="2">Post-dose Time</th> <th rowspan="2">max. $\Delta\Delta\text{QT}_{\text{CSS}}$: Estimate (ms)</th> <th colspan="2">Two-Sided 90% Confidence Interval^(a) (ms)</th> </tr> <tr> <th>lower</th> <th>upper</th> </tr> </thead> <tbody> <tr> <td rowspan="3">PP^(b)</td> <td>BRV 75 mg <i>bid</i></td> <td>4 h</td> <td>0.2</td> <td>-3.9</td> <td>4.3</td> </tr> <tr> <td>BRV 400 mg <i>bid</i></td> <td>12 h</td> <td>-1.1</td> <td>-5.2</td> <td>3.0</td> </tr> <tr> <td>MOX 400 mg</td> <td>4 h</td> <td>12.4</td> <td>8.6</td> <td>16.2</td> </tr> <tr> <td rowspan="3">ITT^(b)</td> <td>BRV 75 mg <i>bid</i></td> <td>4 h</td> <td>-0.1</td> <td>-4.2</td> <td>3.9</td> </tr> <tr> <td>BRV 400 mg <i>bid</i></td> <td>12 h</td> <td>-1.5</td> <td>-5.6</td> <td>2.5</td> </tr> <tr> <td>MOX 400 mg</td> <td>4 h</td> <td>12.3</td> <td>8.5</td> <td>16.1</td> </tr> </tbody> </table> <p>Table N01233-2: Largest Time-Matched Difference Between Active Treatment and Placebo (Maximum $\Delta\Delta\text{QT}_{\text{CF}}$)</p> <table border="1"> <thead> <tr> <th rowspan="2">Population</th> <th rowspan="2">Treatment</th> <th rowspan="2">Post-dose Time</th> <th rowspan="2">max. $\Delta\Delta\text{QT}_{\text{CF}}$: Estimate (ms)</th> <th colspan="2">Two-Sided 90% Confidence Interval^(a) (ms)</th> </tr> <tr> <th>lower</th> <th>upper</th> </tr> </thead> <tbody> <tr> <td rowspan="3">PP^(b)</td> <td>BRV 75 mg <i>bid</i></td> <td>4 h</td> <td>1.0</td> <td>-3.1</td> <td>5.0</td> </tr> <tr> <td>BRV 400 mg <i>bid</i></td> <td>9 h</td> <td>-0.1</td> <td>-4.2</td> <td>4.0</td> </tr> <tr> <td>MOX 400 mg</td> <td>4 h</td> <td>12.2</td> <td>8.4</td> <td>15.9</td> </tr> <tr> <td rowspan="3">ITT^(b)</td> <td>BRV 75 mg <i>bid</i></td> <td>4 h</td> <td>0.8</td> <td>-3.2</td> <td>4.7</td> </tr> <tr> <td>BRV 400 mg <i>bid</i></td> <td>9 h</td> <td>-0.5</td> <td>-4.5</td> <td>3.6</td> </tr> <tr> <td>MOX 400 mg</td> <td>4 h</td> <td>12.3</td> <td>8.6</td> <td>16.0</td> </tr> </tbody> </table>	Population	Treatment	Post-dose Time	max. $\Delta\Delta\text{QT}_{\text{CSS}}$: Estimate (ms)	Two-Sided 90% Confidence Interval ^(a) (ms)		lower	upper	PP ^(b)	BRV 75 mg <i>bid</i>	4 h	0.2	-3.9	4.3	BRV 400 mg <i>bid</i>	12 h	-1.1	-5.2	3.0	MOX 400 mg	4 h	12.4	8.6	16.2	ITT ^(b)	BRV 75 mg <i>bid</i>	4 h	-0.1	-4.2	3.9	BRV 400 mg <i>bid</i>	12 h	-1.5	-5.6	2.5	MOX 400 mg	4 h	12.3	8.5	16.1	Population	Treatment	Post-dose Time	max. $\Delta\Delta\text{QT}_{\text{CF}}$: Estimate (ms)	Two-Sided 90% Confidence Interval ^(a) (ms)		lower	upper	PP ^(b)	BRV 75 mg <i>bid</i>	4 h	1.0	-3.1	5.0	BRV 400 mg <i>bid</i>	9 h	-0.1	-4.2	4.0	MOX 400 mg	4 h	12.2	8.4	15.9	ITT ^(b)	BRV 75 mg <i>bid</i>	4 h	0.8	-3.2	4.7	BRV 400 mg <i>bid</i>	9 h	-0.5	-4.5	3.6	MOX 400 mg	4 h	12.3	8.6	16.0
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Table N01233-3: Single-Dose PK Parameters for Moxifloxacin				
	Parameter	units	MOX 400 mg (N=52)	
			Geomean (CV%)	min – max
	C_{max}	µg/mL	2.40 (26.6%)	1.32 – 4.50
	$AUC_{(0-12h)}$	µg*h/mL	16.6 (21.7%)	10.2 – 25.6
	t_{max}	h	1.5 ^(a)	0.5 – 6.0
Safety	<ul style="list-style-type: none"> TEAEs occurred in 48.9% of subjects, TEAEs were reported in 92.5%, 79.5%, 22.6[^], and 19.2% of the BRV 400 mg bid group, BRV 75 mg bid group, placebo group, and MOX treatment group All TEAEs were mild to moderate in intensity Most common TEAEs in 400 mg BRV group were feeling drunk (45.0%), dizziness (42.5%), asthenia (22.5%), somnolence (15.0%), headache (10.0%), euphoric mood (7.5%), nausea (7.5%), and vomiting (5.0%). Most common TEAEs in 75 mg BRV group were asthenia, somnolence and headache (28.2%, 12.8% and 10.3% of the subjects). 			
Sponsor's Conclusions	<p>The results demonstrate the absence of BRV effects on cardiac repolarization</p> <p>The repeated oral administration of 150 mg and 800 mg BRV in HV did not give rise to any unexpected safety concerns</p>			
Reviewer Comment	<p><i>This study did not give rise to any new BRV safety signals.</i></p> <p><i>The IRT QT consult of IND 70205 / IND (b) (4) reviewed this TQT study (see the review of IND 70205 signed on 03/05/2009 for details).</i></p> <p><i>The overall summary of findings was that no significant effect of BRV was detected in the TQT study. The IRT review provided the following statement regarding organ impairment:</i></p> <p><i>“We note that subjects with severe renal impairment had plasma concentrations of the hydroxyacidic metabolite that were 20-fold higher. The sponsor has not completed their evaluation of the extrinsic (e.g., drug interactions) factors that could increase exposure to brivaracetam in patients (Clinical Pharmacology Table, section 6.1). Therefore, the adequacy of the exposures achieved in this TQT study will be a review issue when additional studies are complete.”</i></p> <p><i>Study N01109 demonstrated that metabolite exposures increased between 324% - 2148% in patients with severe RI compared to healthy volunteers. The exposures were greater patients with severe renal impairment compared to patients in the TQT study. While the accumulation of metabolites in patients with severe RI is not known (since N01109 was a single-dose RI study), the Sponsor has provided safety information for animals that were exposed to metabolite exposures 8.5-25 fold greater than predicted steady-state exposures in patients with severe RI, and for durations of 4 to 13 weeks. As there were no significant cardiac toxicity in these toxicology studies, the use of BRV with no dose adjustment in patients with severe RI is acceptable. Please refer to the ISR for study N01109 for additional details.</i></p>			

4.4.22 N01252: Efficacy – 20, 50, 100 mg/day – LEV allowed (Phase 3)

Study Report#	NCT00490035 / N01252
Title	A multi-center, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 years to 70 years old) with Partial Onset Seizures
Objectives	Primary: Assess efficacy of 20, 50, and 100 mg/day BRV in POS epilepsy patients Secondary: Dose/response, effects on Type IC seizures, safety and tolerability, patient functionality and quality of life Exploratory: patient quality of life, population PK, genotyping for SV2-and-epilepsy-related genes (for pooled analyses)
Study Design	International, double-blind, parallel-group, placebo-controlled, randomized, phase 3 confirmatory study
Duration	24-weeks, 14-weeks exposure to BRV (8 week baseline period, 12 week treatment period, 2 week down-titration period, 2-week study drug-free period)
Dosage and Administration	<ul style="list-style-type: none"> After an 8 week baseline period, subjects were randomized 1:1:1:1 to placebo, BRV 20, 50, or 100 mg/day as oral tablets administered BID (2 equal intakes, morning and evening). Subjects were randomized to the full dose without a titration and were treated for 12 weeks. After the Treatment Period, subjects entered the LTFU study at the recommended starting dose of BRV 50 mg/day, or down-titrated over 2 weeks followed by a 2-week study drug-free period. Subjects were stratified by geographical region (Eastern Europe, Western Europe, India) and for use of Levetiracetam (with or without LEV use at study entry). <p>The diagram illustrates the study timeline. It is divided into four main phases: Baseline Period (8 weeks), Treatment Period (12 weeks), Down-titration Period (2 weeks), and Study Drug Free Period (2 weeks). The baseline period starts at V1 (W-8) and ends at V3 (W0). The treatment period begins at V3 (W0) and ends at V7 (W12). The down-titration period follows from V7 (W12) to V8 (W14), and the study drug-free period ends at V9 (W16). Dosage levels are shown for four groups: D3 (100 mg/d), D2 (50 mg/d), D1 (20 mg/d), and Placebo. Key events include Screening at V1 (W-8), Randomization at V3 (W0), Evaluation at V7 (W12), and Follow-up Studies (N01125/N01199) starting at V9 (W16) with a dosage of 50 mg/d.</p>
PK Assessment	<u>Plasma Samples – BRV:</u> one blood sample at Visit 3 (V3-B), Visit 4 (V4-B), Visit 5 first draw (V5-B) and second draw (V5-B2), Visit 6 first draw (V6-B) and

	<p>second draw (V6-B2), Visit 7 first draw (V7-B) and second draw (V7-B2) and Early Discontinuation Visit (EDV).</p> <p><u>Plasma Samples – AEDs:</u> one blood sample at Visit 1 (V1-B), Visit 3 (V3-B), Visit 4 (V4-B), Visit 5 (V5-B), Visit 6 (V6-B), Visit 7 (V7-B), Early Discontinuation Visit (EDV is a Eurofins Medinet visit identification) and at Safety Visit (SV-B).</p>																				
<p>Bioanalytical Methods</p>	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1" data-bbox="495 472 1339 934"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.6 to 3.8%</td> </tr> <tr> <td>Standards precision</td> <td><5.2%</td> </tr> <tr> <td>QC concentrations</td> <td>30, 300, 900, 3600 µg/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-3.4 to 8.6%</td> </tr> <tr> <td>QC Precision</td> <td>< 7.2%</td> </tr> <tr> <td>LLOQ</td> <td>10 ng/mL</td> </tr> </table> <p>[Reviewer comment: The assay is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL	Standards accuracy	-4.6 to 3.8%	Standards precision	<5.2%	QC concentrations	30, 300, 900, 3600 µg/mL	QC Accuracy	-3.4 to 8.6%	QC Precision	< 7.2%	LLOQ	10 ng/mL
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<p>Population/ Demographics</p>	<p>N=399 epilepsy patients with POS</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female patients with epilepsy age 16 to 70 years 2. Focal epilepsy or epileptic syndrome, history of partial onset seizures 3. Refractory while receiving 1 or 2 co-AEDs (Vagal nerve stimulation allowed, but not counted as a co-AED). Benzodiazepine (BZD) taken more than once a week (for any indication) was considered as a concomitant AED. 4. Females of childbearing potential must use acceptable birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Current or previous use of felbamate within 18 months of visit 1 2. Current use of vigabatrin 3. Use of drugs with possible CNS effects unless stable for 1 month prior to Visit 1 and for whole study period.. 4. Use of drugs that influence BRV metabolism (2C or 3A potent inhibitors) unless stable for 1 more before visit 1 and for entire study duration. 5. Impaired hepatic function (ALAT/SGPT, ASAT/SGOT, ALP, GGT > 3 x ULN) 6. Creatinine CL < 50 mL/min 7. Clinically significant ECG abnormalities 8. Pregnant/lactating women <p>[Reviewer comment: Use of levetiracetam was permitted in this study.]</p>																				
<p>PK Results</p>	<p>The population pharmacokinetics (PK) of brivaracetam (BRV) in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358)</p> <p>PK results from these studies are pooled and provided in the CSR for N01358.</p>																				

Efficacy	<p>Table N01252-1: Primary Efficacy Analysis of Seizure Frequency Per Week Over the Treatment Period</p> <table border="1"> <thead> <tr> <th rowspan="2">Statistics</th> <th rowspan="2">PBO (N=100)</th> <th colspan="3">BRV</th> </tr> <tr> <th>20mg (N=99)</th> <th>50mg (N=99)</th> <th>100mg (N=100)</th> </tr> </thead> <tbody> <tr> <td>n</td> <td>100</td> <td>99</td> <td>99</td> <td>100</td> </tr> <tr> <td>LS means (log transformed) (SE)</td> <td>1.167 (0.042)</td> <td>1.096 (0.042)</td> <td>1.099 (0.042)</td> <td>1.042 (0.042)</td> </tr> <tr> <td>LS means (back transformed)</td> <td>2.211</td> <td>1.993</td> <td>2.002</td> <td>1.836</td> </tr> <tr> <td>Treatment comparison vs PBO</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>% reduction over PBO</td> <td></td> <td>6.8</td> <td>6.5</td> <td>11.7</td> </tr> <tr> <td>95% confidence interval</td> <td></td> <td>-4.8, 17.1</td> <td>-5.2, 16.9</td> <td>0.7, 21.4</td> </tr> <tr> <td>p-value^a</td> <td></td> <td>0.239</td> <td>0.261</td> <td>0.037^b</td> </tr> </tbody> </table> <p>The 100 mg/day big dose level is the only group that demonstrated statistically significant benefit compared to placebo.</p> <p>However, the primary outcome for study N01252 <u>did not achieve statistical significance based on the sequential testing procedure</u>, which required statistical significance at the 0.050 level for BRV 50mg/day versus PBO <i>prior</i> to the testing of BRV 100mg/day and BRV 20mg/day in sequence.</p>	Statistics	PBO (N=100)	BRV			20mg (N=99)	50mg (N=99)	100mg (N=100)	n	100	99	99	100	LS means (log transformed) (SE)	1.167 (0.042)	1.096 (0.042)	1.099 (0.042)	1.042 (0.042)	LS means (back transformed)	2.211	1.993	2.002	1.836	Treatment comparison vs PBO					% reduction over PBO		6.8	6.5	11.7	95% confidence interval		-4.8, 17.1	-5.2, 16.9	0.7, 21.4	p-value ^a		0.239	0.261	0.037 ^b
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p-value ^a		0.239	0.261	0.037 ^b																																								
Safety	<ul style="list-style-type: none"> TEAEs occurred in 53.0% and 60.7% of subjects in the PBO group and BRV group, respectively. The most common TEAEs in BRV vs PBO were the Treatment Period were: headache (13.8% vs 9.0%), somnolence (7.4% vs 6.0%), dizziness (5.7% vs 5.0%), and fatigue (5.0% vs 2.0%), respectively. Headache and fatigue were the two TEAEs that occurred at the highest rates compared to placebo. TEAEs during the Treatment Period was higher in the subjects with concomitant LEV use for both the PBO and BRV overall treatment groups (66.7% and 72.4%, respectively) compared with subjects without concomitant LEV use (50.0% and 57.9%, respectively). The most common <i>drug-related</i> TEAEs in the BRV overall group compared with the PBO group were as follows: headache (6.4% vs 3.0%), somnolence (6.4% vs 6.0%), and fatigue (4.7% vs 2.0%). TEAEs that lead to discontinuation was 4.0% and 4.7% in PBO and BRV groups SAE incidence was 6.0% and 2.3% in PBO and BRV groups 																																											
Sponsor's Conclusions	<ul style="list-style-type: none"> The primary efficacy outcome did not achieve statistical significance, based on the pre-specified statistical testing procedure for 20 mg and 50 mg doses. The comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome (p=0.037). Brivaracetam at doses of 20mg/day, 50mg/day, and 100mg/day was generally well tolerated. 																																											
Reviewer Comment	<ul style="list-style-type: none"> The 50 mg/day dose was statistically significantly better than placebo in study N01253 as well as N01193. However, the 50 mg/day dose was not better than placebo in study N01114 and the current study. Please refer to the medical officer's review for more information about the acceptability of the 50 mg/day bid (25 mg twice per day) dose level. For insight into the population pharmacokinetic analyses and exposure-efficacy analyses, please refer to the pharmacometric portion of this review. 																																											

4.4.23 N01253: Efficacy – 5, 20, 50 mg/day – LEV allowed (Phase 3)

Study Report#	NCT00464269 / N01253
Title	An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 15 years to 70 years old) with Partial Onset Seizures
Objectives	<p><u>Primary:</u> Assess efficacy of 5, 20, and 50 mg/day BRV in POS epilepsy patients</p> <p><u>Secondary:</u> Dose/response, effects on Type IC seizures, safety and tolerability, patient functionality and quality of life</p> <p><u>Exploratory:</u> patient quality of life, population PK, genotyping for SV2-and-epilepsy-related genes (for pooled analyses)</p>
Study Design	International, double-blind, parallel-group, placebo-controlled, randomized, phase 3 confirmatory study
Duration	23 weeks, 13-weeks exposure to BRV (8 weeks baseline period, 12 week treatment period, 1 week down-titration period, 2-week study drug-free period)
Dosage and Administration	<ul style="list-style-type: none"> After an 8-week Baseline Period, subjects were randomized 1:1:1:1 to placebo, BRV 5, 20, or 50 mg/day as oral tablets administered BID (2 equal intakes, morning and evening). Subjects were randomized to the full dose without a titration and were treated for 12 weeks. After the Treatment Period, subjects entered the LTFU study at the recommended starting dose of 50 mg/day or down-titrated over 1 week followed by a 2-week study-drug-free period. <p>The diagram illustrates the study timeline. It is divided into four main phases: Baseline Period (8 weeks), Treatment Period (12 weeks), Down-Titration Period (1 week), and Study Drug Free Period (2 weeks). The Baseline Period includes visits V1 (W-8) and V2 (W-4). Randomization occurs at V3 (W0). The Treatment Period includes visits V4 (W2), V5 (W4), V6 (W8), and V7 (W12). The Down-Titration Period includes a Phone Call at W13. The Study Drug Free Period includes a Safety Visit at W15. Dosage levels are shown for four groups: D3 (50 mg/d), D2 (20 mg/d), D1 (5 mg/d), and Placebo. The D3 group starts at 50 mg/d at V3 and remains constant until V7, then down-titrates to 20 mg/d at W13 and 5 mg/d at W15. The D2 group starts at 20 mg/d at V3 and remains constant until V7, then down-titrates to 5 mg/d at W13 and 5 mg/d at W15. The D1 group starts at 5 mg/d at V3 and remains constant until V7, then down-titrates to 5 mg/d at W13 and 5 mg/d at W15. The Placebo group starts at 5 mg/d at V3 and remains constant until V7, then down-titrates to 5 mg/d at W13 and 5 mg/d at W15. Key events include Screening at V1, Randomization at V3, Evaluation at V7, and Start dosage for Follow-up Study N01199 at W13.</p>
PK Assessment	<p><u>Plasma Samples – BRV:</u> one blood sample at Visit 3 (V3-B), Visit 4 (V4-B), Visit 5 first draw (V5-B) and second draw (V5-B2), Visit 6 first draw (V6-B) and second draw (V6-B2), Visit 7 first draw (V7-B) and second draw (V7-B2) and Early Discontinuation Visit (EDV).</p> <p><u>Plasma Samples – AEDs:</u> one blood sample at Visit 1 (V1-B), Visit 3 (V3-B), Visit 4 (V4-B), Visit 5 (V5-B), Visit 6 (V6-B), Visit 7 (V7-B), Early Discontinuation Visit (EDV is a Eurofins Medinet visit identification) and at</p>

	Safety Visit (SV-B).	
Bioanalytical Methods	HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations	
	Analyte Name	Brivaracetam
	Analyte ID	ucb 34714
	Internal Standard (IS)	(b) (4)
	Standard curve concentrations	10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL
	Standards accuracy	-6.3 to 4.1%
	Standards precision	< 6.5%
	QC concentrations	30, 300, 900, 3600 µg/mL
	QC Accuracy	-4.1 to 8.2%
	QC Precision	< 9.4%
	LLOQ	10 ng/mL
	<i>[Reviewer comment: The assay is acceptable.]</i>	
Population/ Demographics	<p>N=400 epilepsy patients with POS</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Male and female patients with epilepsy age 16 to 70 years 2. Focal epilepsy or epileptic syndrome, history of partial onset seizures 3. Refractory while receiving 1 or 2 co-AEDs (Vagal nerve stimulation allowed, but not counted as a co-AED). Benzodiazepine (BZD) taken more than once a week (for any indication) was considered as a concomitant AED. 4. Females of childbearing potential must use acceptable birth control <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Current or previous use of felbamate within 18 months of visit 1 2. Current use of vigabatrin 3. Use of drugs with possible CNS effects unless stable for 1 month prior to Visit 1 and for whole study period. Benzodiazepines taken more than once/week (for any indication) is considered as a concomitant AED. 4. Use of drugs that influence BRV metabolism (2C or 3A potent inhibitors) unless stable for 1 more before visit 1 and for entire study duration. 5. Impaired hepatic function (ALAT/SGPT, ASAT/SGOT, ALP, GGT > 3 x ULN) 6. Creatinine CL < 50 mL/min 7. Clinically significant ECG abnormalities 8. Pregnant/lactating women <p><i>[Reviewer comment: Use of levetiracetam was permitted in this study.]</i></p>	
PK Results	<p>The population pharmacokinetics (PK) of brivaracetam (BRV) in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358)</p> <p>PK results from these studies are pooled and provided in the CSR for N01358.</p>	

Efficacy	<p>Table N01253-1: Primary Efficacy Analysis Partial Seizure Frequency Per Week Over the Treatment Period</p> <table border="1"> <thead> <tr> <th rowspan="2">Statistics</th> <th rowspan="2">PBO (N=96)</th> <th colspan="3">BRV</th> </tr> <tr> <th>5mg (N=96)</th> <th>20mg (N=99)</th> <th>50mg (N=101)</th> </tr> </thead> <tbody> <tr> <td>n</td> <td>96</td> <td>96</td> <td>99</td> <td>101</td> </tr> <tr> <td>LS means (log-transformed) (SE)</td> <td>1.418 (0.044)</td> <td>1.427 (0.044)</td> <td>1.376 (0.044)</td> <td>1.282 (0.043)</td> </tr> <tr> <td>LS means (back transformed)</td> <td>3.131</td> <td>3.168</td> <td>2.961</td> <td>2.602</td> </tr> <tr> <td colspan="5">Treatment comparison vs PBO</td> </tr> <tr> <td>% reduction over PBO</td> <td>–</td> <td>-0.9</td> <td>4.1</td> <td>12.8</td> </tr> <tr> <td>95% CI</td> <td>–</td> <td>-13.9, 10.6</td> <td>-8.1, 15.0</td> <td>1.7, 22.6</td> </tr> <tr> <td>p-value^a</td> <td>–</td> <td>0.885</td> <td>0.492</td> <td>0.025</td> </tr> </tbody> </table> <p>Only the 50 mg bid group demonstrated a statistically significant efficacy improved compared to placebo.</p>	Statistics	PBO (N=96)	BRV			5mg (N=96)	20mg (N=99)	50mg (N=101)	n	96	96	99	101	LS means (log-transformed) (SE)	1.418 (0.044)	1.427 (0.044)	1.376 (0.044)	1.282 (0.043)	LS means (back transformed)	3.131	3.168	2.961	2.602	Treatment comparison vs PBO					% reduction over PBO	–	-0.9	4.1	12.8	95% CI	–	-13.9, 10.6	-8.1, 15.0	1.7, 22.6	p-value ^a	–	0.885	0.492	0.025
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p-value ^a	–	0.885	0.492	0.025																																								
Safety	<ul style="list-style-type: none"> TEAEs occurred in 70.4% and 75.8% of subjects receiving placebo and BRV, respectively. The most comment AEs with BRV vs PBO were somnolence (15.1% vs 7.1%), dizziness (14.1% vs 9.2%), headache (10.1% vs 14.3%), influenza (6.4% vs 1.0%), nausea (5.7% vs 3.1%), and fatigue (8.7% vs 2.0%). Majority of AEs were mild or moderate TEAEs leading to discontinuation was 2.0%, 8.2%, 5.0%, and 5.9% in the PBO, BRV 5mg/day, BRV 20mg/day, and BRV 50mg/day groups, respectively 																																											
Sponsor's Conclusions	<ul style="list-style-type: none"> The 50 mg/day bid BRV group demonstrated statistically significant improvement over placebo A statistically greater proportion of subjects in the BRV 50mg/day group (32.7%) were 50% responders compared with the PBO group (16.7%; p=0.008). Brivaracetam at doses of 5mg/day, 20mg/day, and 50mg/day was generally well tolerated compared with PBO in this controlled study of subjects aged 16 to 70 years old with POS. 																																											
Reviewer Comment	<ul style="list-style-type: none"> <i>There were no apparent new safety signals in this study.</i> <i>The 50 mg/day dose was statistically significantly better than placebo in this study as well as N01193. However, the 50 mg/day dose was not better than placebo in study N01114 and N01252.</i> <i>Please refer to the medical officer's review for more information about the acceptability of the 50 mg/day bid (25 mg twice per day) dose level.</i> <i>For insight into the population pharmacokinetic analyses and exposure-efficacy analyses, please refer to the pharmacometric portion of this review.</i> 																																											

4.4.24 N01254: Safety – 20, 50, 100, 150 mg/day – LEV allowed

Study Report#	N01254
Title	An international, randomized, double-blind, parallel-group, placebo-controlled, flexible dose study: evaluation of the safety and efficacy of brivaracetam in subjects (≥16 to 70 years old) suffering from localization-related or generalized epilepsy
Objectives	<p><u>Primary:</u> assess the safety and tolerability</p> <p><u>Secondary:</u></p> <ol style="list-style-type: none"> 1. Confirm efficacy 2. Assess effect on quality of life measures 3. Assess effects on Type IC seizures.
Study Design	Randomized, double-blind, parallel-group, placebo-controlled, flexible dose study
Duration	25 weeks (19-week BRV exposure)
Dosage and Administration	<p>After a 4-week Baseline Period (screening visit V02), subjects who entered the Treatment Period were randomized (dose finding period 8 weeks with visit V03, V04 and V06) to one treatment group: 20, 50, 100 and 150 mg/day of Brivaracetam or placebo (tablets, BID).</p> <p>The treatment period at stable dose (maintenance period V08) lasted 8 weeks and at the end of this treatment period, a decision was made on whether the subject enter the LTFU, or entered a Down-titration Period, followed by a 2-week Study Drug Free Period.</p> <p>* Dose escalation to the next higher dose will be at Investigator's discretion during the Dose-Finding Period up to V6 included. One fallback to the immediate lower dose level is also allowed during the Dose-Finding Period for subjects taking doses above BRV 20 mg/day or matching PBO. Once the fallback option has been used, there will be no possibility to resume the previous dose.</p>
PK Assessment	<p><u>Plasma Samples – BRV:</u> one blood sample at Visit 3 (V3-B), Visit 4 (V4-B), Visit 5 first draw (V5-B) and second draw (V5-B2), Visit 6 first draw (V6-B) and second draw (V6-B2), Visit 7 first draw (V7-B) and second draw (V7-B2) and Early Discontinuation Visit (EDV).</p> <p><u>Plasma Samples – AEDs:</u> one blood sample at Visit 1 (V1-B), Visit 3 (V3-B), Visit 4 (V4-B), Visit 5 (V5-B), Visit 6 (V6-B), Visit 7 (V7-B), Early</p>

	Discontinuation Visit (EDV is a Eurofins Medinet visit identification) and at Safety Visit (SV-B).																				
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1" data-bbox="495 289 1339 751"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.4 to 4.3%</td> </tr> <tr> <td>Standards precision</td> <td>< 5.6%</td> </tr> <tr> <td>QC concentrations</td> <td>30, 300, 900, 3600 µg/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-3.9 to 8.1%</td> </tr> <tr> <td>QC Precision</td> <td><9.6%</td> </tr> <tr> <td>LLOQ</td> <td>10 ng/mL</td> </tr> </table> <p>[Reviewer comment: The assay is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	10, 20, 50, 100, 200, 500, 1000, 2000, 4000 ng/mL	Standards accuracy	-4.4 to 4.3%	Standards precision	< 5.6%	QC concentrations	30, 300, 900, 3600 µg/mL	QC Accuracy	-3.9 to 8.1%	QC Precision	<9.6%	LLOQ	10 ng/mL
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QC Accuracy	-3.9 to 8.1%																				
QC Precision	<9.6%																				
LLOQ	10 ng/mL																				
Population/ Demographics	<p>N=480</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female patients with epilepsy age 16 to 70 years 2. Focal epilepsy or epileptic syndrome, history of partial onset seizures 3. Refractory while receiving 1 or 3 co-AEDs (Vagal nerve stimulation allowed, but not counted as a co-AED) stable for 1 month (3 months for phenobarbital and primidone) before V1. Benzodiazepine (BZD) taken more than once a week (for any indication) was considered as a concomitant AED. 4. Females of childbearing potential must use acceptable birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Current or previous use of felbamate within 18 months of visit 1 2. Current use of vigabatrin 3. Use of drugs with possible CNS effects unless stable for 1 month prior to Visit 1 and for whole study period. Benzodiazepines taken more than once/week (for any indication) is considered as a concomitant AED. 4. Use of drugs that influence BRV metabolism (2C or 3A potent inhibitors) unless stable for 1 more before visit 1 and for entire study duration. 5. Impaired hepatic function (ALAT/SGPT, ASAT/SGOT, ALP, GGT > 3 x ULN) 6. Creatinine CL < 50 mL/min 7. Clinically significant ECG abnormalities 8. Pregnant/lactating women <p>[Reviewer comment: Use of <u>levetiracetam</u> was <u>permitted</u> in this study.]</p>																				
PK Results	<p>The population pharmacokinetics (PK) of brivaracetam (BRV) in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358)</p> <p>PK results from these studies are pooled and provided in the CSR for N01358.</p>																				

Efficacy	Table N01254-1: Primary Efficacy Analysis of Seizure Frequency Per Week Over Analysis Periods		
	Period Statistics	PBO (N=108)	BRV (N=323)
	Treatment Period (Dose-Finding + Maintenance)		
	N	108	323
	LS means (log transformed) (SE)	1.286 (0.046)	1.210 (0.030)
	LS means (back transformed)	2.620	2.355
	Treatment comparison vs PBO		
	% reduction over PBO	-	7.3
	95% confidence interval	-	-2.2, 15.9
	p-value ^a	-	0.125
	Dose-Finding Period		
	N	108	323
	LS means (log transformed) (SE)	1.354 (0.045)	1.229 (0.030)
	LS means (back transformed)	2.874	2.417
	Treatment comparison vs PBO		
	% reduction over PBO	-	11.8
	95% confidence interval	-	2.9, 19.9
	p-value ^a	-	0.011
	Maintenance Period		
	N	108	323
	LS means (log transformed) (SE)	1.201 (0.053)	1.171 (0.035)
	LS means (back transformed)	2.324	2.226
	Treatment comparison vs PBO		
	% reduction over PBO	-	3.0
	95% confidence interval	-	-8.7, 13.3
	p-value ^a	-	0.603
	The primary efficacy outcome (seizure reduction during the entire Treatment Period (Dose-Finding Period + Maintenance Period) did not achieve statistical significance at the 0.05 level (p=0.125).		
Safety	<ul style="list-style-type: none"> TEAE rate was 65.3% and 66% in PBO and BRV groups, respectively. The most common TEAEs during the Treatment Period for the BRV group compared with the PBO group were as follows: headache (14.2% vs 19.8%), somnolence (11.1% vs 4.1%), dizziness (8.6% vs 5.8%), fatigue (7.8% vs 4.1%), nausea (5.6% vs 8.3%), convulsion (5.0% vs 3.3%), nasopharyngitis (3.9% vs 6.6%), and back pain (3.1% vs 6.6%). The majority of TEAEs reported during the Treatment Period for the overall Safety Population were mild or moderate in intensity; TEAEs that led to discontinuation 5.0% and 6.4% in PBO and BRV groups SAEs in the Overall Period occurred in 7.4% and 5.6% of the PBO and BRV groups, respectively. 		
Sponsor's Conclusions	<ul style="list-style-type: none"> The primary outcome, % POS reduction compared to placebo during the treatment period, was 7.2% and did not achieve statistical significance. A secondary endpoint, 50% responder rate over the treatment period was statistically significantly improved compared to placebo (30.3% versus 16.7% for BRV versus PBO; p=0.006). Brivaracetam was generally well tolerated. 		

<i>Reviewer Comment</i>	<ul style="list-style-type: none">• <i>There was no signs of new safety signals from this study</i>• <i>The overall effect of BRV (all doses pooled in a single BRV arm) was not statistically significantly superior to placebo over the time course of interest. It is not clear why BRV was superior to placebo during the dose-finding period (up-titration period) but BRV was not superior to placebo during the maintenance period.</i>
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4.4.25 N01256-A: Bioavailability of Oral Tablet Versus IV infusion, and IV bolus (Phase 1)

Study Report#	RPCE07C1525 / N01256
Title	<i>A randomized, monocenter, open-label, three-way crossover, dose availability study of three different formulation of brivaracetam (part I), followed by a non-randomized, monocenter, open-label safety assessment study of four escalating doses of brivaracetam (BRV) administered via two formulations (part II), on healthy volunteers</i>
Objectives	<i>Primary:</i> BA comparison between BRV 10 mg oral tablet versus BRV 10 mg IV-infusion (15 minutes), and BRV 10 mg IV bolus (12 seconds) <i>Secondary:</i> Assess safety and tolerability
Study Design	Monocenter, single dose, open-label, randomized, 3-way crossover study
Duration	6 weeks in Part A (see the ISR for Study N01256-B for details on Part B)
Dosage and Administration	N=24 Subjects received a single dose of each of the three treatments (separated by a 1-week washout): 1. BRV 10 mg oral tablet, 2. BRV 10 mg (50 mg / mL Vial) as a 15-minute IV infusion, 3. BRV 10 mg (50 mg / mL Vial) as a 12-second IV bolus.
PK Assessment	Part I (N01256-A) collected plasma samples for plasma PK analyses. <u>BRV tablet:</u> pre-dose, 15, 30, 45 minutes, and 1, 2, 4, 6, 8, 12, 24, and 36 hours after dosing. <u>BRV infusion and bolus:</u> pre-dose, 5, 10, 15, and 30 minutes, 1, 2, 4, 6, 8, 12, 24, and 36 hours after dosing. PK <u>Analyses:</u> C_{max} , C_T (end of infusion or bolus), t_{max} , AUC, AUC_{0-t} , λ_z , $t_{1/2}$, CL, V_z .
Statistical Analysis	<u>Reference:</u> 10 mg BRV oral tablet <u>Test 1:</u> 10 mg BRV IV (infusion) <u>Test 2:</u> 10 mg BRV IV (bolus) Sponsor assessed bioavailability between Test 1/Reference and Test 2/Reference by computing the 90% CI for the ratio of geometric means of In-transformed parameters AUC, AUC_{0-t} , and C_{max} using a linear mixed-effects model (ANOVA). Sponsor concluded that the bioavailability was comparable if the 90% CI was fully included within the range of 80 to 125% for the primary parameters AUC, AUC_{0-t} , and C_{max} . PK analyses were carried out on the “per protocol” population.

Bioanalytical Methods	HPLC-MS/MS Analytical Methods for Plasma Concentrations				
	Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite
	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1
	Internal Standard (IS)	(b) (4)	(b) (4)		
	Standard curve concentrations	2, 5, 50, 200, 600, 1200, 1800, 2000 ng/mL	1.99, 4.98, 19.9, 49.8, 99.5, 249, 448 ng/mL*	1.86, 4.65, 18.6, 46.5, 93, 232, 418, 465 ng/mL*	1.85, 4.63, 46.3, 185, 556, 1111, 1667, 1852 ng/mL*
	Standards accuracy	- 3.9 to 3.2%	-1.6 to 1.5%	-1.9 to 1.6%	-3.2 to 2.8%
	Standards precision	2.0 to 5.4%	1.9 to 5.1%	1.7 to 4.8%	1.9 to 5.4%
	QC concentrations	6, 75, 1600 ng/mL	5.97, 29.9, 398 ng/mL*	5.58, 27.9, 372 ng/mL*	5.56, 69.4, 1481 ng/mL*
	QC Accuracy	-2.2 to 2.3%	-0.7 to 1.3%	-5.2 to -3.6%	-0.9 to 27%
	QC Precision	5.6 to 7.8%	6.0 to 7.3%	5.4 to 6.9%	7.0 to 9.6%
	LLOQ	50 ng/mL	0.002 µg/mL	0.002 µg/mL	0.002 µg/mL
	<p>*The metabolites are presented as “effective concentrations” (ng eq ucb 34714/mL).</p> <p>IS (b) (4)</p> <p>IS (b) (4)</p> <p>The Sponsor utilized a similar assay method for measuring urine concentration. The Sponsor took a urine sample, diluted it 10-fold with blank plasma, and applied the same assay methodology as was applied for plasma concentration assessment. The Sponsor reports that the LLOQ was the same in urine as in plasma for each species. Please refer to N01256-B for additional details.</p>				
Population/ Demographics	<p>N=24 healthy male and female subjects age 18 to 55 years with BME 18 to 29 kg/m².</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male and female subjects age 18 to 55 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 5. Females of childbearing potential must use adequate birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Pregnant or lactating females 2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness 4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day, or hormonal therapy for females). Use of drugs during clinical trial 5. Heavy caffeine drinker (drinking >5 cups of coffee, tea, etc. per day). 6. Current smoker or had given up smoking in the last 6 months 				

PK Results

Figure N01256A-1: Mean PK Profile After Administration of Single 10 mg BRV as an IV Infusion, IV Bolus, and Oral Tablet

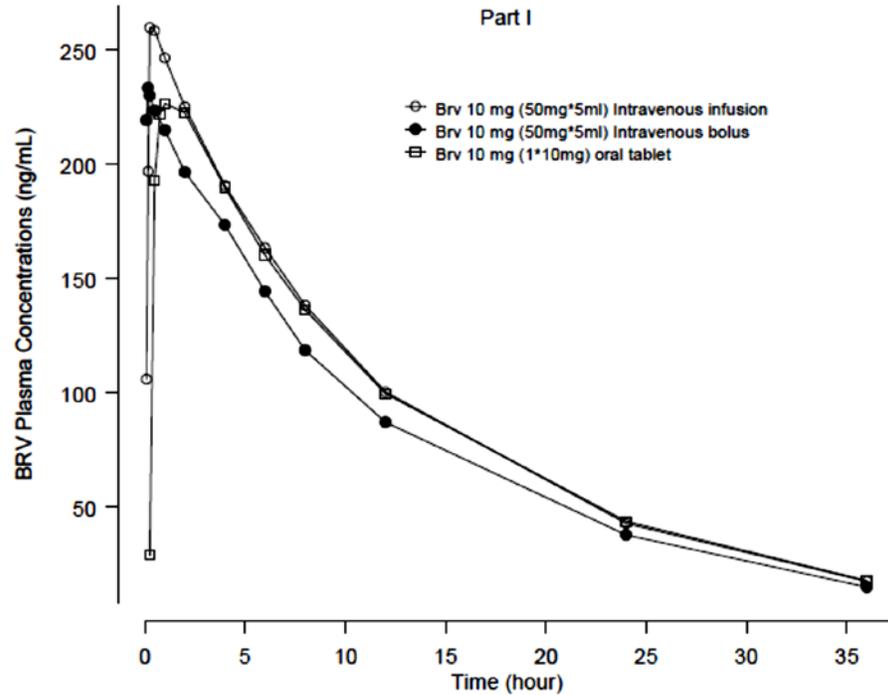


Figure N01256A-2: Mean \pm SD PK Profile After Administration of Single 10 mg BRV as an IV Infusion, IV Bolus, and Oral Tablet

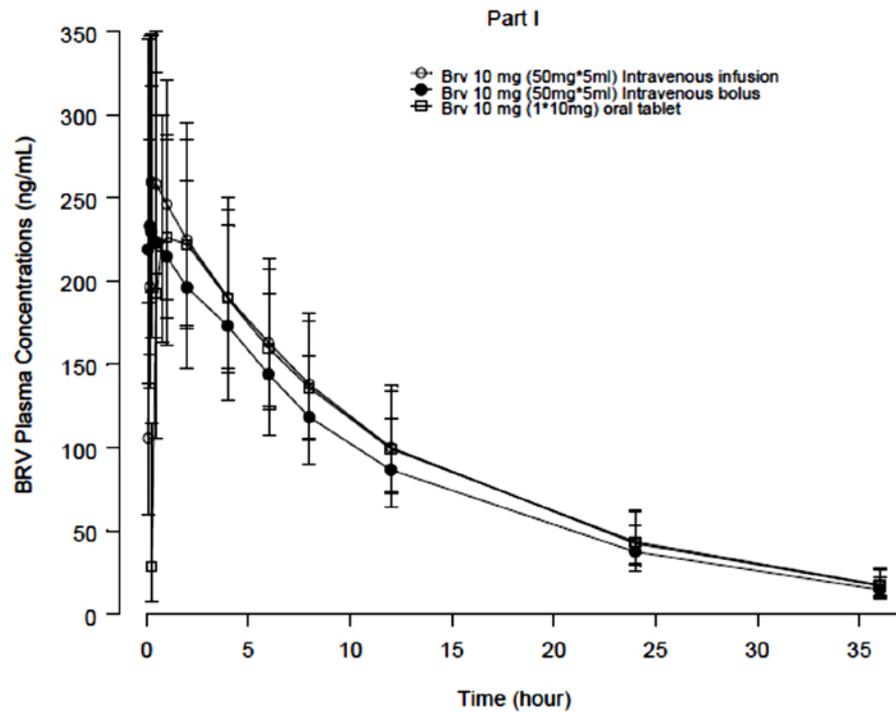


Table N01256A-1: PK Parameters of the Different BRV Formulations (PP Population)

Parameters	Geometric Mean (Geometric CV [%])		
	BRV 10 mg Oral Tablet N = 24	BRV 10 mg IV Infusion N = 24	BRV 10 mg IV Bolus N = 24
AUC(0-t) (ng*h/mL)	3145 (27.8)	3241 (29.6)	2848 (30.0)
AUC (ng*h/mL)	3400 (29.8)	3488 (31.8)	3056 (31.1)
C _{max} (ng/mL)	278 (26.7)	300 (22.1)	262 (34.9)
C _t (ng/mL) ^(a)	NC	259 (30.0)	219 (48.3)
λ _z (1/h)	0.0724 (12.9)	0.0742 (14.3)	0.0746 (13.0)
t _½ (h)	9.57 (12.9)	9.34 (14.3)	9.30 (13.0)
CL/F or CL (L/h) ^(b)	2.94 (29.8)	2.97 (31.9)	3.22 (33.4)
V _Z /F or V _Z (L) ^(b)	40.6 (22.9)	40.1 (24.1)	43.2 (30.6)
	Median (range)		
t _{max} (h)	0.63 (0.25 – 2.0)	0.5 (0.08 – 2.0)	0.16 (0.08 – 0.99)

^(a) t = 5 min for bolus; t = 15 min for infusion
^(b) For IV administrations, actual doses were used.
 NC = not computed

Table N01256A-2: Comparative Bioavailability Assessment for BRV IV Infusion

Parameters (Units)	Test 1 ^(a) BRV IV Infusion	Reference ^(a) BRV Oral Tablet	CV ^(b) (%)	Test 1 versus Reference ^(c)	
				Point Estimate	90% CI
AUC(0-t) (ng*h/mL)	3241 (2857; 3676)	3145 (2773; 3568)	8.67	103.0	(98.80; 107.5)
AUC (ng*h/mL)	3488 (3055; 3982)	3400 (2978; 3881)	8.66	102.6	(98.38; 107.0)
C _{max} (ng/mL)	299.9 (265.9; 338.1)	277.7 (246.3; 313.1)	17.08	108.0	(99.46; 117.2)

^(a) Geometric LSMs (95% CI)
^(b) Intra-subject variability
^(c) Ratio of LSMs (%) and 90% CI derived from ANOVA

Table N01256A-3: Comparative Bioavailability Assessment for BRV IV Bolus

Parameters (Units)	Test 2 ^(a) BRV IV Bolus	Reference ^(a) BRV Oral Tablet	CV ^(b) (%)	Test 2 versus Reference ^(c)	
				Point Estimate	90% CI
AUC(0-t) (ng*h/mL)	2848 (2511; 3231)	3145 (2773; 3568)	8.67	90.55	(86.83; 94.43)
AUC (ng*h/mL)	3056 (2676; 3489)	3400 (2978; 3881)	8.66	89.88	(86.19; 93.72)
C _{max} (ng/mL)	261.8 (232.2; 295.3)	277.7 (246.3; 313.1)	17.08	94.29	(86.85; 102.4)

^(a) Geometric LSMs (95% CI)
^(b) Intra-subject variability
^(c) Ratio of LSMs (%) and 90% CI derived from ANOVA

Safety Results

All TEAE were mild to moderate in intensity and all resolved before end of the study. The most frequent TEAE were headache (20.8%), somnolence (12.5%), and fatigue (16.7%). Sponsor states that the incidence of these events was almost similar for the 3 BRV formulations.

Sponsor's Conclusions	Oral 10 mg BRV tablets are bioequivalent to 10 mg BRV administered as an IV infusion (15-minute infusion duration) or IV bolus (12-second infusion duration). About 2/3 of the subjects reached T _{max} after the end of the IV administration. Sponsor states that this may be due to the equilibration of BRV between blood cells and plasma since BRV is distributed into the blood cells. Sponsor states that similar findings have been reported after IV administration of levetiracetam (the precursor of BRV, in the same family of compounds).
Reviewer Comment	<p><i>The observation of the mean C_{max} achieved after IV bolus (12 second infusion) was lower than the mean C_{max} achieved after IV infusion (15 minute infusion) is unexpected. The reason for this finding is not clear. Rapid distribution into red blood cells as well as solution precipitation upon injection may be factors contributing to the lower C_{max} after a bolus compared to an infusion.</i></p> <p><i>The clinical pharmacology review of NDA 21872 signed on 12/22/2005 indicates that C_{max} values for levetiracetam (the precursor to brivaracetam) were comparable after oral administration and I.V. administration (e.g. 47.9 ± 13.1 µg/mL after 1500 mg oral LEV tablets and 50.90 ± 20.0 µg/mL after 1500 mg I.V. LEV).</i></p>

4.4.26 N01256-B: Safety and PK of 4 escalating Single IV Doses (Phase 1)

Study Report#	RPCE07C1525 / N01256																																	
Title	A randomized, monocenter, open-label, three-way cross-over, dose availability study of three different formulations of brivaracetam (Part I), followed by a non-randomized monocenter, open-label safety assessment study of four escalating doses of brivaracetam (BRV) administered via two formulations (Part II), on healthy volunteers																																	
Objectives	<p><u>Primary</u>: Assess safety and tolerability of single BRV doses of 25, 50, 100, and 150 mg administered as 15-minute IV infusion and as an IV bolus</p> <p><u>Secondary</u>: Assess PK of BRV, including an exploration of dose proportionality</p>																																	
Study Design	Monocenter, dose escalation, non-randomized, open-label study in 4 consecutive groups of 6 subjects (3 males, 3 females)																																	
Duration	5 weeks in Part B (see the ISR for Study N01256-A for details on Part A).																																	
Dosage and Administration	<p>25 mg, 50 mg, 100 mg, and 150 mg in 50 mg / 5 mL vials administered as IV infusion and IV bolus.</p> <p>Each individual subject receives two administrations (IV infusion followed by IV bolus) of a single dose of BRV 25, 50, 100, or 150 mg separated by at least one-week washout.</p>																																	
PK Assessment	<p>Brivaracetam PK was assessed for all doses and all regimens. Metabolite PK was assessed for the 150 mg IV bolus only.</p> <p><u>Plasma sampling times for 150 mg IV bolus</u>: Pre-dose, 5, 10, 15, 30 minutes, and 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours post-dose</p> <p><u>Plasma sampling times for all other doses and regimens</u>: Pre-dose, 5, 10, 15, 30 minutes, and 1, 2, 4, 6, 8, 12, 24, and 36 hours post-dose</p> <p><u>Urine Sample Intervals (150 mg IV bolus)</u>: 0-12 h, 12-24 h, 24-48 h, 48-72 h post-dose.</p> <p><u>PK Analyses</u>: <i>For BRV (all doses, all regimens)</i>: Cmax, CT (end of infusion/bolus), AUC(0-t), AUC, tmax, λz, t1/2, CL, Vz <i>For both BRV and metabolites (150 mg IV bolus)</i>: Ae, fe, CLR <i>For metabolites (150 mg IV bolus)</i>: Cmax, AUC(0-t), AUC, tmax, λz, t1/2</p>																																	
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for Urine Concentrations</p> <table border="1"> <thead> <tr> <th>Analyte Name</th> <th>Brivaracetam</th> <th>Carboxylic Acid Metabolite</th> <th>Hydroxy Metabolite</th> <th>Hydroxy Acid Metabolite</th> </tr> </thead> <tbody> <tr> <td>Analyte ID</td> <td>ucb 34714</td> <td>ucb 42145</td> <td>ucb-100406-1</td> <td>ucb-107092-1</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> <td colspan="3">(b) (4)</td> </tr> <tr> <td colspan="5" style="text-align: center;"><i>Matrix Effect</i></td> </tr> <tr> <td>QC concentrations</td> <td>60,750, 16000 ng/mL</td> <td>60, 300, 4000 ng/mL*</td> <td>60, 300, 4000 ng/mL*</td> <td>60,750, 16000 ng/mL*</td> </tr> <tr> <td>QC Accuracy</td> <td>87.4 – 101.2 %</td> <td>87.4 – 97.7%</td> <td>85.7 – 95.2%</td> <td>85.8 – 93.5 %</td> </tr> </tbody> </table>				Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1	Internal Standard (IS)	(b) (4)	(b) (4)			<i>Matrix Effect</i>					QC concentrations	60,750, 16000 ng/mL	60, 300, 4000 ng/mL*	60, 300, 4000 ng/mL*	60,750, 16000 ng/mL*	QC Accuracy	87.4 – 101.2 %	87.4 – 97.7%	85.7 – 95.2%	85.8 – 93.5 %
Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite																														
Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1																														
Internal Standard (IS)	(b) (4)	(b) (4)																																
<i>Matrix Effect</i>																																		
QC concentrations	60,750, 16000 ng/mL	60, 300, 4000 ng/mL*	60, 300, 4000 ng/mL*	60,750, 16000 ng/mL*																														
QC Accuracy	87.4 – 101.2 %	87.4 – 97.7%	85.7 – 95.2%	85.8 – 93.5 %																														

QC Precision	6.5 - 10.4 %	5.5 – 8.5%	3.2 – 8.6%	6.7 – 8.4 %
<i>1000-fold Dilution of a 20,000 ng/mL Sample (Blank Human Citrated Plasma)</i>				
QC Accuracy	84.8, 102.8%	93.6%	97.1%	105%
QC Precision	4.4, 24.0%	7.8 - 22.8%	4.4%	7.7%
<i>2000-fold Dilution of a 20,000 ng/mL Sample (Blank Human Citrated Plasma)</i>				
QC Accuracy	98.8%	95.8%	97.1%	95.0%
QC Precision	4.2%	6.0%	4.4%	4.6%
<i>4000-fold Dilution of a 100,000 ng/mL Sample (Blank Human Citrated Plasma)</i>				
QC Accuracy	---	---	---	95.7%
QC Precision	---	---	---	8.2%
<i>8000-fold Dilution of a 100,000 ng/mL Sample (Blank Human Citrated Plasma)</i>				
QC Accuracy	---	---	---	96.7%
QC Precision	---	---	---	2.1%
LLOQ	20 ng/mL	19.9 µg/mL	18.6 µg/mL	18.5 µg/mL

*The metabolites are presented as “effective concentrations” (ng eq ucb 34714/mL).
 IS (b) (4)
 IS (b) (4)

[Reviewer comment: The urine assay is validated.]

Population/ Demographics	N=24 healthy male and female subjects, age 18 to 55 years, with BMI between 18 and 29 kg/m ² . Same inclusion/exclusion as in study report N01256-A.
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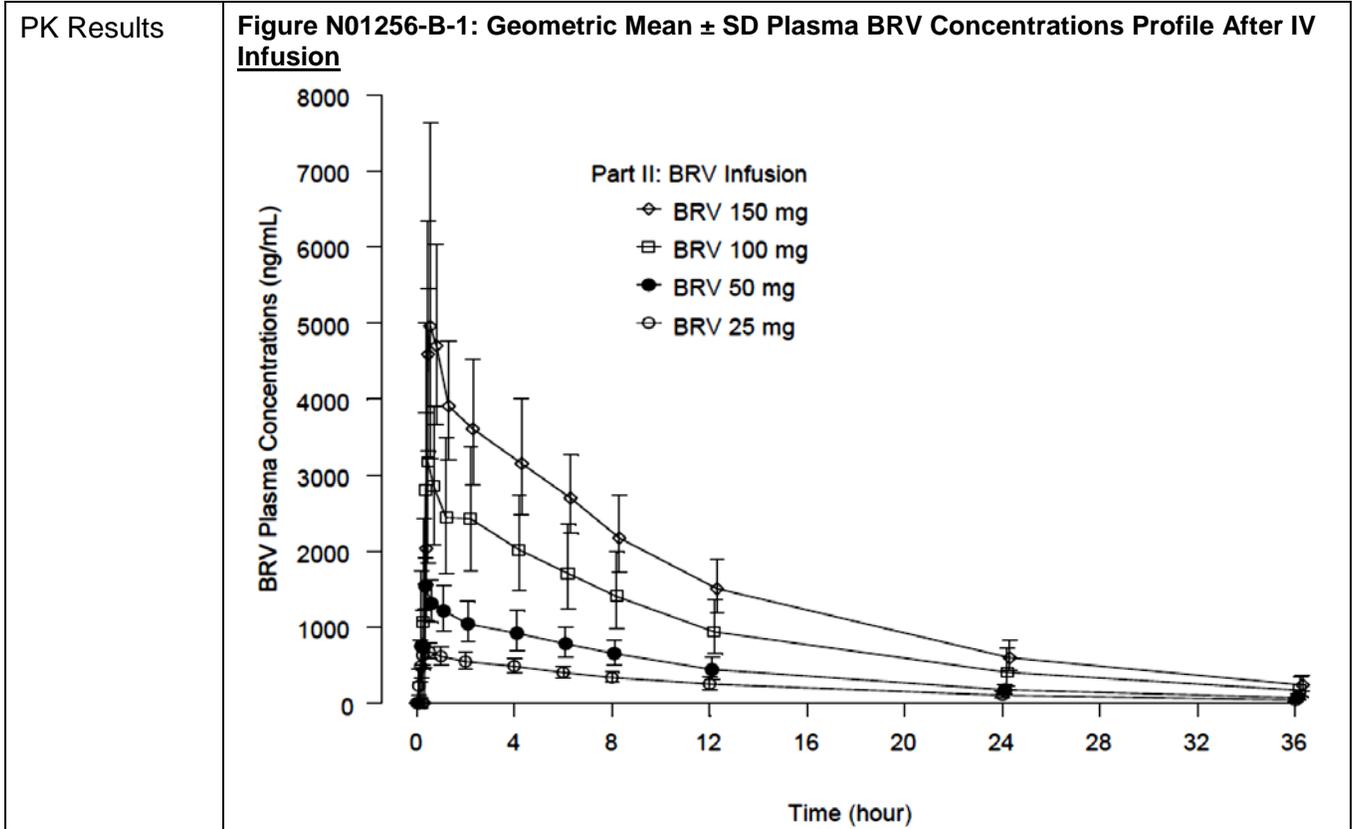


Figure N01256-B-2: Geometric Mean ± SD Plasma BRV Concentrations Profile After IV Bolus

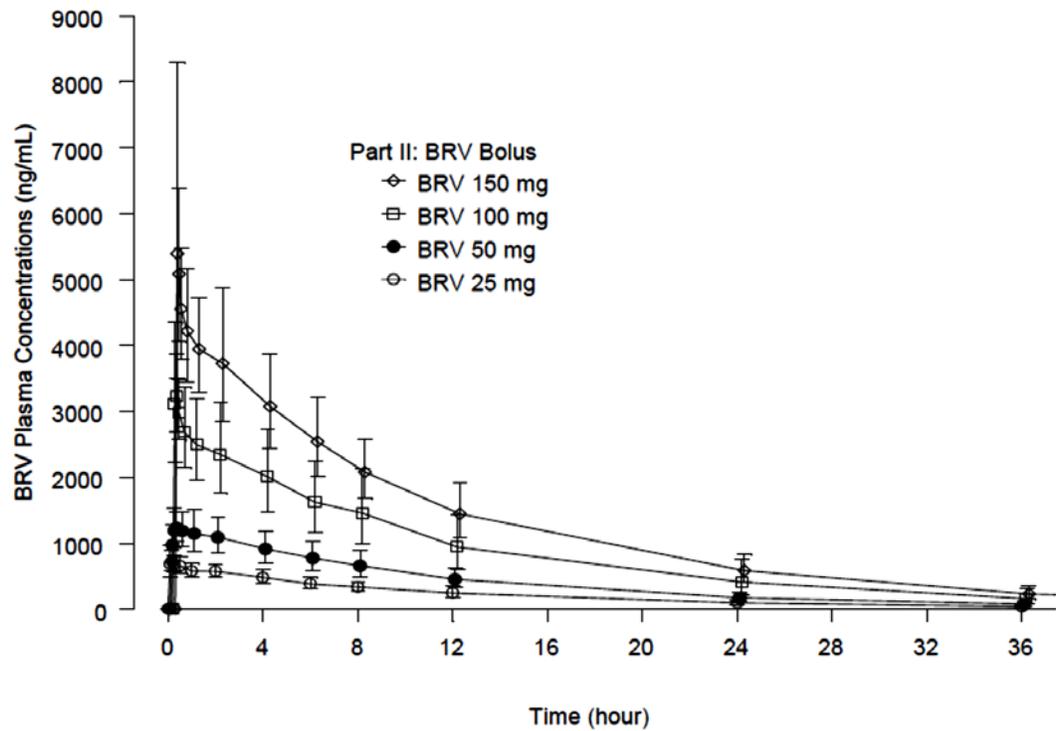


Table N01256-B-1: BRV Plasma PK Parameters After IV Infusion (PP population)

Parameter	Geometric mean (geo CV [%])			
	25 mg IV infusion N=6	50 mg IV infusion N=6	100 mg IV infusion N=6	150 mg IV infusion N=6
AUC(0-t) (ng*h/mL)	8001 (25.1)	14872 (27.5)	32622 (40.5)	50517 (24.0)
AUC (ng*h/mL)	8526 (27.8)	15865 (29.0)	35164 (44.1)	53758 (25.8)
C _{max} (ng/mL)	754 (5.64)	1627 (17.2)	3361 (48.4)	5568 (37.9)
C _T (ng/mL)	626 (21.2)	1539 (22.0)	3171 (58.5)	4956 (45.3)
λ _z (1/h)	0.0772 (14.8)	0.0776 (13.0)	0.0730 (19.7)	0.0772 (14.0)
t _{1/2} (h)	8.97 (14.8)	8.94 (13.0)	9.50 (19.7)	8.98 (14.0)
CL (L/h)	2.95 (27.8)	3.13 (29.1)	2.81 (44.3)	2.81 (25.7)
V _z (L)	38.2 (15.4)	40.3 (24.8)	38.5 (25.5)	36.4 (17.5)
	Median (Range)			
t _{max} (h)	0.50 (0.17-1.0)	0.25 (0.08-0.5)	0.25 (0.25-0.50)	0.50 (0.25-0.5)

C_T = concentration at 15 min, CV=coefficient of variation, geo=geometric, N=number of subjects

Table N01256-B-2: BRV Plasma PK Parameters After IV Bolus (PP population)

Parameter	Geometric mean (geo CV [%])			
	25 mg IV bolus N=6	50 mg IV bolus N=6	100 mg IV bolus N=6	150 mg IV bolus N=6
AUC(0-t) (ng*h/mL)	7885 (26.7)	14852 (29.8)	32746 (39.8)	52622 (27.1)
AUC (ng*h/mL)	8413 (29.5)	15849 (31.2)	34968 (42.7)	52844 (27.2)
C _{max} (ng/mL)	793 (26.2)	1295 (20.9)	3623 (15.8)	5910 (34.7)
C _T (ng/mL)	685 (34.7)	972 (28.4)	3110 (34.4)	5391 (45.1)
λ _z (1/h)	0.0768 (15.4)	0.0785 (12.0)	0.0769 (14.3)	0.0764 (9.97)
t _{1/2} (h)	9.03 (15.4)	8.83 (12.0)	9.02 (14.3)	9.08 (9.97)
CL (L/h)	2.88 (25.8)	3.14 (30.3)	2.84 (43.0)	2.78 (27.3)
V _z (L)	37.5 (12.1)	40.1 (26.4)	36.9 (27.5)	36.4 (25.0)
Median (Range)				
t _{max} (h)	0.16 (0.08-0.5)	0.38 (0.08-1.0)	0.13 (0.08-0.25)	0.08 (0.07-0.25)

C_T = concentration at 5 min, CV=coefficient of variation, geo=geometric, N=number of subjects

Table N01256-B-3: BRV Plasma PK Proportionality Assessment for IV Bolus and IV Infusion (PP population)

Parameter	Slope	Point Estimate for Slope	90% Confidence Interval
IV Infusion – Dose proportionality			
AUC (ng*h/mL)	Dose effect ^(a)	1.041	[0.885, 1.197]
AUC(0-t) (ng*h/mL)	Dose effect ^(a)	1.039	[0.895, 1.184]
C _{max} (ng/mL)	Dose effect ^(a)	1.105	[0.953, 1.257]
IV Infusion – Dose Independence			
CL (L/h)	Dose effect ^(b)	-0.041	[-0.197, 0.115]
t _{1/2} (h)	Dose effect ^(b)	0.013	[-0.064, 0.090]
IV Bolus – Dose proportionality			
AUC (ng*h/mL)	Dose effect ^(a)	1.035	[0.881, 1.189]
AUC(0-t) (ng*h/mL)	Dose effect ^(a)	1.061	[0.914, 1.207]
C _{max} (ng/mL)	Dose effect ^(a)	1.149	[1.014, 1.284]
IV Bolus – Dose Independence			
CL (L/h)	Dose effect ^(b)	-0.035	[-0.189, 0.119]
t _{1/2} (h)	Dose effect ^(b)	0.008	[-0.056, 0.071]

^(a) if dose is proportional, slope should be equal to 1

^(b) if no dose effect, slope should be equal to 0

Figure N01256-B-3: Geometric Mean Plasma Concentration Profiles for BRV and Metabolites after BRV 150 mg IV Bolus (PP Population)

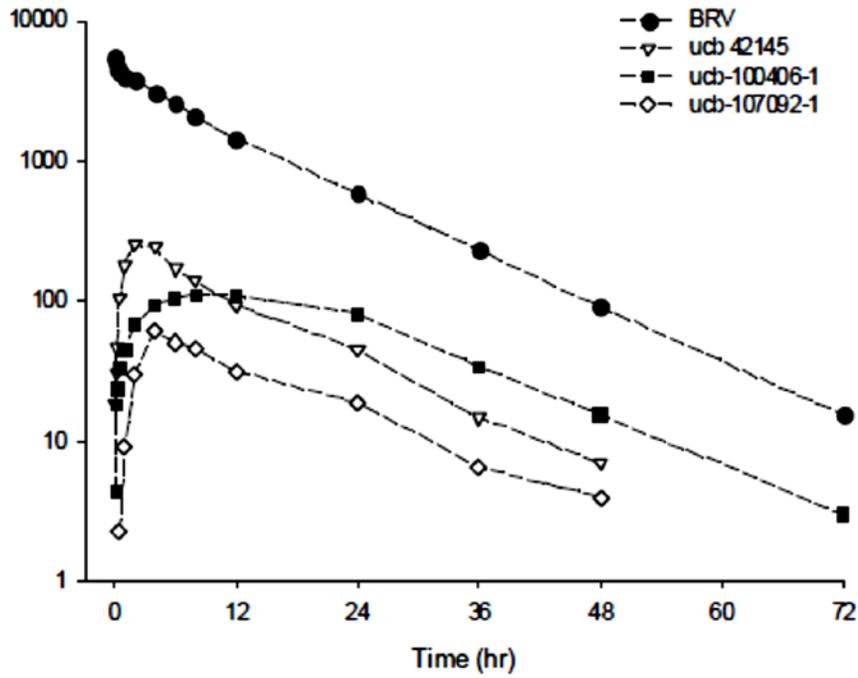


Figure N01256-B-4: Geometric Mean Cumulative Urinary Excretion Profiles for BRV and Metabolites After BRV 150 mg IV Bolus (PP Population)

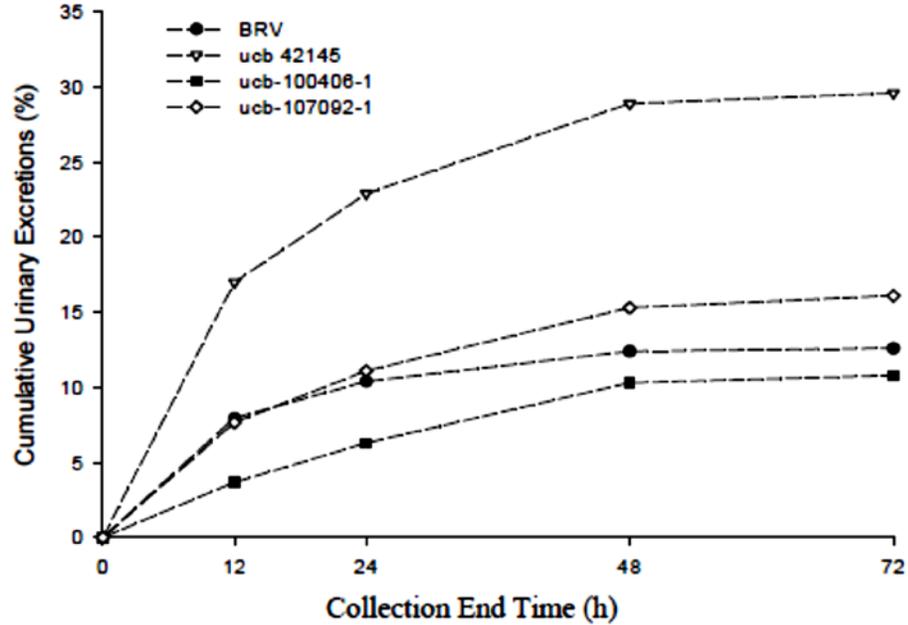


Table N01256-B-4: BRV and Metabolite Plasma PK Parameters and Urinary PK Parameters After BRV 150 mg IV Bolus (PP population)				
Parameter	Geometric mean (geo CV [%])			
	BRV N=6	ucb-100406-1 N=6	ucb 42145 N=6	ucb-107092-1 N=6
AUC(0-t)(ng eq 34714 ³ h/mL)	52622 (27.1)	3435 (36.1)	3366 (7.28)	994 (17.3)
AUC (ng eq 34714 ³ h/mL)	52844 (27.2)	3481 (35.9)	3453 (6.07)	1060 (16.6)
C _{max} (ng eq 34714/mL)	5910 (34.7)	116 (35.4)	275 (15.1)	61.7 (20.8)
λ _z (1/h)	0.0764 (9.97)	0.0681 (9.89)	0.0728 (11.0)	0.0612 (8.45)
t _{1/2} (h)	9.08 (9.97)	10.2 (9.89)	9.53 (11.0)	11.3 (8.45)
Ae _(0-72h) (mg)	18.5 (60.7)	15.8 (28.2)	43.6 (14.2)	23.6 (14.0)
fe _(0-72h) (%)	12.6 (60.5)	10.8 (28.1)	29.6 (14.3)	16.1 (14.0)
CL _R (L/h)	0.350 (45.2)	4.55 (9.88)	12.6 (10.6)	22.3 (8.40)
CL _R (mL/min)	5.84 (45.2)	75.9 (9.88)	210 (10.6)	372 (8.40)
CL _R (mL/min/kg)	0.08 (53.3)	1.09 (16.7)	3.02 (23.8)	5.34 (21.6)
CL _R (mL/min/1.73 m ²)	5.53 (49.5)	71.9 (10.6)	199 (16.7)	352 (14.2)
Median (Range)				
t _{max} (h)	0.08 (0.07-0.25)	8.00 (8.00-12.0)	2.00 (2.00-4.02)	4.00 (3.97-4.02)
CV=coefficient of variation, geo=geometric, N=number of subjects				
Safety	<ol style="list-style-type: none"> All TEAEs were mild to moderate, none lead to early discontinuation, no new safety findings were found (related to known BRV safety profile) There were no SAEs reported TEAEs with overall frequency > 10.0% were: somnolence (87.5% of subjects), fatigue (54.2%), dizziness (33.3%), feeling drunk (25.0%), and dysgeusia (25.0%). All TEAE resolved before the end of the study 			
Sponsor's Conclusions	<ul style="list-style-type: none"> Single doses of BRV (25 mg to 150 mg) administered via IV infusion or IV bolus was safe and well-tolerated in this population of n=24 healthy male and female subjects BRV PK parameters after IV infusion and IV bolus were similar AUC and AUC0-t were proportional for single doses of 25 mg to 150 mg 			
Reviewer Comment	<ul style="list-style-type: none"> C_{max} value achieved after IV bolus was the only PK parameter that did not meet criteria for proportionality as the 90% CI of the slope did not include 1 (e.g. 1.014 to 1.284). The variability of urinary BRV PK parameters was higher (e.g. 45.2% for CL_R, 60.5% for fe_(0-72h), and 60.7% for Ae_{0-72h}) than the urinary PK parameters for the metabolites or plasma BRV PK parameters. The observed variability after IV administration is comparable to that following oral administration. The 150 mg IV bolus single-dose and 150 mg IV infusion single-dose showed a greater than proportional increase in C_{max}. (UL of 90% CI for C_{max} proportionality coefficient was 1.284). However, the safety data are supportive of the use of a 200 mg/day IV single dose. 			

4.4.27 N01258: IV bolus / infusion safety trial (Phase 3)

Study Report#	N01258																				
Title	A multicenter, open-label, four-arm, randomized trial evaluating the safety and tolerability of brivaracetam intravenous infusion and bolus, administered in bid regimen as an adjunctive antiepileptic treatment in subjects from 16 to 70 years suffering from epilepsy																				
Objectives	<i>Primary:</i> Assess safety and tolerability of BRV administered as an IV bolus or IV infusion <i>Exploratory:</i> Collect data on healthcare resource utilization																				
Study Design	Multicenter, open-label, four-arm, randomized, parallel group study with a double-blind placebo-controlled run-in period.																				
Duration	61 days (40 days maximum treatment exposure: 1 week double-blind PBO or BRV oral tablet, 4.5 days IV treatment infusion or bolus, 4 week down-titration period [or immediate switch to LTFU study], 2-weeks Study-Drug-Free Period for patients who did not enter LTFU or discontinued prematurely)																				
Dosage and Administration	<p>Patients underwent a run-in phase where they were randomized to receive blinded oral study substance (BRV 200 mg/day administered as 100 mg BID or matching placebo) for 7 days followed by open-label IV BRV 200 mg/day administered as 100 mg BID for 4.5 days. IV administration was either IV bolus (a 2-minute infusion duration) or IV infusion (15-minute infusion duration). Subjects were randomized 1:1:1:1 to receive:</p> <p>a) PBO/BRV bolus, b) PBO/BRV infusion, c) BRV/BRV bolus, d) BRV/BRV infusion (during run-in period / during evaluation period, respectively).</p> <p>After completion of study, Patients had the option to enter into study N01379 (long-term follow-up) at a dose of 200 mg/day (100 mg BID). Patients who did not enter study N01379 or who discontinued prematurely were down titrated over a 4-week period and underwent a final safety visit after a 2-week Study-Drug-Free period.</p>																				
PK Assessment	<p><u>Plasma samples for BRV PK:</u> Visit 3 (Day 8/iv), 5 min pre-dose, 15 min post dose Visit 7 (Day 12/iv), 5 min pre-dose, 15 min post-dose</p> <p><u>Plasma BRV PK Analyses:</u> Geometric mean and geometric CV of concentrations at each visit</p>																				
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	<p>[Reviewer comment: The assay is validated.]</p>
Population/ Demographics	<p>N=105 adults receiving 1 or 2 concomitant AEDs for epilepsy (no formal sample size calculation was performed)</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none">1. Male and female patients with epilepsy age 16 to 70 years (in countries where children age < 18 were permitted to participate) weighing ≥ 40 kg2. Subjects who were uncontrolled while treated with 1 to 2 permitted concomitant AEDs. AEDs must be stable and optimal dosage at least 1 month prior to Visit 1 (3 months for phenobarbital or primidone) an expected to remain stable during the run-in.3. Female subjects must not be pregnant and must be using an acceptable form of birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none">1. If using felbamate, less than 18 months continuous exposure before Visit 12. Use of vigabatrin3. Concomitant medications with relevant CNS effects except if stable for at least 1 month before Visit 1 (and expected to remain stable during study).4. Use of any drug that significantly influences BRV metabolism (e.g. potent inducers or inhibitors of CYP2C or CYP3A) except if the dose had been kept stable at last 1 month before Visit 1 (and is expected to remain stable during study).5. Severe renal impairment6. Impaired hepatic function (ALT/SGPT, AST/SGOT, alkaline phosphatase, gamma-glutamyltransferase [GGT] > 3 x ULN). A GGT > 3 x ULN would only be accepted if attributable to hepatic enzyme induction caused by AEDs and other hepatic enzymes < 3 x ULN.7. In Czech Republic sites: values of ALT/SGPT, AST/SGOT, alkaline phosphatase > 2 x ULN8. CRCL < 50 mL/min9. Pregnant or lactating women10. Subjects previously treated with BRV

PK Results	Table N01258-1: Brivaracetam Plasma Concentrations by Treatment Group and Visit (PK-PPS Population)				
	Treatment group Visit Time point	n	n>LOQ	Geometric mean (µg/mL)	Geometric CV (%)
	PBO/BRV bolus (N=25)				
	Visit 3 (Day 8/iv)				
	5min predose	24	0	NC	NC
	15min postdose	25	24	<2.21	116.05
	Visit 7 (Day 12/iv)				
	5min predose	25	25	1.00	54.59
	15min postdose	25	25	3.42	47.97
	PBO/BRV infusion (N=26)				
	Visit 3 (Day 8/iv)				
	5min predose	26	2	NC	NC
	15min postdose	26	25	<2.06	102.26
	Visit 7 (Day 12/iv)				
	5min predose	25	25	0.82	54.96
	15min postdose	25	25	3.30	38.00
	EDV	1	1	0.39	NC
	BRV/BRV bolus (N=27)				
	Visit 3 (Day 8/iv)				
	5min predose	26	26	1.20	60.55
	15min postdose	27	27	4.05	31.37
	Visit 7 (Day 12/iv)				
	5min predose	27	27	0.91	49.76
	15min postdose	27	27	3.32	25.70
	BRV/BRV infusion (N=26)				
	Visit 3 (Day 8/iv)				
	5min predose	26	26	1.13	70.51
15min postdose	26	26	3.87	119.95	
Visit 7 (Day 12/iv)					
5min predose	26	26	0.72	61.23	
15min postdose	26	26	2.88	36.88	
Safety	<ol style="list-style-type: none"> TEAE rate ranged from 73.1% to 77.8% across the treatment arms The most common TEAE were <i>somnolence</i> (29.5% of subjects) and <i>dizziness</i> (14.3%) One subject in BRV/BRV bolus group reported a severe TEAE (vertigo and nausea) and the rest of the TEAE were mild or moderate 				
Sponsor's Conclusions	<ul style="list-style-type: none"> IV bolus or IV infusion were well-tolerated regardless of an initiation or conversion scheme TEAE profile was comparable between the initiation scheme group and the conversion group 				

	<ul style="list-style-type: none">• BRV plasma concentrations were similar across treatment groups regardless of whether subjects received IV bolus or IV infusion.• BRV concentrations were 83% to 88% higher after 5 days of IV infusion than on Day 1 of IV infusion (a difference that is consistent with the expected accumulation factor).
<i>Reviewer comments</i>	<ul style="list-style-type: none">• <i>In study N01067 (repeat dose PK study), subjects with repeat oral BRV 100 mg bid were associated with about 3.5 µg/mL C_{max} after 14 days of repeat dose. The maximum concentrations associated with the IV formulation are comparable considering the PK variability observed in the current study and in study N01067.</i>• <i>Exposures were marginally greater in groups that received IV bolus compared to those who received IV infusion.</i>• <i>The current study and N01067 show a comparable safety profile.</i>• <i>Overall, this study is supportive of IV bolus or IV infusion of 100 mg bid BRV.</i>

4.4.28 N01259: DDI – Gemfibrozil and Rifampicin (Phase 1)

Study Report#	RPCE06K1223 / Study N01259																																																																																			
Title	Monocenter, open-label, randomized, 2x2-way cross-over study to assess the effects of Gemfibrozil and Rifampicin on the pharmacokinetics of Brivaracetam, a CYP2C8 substrate, in healthy male subjects																																																																																			
Objectives	<p><u>Primary:</u> Assess whether steady-state gemfibrozil (2C8 inhibitor) or steady-state rifampicin (2C8 inducer) affect single-dose BRV PK</p> <p><u>Secondary:</u> Gain information about BRV safety</p>																																																																																			
Study Design	Randomized, open-label, 2x2-way crossover, oral, single dose study																																																																																			
Duration	9 weeks																																																																																			
Dosage and Administration	<p><u>Gemfibrozil sub-study:</u> screening 3 weeks; 2 treatment periods: treatment A (Brivaracetam alone): 4 days, treatment B (Brivaracetam + Gemfibrozil): 7 days; wash-out 2 weeks; discharge 1 week.</p> <p><u>Rifampicin sub-study:</u> screening 3 weeks; 2 treatment periods: Treatment C (Brivaracetam alone): 4 days, Treatment D (Brivaracetam + Rifampicin): 8 days; wash-out 4 weeks; discharge 1 week.</p>																																																																																			
PK Assessment	<p><u>Plasma Samples – BRV + Metabolites:</u> pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 6, 9, 12, 24, 36, 48 and 72 h post-dose brivaracetam.</p> <p><u>Urine Samples – BRV + Metabolites:</u> 0-12h, 12-24h, 24-48h and 48-72h</p> <p><u>PK Analyses:</u> Cmax, tmax, AUC(0-t), AUC, t1/2, Ae(0-72h), CL/F, Vz/F</p>																																																																																			
Bioanalytical Methods	<p>Urine samples were diluted 10-fold with human citrated plasma prior to analysis.</p> <p>HPLC-MS/MS Analytical Methods for Plasma and Urine Concentrations</p> <table border="1"> <thead> <tr> <th>Analyte Name</th> <th>Brivaracetam</th> <th>Carboxylic Acid Metabolite</th> <th>Hydroxy Metabolite</th> <th>Hydroxy Acid Metabolite</th> </tr> </thead> <tbody> <tr> <td>Analyte ID</td> <td>ucb 34714</td> <td>ucb 42145</td> <td>ucb-100406-1</td> <td>ucb-107092-1</td> </tr> <tr> <td>Internal Standard</td> <td>(b) (4)</td> <td>(b) (4)</td> <td>(b) (4)</td> <td>(b) (4)</td> </tr> <tr> <td colspan="5" style="text-align: center;"><i>Plasma</i></td> </tr> <tr> <td>Standard curve concentrations</td> <td>2.00 to 2000 ng/mL</td> <td>1.99 to 498 ng/mL*</td> <td>1.86 to 465 ng/mL*</td> <td>1.85 to 1852 ng/mL*</td> </tr> <tr> <td>Standards accuracy</td> <td>-4.1 to 2.5%</td> <td>-2 to 2.5%</td> <td>-3.2 to 2.3%</td> <td>-2.7 to 3.5%</td> </tr> <tr> <td>Standards precision</td> <td>1.9 to 5.2%</td> <td>2.1 to 5.1%</td> <td>1.9 to 4.5%</td> <td>2.1 to 5.6%</td> </tr> <tr> <td>QC concentrations</td> <td>6.00, 75.0 and 1600 ng/mL</td> <td>5.97, 29.9, 398 ng/mL*</td> <td>5.58, 27.9, 372 ng/mL*</td> <td>5.56, 69.4, 1481 ng/mL*</td> </tr> <tr> <td>QC Accuracy</td> <td>0.4 to 5.5%</td> <td>0.0 to 2.5%</td> <td>-0.7 to 1.6%</td> <td>-0.9 to 2.3%</td> </tr> <tr> <td>QC Precision</td> <td>6.3 to 7.8%</td> <td>7.2 to 10.0%</td> <td>5.3 to 8.4%</td> <td>6.9 to 13.7%</td> </tr> <tr> <td>LLOQ</td> <td>2.00 ng/mL</td> <td>1.99 ng/mL*</td> <td>1.86 ng/mL*</td> <td>1.85 ng/mL*</td> </tr> <tr> <td colspan="5" style="text-align: center;"><i>Urine</i></td> </tr> <tr> <td>Conc Used in QC Dilution</td> <td>1600 ng/mL</td> <td>398 ng/mL*</td> <td>372 ng/mL*</td> <td>1481 ng/mL*</td> </tr> <tr> <td>5-fold dilution Accuracy</td> <td>7.1%</td> <td>2.0%</td> <td>3.9%</td> <td>4.6%</td> </tr> <tr> <td>20-fold dilution Accuracy</td> <td>2.5%</td> <td>-6.2%</td> <td>-2.3%</td> <td>-0.6%</td> </tr> <tr> <td>LLOQ</td> <td>20.0 ng/mL</td> <td>19.9 ng/mL*</td> <td>18.6 ng/mL*</td> <td>18.5 ng/mL*</td> </tr> </tbody> </table>				Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1	Internal Standard	(b) (4)	(b) (4)	(b) (4)	(b) (4)	<i>Plasma</i>					Standard curve concentrations	2.00 to 2000 ng/mL	1.99 to 498 ng/mL*	1.86 to 465 ng/mL*	1.85 to 1852 ng/mL*	Standards accuracy	-4.1 to 2.5%	-2 to 2.5%	-3.2 to 2.3%	-2.7 to 3.5%	Standards precision	1.9 to 5.2%	2.1 to 5.1%	1.9 to 4.5%	2.1 to 5.6%	QC concentrations	6.00, 75.0 and 1600 ng/mL	5.97, 29.9, 398 ng/mL*	5.58, 27.9, 372 ng/mL*	5.56, 69.4, 1481 ng/mL*	QC Accuracy	0.4 to 5.5%	0.0 to 2.5%	-0.7 to 1.6%	-0.9 to 2.3%	QC Precision	6.3 to 7.8%	7.2 to 10.0%	5.3 to 8.4%	6.9 to 13.7%	LLOQ	2.00 ng/mL	1.99 ng/mL*	1.86 ng/mL*	1.85 ng/mL*	<i>Urine</i>					Conc Used in QC Dilution	1600 ng/mL	398 ng/mL*	372 ng/mL*	1481 ng/mL*	5-fold dilution Accuracy	7.1%	2.0%	3.9%	4.6%	20-fold dilution Accuracy	2.5%	-6.2%	-2.3%	-0.6%	LLOQ	20.0 ng/mL	19.9 ng/mL*	18.6 ng/mL*	18.5 ng/mL*
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	<p>*The metabolites are presented as “effective concentrations” (ng eq ucb 34714/mL). IS (b) (4) IS (b) (4) [Reviewer comment: The assay is validated.]</p>
<p>Population/ Demographics</p>	<p>N=51 <u>Inclusion Criteria:</u> 1. Healthy male subjects age 18 to 55 years 2. ECG read as normal or abnormal but not clinically significant 3. Laboratory tests are within reference range or outside the reference range but not clinically significant <u>Exclusion Criteria:</u> 1. Hepatic, renal, gastrointestinal, or other condition that may affect ADME of drugs or constitute a risk factor when taking study medication 2. Any significant chronic or acute illness 3. Any drug treatment, prescription or non-prescription taken ≤ 14 days prior to first study drug intake (paracetamol [acetaminophen] up to 2 g/day is permitted) 4. Use of any hepatic enzyme inducing drug (e.g., glucocorticoids, phenobarbital, isoniazid) ≤ 2 months prior to first administration 5. Heavy caffeine drinker 6. Heavy caffeine drinker 7. Grapefruit product consumption ≤ 14 days prior to inclusion in trial 8. Smokers (quit less than 6 months prior to study)</p>
<p>PK Results</p>	<p>Figure N01259-1: Geometric Mean Plasma Concentration Profile of <u>BRV, ucb-100406-1 (hydroxy metabolite), ucb 42145 (carboxylic acid metabolite) and ucb 107092-1 (hydroxyacid metabolite)</u> With GFZ versus Without GFZ</p> <p>Summary of GFZ effect on PK BRV and metabolites: <u>BRV</u>: no significant effect <u>hydroxy metabolite ucb-100406-1</u>: C_{max}: 19%↑, AUC: 18%↑, Ae₍₀₋₇₂₎: 13%↑ <u>carboxylic acid metabolite (ucb 42145)</u>: C_{max}: 17%↑, AUC: 11%↑, Ae₍₀₋₇₂₎: 11%↑ <u>hydroxyacid metabolite ucb-107092-1</u>: C_{max}: 48%↓, AUC: 35%↓, Ae₍₀₋₇₂₎: 40%↓.</p>

Table N01259-1: Effect of GFZ on BRV and Metabolite PK

Parameter (unit)	Reference ^a GeoMean (95% CI) BRV 150mg		Test ^a GeoMean (95% CI) BRV 150mg with GFZ 600mg bid		CV _{res} (%) ^b	Test vs reference ^c	
	N		N			PE	90% CI
BRV							
C _{max} (µg/mL)	25	4.14 (3.77; 4.54)	26	4.16 (3.80; 4.56)	15.0	1.01	0.937; 1.08
t _{max} (h)	25	0.5 (0.25; 2)	26	0.6 (0.25; 2)	NA	0.00	-0.13; 0.13
AUC (µg.h/mL)	25	41.2 (38.7; 43.9)	26	39.2 (36.7; 41.7)	4.67	0.950	0.929; 0.972
AUC(0-t) (µg.h/mL)	25	41.1 (38.6; 43.8)	26	39.1 (36.7; 41.6)	4.71	0.950	0.929; 0.972
CL/F (mL/min/kg)	25	0.790 (11.8)	26	0.834 (12.8)	NC	NC	NC
Carboxylic acid metabolite (ucb 42145)							
C _{max} (µg/mL)	25	0.243 (0.223; 0.265)	26	0.285 (0.262; 0.310)	17.1	1.17	1.08; 1.27
t _{max} (h)	25	3 (1.5-6)	26	3 (2-6)	NA	0	0; 0.75
AUC (µg.h/mL)	25	3.27 (2.99; 3.58)	26	3.61 (3.30; 3.94)	9.76	1.10	1.05; 1.16
AUC(0-t) (µg.h/mL)	25	3.21 (2.93; 3.51)	26	3.55 (3.25; 3.88)	9.86	1.11	1.06; 1.16
Hydroxy metabolite (ucb-100406-1)							
C _{max} (µg/mL)	25	0.154 (0.127; 0.187)	26	0.183 (0.150; 0.222)	9.55	1.19	1.13; 1.24
t _{max} (h)	25	9 (6-12)	26	9 (1-12)	NA	0.00	-1.5; 0
AUC (µg.h/mL)	25	4.19 (3.52; 5.00)	26	4.94 (4.14; 5.89)	7.12	1.18	1.14; 1.22
AUC(0-t) (µg.h/mL)	25	4.13 (3.45; 4.94)	26	4.87 (4.07; 5.83)	7.39	1.18	1.14; 1.22
Hydroxyacid metabolite (ucb-107092-1)							
C _{max} (µg/mL)	25	0.048 (0.042; 0.055)	26	0.025 (0.022; 0.028)	23.5	0.516	0.462; 0.578
t _{max} (h)	25	6 (6-9)	26	6 (3-12)	NA	0.00	0; 0
AUC (µg.h/mL)	25	0.968 (0.872; 1.08)	26	0.634 (0.572; 0.703)	16.2	0.655	0.606; 0.707
AUC(0-t) (µg.h/mL)	25	0.908 (0.800; 1.03)	26	0.553 (0.488; 0.627)	21.2	0.609	0.551; 0.674

Sponsor reports that the effects of GFZ on the metabolites can be explained as follows (in reference to the metabolic diagram below):

1. Pathway [2] is estimated to account for less than 10% of the total clearance. A high magnitude of inhibition by CYP2C8 inhibitor was thus not expected.
2. Hydrolysis (pathways [1] and [3]) is not CYP-dependent and can be assumed to be unaffected by GFZ.
3. The existence of pathway [4] is not only evidenced but also suggested to be CYP2C8-dependent, as evidenced by the 35-40% decrease in formation of ucb-107092-1 in presence of GFZ. Blockade of ucb-107092-1 formation from ucb 42145 by GFZ may result in a shift to the ucb-100406-1 pathway for the formation of ucb-107092-1.

Figure N01259-2: Proposed Metabolic Pathway Based on Current Study Results

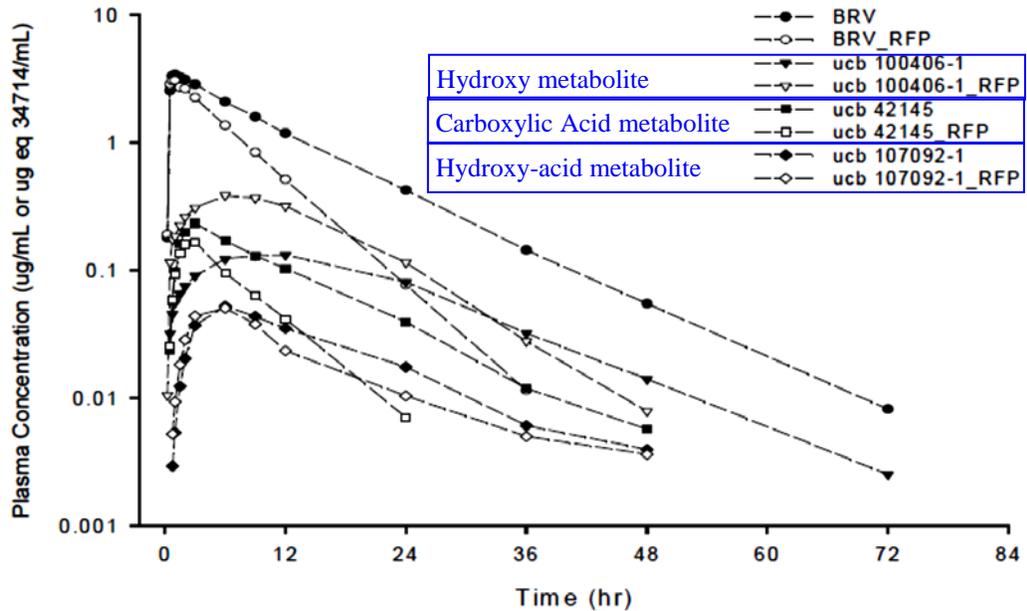
(b) (4)

[Reviewer comment: The metabolic pathways described in the figure above are not the final pathways. The Sponsor has subsequently updated the proposed metabolic pathways. The updated metabolic pathway provided by the Sponsor indicates that:

- Amidase is responsible for hydrolysis reactions [1] and [3]
- 2C8 is the main enzyme responsible for [2]
- CYP2C9 is responsible for [4], (b) (4)

Please refer to the comments at the end of the review for additional details.]

Figure N01259-3: Geometric Mean Plasma Concentration Profile of BRV, ucb-100406-1 (hydroxy metabolite), ucb 42145 (carboxylic acid metabolite) and ucb 107092-1 (hydroxyacid metabolite) With RFP versus Without RFP



Summary of RFP effect on PK BRV and metabolites:

BRV: Cmax: 11%↓, AUC: 45%↓,

hydroxy metabolite ucb-100406-1: Cmax: 3 fold↑, AUC: 2 fold↑, Ae(0-72): 2 fold↑

carboxylic acid metabolite (ucb 42145): Cmax: 24%↓, AUC: 53%↓, Ae(0-72): 57%↓

hydroxyacid metabolite ucb-107092-1: Cmax: 2.5%↓, AUC: 10%↓, Ae(0-72): 17%↓

Table N01259-2: Effect of RFP on BRV and Metabolite PK

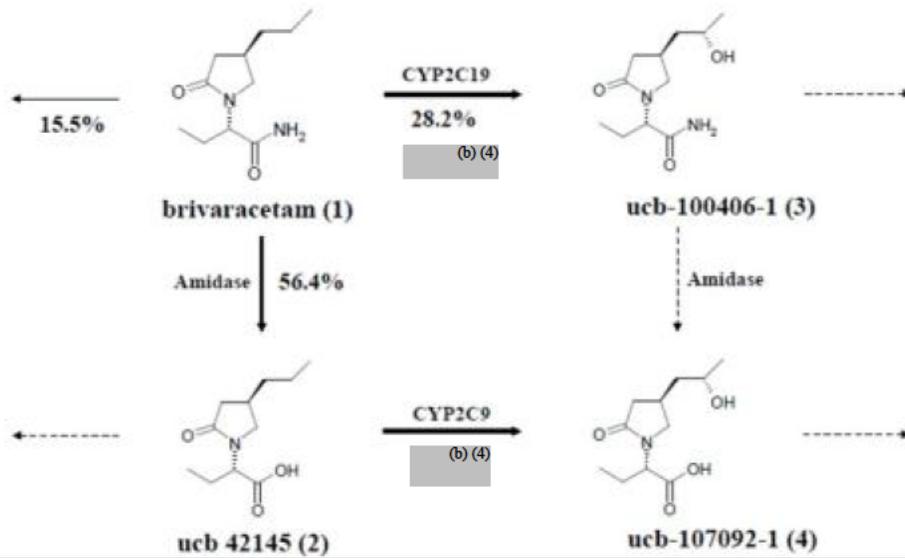
Parameter (unit)	Reference ^a GeoMean (CV%) BRV 150mg (N=26)	Test ^a GeoMean (CV%) BRV 150mg with RFP 600mg (N=26)	CV _{res} (%) ^b	Test vs reference ^c	
				PE	95% CI
BRV					
C _{max} (µg/mL)	4.22 (3.84; 4.64)	3.74 (3.40; 4.11)	14.1	0.887	0.830; 0.948
t _{max} (h)	0.75 (0.25; 3)	0.6 (0.25; 2)	NA	-0.01	-0.25; 0.13
AUC (µg.h/mL)	41.2 (38.1; 44.6)	22.8 (21.1; 24.7)	8.23	0.554	0.533; 0.576
AUC(0-t) (µg.h/mL)	41.1 (38.0; 44.5)	22.8 (21.1; 24.7)	8.31	0.555	0.533; 0.577
CL/F (mL/min/kg)	0.803 (14.5)	1.45 (19.8)	NC	NC	NC
Carboxylic acid metabolite ucb 42145					
C _{max} (µg/mL)	0.242 (0.219; 0.267)	0.184 (0.166; 0.203)	15.3	0.761	0.708; 0.818
t _{max} (h)	3 (2-6)	2 (1.5-3)	NA	-0.5	-1; -0.5
AUC (µg.h/mL)	3.23 (2.90; 3.59)	1.51 (1.36; 1.68)	10.7	0.468	0.445; 0.492
AUC(0-t) (µg.h/mL)	3.16 (2.84; 3.52)	1.48 (1.33; 1.65)	10.6	0.468	0.445; 0.492
Hydroxy metabolite ucb-100406-1					
C _{max} (µg/mL)	0.137 (0.112; 0.167)	0.419 (0.343; 0.512)	29.2	3.06	2.68; 3.51
t _{max} (h)	12 (0.5-12)	6 (6-9)	NA	-4.5	-4.5; -3
AUC (µg.h/mL)	3.77 (3.08; 4.61)	7.80 (6.38; 9.54)	15.7	2.07	1.92; 2.23
AUC(0-t) (µg.h/mL)	3.69 (3.01; 4.53)	7.71 (6.28; 9.46)	16.1	2.09	1.94; 2.25
Hydroxyacid metabolite ucb-107092-1					
C _{max} (µg/mL)	0.053 (0.048; 0.058)	0.052 (0.047; 0.057)	12.7	0.974	0.917; 1.03
t _{max} (h)	6 (6-12)	6 (3-6)	NA	-1.5	-1.5; 0
AUC (µg.h/mL)	1.04 (0.958; 1.12)	0.934 (0.863; 1.01)	7.60	0.902	0.868; 0.938
AUC(0-t) (µg.h/mL)	0.976 (0.899; 1.06)	0.854 (0.786; 0.927)	9.56	0.874	0.836; 0.915

Safety
 Dizziness and fatigue were the most frequent TEAEs.
GFZ sub-study: Dizziness occurred in the 76% of subjects in BRV group and 76.9% of GFZ + BRV group, 3.8% of the GFZ group. Fatigue occurred in 24%, 0%, and 19% of the BRV, GFZ, and BRV+GFZ groups, respectively.
RFP sub-study: Dizziness occurred in the 69.2% of subjects in BRV group and 73.1% of RFP + BRV group, 3.8% of the RFP group. Fatigue occurred in 23.1%, 19.2%, and 26.9% of the BRV, RFP, and BRV+RFP groups, respectively.
 There was a pruritic rash in the GFZ treatment group that was severe and led to study termination. All other TEAEs were mild to moderate.

- Sponsor's Conclusions**
- Based on RFP sub-study, BRV is subject to interact with CYP inducers
 - Based on GFZ sub-study, BRV interactions with 2C8 inhibitors are minor
 - The TEAEs observed during the study are consistent with AEs usually reported for BRV
 - BRV was well-tolerated

Reviewer Comment
This study provided insight into BRV metabolism. Sponsor has subsequently modified the conclusions from this clinical study report. The final metabolic pathway proposed by the Sponsor is found below.

Figure N01259-4: Sponsor's Final Proposal of BRV Metabolic Pathways



The Sponsor has since proposed 2C19 and 2C9 (b) (4) for metabolism of BRV and metabolism of ucb 42145. The final metabolic pathway will help with the interpretation of the GFZ and RFP sub-studies.

For interpretation of GFZ and RFP sub-studies, this reviewer assumes that neither GFZ or RFP affect the metabolic activity of the amidase enzymes involved in BRV metabolism.

GFZ Sub-study:

Gemfibrozil is a potent inhibitor of 2C8 and also inhibits OATP1B1.

If BRV were a 2C8 substrate, then BRV exposures would be expected to be significantly reduced in the presence of GFZ, a 2C8 inhibitor. However, BRV exposures were not significantly reduced by GFZ (gmean AUC_{0-∞} reduced from 41.4 to 39.2 µg*h/mL), a finding that does not support the notion that BRV is a 2C8 substrate.

Hydroxy metabolite --- ucb-100406-1: If conversion from BRV into ucb-100406-1 is mediated chiefly by 2C8 (b) (4) then GFZ (a 2C8 inhibitor) would be expected to result in increased ucb-100406-1 exposures.

Sponsor reports a "slight" increase in plasma concentration and urinary excretion of ucb-100406-1 (C_{max}: 19%↑, AUC: 18%↑, Ae(0-72): 13%↑). Gemfibrozil is listed as a "strong inhibitor" of 2C8 (defined as being expected to cause ≥ 5-fold increase in AUC of a 2C8 substrate). As such, an increase of this magnitude, in combination with the minor change of BRV exposures by GFZ, does not support the notion that 2C8 is the chief enzyme responsible for conversion of BRV into ucb-100406-1.

Carboxylic acid metabolite --- ucb 42145: If 2C8 responsible for conversion of ucb42145 into ucb107092-1, then a GFZ (a 2C8 inhibitor) would expected to increase the exposures of ucb42145. Sponsor reports an increase in ucb42145

(Cmax: 17%↑, AUC: 11%↑, Ae(0-72): 11%↑).

Hydroxyacid metabolite --- ucb-107092-1: If 2C8 responsible for conversion of ucb42145 into ucb107092-1, then a GFZ (a 2C8 inhibitor) would expected to reduce the exposures of ucb-107092-1. Sponsor reports that ucb-107092-1 significantly decreased (Cmax: 48%↓, AUC: 35%↓, Ae(0-72): 40%↓) with concomitant GFZ.

The ucb 42145 exposure increase and ucb-107092-1 decrease with GFZ appears to be consistent with the notion that 2C8 is the chief enzyme responsible for conversion of ucb 42145 into ucb 107092-1. However, results of sub study with RFP, an inducer of 2C8, do not support the idea that 2C8 is the main enzyme for conversion of ucb 42145 into ucb 107092-1 (see the discussion below for the RFP substudy).

RFP Sub-study:

Rifampicin (known as rifampin in the United State) is a moderate inducer of 2C8, 2C19, and 2B6. Rifampicin is a strong inducer of CYP3A. Rifampin is known to induce P-gp and inhibit OATP1B1 and OATP1B3.

The BRV exposures were significantly reduced by RFP. Overall, this rifampin sub-study provided the following insights into the BRV metabolism:

Hydroxy metabolite --- ucb-100406-1: As RFP is known to induce 2C19, the reduction in BRV exposures and increase in the ucb-100406-1 exposure (Cmax: 3 fold↑, AUC: 2 fold↑, Ae(0-72): 2 fold↑) observed with concomitant RFP is supportive of the notion that 2C19 catalyzes the conversion from BRV to ucb-100406-1. This clinical finding is consistent with non-clinical findings. In microsomes, formation of the hydroxy metabolite ucb-100406-1 was found to mainly supported by CYP2C19 (study NCD1998).

Carboxylic acid metabolite --- ucb 42145: If metabolism of 42145 was catalyzed chiefly by CYP2C8 ((b) (4)), then ucb 42145 concentration would be expected to decrease with concomitant RFP. However, RFP increased carboxylic acid metabolite ucb 42145 exposure (Cmax: 3 fold↑, AUC(0-t) and AUC: 2 fold↑, Ae(0-72): 2 fold ↑, t1/2: 30% ↓). This increase in ucb 42145 with concomitant RFP does not support the idea that 2C8 metabolizes ucb 42145.

Hydroxyacid metabolite --- ucb-107092-1: If formation of ucb 107092-1 was catalyzed chiefly by CYP2C8 ((b) (4)), then ucb 107092-1 concentration would be expected to increase with RFP (a moderate 2C8 inducer). However, the ucb 107092-1 exposure (e.g. decrease in AUC_{0-t}, decrease in AUC_{0-∞}, and decrease in Ae₀₋₇₂, though the 90% CI for the ratios were included in the 80-125% range). Overall, the RFP sub-study results do not support the notion that CYP2C8 mediates the conversion of ucb 42145 into ucb-107092-1.

Sponsor has subsequently performed non-clinical study NCD1674 which confirms that the oxidation of the carboxylic acid metabolite ucb 42145 into the hydroxyacid metabolite ucb-107092-1 was found to be primarily mediated by CYP2C9. In light of the findings from NCD1674, and as RFP does not alter 2C9 activity, then the results of the RFP sub-study in N01259 are consistent with the idea that 2C9 mediates conversion from ucb 42145 into ucb-107092-1.

Going back to the GFZ sub-study results, as 2C9 is likely the main enzyme involved in conversion of conversion of ucb 42145 into ucb 107092-1, it is not clear why GFZ caused an increase in ucb 42145 exposure and a decrease in ucb-107092-1 exposure.

The BRV dose should be doubled when used concomitantly with rifampicin.

4.4.29 N01261: DDI – Midazolam (Phase 1)

Study Report#	RPCE06F2303 / N01261																					
Title	Single-centre, open-label, Phase 1 study to assess the effects of a repeated administration of brivaracetam on CYP3A4 activity in healthy male subjects using midazolam as a probe.																					
Objectives	<p><u>Primary:</u> Assess effect repeated BRV administration (3 dose levels) on 3A4 activity (using midazolam [MDZ] as a probe)</p> <p><u>Secondary:</u> Assess safety and tolerability of concomitant BRV and MDZ administration</p>																					
Study Design	Open-label, randomized trial to assess the effect of steady-state BRV (5, 50, or 150 mg/day) on the PK of MDZ (7.5 mg single dose).																					
Duration	21 days (three study periods each separated by a 7-day period for MDZ to washout; 6.5 days receiving BRV [Day 8 to Day 14], three single doses of MDZ [Day 1, Day 13, Day 20]).																					
Dosage and Administration	<p><u>MDZ:</u> Day 1, 13, and 20 subjects receive a single 7.5 mg MDZ dose at 8:30 am</p> <p><u>BRV:</u> Starting Day 8 (after a 7-day washout from the first single-dose of MDZ) until Day 14, subjects received BRV 5, 50, 150 mg/day (2.5 mg, 25 mg, or 75 mg twice daily at 8:00 am and 8:00 pm).</p> <p><u>Fasting:</u> On days 8, 13, and 20, the morning dose was taken in the fasting condition. On MDZ days, the subjects remained fasted until 4 hours-post MDZ dose.</p>																					
PK Assessment	<p><u>BRV:</u> A trough plasma sample was collected pre-dose in the morning of Days 8, 11, 12, 13, and 14 (5 samples total for each patient for BRV).</p> <p><u>MDZ:</u> On Days 1, 13, and 20, samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24</p> <p><u>PK Analyses:</u></p> <p><i>MDZ and its metabolite:</i> C_{max}, t_{max}, AUC(0-t) , AUC, t_{1/2}, λ_z.</p> <p><i>MDZ only:</i> CL/F, V_z/F.</p> <p><i>metabolic ratio OH-Midazolam/ Midazolam:</i> AUC (if applicable, otherwise AUC(0-t))</p> <p><i>BRV:</i> morning trough levels determined on Days 8, 11, 12, 13, and 14</p>																					
Bioanalytical Methods	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-10.50 to 5.00%</td> </tr> <tr> <td>Standards precision</td> <td>1.64 to 5.86%</td> </tr> <tr> <td>QC concentrations</td> <td>25, 150, 1800 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-6.67 to 7.2%</td> </tr> <tr> <td>QC Precision</td> <td>1.88 to 6.27%</td> </tr> <tr> <td>LLOQ</td> <td>0.05 µg/mL</td> </tr> </table>		Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL	Standards accuracy	-10.50 to 5.00%	Standards precision	1.64 to 5.86%	QC concentrations	25, 150, 1800 ng/mL	QC Accuracy	-6.67 to 7.2%	QC Precision	1.88 to 6.27%	LLOQ	0.05 µg/mL
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QC Precision	1.88 to 6.27%																					
LLOQ	0.05 µg/mL																					

HPLC-MS/MS Analytical Methods for MDZ and MDZ-OH Plasma Concentrations

Analyte Name	Midazolam	1-hydroxymidazolam
Analyte ID	MDZ	MDZ-OH
Internal Standard (IS)	(b) (4)	
Standard curve concentrations	0.1, 0.5, 1, 5, 10, 50, 75, 100 ng/mL	
Standards accuracy	-2.2 to 2.13%	-3.00 to 3.33%
Standards precision	3.22 to 5.00%	3.24 to 6.7%
QC concentrations	0.3, 30, 80 ng/mL	
QC Accuracy	-0.67 to 6.75%	-9.00 to -0.25%
QC Precision	2.97 to 5.30%	3.97 to 6.78%
LLOQ	0.1 ng/mL	0.1 ng/mL

[Reviewer comment: The assays are acceptable.]

**Population/
Demographics**

N=41
Inclusion Criteria: healthy male volunteers age 18 to 55 years, BMI between 19.0 and 28.8 kg/m². Clinical laboratory tests or ECG should be considered normal or may have values outside the accepted range if the values are of no clinical significance.
Exclusion Criteria: consumption of grapefruit ≤ 14 days before inclusion in trial, use of enzyme-inducing drug within 2 months of first study drug intake, any prescription or non-prescription medication taken within 14 days preceding first study drug intake.

PK Results

Figure N01261-1: Geometric Mean (± SD) MDZ Plasma Concentration in the 2.5 mg bid BRV Group

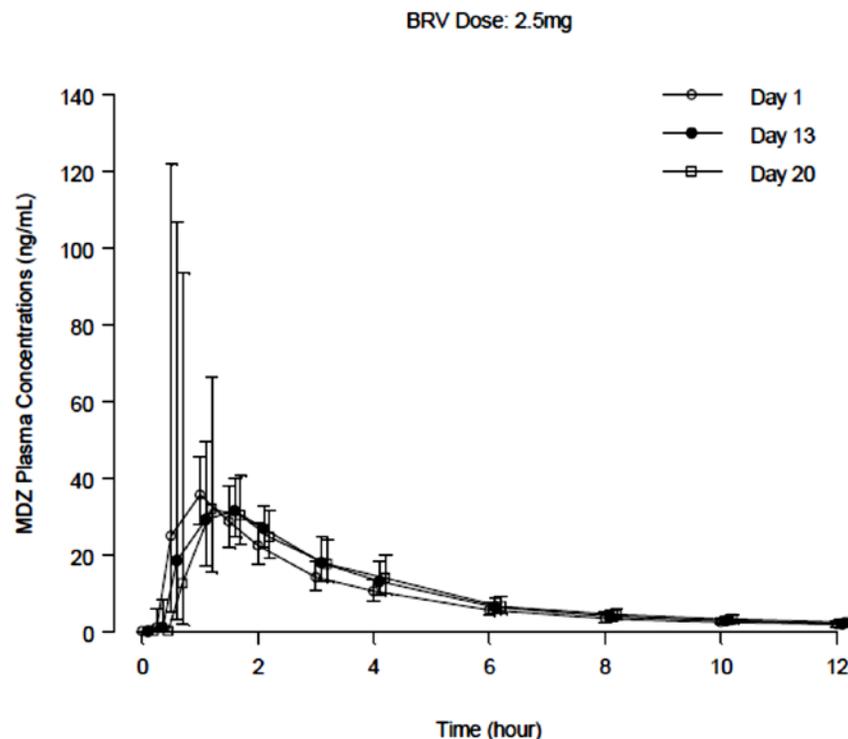


Figure N01261-2: Geometric Mean (\pm SD) MDZ Plasma Concentration in the 25 mg bid BRV Group

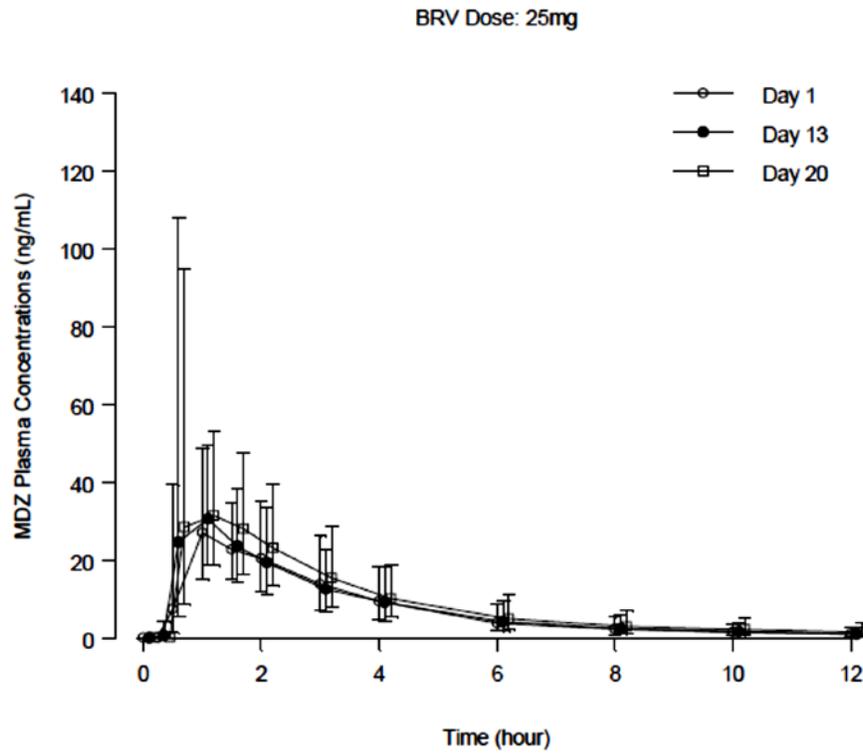


Figure N01261-3: Geometric Mean (\pm SD) MDZ Plasma Concentration in the 75 mg bid BRV Group

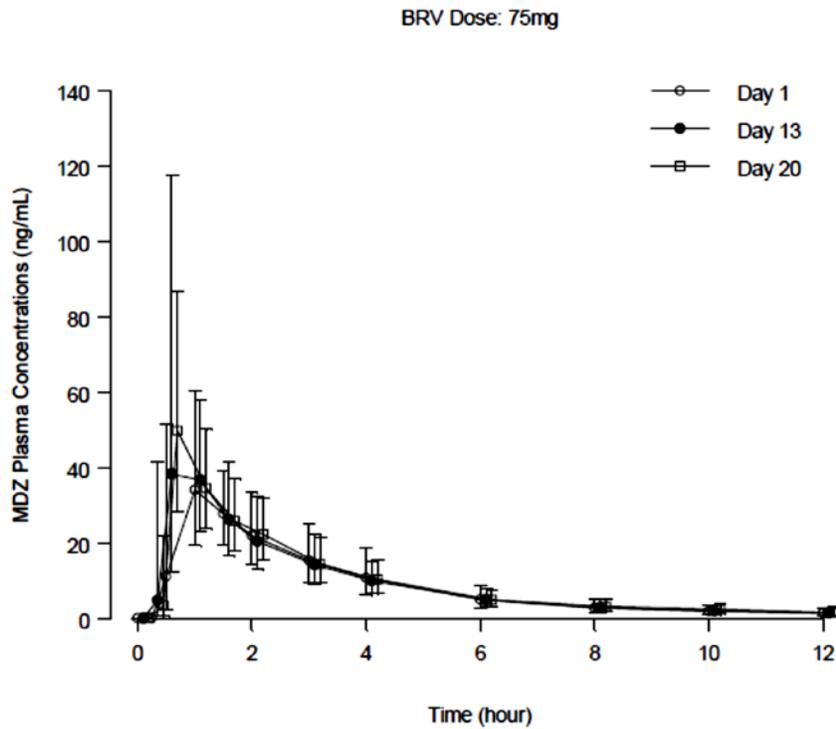


Table N01261-1: Geometric Mean (%CV) MDZ PK Parameters By Day and By BRV Treatment Group

PK parameters	Treatment Day	BRV		
		2.5 mg <i>b.i.d.</i> (N=14)	25 mg <i>b.i.d.</i> (N=14)	75 mg <i>b.i.d.</i> (N=14)
C_{max} (ng/mL)	Day 1	50.61 (39.5)	37.37 (45.9)	42.94 (45.5)
	Day 13	50.91 (33.5)	43.92 (62.6)	63.86 (58.0)
	Day 20	47.01(52.0)	52.52 (57.3)	54.11 (46.3)
AUC (ng.h/mL)	Day 1	138.3 (28.6)	107.5 (60.1)	126.3 (46.8)
	Day 13	153.4 (22.6)	112.6 (67.1)	137.0 (45.9)
	Day 20	155.9 (28.7)	135.5 (63.6)	138.7 (38.8)
AUC _(0-t) (ng.h/mL)	Day 1	134.5 (27.6)	105.2 (58.6)	123.0 (45.4)
	Day 13	149.0 (21.6)	110.1(65.9)	134.3 (44.7)
	Day 20	150.7(28.0)	132.8 (62.9)	135.5 (37.0)
t_{max} (h)	Day 1	0.5 (0.5-1.5)	1.0 (0.25-3.0)	1.0 (0.5-4.0)
	Day 13	0.5 (0.5-2.0)	0.5 (0.5-2.0)	0.5 (0.25-1.0)
	Day 20	1.0 (0.5-2.0)	0.5 (0.25-2.0)	0.5 (0.25-1.0)
$t_{1/2}$ (h)	Day 1	5.167 (33.9)	4.361 (34.4)	5.060 (29.6)
	Day 13	5.385 (26.8)	4.408 (35.8)	4.661(25.8)
	Day 20	5.280 (31.5)	4.345 (29.6)	5.093 (24.0)
λ_z	Day 1	0.1342 (33.9)	0.1589 (34.4)	0.1370 (29.6)
	Day 13	0.1287 (26.8)	0.1573 (35.8)	0.1487 (25.8)
	Day 20	0.1313 (31.5)	0.1595 (29.6)	0.1361 (24.0)
CL/F (mL/min/kg)	Day 1	11.21 (28.4)	16.09 (63.1)	13.06 (41.7)
	Day 13	10.07 (27.2)	15.36 (72.2)	12.04 (44.4)
	Day 20	9.908 (23.2)	12.77 (65.4)	11.89 (35.7)
V_z/F (L/kg)	Day 1	5.014 (31.1)	6.076 (44.2)	5.721 (35.6)
	Day 13	4.694 (31.0)	5.861 (45.8)	4.857 (30.1)
	Day 20	4.529 (28.6)	4.804 (52.9)	5.240 (22.4)

In BRV 2.5 mg *b.i.d.* group, N=13 for Day 13 and Day 20

Table N01261-2: Geometric Mean (%CV) OH-MDZ PK Parameters By Day and By BRV Treatment Group

PK parameters	Treatment Day	BRV		
		2.5 mg <i>b.i.d.</i> (N=14)	25 mg <i>b.i.d.</i> (N=14)	75 mg <i>b.i.d.</i> (N=14)
C_{max} (ng/mL)	Day 1	17.27 (51.9)	16.22 (51.1)	17.02 (47.4)
	Day 13	14.51 (66.7) ^(a)	17.61 (63.9)	21.85 (54.7)
	Day 20	14.57 (84.9) ^(a)	19.76 (59.7)	20.89 (54.8)
AUC (ng.h/mL)	Day 1	40.56 (41.6)	43.20 (40.3) ^(b)	44.88 (29.6)
	Day 13	38.74 (42.2) ^(b)	44.12 (38.4) ^(a)	46.88 (33.0)
	Day 20	38.38 (49.6) ^(a)	46.30 (43.1) ^(c)	47.92 (34.9)
AUC _(0-t) (ng.h/mL)	Day 1	38.59 (41.3)	40.19 (41.8)	42.94 (28.7)
	Day 13	36.04 (41.7) ^(a)	40.40 (42.2)	44.90 (33.8)
	Day 20	36.74 (52.6) ^(a)	44.71 (44.2)	46.40 (35.3)
t_{max} (h)	Day 1	0.5 (0.5-1.5)	1.0 (0.5-2.0)	1.0 (0.5-4.0)
	Day 13	0.5 (0.5-2.0) ^(a)	0.5 (0.5-1.5)	0.5 (0.25-1.0)
	Day 20	1.0 (0.5-2.0) ^(a)	0.5 (0.5-2.0)	0.5 (0.5-1.0)
$t_{1/2}$ (h)	Day 1	6.321 (39.8)	6.963 (24.9) ^(b)	6.410 (37.2)
	Day 13	5.741 (25.3) ^(b)	5.951 (27.5) ^(a)	5.922 (35.6)
	Day 20	5.394 (22.0) ^(a)	6.382 (15.6) ^(c)	6.185 (23.7)
λ_z	Day 1	0.1097 (39.8)	0.09955 (24.9) ^(b)	0.1081 (37.2)
	Day 13	0.1207 (25.3) ^(b)	0.1165 (27.5) ^(a)	0.1170 (35.6)
	Day 20	0.1285 (22.0) ^(a)	0.1086 (15.6) ^(c)	0.1121 (23.7)

Table N01261-3: Geometric Mean (%CV) of [AUC(OH-MDZ) / AUC(MDZ)] ratios By Day and By BRV Treatment Group

	Treatment Day	BRV		
		2.5 mg b.i.d. (N=14)	25 mg b.i.d. (N=14)	75 mg b.i.d. (N=14)
AUC(OH-MDZ)/AUC(MDZ)	Day 1	0.2933 (27.7)	0.3915 (59.3)	0.3555 (39.2)
	Day 13	0.2449 (38.5) ^(a)	0.3732 (63.5)	0.3422 (33.9)
	Day 20	0.2462 (33.5) ^(a)	0.3421 (46.7)	0.3454 (39.6)

[Reviewer comment: The ratio of midazolam metabolite-to-parent is comparable within a BRV dose group over time. The ratio increases with increasing BRV dose.]

Table N01261-4: Statistical Comparison of MDZ PK Parameters On Days 13 and Day 20 versus Day 1 By BRV Treatment Group

Parameters	Treatment Day	BRV		
		2.5 mg b.i.d.	25 mg b.i.d.	75 mg b.i.d.
C _{max} (ng/mL)	Day 13	101.5 (80.04 ; 128.7)	117.5 (93.25 ; 148.1)	148.7 (118.0 ; 187.4)
	Day 20	93.46 (71.48 ; 122.2)	140.6 (108.2 ; 182.6)	126.0 (96.99 ; 163.8)
AUC (ng.h/mL)	Day 13	112.0 (99.78 ; 125.7)	104.8 (93.70 ; 117.2)	108.5 (97.03 ; 121.3)
	Day 20	113.9 (101.4 ; 127.8)	126.0 (112.7 ; 140.9)	109.9 (98.27 ; 122.8)
AUC _(0-t) (ng.h/mL)	Day 13	112.0 (99.84 ; 125.7)	104.7 (93.64 ; 117.0)	109.2 (97.69 ; 122.0)
	Day 20	113.9 (100.9 ; 127.1)	126.2 (112.9 ; 141.1)	110.1 (98.51 ; 123.1)
t _{max} (h)	Day 13	0.50 (-0.50 ; 1.50)	-0.50 (-0.75 ; 0.00)	-0.63 (-2.00 ; -0.50)
	Day 20	0.50 (-0.25 ; 0.50)	-0.25 (-0.75 ; 0.25)	-0.50 (-0.75 ; -0.38)

[Reviewer comment: Overall, midazolam exposures tend to increase with concomitant BRV administration. However, there isn't a clear trend of MDZ exposure increase over time or with dose. For example, the AUC_{0-t} and AUC_{0-∞} MDZ increases are lower for the 75 mg bid BRV group than for 2.5 or 25 mg bid BRV group.]

Table N01261-5: Statistical Comparison of OH-MDZ PK Parameters On Days 13 and Day 20 versus Day 1 By BRV Treatment Group

	Treatment Day	BRV		
		2.5 mg b.i.d.	25 mg b.i.d.	75 mg b.i.d.
C _{max} (ng/mL)	Day 13	86.19 (64.92 ; 114.4)	108.6 (82.39 ; 143.1)	128.4 (97.40 ; 169.2)
	Day 20	86.05 (63.21 ; 117.2)	121.9 (90.18 ; 164.7)	122.7 (90.82 ; 165.9)
AUC (ng.h/mL)	Day 13	97.64 (86.62 ; 110.1)	99.21 (88.04 ; 111.8)	104.4 (93.36 ; 116.9)
	Day 20	98.56 (89.02 ; 109.1)	109.4 (97.69 ; 122.5)	106.8 (96.75 ; 117.8)
AUC _(0-t) (ng.h/mL)	Day 13	97.18 (86.51 ; 109.2)	100.5 (89.83 ; 112.5)	104.6 (93.43 ; 117.0)
	Day 20	99.32 (89.59 ; 110.1)	111.2 (100.7 ; 122.9)	108.1 (97.82 ; 119.4)
t _{max} (h)	Day 13	0.50 (-0.50 ; 1.50)	-0.50 (-0.75 ; 0.00)	-0.63 (-2.00 ; -0.50)
	Day 20	0.50 (0.00 ; 0.50)	-0.50 (-0.75 ; 0.25)	-0.50 (-2.00 ; 0.00)

Table N01261-6: Statistical Comparison of [AUC(OH-MDZ) / AUC(MDZ)] ratios On Days 13 and Day 20 versus Day 1 By BRV Treatment Group

Ratio	Treatment Day	BRV		
		2.5 mg b.i.d.	25 mg b.i.d.	75 mg b.i.d.
Ratio	Day 13	86.11 (76.91 ; 96.41)	95.33 (85.47 ; 106.3)	96.27 (86.31 ; 107.4)
	Day 20	86.50 (76.68 ; 97.59)	87.37 (77.76 ; 98.18)	97.17 (86.48 ; 109.2)

Safety

The majority of AEs were related to somnolence and thought to be related to MDZ. Severe somnolence was reported by the majority of subjects after each MDZ intake. Severe diplopia was reported in 3 subjects (7%) after receiving MDZ while at SS BRV. No SAEs or significant AE occurred. No new observations related to the known BRV safety profile were found

Sponsor's

- This study suggests the absence of 3A4 induction by BRV (2.5, 25, and 75 mg

Conclusions	bid) at steady state using midazolam as a probe. <ul style="list-style-type: none">Repeat administration of BRV (2.5, 25, and 75 mg bid) with concomitant midazolam 7.5 mg/day during 6.5 days was well-tolerated
<i>Reviewer Comment</i>	<ul style="list-style-type: none"><i>As midazolam is considered to be a sensitive 3A4 substrate by the agency, these results support the claim that repeat BRV 2.5, 25, and 75 mg bid do not result in 3A4 induction.</i><i>Results from study N01067 are consistent with this finding, as there was no clear evidence to support 3A4 induction by BRV.</i>

4.4.30 N01263: Pediatric Open-Label PK, Safety, and Efficacy Trial with Titration (Phase 2a)

Study Report#	N01263
Title	Open-Label, Single-Arm, Multicenter, Pharmacokinetic, Safety, and Efficacy Study of Adjunctive Administration of Brivaracetam in Subjects from ≥1 Month to <16 Years Old with Epilepsy
Objectives	<u>Primary:</u> Assess SS PK of BRV and metabolites in pediatric patients, assess relationship to developmental variables, assess need for dosing adaptation <u>Secondary:</u> Further characterize safety and tolerability, assess preliminary efficacy information in pediatric subjects
Study Design	This was a Phase 2a, open-label, single-arm, multicenter (29 sites in US, Mexico, and EU [Belgium, Czech Republic, Poland, and Spain]), fixed 3-step up-titration study in subjects with epilepsy evaluating the PK, safety, and efficacy of BRV. Subjects may be eligible to continue into the long-term follow-up study (N01266) after completion of N01263.
Duration	49 days (with 35 days total exposure to BRV, including 2-weeks up-titration, 1-week
Dosage and Administration	After a 1-week baseline period, subjects underwent a 3-week Evaluation Period with weekly fixed 3-step up-titration of the BRV dose. Subjects received brivaracetam oral solution (1 mg/mL) or brivaracetam oral solution (10 mg/mL) via a polypropylene syringe. <u>Up-Titration:</u> Brivaracetam oral solution was administered at weekly increasing doses: 0.4mg/kg, 0.8mg/kg, and 1.6mg/kg bid for subjects ≥8 years of age, and 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg bid for subjects <8 years of age, from Week 1 (V3) to Week 3 (V5). <u>Down-Titration:</u> Upon completion of the study (Day 21, V5), unless patients continue into LTFU study N01266, subjects underwent a 2-week down-titration period with weekly dose decreases: 0.8mg/kg and 0.4mg/kg bid for subjects ≥8 years of age, and 1.0mg/kg and 0.5mg/kg bid for subjects <8 years of age If subjects reached the maximum dose (1.6 mg/kg bid or 2.0 mg/kg bid for subjects ≥ 8 years or < 8 years), down-titration was 2 weeks. If subjects reached only the intermediate dose, down-titration was 1 week. Subjects exiting the study were also to be down-titrated in the same manner.
PK Assessment	PK of BRV and metabolites was assessed in plasma. <u>Plasma PK Samples:</u> Two to three blood samples were acquired on Day 7 (V3), Day 14 (V4), and Day 21 (V5) or early discontinuation. Sponsor planned to acquire a PK sample at the time of an SAE. If patients arrived at the CRU in the early morning, one sample was acquired pre-dose and 1 sample between 1-2 hours post-dose (with an optional 3 rd sample at a later or intervening time). Patients who arrived in the later morning or afternoon visit provided 2 PK samples at least 2 hours apart from each other (with an option 3 rd pk sample at a later or intervening time). <u>PK Analyses:</u> Pediatric exposures were summarized by age group and time of

	<p>samples. The pediatric data were also included in the population PK analyses (report #CL0187). Please refer to the pharmacometric review in the QBR for additional details).</p>																																																		
<p>Bioanalytical Methods</p>	<p>HPLC-MS/MS Analytical Methods for <i>PL</i>asma Concentrations</p> <table border="1" data-bbox="365 357 1393 1045"> <thead> <tr> <th>Analyte Name</th> <th>Brivaracetam</th> <th>Carboxylic Acid Metabolite</th> <th>Hydroxy Metabolite</th> <th>Hydroxy Acid Metabolite</th> </tr> </thead> <tbody> <tr> <td>Analyte ID</td> <td>ucb 34714</td> <td>ucb 42145</td> <td>ucb-100406-1</td> <td>ucb-107092-1</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> <td colspan="3">(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td colspan="4">2, 5, 50, 200, 600, 1200, 1800, 2000 ng/mL</td> </tr> <tr> <td>Standards Accuracy</td> <td>-5.5 to 6.8%</td> <td>-1.5 to 1.7%</td> <td>-1.4 to 2.6%</td> <td>-2.9 to 3.0%</td> </tr> <tr> <td>Standards precision</td> <td>1.2 to 3.2%</td> <td>0.9 to 3.8%</td> <td>1.2 to 2.8%</td> <td>1.3 to 3.8%</td> </tr> <tr> <td>QC concentrations</td> <td>6, 75, 160 ng/mL</td> <td>6, 30, 400 ng/mL</td> <td>6, 30, 400 ng/mL</td> <td>6, 70, 1500 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-3.3 to 6.1%</td> <td>-2.1 to -0.5%</td> <td>-6.3 to -5.1%</td> <td>-1.4 to 3.1%</td> </tr> <tr> <td>QC Precision</td> <td>2.7 to 9.3%</td> <td>2.3 to 4.2%</td> <td>2.8 to 8.8%</td> <td>2.9 to 4.1%</td> </tr> <tr> <td>LLOQ</td> <td>20 ng/mL</td> <td>19.9 µg/mL</td> <td>18.6 µg/mL</td> <td>18.5 µg/mL</td> </tr> </tbody> </table> <p>*The metabolites are presented as “effective concentrations” (ng eq ucb 34714/mL). IS (b) (4) IS (b) (4)</p> <p>[Reviewer comment: The plasma and assay for BRV is acceptable.]</p>	Analyte Name	Brivaracetam	Carboxylic Acid Metabolite	Hydroxy Metabolite	Hydroxy Acid Metabolite	Analyte ID	ucb 34714	ucb 42145	ucb-100406-1	ucb-107092-1	Internal Standard (IS)	(b) (4)	(b) (4)			Standard curve concentrations	2, 5, 50, 200, 600, 1200, 1800, 2000 ng/mL				Standards Accuracy	-5.5 to 6.8%	-1.5 to 1.7%	-1.4 to 2.6%	-2.9 to 3.0%	Standards precision	1.2 to 3.2%	0.9 to 3.8%	1.2 to 2.8%	1.3 to 3.8%	QC concentrations	6, 75, 160 ng/mL	6, 30, 400 ng/mL	6, 30, 400 ng/mL	6, 70, 1500 ng/mL	QC Accuracy	-3.3 to 6.1%	-2.1 to -0.5%	-6.3 to -5.1%	-1.4 to 3.1%	QC Precision	2.7 to 9.3%	2.3 to 4.2%	2.8 to 8.8%	2.9 to 4.1%	LLOQ	20 ng/mL	19.9 µg/mL	18.6 µg/mL	18.5 µg/mL
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<p>Population/ Demographics</p>	<p>N=97 subjects were included in the full analysis set (n=96 had complete PK data). <u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male or female patients with epilepsy ≥ 1 month to < 16 years. Enrollment was stratified by age (at least n=30 age < 23 months, a least n=30 age 2 to 11 years, no more than 30 age 12 to < 16 years). 2. Epilepsy was localization-related, generalized, or undetermined whether focal or generalized epileptic syndrome, and other symptomatic generalized epilepsies 3. Received stable doses of 1 to 3 concomitant AEDs (stable for ≥ 7 days prior to V1 and through the last PK sample), no additions or deletions of AEDs during the study were permitted. Benzodiazepine use for more than 1 week was considered a concomitant medication. 4. Female subjects without childbearing potential (premenarcheal or surgically sterile) were eligible. <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Concomitant use of levetiracetam within 4 weeks of V1 2. Status epilepticus 3. Pregnant or nursing females. 4. Subject had an underlying disease or was receiving a treatment that may have interfered with the absorption, distribution, metabolism, and elimination of the study drug. 																																																		

	<p>5. Subject had any clinically significant deviations from reference range values for laboratory parameters as determined by the Investigator.</p> <p>6. Subject had impaired hepatic function:</p> <ul style="list-style-type: none">• Alanine aminotransferase/serum glutamic pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or ALP of more than 2x the upper limit of normal (ULN), or total bilirubin of more than 2xULN.• Gamma-glutamyltransferase values of more than 3xULN. A result of GGT exceeding 3xULN could only be accepted if attributable to hepatic enzyme induction caused by concomitant antiepileptic treatment and if other hepatic enzymes were below 2xULN.
PK Results	<p>(b) (4)</p>

Efficacy	(b) (4)
Safety	TEAEs were reported in 66.7% of subjects. The most common AEs were convulsion (10.1%), and somnolence, irritability, and pyrexia (8.1% each). The most common <i>drug-related</i> TEAEs were somnolence (7.1% and decreased appetite (6.1%). Convulsions were reported during the Post-Treatment Period but not during the Down-Titration Period and Sponsor considered potentially related to withdrawal or rebound phenomena. Discontinuation due to TEAE occurred in 6.1% of subjects (2 subjects (2.0%) discontinued due to aggression).
Sponsor's Conclusions	<p><u>Efficacy:</u> (b) (4)</p> <p><u>Safety:</u> BRV was generally well-tolerated. Safety profile was consistent with what is known about BRV in adults, except dizziness incidence was greater than in adults.</p> <p><u>PK:</u> (b) (4)</p>
Reviewer Comment	<ul style="list-style-type: none">• <u>Efficacy:</u> Please refer to the clinical review by Dr. Steven Dinsmore for comments on the interpretation of the efficacy data.• <u>Safety:</u> The safety profile is consistent with the type of AEs observed in other BRV trials. <p><u>PK:</u> (b) (4)</p>

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)



(b) (4)

4.4.31 N01282: DDI – LVN+EES (Phase 1)

Study Report#	RPCE06J2901 / N01282
Title	Interaction study between brivaracetam 50mg twice daily and a combined oral contraceptive containing 30µg ethinylestradiol and 150µg levonorgestrel in healthy female subjects
Objectives	<p><u>Primary:</u> Assess the effect of BRV on oral contraceptive (OC) PK</p> <p><u>Secondary:</u></p> <ol style="list-style-type: none"> 1. Assess impact of BRV on spotting/bleed (via person diary), 2. Assess effect of OC on BRV PK 3. Gain information on safety and tolerability of concomitant BRV + OC
Study Design	Double-blind, placebo-controlled, randomized, two-way crossover, multiple oral dose interaction study
Duration	24 weeks
Dosage and Administration	<p>The study was conducted in two centers in France and utilized the approved OC product was Minidril® (or approved equivalent). The OC was taken for a minimum of 2 cycles prior to cycle 1. The cycles consisted of 21 days of OC administration followed by an OC-free period of 7 days. For each subject, the study lasted a maximum of 24 weeks from Screening Visit to Discharge Visit:</p> <ul style="list-style-type: none"> • Screening Visit: maximal 3 weeks before the first OC administration • Cycle 1 (4 weeks): baseline contraception cycle <ul style="list-style-type: none"> • Cycle 2 (4 weeks): treatment cycle, according to randomization • Cycle 3 (4 weeks): contraception (wash-out) cycle • Cycle 4 (4 weeks): treatment cycle, according to randomization • Cycle 5 (4 weeks): follow-up contraception cycle • Discharge Visit: maximal 1 week after the end of Cycle 5 <p>Ethinylestradiol 30µg and levonorgestrel 150µg were administered once daily from Day 1 to Day 21 throughout Cycle 1 to Cycle 5.</p> <p>BRV 50 mg twice daily or placebo was administered from Day 1 to Day 21 in the morning during Cycle 2 and Cycle 4</p>
PK Assessment	<p>The following PK samples are acquired during <u>Cycle 2</u> and <u>Cycle 4</u>:</p> <p><u>Plasma PK Samples – BRV:</u> <i>Trough:</i> morning of Day 3, 8, 14, 18, 20, and 29 (prior to administration) <i>Rich:</i> Day 20 from predose up to 12 hours postdose (predose, 30min, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12h postdose).</p> <p><u>Plasma PK Samples – LVN+EES:</u> Day 20 from predose up to 24 hours postdose (predose, 30min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24h postdose). The 24-hour sample was obtained before the morning-dose on Day 21.</p> <p><u>PK Analyses:</u> Day 20 Cmax, tmax, Cmin, AUCtau, and CLss/F for BRV, EES, and LVN</p>

Bioanalytical Methods	HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations		
	Analyte Name	Brivaracetam	
	Analyte ID	ucb 34714	
	Internal Standard (IS)	(b) (4)	
	Standard curve concentrations	50.0 100 250 500 750 1000 1500 2000 ng/mL	
	Standards accuracy	-2.4 to 2.7%	
	Standards precision	0.9 to 4.7%	
	QC concentrations	150, 600, 1750 ng/mL	
	QC Accuracy	-4.5 to -1.0%	
	QC Precision	3.3 to 3.7%	
	LLOQ	0.05 µg/mL	
	HPLC-MS/MS Analytical Methods for EES and LVN Plasma Concentrations		
	Analyte Name	Ethinylestradiol	Levonorgestrel
	Analyte ID	EES	LVN
	Internal Standard (IS)	(b) (4)	(b) (4)
	Standard curve concentrations	10.0 – 500 pg/mL	50-25000 pg/mL
	Standards accuracy	-6.44 to 5.79%	-3.98 to 6.29%
	Standards precision	0.41 to 14.68%	0.03 to 14.11%
	QC concentrations	30, 150, 400 pg/mL	150, 2500, 20000 pg/mL
	QC Accuracy	-2.52 to 0.40%	-2.41 to 1.47%
	QC Precision	3.9 to 7.05%	7.16 to 7.89%
	LLOQ	10 pg/mL	50 pg/mL
	[Reviewer comment: The assays are acceptable.]		
Population/ Demographics	N=28 <u>Inclusion criteria:</u> <ol style="list-style-type: none"> 1. Healthy, nonsmoking, premenopausal, non-pregnant and non-lactating female subjects at 18 to 40 years 2. Receiving OC of interest (EES 30µg and LVN 150µg, Minidril or equivalent eg, Ludeal®, Microgynon30®) for at least 2 consecutive cycles prior to Cycle 1 3. Use of additional appropriate birth control method 4. ECG considered normal or abnormal but not clinically significant 5. Clinical laboratory tests within reference range or outside range but not clinically significant. <u>Exclusion criteria:</u> <ol style="list-style-type: none"> 1. Hepatic, renal, gastrointestinal or other disorder capable of altering ADME of drugs (or causing a risk factor for use of the medication) 2. Clinically significant chronic or acute illness 3. Contraindication to prescription Minidril 4. Any prescription or OTC medications including herbs within 14 days before study drug administration in cycle 1 (paracetamol [acetaminophen] up to 2 g/day is permitted) 		

5. Blood pressure and heart rate outside normal range (unless clinically not significant)
6. Current tobacco smoker
7. Heavy caffeine drinker

PK Results

Figure N01282-1: Geometric Mean (\pm SD) EES Concentration on Day 20 of EES+LVN+BRV Versus Day 20 of EES+LVN+Placebo

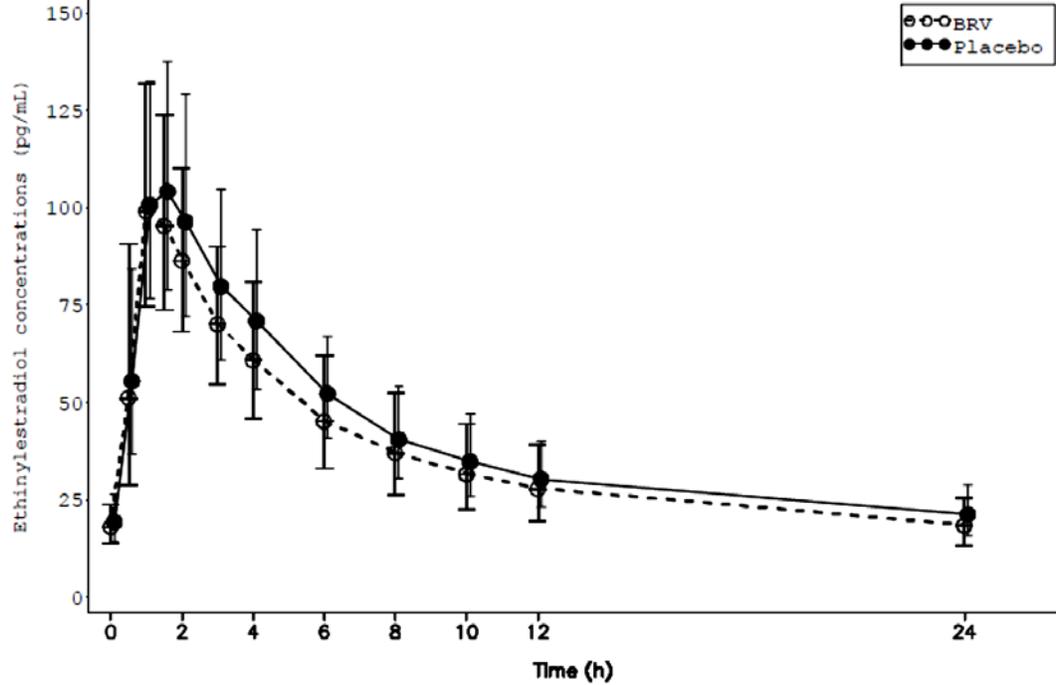


Figure N01282-2: Geometric Mean (\pm SD) LVN Concentration on Day 20 of EES+LVN+BRV Versus Day 20 of EES+LVN+Placebo

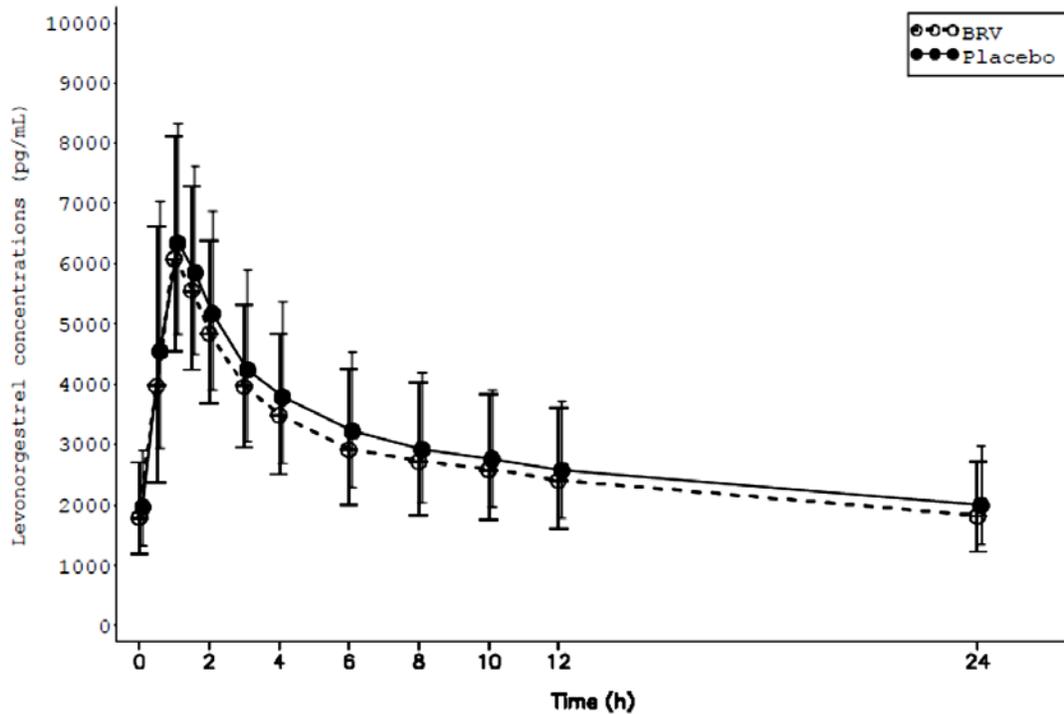


Table N01282-1: Statistical Comparison of EES PK Parameters and LVN PK Parameters On Day 20 of EES+LVN+BRV Versus Day 20 of EES+LVN+Placebo

Oral contraceptive	Parameters (units)	Reference ^(a) OC with PBO	Test ^(a) OC with BRV	CV ^(b) (%)	Reference <i>versus</i> Test ^(c)	
					Point Estimate	90% CI
Ethinylestradiol	AUC _τ (pg*h/mL)	989 (889; 1100)	893 (803; 994)	9.95	90.3	85.9; 95.0
	C _{max} (pg/mL)	110 (98.4; 123)	105 (94.3; 118)	16.1	95.8	88.4; 104
	t _{max} (h)	1.50 (1.00; 2.00)	1.00 (0.50; 2.00)	NA	-0.29	-0.50; -0.25
Levonorgestrel	AUC _τ (ng*h/mL)	70.8 (61.8; 81.0)	65.3 (57.1; 74.7)	9.91	92.3	87.8; 97.0
	C _{max} (ng/mL)	6.53 (5.86; 7.29)	6.20 (5.56; 6.92)	9.06	94.9	90.7; 99.4
	t _{max} (h)	1.00 (0.50; 2.00)	1.00 (0.50; 3.00)	NA	0.00	-0.25; 0.00

BRV=brivaracetam; CI=confidence interval; CV%=coefficient of variation; NA=not applicable; OC=oral contraceptive; PBO=placebo

^(a) Geometric least squares means (95% CI); for t_{max}: median (range)

^(b) Intra-subject variability

^(c) Ratio of least squares means (%) and 90% CI derived from ANOVA

Table N01282-2: Geometric Mean (± SD) BRV PK Parameters On Day 20 of EES+LVN+BRV

Parameter (unit)	Geometric mean (CV%) N=24
C _{max} (µg/mL)	2.55 (14.1)
AUC _τ (µg*h/mL)	18.8 (13.6)
C _{min} (µg/mL)	0.936 (20.7)
CL _{ss} /F (mL/min/kg)	0.715 (13.6)
	Median (range)
t _{max} (h)	1.0 (0.5-2.0)

CV=coefficient of variation

Source: Table 14.2.2:3

- PK Parameters of EES were similar when OC was administered with either PBO or BRV (C_{max}, AUC_τ, C_{min}, CL_{ss}/F), as the 90% CI were entirely contained within the 80-125% no-effect boundaries.
- BRV trough concentrations on Day 20 of co-administration with OC were comparable to Day 29 (after the 7-day washout of OC).

Safety

- AEs were reported in 64% of subjects receiving BRV + OC and in 41% of subjects receiving placebo + OC.
- There were 18 AEs during OC administration, 53 during co-administration of 50mg BRV bid and OC, 26 during co-administration of PBO and OC and 8 in the wash-out periods
- All but 2 AEs (which occurred in the placebo arm) were mild to moderate in intensity
- During BRV + OC administration the most common TEAEs were dizziness (40%), headache (24%), somnolence (28%), and asthenia (20%). These adverse events were less frequent (or did not occur) before and after BRV administration.

Sponsor's Conclusions	<ul style="list-style-type: none">• The absence of a PK interaction of 50 mg BRV bid <u>on OC</u> can be concluded.• Based on a comparison of BRV trough levels after 1 week of OC wash-out, the absence of a PK interaction of OC <u>on BRV</u> can be concluded.• Co-administration of 50 mg bid BRV over 28 days with the OC containing 30µg ethinylestradiol and 150µg levonorgestrel was safe and well tolerated
Reviewer Comment	<ul style="list-style-type: none">• <i>The study results suggest <u>50 mg BRV bid</u> does not interact with oral contraceptives consisting of 30 µg ethinylestradiol and 150µg levonorgestrel.</i>• <i>The dose in this study was <u>50 mg bid BRV</u>, whereas study N01080 administered <u>200 mg bid BRV</u>. While the 50 mg BRV dose in the current study did not alter the OC PK, OC exposures were reduced in study N01080. It is possible that BRV doses greater than 50 mg bid can reduce exposures of both EES as well as LVN.</i>• <i>Please refer to study N01080 ISR for additional discussion regarding DDI with OC.</i>

4.4.32 N01287: BA/BE of BRV Capsule, Tablet, and Oral Solution with Food Effect

Study Report #	N01287																				
Title	Monocenter, open-label, randomized, five-way cross-over relative bioavailability/bioequivalence study of brivaracetam solid oral formulations (capsule and tablet) using as reference brivaracetam oral solution with assessment of food effect on brivaracetam tablet formulation.																				
Objectives	<p><u>Primary:</u></p> <ol style="list-style-type: none"> 1. Assess relative BA of oral capsules (2 x 25 mg, 50 mg), oral tablets (50 mg) vs. an oral solution (reference) 2. Assess BE of oral capsules (2 x 25 mg, 50 mg) vs oral tablets (reference) 3. Assess absorption rate and extent for 50 mg oral tablets in fed versus fasted state <p><u>Secondary:</u> Assess safety</p>																				
Study Design	Monocenter, open-label, randomized, five-way crossover relative BA/BE study																				
Duration	9 weeks (3 weeks screening, 4 weeks treatment [5 treatment period], each consisting of 4 days, ≥ 7 day washout, discharge 1 week later)																				
Dosage and Administration	<p>The following treatments were administered in a randomized order in this 5-period cross-over study:</p> <ol style="list-style-type: none"> 1) BRV 1 x 50 mg oral solution – single dose, fasted (reference) 2) BRV 2 x 25 mg oral capsule – single dose, fasted (test) 3) BRV 1 x 50 mg oral capsule – single dose, fasted (test) 4) BRV 1 x 50 mg oral tablet – single dose, fasted (test) 5) BRV 1 x 50 mg oral tablet – single dose, fed (test) <p>A single dose was administered on Day 1, 8, 15, 22, and 29 following an overnight fast of at least 10 hours. For the food effect assessment, the 50-mg tablet was administered 30 minute after the start of a high-fat breakfast. The oral solution was preparing using a powder and mixed on-site.</p>																				
PK Assessment	<p><u>Plasma PK Samples:</u> pre-dose, 5 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 6 h, 9 h, 12 h, 24 h, 36 h and 48 h post-dose.</p> <p><u>Analyses:</u> C_{max}, AUC_{0-t}, AUC, t_{max}, t_{1/2}, CL/F, V_Z/F. Relative BA and BE were based upon the 90% CI of the log-transformed geometric mean ratio (GMR) for C_{max}, AUC_{0-t}, AUC. BE for test-vs-reference as well as food effect for the tablet were assessed using 0.8-1.25 no-effect boundaries.</p>																				
Bioanalytical Methods	<p style="text-align: center;">HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>2.00, 5.00, 50.0, 200, 600, 1200, 1800 and 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-5.6 to 3.4%</td> </tr> <tr> <td>Standards precision</td> <td>2 to 6.4%</td> </tr> <tr> <td>QC concentrations</td> <td>6.00, 75.0 and 1600 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-1.3 to 5.7%</td> </tr> <tr> <td>QC Precision</td> <td>6 to 7.9%</td> </tr> <tr> <td>LLOQ</td> <td>2.00 ng/mL</td> </tr> </table>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	2.00, 5.00, 50.0, 200, 600, 1200, 1800 and 2000 ng/mL	Standards accuracy	-5.6 to 3.4%	Standards precision	2 to 6.4%	QC concentrations	6.00, 75.0 and 1600 ng/mL	QC Accuracy	-1.3 to 5.7%	QC Precision	6 to 7.9%	LLOQ	2.00 ng/mL
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QC Accuracy	-1.3 to 5.7%																				
QC Precision	6 to 7.9%																				
LLOQ	2.00 ng/mL																				

	<p>[Reviewer comment: The assay is acceptable.]</p>																																								
<p>Population / Demographics</p>	<p>N=25 healthy male and female volunteers age 18-55 years.</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male or female subjects age 18 to 55 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 5. Females must use adequate birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Female subjects must not be pregnant or lactating 2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness 4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical trial 5. Use of any hepatic enzyme inducing drug within 2 months before the first administration, 6. Heavy caffeine drinker (drinking >5 cups of coffee, tea, etc. per day), 7. Current smoker or had given up smoking in the last 6 months 																																								
<p>PK Results</p>	<p>Figure N01287-1: Geometric Mean Plasma Concentrations After Single 50 mg BRV Doses of Oral solution, Oral Capsules, and Oral Tablets In Healthy Volunteers in a Fasted State</p> <table border="1"> <caption>Approximate data points from Figure N01287-1</caption> <thead> <tr> <th>Time (hour)</th> <th>Treatment A (50mg solution) (µg/mL)</th> <th>Treatment B (2x25mg capsules) (µg/mL)</th> <th>Treatment C (50mg capsule) (µg/mL)</th> <th>Treatment D (50mg tablet) (µg/mL)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>1</td> <td>1.5</td> <td>1.4</td> <td>1.4</td> <td>1.4</td> </tr> <tr> <td>2</td> <td>1.2</td> <td>1.15</td> <td>1.15</td> <td>1.15</td> </tr> <tr> <td>4</td> <td>1.0</td> <td>0.95</td> <td>0.95</td> <td>0.95</td> </tr> <tr> <td>6</td> <td>0.8</td> <td>0.75</td> <td>0.75</td> <td>0.75</td> </tr> <tr> <td>9</td> <td>0.6</td> <td>0.55</td> <td>0.55</td> <td>0.55</td> </tr> <tr> <td>12</td> <td>0.5</td> <td>0.45</td> <td>0.45</td> <td>0.45</td> </tr> </tbody> </table>	Time (hour)	Treatment A (50mg solution) (µg/mL)	Treatment B (2x25mg capsules) (µg/mL)	Treatment C (50mg capsule) (µg/mL)	Treatment D (50mg tablet) (µg/mL)	0	0.0	0.0	0.0	0.0	1	1.5	1.4	1.4	1.4	2	1.2	1.15	1.15	1.15	4	1.0	0.95	0.95	0.95	6	0.8	0.75	0.75	0.75	9	0.6	0.55	0.55	0.55	12	0.5	0.45	0.45	0.45
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<p>PK Results</p>	<p>Figure N01287-2: Geometric Mean Plasma Concentrations After Single 50 mg BRV Doses of Oral Tablets In Healthy Volunteers in a Fasted State Versus Fed State</p> <p>The graph plots Brivaracetam Plasma Concentrations (µg/mL) on the y-axis (0.0 to 3.0) against Time (hour) on the x-axis (0 to 48). Two data series are shown: Treatment E (50mg tablet fed) represented by solid circles and a solid line, and Treatment D (50mg tablet fasted) represented by open squares and a dashed line. Both series show a rapid increase in concentration, peaking at 1 hour, followed by a gradual decline. Treatment E reaches a higher peak concentration of approximately 1.2 µg/mL, while Treatment D peaks at approximately 1.0 µg/mL. Both concentrations converge to near zero by 48 hours. Error bars represent standard deviation.</p>																																																	
<p>PK Results</p>	<p>Table N01287-1: PK Parameters after a single dose of 50 mg oral solution, 2 x 25 mg capsules, 50 mg capsule, and 50 mg tablets under <i>fasting</i> conditions</p> <table border="1"> <thead> <tr> <th rowspan="2">PK parameters</th> <th colspan="4">GeoMean (GeoCV%)</th> </tr> <tr> <th>Treatment A: BRV 50 mg Solution (N=23)</th> <th>Treatment B: BRV 2x25 mg Capsules (N=25)</th> <th>Treatment C: BRV 50 mg Capsule (N=25)</th> <th>Treatment D: BRV 50 mg Tablet (N=24)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>1.62 (18.0)</td> <td>1.62 (21.1)</td> <td>1.55 (22.5)</td> <td>1.68 (25.5)</td> </tr> <tr> <td>t_{max} (hr)^(a)</td> <td>0.5 (0.25-1.5)</td> <td>0.5 (0.5-2.0)</td> <td>0.75 (0.25-3.0)</td> <td>0.5 (0.25-3.0)</td> </tr> <tr> <td>AUC(0-t) (µg.h/mL)</td> <td>16.1 (24.5)</td> <td>15.9 (23.9)</td> <td>16.1 (27.7)</td> <td>16.2 (25.3)</td> </tr> <tr> <td>AUC (µg.h/mL)</td> <td>16.6 (25.5)</td> <td>16.4 (25.0)</td> <td>16.6 (28.7)</td> <td>16.7 (26.3)</td> </tr> <tr> <td>λ_z (1/hr)</td> <td>0.0751 (15.8)</td> <td>0.0752 (16.3)</td> <td>0.0775 (17.0)</td> <td>0.0765 (16.2)</td> </tr> <tr> <td>$t_{1/2}$ (hr)</td> <td>9.23 (15.8)</td> <td>9.22 (16.3)</td> <td>8.94 (17.0)</td> <td>9.06 (16.2)</td> </tr> <tr> <td>CL/F (L/hr)</td> <td>3.02 (25.5)</td> <td>3.05 (25.0)</td> <td>3.02 (28.7)</td> <td>2.99 (26.3)</td> </tr> <tr> <td>V_z/F (L)</td> <td>40.2 (19.9)</td> <td>40.6 (17.2)</td> <td>38.9 (19.7)</td> <td>39.1 (18.9)</td> </tr> </tbody> </table> <p>^(a) t_{max} (hr) values are median (min-max); GeoCV%: geometric coefficient of variation, N: number of subjects (Source data: Table 14.2.1.2)</p>	PK parameters	GeoMean (GeoCV%)				Treatment A: BRV 50 mg Solution (N=23)	Treatment B: BRV 2x25 mg Capsules (N=25)	Treatment C: BRV 50 mg Capsule (N=25)	Treatment D: BRV 50 mg Tablet (N=24)	C_{max} (µg/mL)	1.62 (18.0)	1.62 (21.1)	1.55 (22.5)	1.68 (25.5)	t_{max} (hr) ^(a)	0.5 (0.25-1.5)	0.5 (0.5-2.0)	0.75 (0.25-3.0)	0.5 (0.25-3.0)	AUC(0-t) (µg.h/mL)	16.1 (24.5)	15.9 (23.9)	16.1 (27.7)	16.2 (25.3)	AUC (µg.h/mL)	16.6 (25.5)	16.4 (25.0)	16.6 (28.7)	16.7 (26.3)	λ_z (1/hr)	0.0751 (15.8)	0.0752 (16.3)	0.0775 (17.0)	0.0765 (16.2)	$t_{1/2}$ (hr)	9.23 (15.8)	9.22 (16.3)	8.94 (17.0)	9.06 (16.2)	CL/F (L/hr)	3.02 (25.5)	3.05 (25.0)	3.02 (28.7)	2.99 (26.3)	V_z/F (L)	40.2 (19.9)	40.6 (17.2)	38.9 (19.7)	39.1 (18.9)
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	<p>Table N01287-2: PK Parameters for 50 mg BRV tablet after a single dose under <i>fasting and fed</i> conditions</p> <table border="1"> <thead> <tr> <th rowspan="2">PK parameters</th> <th colspan="2">GeoMean (GeoCV %)</th> </tr> <tr> <th>BRV 50 mg tablet fasted (N=24)</th> <th>BRV 50 mg tablet fed (N=25)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>1.68 (25.5)</td> <td>1.03 (29.6)</td> </tr> <tr> <td>t_{max} (hr)^(a)</td> <td>0.5 (0.25-3.0)</td> <td>3.0 (0.5-9.0)</td> </tr> <tr> <td>AUC(0-t) (µg.h/mL)</td> <td>16.2 (25.3)</td> <td>15.0 (29.4)</td> </tr> <tr> <td>AUC (µg.h/mL)</td> <td>16.7 (26.3)</td> <td>15.6 (30.1)</td> </tr> <tr> <td>λ_z (1/hr)</td> <td>0.0765 (16.2)</td> <td>0.0762 (16.6)</td> </tr> <tr> <td>t_{1/2} (hr)</td> <td>9.06 (16.2)</td> <td>9.10 (16.6)</td> </tr> <tr> <td>CL/F (L/hr)</td> <td>2.99 (26.3)</td> <td>3.21 (30.1)</td> </tr> <tr> <td>V_z/F (L)</td> <td>39.1 (18.9)</td> <td>42.2 (25.7)</td> </tr> </tbody> </table> <p>^(a) t_{max} (hr): values are median (min-max) GeoCV%: geometric coefficient of variation, N: number of subjects Source data: Table 14.2.1:2</p>	PK parameters	GeoMean (GeoCV %)		BRV 50 mg tablet fasted (N=24)	BRV 50 mg tablet fed (N=25)	C _{max} (µg/mL)	1.68 (25.5)	1.03 (29.6)	t _{max} (hr) ^(a)	0.5 (0.25-3.0)	3.0 (0.5-9.0)	AUC(0-t) (µg.h/mL)	16.2 (25.3)	15.0 (29.4)	AUC (µg.h/mL)	16.7 (26.3)	15.6 (30.1)	λ _z (1/hr)	0.0765 (16.2)	0.0762 (16.6)	t _{1/2} (hr)	9.06 (16.2)	9.10 (16.6)	CL/F (L/hr)	2.99 (26.3)	3.21 (30.1)	V _z /F (L)	39.1 (18.9)	42.2 (25.7)
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<p>PK Results</p>	<p>Table N01287-3: BA Comparison for a 50 mg BRV Tablet After a Single Dose Under <i>Fasting and Fed</i> Conditions</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Treatment Ratio</th> <th>Point Estimate for Ratio</th> <th>90% Confidence Interval</th> <th>ANOVA CV (%)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>fed/ fasting</td> <td>62.56</td> <td>[57.36, 68.23]</td> <td>18.35</td> </tr> <tr> <td>AUC (µg*h/mL)</td> <td>fed/ fasting</td> <td>94.52</td> <td>[89.30, 100.04]</td> <td>11.94</td> </tr> <tr> <td>AUC(0-t) (µg*h/mL)</td> <td>fed/ fasting</td> <td>94.02</td> <td>[88.86, 99.48]</td> <td>11.88</td> </tr> <tr> <td>t_{max} (h)</td> <td>fed/ fasting</td> <td>3.00</td> <td>[2.13, 3.88]</td> <td>NA</td> </tr> </tbody> </table> <p>Fed: brivaracetam 50 mg oral tablet under fed conditions; fasted: brivaracetam 50 mg oral tablet under fed conditions; CV=ANOVA residual error, representing intrasubject variability; PP=Per Protocol Population; Point estimate (90% confidence interval) for the geometric lsmear ratio (%) derived from ANOVA; for t_{max}: median point estimate (90% no parametric confidence interval) of the difference Test-Reference; NA: not applicable</p>	Parameter	Treatment Ratio	Point Estimate for Ratio	90% Confidence Interval	ANOVA CV (%)	C _{max} (µg/mL)	fed/ fasting	62.56	[57.36, 68.23]	18.35	AUC (µg*h/mL)	fed/ fasting	94.52	[89.30, 100.04]	11.94	AUC(0-t) (µg*h/mL)	fed/ fasting	94.02	[88.86, 99.48]	11.88	t _{max} (h)	fed/ fasting	3.00	[2.13, 3.88]	NA				
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PK Results	<p>Table N01287-4: BE Assessment Under Fed Conditions for Single Doses of Oral Solution, Oral Tablet, and Oral Capsules</p> <table border="1"> <thead> <tr> <th>PK Parameter</th> <th>Treatment Ratio</th> <th>Point Estimate for Ratio</th> <th>90% Confidence Interval</th> <th>ANOVA CV (%)</th> </tr> </thead> <tbody> <tr> <td rowspan="5">C_{max} (µg/mL)</td> <td>2 x 25 mg cap/50 mg sol</td> <td>101.0</td> <td>[92.47, 110.3]</td> <td rowspan="5">18.35</td> </tr> <tr> <td>50 mg cap/50 mg sol</td> <td>96.57</td> <td>[88.43, 105.5]</td> </tr> <tr> <td>50 mg tab/50 mg sol</td> <td>103.4</td> <td>[94.60, 113.0]</td> </tr> <tr> <td>2x25 mg cap/50 mg tab</td> <td>97.68</td> <td>[89.57, 106.5]</td> </tr> <tr> <td>50 mg cap/50 mg tab</td> <td>93.41</td> <td>[85.65, 101.9]</td> </tr> <tr> <td rowspan="5">AUC (µg.h/mL)</td> <td>2 x 25 mg cap/ 50 mg sol</td> <td>100.2</td> <td>[94.59, 106.1]</td> <td rowspan="5">11.94</td> </tr> <tr> <td>50 mg cap/50 mg sol</td> <td>101.3</td> <td>[95.66, 107.3]</td> </tr> <tr> <td>50 mg tab/50 mg sol</td> <td>100.7</td> <td>[95.00, 106.7]</td> </tr> <tr> <td>2x25 mg cap/50 mg tab</td> <td>99.52</td> <td>[94.03, 105.3]</td> </tr> <tr> <td>50 mg cap/50 mg tab</td> <td>100.6</td> <td>[95.10, 106.5]</td> </tr> <tr> <td rowspan="5">AUC(0-t) (µg.h/mL)</td> <td>2 x 25 mg cap/ 50 mg sol</td> <td>100.1</td> <td>[94.51, 106.0]</td> <td rowspan="5">11.88</td> </tr> <tr> <td>50 mg cap/50 mg sol</td> <td>101.5</td> <td>[95.82, 107.5]</td> </tr> <tr> <td>50 mg tab/50 mg sol</td> <td>100.8</td> <td>[95.14, 106.8]</td> </tr> <tr> <td>2x25 mg cap/50 mg tab</td> <td>99.30</td> <td>[93.85, 105.1]</td> </tr> <tr> <td>50 mg cap/50 mg tab</td> <td>100.7</td> <td>[95.10, 106.5]</td> </tr> <tr> <td rowspan="5">t_{max} (hr)</td> <td>2 x 25 mg cap - 50 mg sol</td> <td>0.44</td> <td>[0.25 - 0.88]</td> <td rowspan="5">NA^(a)</td> </tr> <tr> <td>50 mg cap - 50 mg sol</td> <td>0.38</td> <td>[0.25 - 0.50]</td> </tr> <tr> <td>50 mg tab - 50 mg sol</td> <td>0.25</td> <td>[0.14 - 0.38]</td> </tr> <tr> <td>2x25 mg cap - 50 mg tab</td> <td>0.13</td> <td>[-0.14 - 0.48]</td> </tr> <tr> <td>50 mg cap - 50 mg tab</td> <td>0.15</td> <td>[-0.13 - 0.36]</td> </tr> </tbody> </table> <p>2x25 mg cap: brivaracetam 2x25 mg oral capsules, 50 mg sol: brivaracetam 50 mg oral solution, 50 mg cap: brivaracetam 50 mg oral capsule, 50 mg tab: brivaracetam 50 mg oral tablet; CV=ANOVA residual error, representing intra-subject variability; PP=Per Protocol Population; Point estimate (90% confidence interval) for the geometric lsmear ratio (%) derived from ANOVA, for t_{max}: median point estimate (90% non-parametric confidence interval) of the difference Test-Reference</p>	PK Parameter	Treatment Ratio	Point Estimate for Ratio	90% Confidence Interval	ANOVA CV (%)	C_{max} (µg/mL)	2 x 25 mg cap/50 mg sol	101.0	[92.47, 110.3]	18.35	50 mg cap/50 mg sol	96.57	[88.43, 105.5]	50 mg tab/50 mg sol	103.4	[94.60, 113.0]	2x25 mg cap/50 mg tab	97.68	[89.57, 106.5]	50 mg cap/50 mg tab	93.41	[85.65, 101.9]	AUC (µg.h/mL)	2 x 25 mg cap/ 50 mg sol	100.2	[94.59, 106.1]	11.94	50 mg cap/50 mg sol	101.3	[95.66, 107.3]	50 mg tab/50 mg sol	100.7	[95.00, 106.7]	2x25 mg cap/50 mg tab	99.52	[94.03, 105.3]	50 mg cap/50 mg tab	100.6	[95.10, 106.5]	AUC(0-t) (µg.h/mL)	2 x 25 mg cap/ 50 mg sol	100.1	[94.51, 106.0]	11.88	50 mg cap/50 mg sol	101.5	[95.82, 107.5]	50 mg tab/50 mg sol	100.8	[95.14, 106.8]	2x25 mg cap/50 mg tab	99.30	[93.85, 105.1]	50 mg cap/50 mg tab	100.7	[95.10, 106.5]	t_{max} (hr)	2 x 25 mg cap - 50 mg sol	0.44	[0.25 - 0.88]	NA ^(a)	50 mg cap - 50 mg sol	0.38	[0.25 - 0.50]	50 mg tab - 50 mg sol	0.25	[0.14 - 0.38]	2x25 mg cap - 50 mg tab	0.13	[-0.14 - 0.48]	50 mg cap - 50 mg tab	0.15	[-0.13 - 0.36]
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PK Results	<p>BE Conclusions:</p> <ol style="list-style-type: none"> In fasted state, PK parameters and PK profiles were similar for all 4 treatment arms (50 mg solution, 50 mg capsule, 2 x 25 mg capsule, and 50 mg tablet) Bioequivalence of capsules (2x25 mg and 50 mg) vs. solution, tablet vs. solution, capsules (2x25 mg and 50 mg) vs. tablet can be concluded. <p>Food Effect Conclusions:</p> <ol style="list-style-type: none"> Food intake reduced C_{max} by 37% and delayed t_{max} by 3.0 hours. Food intake did not significantly affect AUC, AUC_{0-t}, or other PK parameters 																																																																									
Safety	<p>Assessments: AEs, physical examination, vital signs, ECG, laboratory tests</p> <p>Results: 96% of subjects experienced a TEAE. Dizziness, somnolence, asthenia were the most commonly-reported. All TEAEs were mild (except for two TEAEs not-related to study drug). All AEs were resolved by the end of the study. No SAEs were reported, and none of the reported TEAEs led to treatment discontinuation.</p>																																																																									
Sponsor's Conclusions	<ol style="list-style-type: none"> The four formulations were BE. Food (high-fat meal) reduced rate of absorption 37% but did not affect absorption extent of 50 mg tablet. AEs observed during this study were consistent with AEs usually reported for BRV Brivaracetam was well safe and well-tolerated 																																																																									
Reviewer Comment	<p>BE Assessments:</p> <ol style="list-style-type: none"> The C_{max}, AUC, AUC_{0-t} BE comparisons among the arms (of capsules [2x25 mg and 50 mg] vs. solution, tablet vs. solution, capsules [2x25 mg and 50 mg] vs. tablet) support BE among the 4 arms (the 90% CI was contained in the no-effect boundaries for all comparisons). Among the formulations compared for the BE assessments, t_{max} typically differed 																																																																									

	<p>by 30 minutes (and up to 1 hour when comparing capsules to oral solution). The difference in T_{max} is not likely to result in a clinically significant reduction of safety or efficacy.</p> <p>Food Effect Assessments:</p> <ol style="list-style-type: none"><li data-bbox="342 323 1477 422">3. The key effects of food are a 37% decrease in C_{max} and a 3 hour delay in t_{max} after a single 50 mg BRV tablet. Based on the exposure-response analyses, BRV tablets can be administered without regard to food.<li data-bbox="342 422 1477 556">4. The safety profile is consistent with other BRV studies. No new safety signals were observed. The safety profile for this trial supports single-dose administration of BRV tablets with or without food intake. The safety profile is supportive of single 50 mg doses of oral solution, 1 x 50 mg capsule, and 2 x 25 mg capsules.
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4.4.33 N01296: BE of Oral Tablet and Oral Solution

Study Report#	Protocol RPCE07E3112 / Study N01296																				
Title	Randomized, monocenter, open-label, two-way cross-over, single dose bioequivalence study of two different formulations of brivaracetam in healthy fasting subjects.																				
Objectives	<u>Primary:</u> Compare BA of (b) (4)% BRV solution (test) vs BRV 50 mg tablet (ref) <u>Secondary:</u> Assess safety and tolerability of BRV oral solution																				
Study Design	Randomized, single-center, open-label, two-way crossover BA study																				
Duration	Two administrations of a single dose, separated by at least 1 week. PK samples occur for up to 36 hours.																				
Dosage and Administration	Subjects received a single dose of 50 mg (b) (4)% (10 mg/ml) BRV solution (test) and a single dose of 50 mg BRV oral film-coated tablet (reference). Subjects received the two treatments in a random order and separated by a 7-day washout period.																				
PK Assessment	<u>Plasma Samples:</u> pre-dose, 15, 30, 45 minutes, and 1, 1.5, 2, 3, 6, 9, 12, 24, and 36 hours post dose. <u>Analyses:</u> C _{max} , AUC _{0-t} , AUC, t _{max} , λ _z , t1/2, CL/F, V _z /F. BE was based upon the 90% CI of the log-transformed geometric mean ratio (GMR) for C _{max} , AUC _{0-t} , AUC. BE for test-vs-reference was assessed using 0.8-1.25 no-effect boundaries.																				
Bioanalytical Methods	<p style="text-align: center;">HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>2, 5, 50, 200, 600, 1200, 1800, 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-2.4 to 2.0%</td> </tr> <tr> <td>Standards precision</td> <td>1.8 to 5.3%</td> </tr> <tr> <td>QC concentrations</td> <td>6, 75, 1600 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-1.9 to 3.9%</td> </tr> <tr> <td>QC Precision</td> <td>5.4 to 6.0%</td> </tr> <tr> <td>LLOQ</td> <td>2 ng/mL</td> </tr> </table> <p>[Reviewer comment: The BRV plasma assay is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	2, 5, 50, 200, 600, 1200, 1800, 2000 ng/mL	Standards accuracy	-2.4 to 2.0%	Standards precision	1.8 to 5.3%	QC concentrations	6, 75, 1600 ng/mL	QC Accuracy	-1.9 to 3.9%	QC Precision	5.4 to 6.0%	LLOQ	2 ng/mL
Analyte Name	Brivaracetam																				
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QC concentrations	6, 75, 1600 ng/mL																				
QC Accuracy	-1.9 to 3.9%																				
QC Precision	5.4 to 6.0%																				
LLOQ	2 ng/mL																				
Population/ Demographics	N=24 healthy male and female subjects age 18 to 55 years <u>Inclusion Criteria:</u> <ol style="list-style-type: none"> 1. Male or female subjects age 18 to 55 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 5. Females must use adequate birth control <u>Exclusion Criteria:</u> <ol style="list-style-type: none"> 1. Female subjects must not be pregnant or lactating 2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness 4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical 																				

- trial
5. Use of any hepatic enzyme inducing drug within 2 months before the first administration,
 6. Heavy caffeine drinker (drinking >5 cups of coffee, tea, etc. per day),
 7. Current smoker or had given up smoking in the last 6 months

PK Results

Figure N01296-1: Geometric Mean PK Profiles for 50 mg oral solution and 50 mg oral tablet

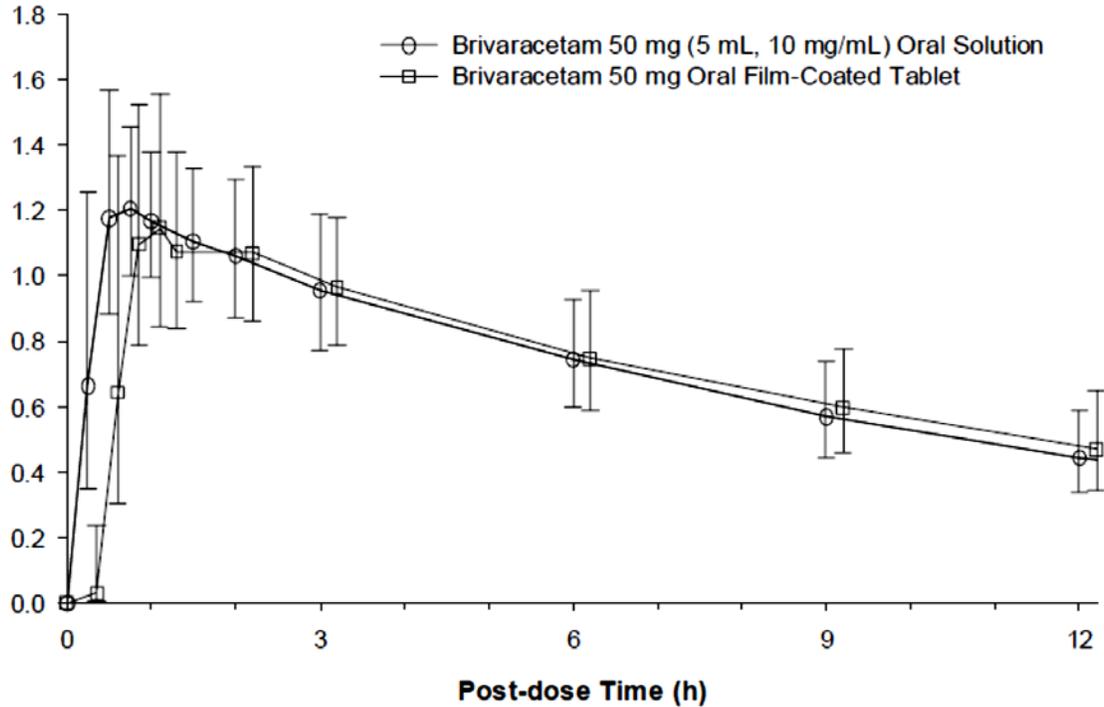


Table N01296-1: Geometric Mean (%CV) PK Parameters for 50 mg oral solution and 50 mg oral tablet

Parameters (Units)	Geometric mean ^(b) (geometric CV [%] BRV=brivaracetam; CV=coefficient of variation; PP=per protocol ^(a))	
	Reference BRV oral film-coated tablet N=24	Test: BRV oral solution N=24
C _{max} (µg/mL)	1.32 (18.1)	1.39 (21.1)
t _{max} (h) ^(b)	1.00 (0.25-3.00)	0.63 (0.25-2.00)
AUC(0-t) (µg*h/mL)	14.6 (28.5)	14.4 (25.7)
AUC (µg*h/mL)	15.6 (31.6)	15.3 (28.7)
λ _z (1/h)	0.07724 (19.4)	0.07929 (19.5)
t _{1/2} (h)	8.97 (19.4)	8.74 (19.5)
CL/F (L/h)	3.20 (31.6)	3.25 (28.5)
V _z /F (L)	41.4 (19.2)	40.9 (14.3)

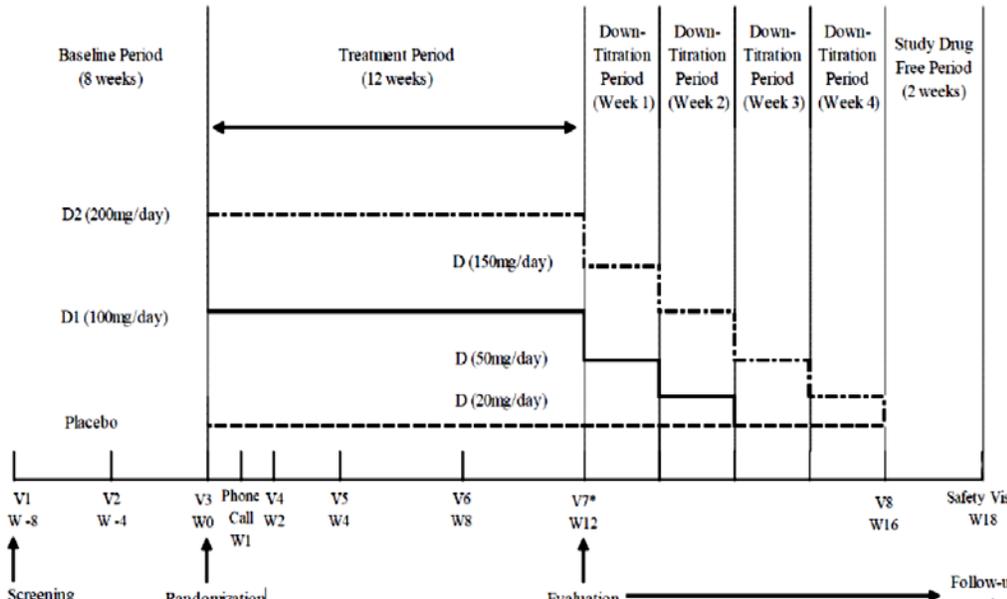
BRV=brivaracetam; CV=coefficient of variation; PP=per protocol

^(a) Geometric CV (%) = 100 x sqrt (exp [SD²]-1), where SD is the standard deviation of the log-transformed data

^(b) for t_{max} median (range) was used

	Table N01296-2: BE Assessment for 50 mg oral solution and 50 mg oral tablet					
	Parameter (Unit)	Test ^(a) BRV oral solution	Reference ^(a) BRV oral tablet	CV (%) ^(b)	Test / Reference ^(c)	
					Point estimate	90% CI
	AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)	15.3 (13.5; 17.4)	15.6 (13.8; 17.8)	4.01	98.15	(96.22; 100.12)
	AUC(0-t) ($\mu\text{g}\cdot\text{h}/\text{mL}$)	14.4 (12.8; 16.1)	14.6 (13.0; 16.3)	4.07	98.89	(96.91; 100.90)
	C _{max} ($\mu\text{g}/\text{mL}$)	1.39 (1.28; 1.51)	1.32 (1.22; 1.43)	13.0	105.72	(99.16; 112.71)
	t _{max} (h)	0.63 (0.25; 2.00)	1.00 (0.25; 3.00)	NC	-0.25	(-0.50; -0.13)
	BRV=brivaracetam; CI=confidence interval; CV=coefficient of variation; NC=not computed; PP=per protocol (a) Geometric least squares mean (95% confidence interval); for t _{max} : median (min-max) (b) CV (%): ANOVA residual error, representing intra-subject variability (c) Point estimate (90% confidence interval) for the Test/Reference geometric least squares mean ratio (%) derived from ANOVA; for t _{max} : median point estimate (90% nonparametric confidence interval) of the difference Test-Reference (h)					
Safety	<p><u>Assessments:</u> AEs, physical examinations, vital signs, ECG, laboratory tests</p> <p><u>Results:</u> 83% of subject's experienced a TEAE with fatigue (62.5%), dizziness (41.7%), somnolence (41.7%), feeling drunk (16.7%), nausea (12.5%) and blurred vision (8.3%) being most common. No severe or serious AEs or deaths were reported. No clinically relevant changes in laboratory or ECGs parameters were observed. AE profile was comparable to that observed in study N01287 (which used the same dose). The two formulations had a comparable AE profile.</p>					
Sponsor's Conclusions	<p><u>PK Conclusions:</u></p> <ol style="list-style-type: none"> Geometric mean BRV concentration profiles and PK parameters were similar between tablet and oral solution. Tmax occurred 30 minutes earlier for the oral solution than for the oral tablets. Single doses of 50 mg BRV tablets and 50 mg oral solution are bioequivalent in terms of C_{max}, AUC_{0-t}, and AUC. <p><u>Safety conclusions:</u> The single doses of both treatments were well tolerated and safe in this study.</p>					
Reviewer Comment	<p><u>PK Conclusions:</u> The reviewer concurs with the Sponsor's PK conclusions.</p> <p><u>Safety conclusions:</u> This study is supportive of single-doses of 50 mg oral solution or a 50 mg oral tablet use.</p>					

4.4.34 N01358: Efficacy – 100, 200 mg/day – No LEV (Phase 3)

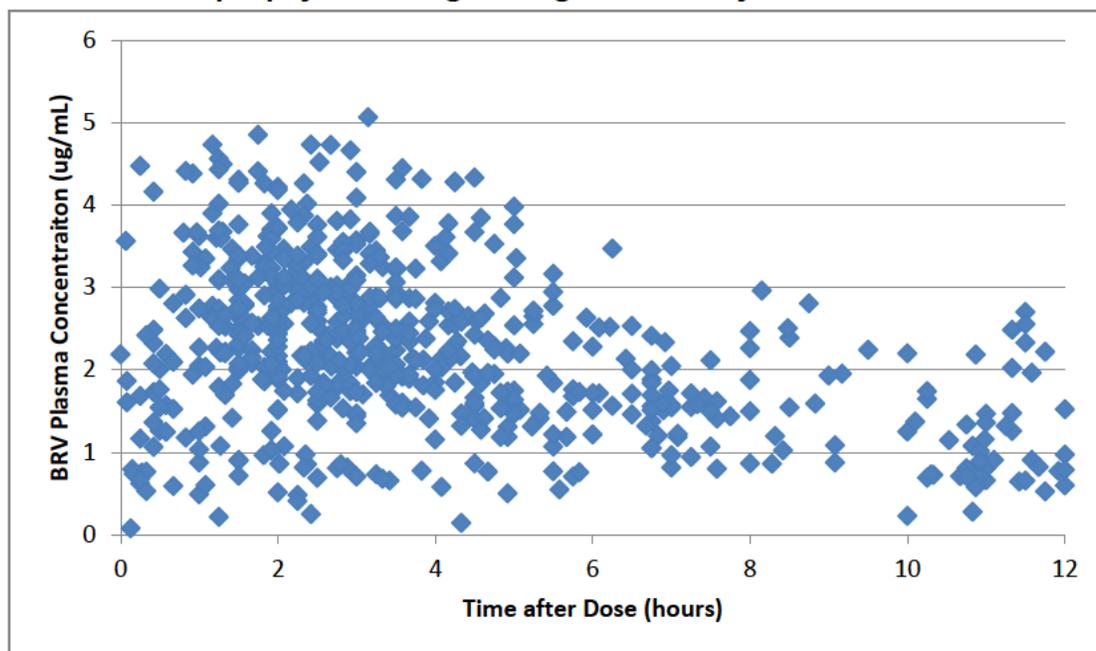
Study Report#	NCT01261325 / N01358
Title	A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of brivaracetam in subjects (≥ 16 to 80 years old) with partial-onset seizures
Objectives	<p><u>Primary:</u> Assess efficacy of 100 and 200 mg/day BRV in POS epilepsy patients</p> <p><u>Secondary:</u> Safety and tolerability</p> <p><u>Exploratory:</u> patient quality of life, self-reported health status</p>
Study Design	International, double-blind, parallel-group, placebo-controlled, randomized, phase 3 confirmatory study
Duration	26 weeks, 16-week exposure to BRV (8 week baseline period, 12-week treatment period, 4-week down titration period, 2-week study)
Dosage and Administration	<p>After an 8 week baseline period, subjects were randomized 1:1:1 to placebo, BRV 100, or 200 mg/day as oral tablets administered BID (2 equal intakes administered twice daily). Subjects were randomized to the full dose without a titration and were treated for 12 weeks.</p> <p>Subjects were stratified by country, previous LEV use (never used LEV vs. prior use of LEV), and number of AEDs previously used but discontinued prior to study entry (≤ 2 versus > 2 AEDs).</p>  <p>The diagram illustrates the study timeline. It is divided into three main phases: a Baseline Period (8 weeks) from V1 (W-8) to V3 (W0), a Treatment Period (12 weeks) from V3 (W0) to V7* (W12), and a Down-Titration Period (Week 1-4) from V7* (W12) to V8 (W16). The Treatment Period is further divided into four Down-Titration Periods (Week 1, Week 2, Week 3, Week 4). Dosages are shown for three groups: D2 (200mg/day), D1 (100mg/day), and Placebo. The D2 group starts at 200mg/day and titrates down to 150mg/day by Week 1, then to 100mg/day by Week 2, 50mg/day by Week 3, and 20mg/day by Week 4. The D1 group starts at 100mg/day and titrates down to 50mg/day by Week 1, then to 20mg/day by Week 2. The Placebo group remains at 0mg/day throughout. Visits are marked at V1 (W-8), V2 (W-4), V3 (W0), V4 (W2), V5 (W4), V6 (W8), V7* (W12), V8 (W16), and Safety Visit (W18). Key events include Screening at V1, Randomization at V3, and Evaluation at V7*. The study ends with a Safety Visit at W18.</p>
PK Assessment	<p><u>Plasma Samples for BRV:</u></p> <ul style="list-style-type: none"> One blood sample per visit was obtained for BRV from Visit 3 onwards. For Visit 4, 5, 6, 7 or early discontinuation visit (EDV [in case the subject exits the study prematurely]), the investigator collected samples at different times postdose to cover the 0 to 12 hour dosing interval (for example, between 0 to 2 hours postdose, 2 to 4 hours postdose, 4 to 8 hours postdose, and 8 to 12 hours postdose). <p><u>Plasma Samples for Co-Meds:</u> Visit 1, 3, 5, 7 or at the EDV</p> <p><u>PK Analyses:</u> The PK data were included in the population PK analyses.</p>

<p>Bioanalytical Methods</p>	<p>HPLC-MS/MS Analytical Methods for BRV Plasma Concentrations</p> <table border="1" data-bbox="495 210 1339 682"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>5, 10, 20, 40, 80, 200, 450, 500 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-8.1 to 6.2%</td> </tr> <tr> <td>Standards precision</td> <td>< 5.1%</td> </tr> <tr> <td>QC concentrations</td> <td>15, 50, 400 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-5.8 to 7.2%</td> </tr> <tr> <td>QC Precision</td> <td>< 7.1%</td> </tr> <tr> <td>LLOQ</td> <td>10 ng/mL</td> </tr> </table> <p>[Reviewer comment: The assay is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	5, 10, 20, 40, 80, 200, 450, 500 ng/mL	Standards accuracy	-8.1 to 6.2%	Standards precision	< 5.1%	QC concentrations	15, 50, 400 ng/mL	QC Accuracy	-5.8 to 7.2%	QC Precision	< 7.1%	LLOQ	10 ng/mL
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LLOQ	10 ng/mL																				
<p>Population/ Demographics</p>	<p>n=768 patients with epilepsy with POS (n=263 received placebo, n=254 received BRV 100 mg/day, and n=251 received BRV 200 mg/day)</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 5. Male and female patients with epilepsy age 16 to 80 years 6. Focal epilepsy or epileptic syndrome, history of partial onset seizures 7. Refractory while receiving 1 or 2 co-AEDs (Vagal nerve stimulation allowed, but not counted as a co-AED) stable for 1 month (3 months for phenobarbital and primidone) before V1. Benzodiazepine (BZD) taken more than once a week (for any indication) was considered as a concomitant AED. 8. Females of childbearing potential must use acceptable birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 9. Current or previous use of felbamate within 18 months of visit 1 10. Current use of vigabatrin 11. Use of drugs with possible CNS effects unless stable for 1 month prior to Visit 1 and for whole study period. Benzodiazepines taken more than once/week (for any indication) is considered as a concomitant AED. 12. Use of drugs that influence BRV metabolism (2C or 3A potent inhibitors) unless stable for 1 more before visit 1 and for entire study duration. 13. Impaired hepatic function (ALAT/SGPT, ASAT/SGOT, ALP, GGT > 3 x ULN) 14. Creatinine CL < 50 mL/min 15. Clinically significant ECG abnormalities 16. Pregnant/lactating women 17. Current use of levetiracetam 18. Use of levetiracetam within 90 days prior to visit 1 																				
<p>PK Results</p>	<p>The population pharmacokinetics (PK) of brivaracetam (BRV) in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358)</p> <p>Concomitant administration of carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB) could result in 34.8%, 26.8%, and 23.9% increase in mean BRV clearance and correspondingly 26%, 21%, and 19% decrease in BRV plasma concentration, respectively.</p>																				

	<p>the sponsor's proposal of no dose adjustment for these three concomitant AEDs is acceptable since the changes in BRV exposure when co-administrated with CBZ, PHT, or PB are all less than 30% and the exposure-response relationship for efficacy does not warrant a dose adjustment.</p> <p>[Reviewer comment: For additional details, please refer to the pharmacometric review section.]</p>																								
Efficacy	<p>Table N01358-1: Percent Reduction over PBO in the 28-day adjusted POS Frequency</p> <table border="1" data-bbox="365 514 1453 814"> <thead> <tr> <th>Statistics</th> <th>PBO N=259</th> <th>BRV 100mg/day N=252</th> <th>BRV 200mg/day N=249</th> </tr> </thead> <tbody> <tr> <td>Number of subjects analyzed</td> <td>259</td> <td>252</td> <td>249</td> </tr> <tr> <td>Back-transformed LS means</td> <td>9.2</td> <td>6.9</td> <td>6.8</td> </tr> <tr> <td>Percent reduction over PBO</td> <td>-</td> <td>22.8</td> <td>23.2</td> </tr> <tr> <td>95% CI (LL, UL)</td> <td>-</td> <td>(13.3, 31.2)</td> <td>(13.8, 31.6)</td> </tr> <tr> <td>p-value^a</td> <td>-</td> <td><0.001*</td> <td><0.001*</td> </tr> </tbody> </table>	Statistics	PBO N=259	BRV 100mg/day N=252	BRV 200mg/day N=249	Number of subjects analyzed	259	252	249	Back-transformed LS means	9.2	6.9	6.8	Percent reduction over PBO	-	22.8	23.2	95% CI (LL, UL)	-	(13.3, 31.2)	(13.8, 31.6)	p-value ^a	-	<0.001*	<0.001*
Statistics	PBO N=259	BRV 100mg/day N=252	BRV 200mg/day N=249																						
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95% CI (LL, UL)	-	(13.3, 31.2)	(13.8, 31.6)																						
p-value ^a	-	<0.001*	<0.001*																						
Safety	<ul style="list-style-type: none"> • TEAE rate was 59.4%, 68.4%, and 66.8% in the PBO, 100 mg/day, and 200 mg/day groups. • The majority of TEAEs were mild or moderate • Somnolence, dizziness, fatigue, and headache were the most common TEAEs • Somnolence, dizziness, and fatigue were more common in the BRV group (18.1, 12.3%, 9.5%) compared to the PBO group, (7.7%, 5.0%, 3.8%). • Headache occurred in 7.4% and 8.4% of PBO and BRV groups. • Dizziness and fatigue were more common in the 200 mg group (14.4% and 11.6%) than the 100 mg group (10.3% and 7.5%). 																								
Sponsor's Conclusions	<ul style="list-style-type: none"> • BRV 100 mg/day and 200 mg/day showed clinically relevant and statistically significant reduction in POS in USA and EU • Secondary efficacy analyses support BRV efficacy in POS patients • BRV 100 mg/day and 200 mg/day were well-tolerated when administered as an adjunctive therapy in the POS adult population • The most commonly reported TEAEs somnolence, dizziness, fatigue, and headache 																								

Reviewer
Comment

Figure N01358-2: Scatter Plot of Steady-State BRV Plasma Concentrations in Patients with Epilepsy Receiving 200 mg BID in Study N01358



The PK variability is broad, but peak BRV plasma concentrations appear to be no more than approximately 5 $\mu\text{g}/\text{mL}$ at steady-state (5.3 $\mu\text{g}/\text{mL}$ is the maximum concentration reported).

Exposure-Response analyses for efficacy suggest that increasing the dose beyond 200 mg/day is not likely to result in a clinically significant increase in efficacy.

4.4.35 EP0007: BE of Commercial and Oral Tablets, BA of Tablet and IV Bolus (Phase 1)

Study Report#	EP0007
Title	A randomized, single-center, open-label, 5-way crossover, single-dose bioavailability/bioequivalence comparison of brivaracetam oral tablets (10 mg, 50 mg, 75 mg, and 100 mg) and brivaracetam intravenous bolus injection (100 mg) in healthy volunteers
Objectives	<i>Primary:</i> Assess BE of commercial formulation BRV 10, 75, and 100 mg (test) to clinical development formulation BRV 50 mg (reference) under fasted conditions <i>Secondary:</i> Assess BA of BRV 100 mg 2-minute IV bolus versus BRV 100 mg and 50 mg oral tablets under fasted conditions
Study Design	Randomized, single-center, open-label, 5-way crossover BE/BA study (5-way Latin Square design)
Duration	59 days (9 weeks) for each subject
Dosage and Administration	<u>Commercial Formulation:</u> 10, 75, or 100 mg BRV tablets, 100 mg BRV IV bolus <u>Clinical development Formulation:</u> 50 mg BRV tablet Each of 5 Treatment Periods consisted of 3 days during which similar assessments were conducted. Subjects check into the clinical the afternoon prior to the day of BRV administration. The next day, a BRV oral tablet, or a 2-minute IV bolus BRV injection was administered in the morning. The injection as administered using a syringe and slow push (10 mL of a 10 mg/mL solution). Each dose level for the tablet administrations was administered as a single tablet. Following BRV administration, subjects were observed for up to 48 hours after which they were discharged. A wash-out period of a last 7 days separated subsequent drug administrations. Final discharge took place between day 3 and Day 11 of the final Treatment Period.
PK Assessment	<u>Plasma samples:</u> Predose, 5, 15, and 30 minutes, and 1, 1.5, 2, 3, 6, 9, 12, 24, 36, and 48 hours postdose. <u>PK Parameters:</u> C_{max} , C_{max} normalized to the 50 mg reference treatment ($C_{max,norm}$), AUC_{0-t} , $AUC_{0-t,norm}$, $AUC_{0-\infty}$, $AUC_{0-\infty,norm}$, %AUC extrapolated, $t_{1/2}$, t_{max} , CL/F, V_z/F
Statistical Analysis	$C_{max,norm}$, $AUC_{0-t,norm}$, and $AUC_{0-\infty,norm}$ were analyzed using an NOVA on the logarithmic scale. The model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Point estimates of geometric mean ratios and 90% confidence intervals were derived for each test formulation versus the reference formulation. Bioequivalence was concluded if the 90% CI was within the range of 80.00% and 125.00%. Primary analyses were performed with and without a potency adjustment. The potency adjustment refers to an adjustment to the batch strength formulation as specified in the batch release certificate. Potency adjustment correction was performed before dose normalization. For example: $AUC_{corr} = AUC \times (\%potency)/(100\%)$ $AUC_{corr,norm} = AUC_{corr} \times 50 \text{ m} / D$ (where D is nominal dose in mg)

<p>Bioanalytical Methods</p>	<p style="text-align: center;">HPLC-MS/MS Analytical Methods for <i>Plasma</i> Concentrations</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>2.00, 5.00, 50.0, 200, 600, 1200, 1800 and 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-2.0 to 2.5%</td> </tr> <tr> <td>Standards precision</td> <td>0.8 to 5.5%</td> </tr> <tr> <td>QC concentrations</td> <td>6.00, 75.0 and 1600 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>0.6 to 2.7%</td> </tr> <tr> <td>QC Precision</td> <td>1.5 to 4.0%</td> </tr> <tr> <td>LLOQ</td> <td>2.00 ng/mL</td> </tr> </table>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	2.00, 5.00, 50.0, 200, 600, 1200, 1800 and 2000 ng/mL	Standards accuracy	-2.0 to 2.5%	Standards precision	0.8 to 5.5%	QC concentrations	6.00, 75.0 and 1600 ng/mL	QC Accuracy	0.6 to 2.7%	QC Precision	1.5 to 4.0%	LLOQ	2.00 ng/mL
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Internal Standard (IS)	(b) (4)																				
Standard curve concentrations	2.00, 5.00, 50.0, 200, 600, 1200, 1800 and 2000 ng/mL																				
Standards accuracy	-2.0 to 2.5%																				
Standards precision	0.8 to 5.5%																				
QC concentrations	6.00, 75.0 and 1600 ng/mL																				
QC Accuracy	0.6 to 2.7%																				
QC Precision	1.5 to 4.0%																				
LLOQ	2.00 ng/mL																				
<p>Population/ Demographics</p>	<p>N=25</p> <p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Male or female subjects age 18 to 55 years 2. Good physical and mental health 3. ECG is normal or abnormal but not clinically significant 4. Laboratory test results are within the reference range 5. Females must use adequate birth control <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Female subjects must not be pregnant or lactating 2. hepatic, renal, gastrointestinal or other disorder that may affect drug ADME or constitute a risk factor when taking the study drug 3. Concomitant or chronic acute illness 4. Any drug treatment, prescription or OTC, within 14 days of first study drug intake (except for paracetamol [acetaminophen] ≤ 2 g/day). Use of drugs during clinical trial 5. Use of any hepatic enzyme inducing drug within 2 months before the first administration, 6. Heavy caffeine drinker (drinking >5 cups of coffee, tea, etc. per day), 7. Use of tobacco products within 60 days prior to first drug administration 																				
<p>Restrictions</p>	<p>Paracetamol (acetaminophen) was permitted up at most every 6 to 8 hours, not exceeding 2 g/day, and with a total of no more than 10 g per 14 days. Subjects were to refrain from consuming grapefruit, grapefruit juice, grapefruit-containing products, and star fruit from 7 days before first drug administration until final discharge. Smoking was prohibited from screening until final discharge.</p>																				

PK Results

Figure EP0007-1: Geometric mean BRV plasma concentration vs Time By Dose

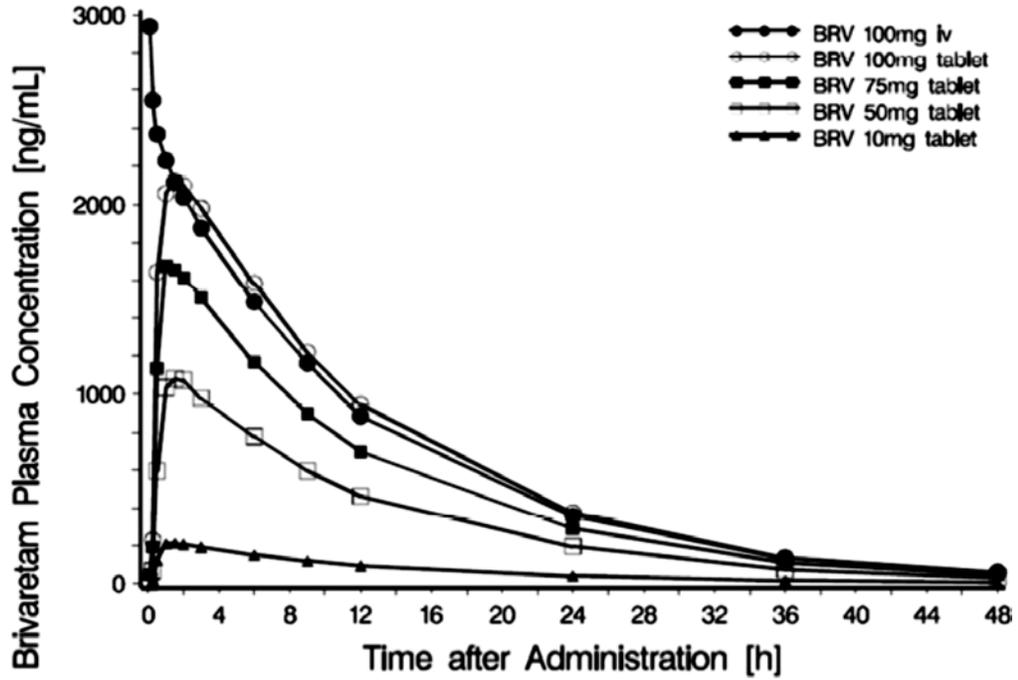


Figure EP0007-2: Geometric mean BRV plasma concentration vs Time By Dose (0 to 6 hours)

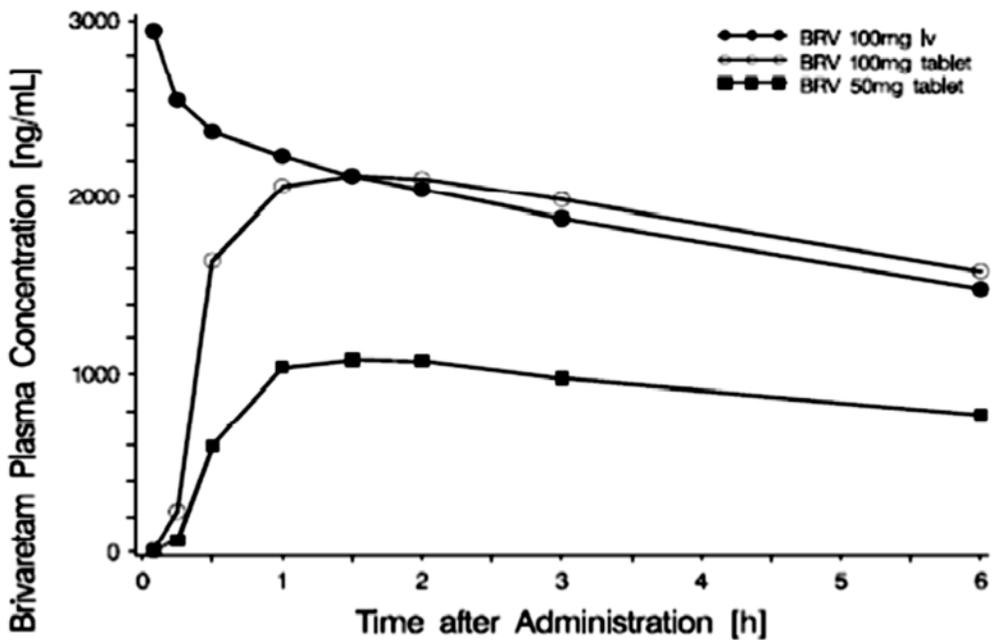


Table EP0007-1: PK Parameters for BRV by Treatment

Parameter (unit)	BRV				
	10mg tablet n=25	50mg tablet n=25	75mg tablet n=25	100mg tablet n=24	100mg iv n=25
	Geometric mean (geometric CV [%])				
AUC (h.ng/mL)	3123 (25.6)	15712 (25.7)	23791 (24.9)	31491 (25.0)	31042 (24.8)
AUC _{norm} (h.ng/mL)	15615 (25.6)	15712 (25.7)	15861 (24.9)	15746 (25.0)	15521 (24.8)
AUC _(0-t) (h.ng/mL)	3015 (24.4)	15227 (24.9)	23099 (24.0)	30652 (24.1)	30193 (23.9)
AUC _{(0-t)norm} (h.ng/mL)	15073 (24.4)	15227 (24.9)	15399 (24.0)	15326 (24.1)	15097 (23.9)
C _{max} (ng/mL)	240 (21.4)	1236 (27.8)	1941 (23.9)	2570 (22.4)	3170 (35.3)
C _{max, norm} (ng/mL)	1198 (21.4)	1236 (27.8)	1294 (23.9)	1285 (22.4)	1585 (35.3)
CL/F (L/h)	3.20 (25.6)	3.18 (25.7)	3.15 (24.9)	3.18 (25.0)	3.22 (24.8)
Vz/F (L)	44.5 (18.7)	42.9 (21.8)	41.9 (20.6)	40.9 (20.0)	42.3 (20.1)
t _{1/2} (h)	9.64 (14.8)	9.34 (12.8)	9.20 (13.0)	8.92 (13.8)	9.11 (13.9)
	Median (range)				
%AUC (%)	2.9 (1.2, 7.1)	2.7 (1.4, 7.3)	2.5 (1.3, 6.9)	2.3 (0.9, 5.5)	2.2 (1.1, 7.5)
t _{max} (h)	1.00 (0.50, 2.00)	1.00 (0.25, 2.00)	1.00 (0.25, 3.00)	1.00 (0.50, 3.00)	0.08 (0.08, 1.50)

*normalized PK parameters were normalized to 50 mg (dose of reference treatment)

[Reviewer comment: Based on the data in the tablet above, the ratio of exposures for 100 mg oral tablets to 100 mg IV based on AUC_{0-∞}, AUC_{norm}, AUC_{0-t} and AUC_{0-tnorm} is approximately 1.014 to 1.015. As such, the absolute oral bioavailability of BRV oral tablets is approximately 100%.]

Table EP0007-2: Results of BA/BE Analyses for Dose-Normalized PK Parameters

Parameter (unit)	Treatment	n	Statistic				
			LS-mean	95% CI	Ratio ^a	Estimate	90% CI
AUC _{norm} (h.ng/mL)	BRV 10mg tablet	25	15615	14096, 17298	10/50	0.9938	0.9728, 1.0153
	BRV 50mg tablet	25	15712	14184, 17405	--	--	--
	BRV 75mg tablet	25	15861	14318, 17570	75/50	1.0094	0.9881, 1.0313
	BRV 100mg tablet	24	15981	14425, 17704	100/50	1.0171	0.9953, 1.0394
	BRV 100mg iv	25	15521	14011, 17194	100iv/100	0.9712	0.9504, 0.9925
					100iv/50	0.9878	0.9669, 1.0092
AUC _{(0-t)norm} (h.ng/mL)	BRV 10mg tablet	25	15073	13667, 16624	10/50	0.9899	0.9695, 1.0107
	BRV 50mg tablet	25	15227	13807, 16794	--	--	--
	BRV 75mg tablet	25	15399	13963, 16984	75/50	1.0113	0.9905, 1.0326
	BRV 100mg tablet	24	15561	14109, 17164	100/50	1.0219	1.0006, 1.0437
	BRV 100mg iv	25	15097	13688, 16650	100iv/100	0.9701	0.9499, 0.9908
					100iv/50	0.9914	0.9710, 1.0123
C _{max, norm} (ng/mL)	BRV 10mg tablet	25	1198	1095, 1310	10/50	0.9693	0.8969, 1.0477
	BRV 50mg tablet	25	1236	1130, 1352	--	--	--
	BRV 75mg tablet	25	1294	1183, 1415	75/50	1.0469	0.9686, 1.1315
	BRV 100mg tablet	24	1306	1192, 1430	100/50	1.0564	0.9764, 1.1429
	BRV 100mg iv	25	1585	1449, 1734	100iv/100	1.2142	1.1222, 1.3136
					100iv/50	1.2826	1.1867, 1.3863

*normalized PK parameters were normalized to 50 mg (dose of reference treatment). The 100 mg IV injection was used as a test treatment against the reference BRV 50 mg and 100 mg tablets

Table EP0007-3: Results of Potency-Adjusted BA/BE Analyses for Dose-Normalized PK Parameters

Parameter (unit)	Treatment	n	Potency (%)	LS-mean	95% CI	Statistic		
						Ratio ^a	Estimate	90% CI
AUC _{corr, norm} (h.ng/mL)	BRV 10mg tablet	25	99.8	15584	14068,17263	10/50	0.9820	0.9612, 1.0033
	BRV 50mg tablet	25	101.0	15869	14325,17579	--	--	--
	BRV 75mg tablet	25	98.0	15543	14031,17218	75/50	0.9795	0.9587, 1.0007
	BRV 100mg tablet	24	100.7	16093	14526,17828	100/50	1.0141	0.9923, 1.0363
	BRV 100mg iv	25	101.6	15769	14235,17469	100iv/100 100iv/50	0.9799 0.9937	0.9589, 1.0014 0.9727, 1.0152
AUC _(0-q) corr, norm (h.ng/mL)	BRV 10mg tablet	25	99.8	15043	13640,16591	10/50	0.9781	0.9580, 0.9987
	BRV 50mg tablet	25	101.0	15380	13945,16962	--	--	--
	BRV 75mg tablet	25	98.0	15091	13684,16644	75/50	0.9813	0.9610, 1.0019
	BRV 100mg tablet	24	100.7	15670	14207,17284	100/50	1.0189	0.9976, 1.0406
	BRV 100mg iv	25	101.6	15338	13907,16916	100iv/100 100iv/50	0.9788 0.9973	0.9584, 0.9997 0.9768, 1.0183
C _{max, corr, norm} (ng/mL)	BRV 10mg tablet	25	99.8	1196	1093,1308	10/50	0.9578	0.8862, 1.0352
	BRV 50mg tablet	25	101.0	1248	1141,1365	--	--	--
	BRV 75mg tablet	25	98.0	1268	1159,1387	75/50	1.0158	0.9399, 1.0979
	BRV 100mg tablet	24	100.7	1315	1201,1440	100/50	1.0532	0.9735, 1.1395
	BRV 100mg iv	25	101.6	1611	1473,1761	100iv/100 100iv/50	1.2250 1.2902	1.1323, 1.3254 1.1937, 1.3945

PK Conclusions

1. T_{max} was about 1.5 hours for 10, 50, 100 mg tablets and 1.0 hours for the 75 mg tablet. Tmax was 0.08 hours for IV administration.
2. Normalized AUC, CL/F, V_z/F were comparable across all BRV doses and routes of administration.
3. The analysis results were similar for the primary PK parameters with and without potency adjustments for the 10, 75, and 100 mg tablet compared with the reference formulation (BRV 50 mg tablet). As the 90% CI was within the 0.8-1.25 no effect boundaries for these comparisons, the results demonstrated BE between the tested strengths of the commercial tablets with the clinical development reference tablet (50 mg tablet).
4. C_{max, norm} was comparable for all oral doses but was greater for the IV bolus.
5. The 10 mg and 50 mg BRV tablets were BE after correcting for measured drug content (in terms of potency).

Safety

1. All TEAEs mild or moderate, no severe TEAEs were reported,
2. TEAEs occurred in 96% of subjects with similar incidence between BRV 50, 75, 100 mg tablets (58.3%) and BRV 100 mg IV (64%). The 10 mg tablet group had There were TEAEs in 44% of subjects in the 10 mg tablet arm.
3. The most common TEAEs were dizziness (52%), fatigue (48%), and headache (36%).
4. TEAEs reported as severe, serious, or leading to subject discontinuation; no deaths occurred

Sponsor's Conclusions

1. The 3 commercial BRV tablets (10, 74, and 100 mg) were BE to the 50 mg BRV clinical development tablet.
2. The 100 mg IV bolus had comparable bioavailability to with the 50 mg and 100 mg tablets in terms of AUC_{norm} (dose-normalized AUC) but had 20% greater C_{max, norm} compared to 50 mg and 100 mg tablets.
3. Single BRV IV doses of 100 mg were generally well-tolerated.

Reviewer Comment

1. The results when adjusting for potency of the release batch are comparable to the results when not adjusting for potency of the batch.
2. The data support the BE of the different tablet strengths, between commercial and clinical development formulation, and between IV and tablets (except for C_{max}).
3. The IV formulations have 30-40% greater C_{max} than the C_{max} after oral tablet administration. As IV brivaracetam will be used in an in-patient setting, and as the adverse events are dizziness, fatigue, and headache, and as the concentrations from IV are only higher than the oral exposure for about 1.5 hours (see Figure EP0007-2), a dose adjustment for IV administration is not necessary.
4. The available safety data support the use of single 100 mg BRV IV bolus doses.

4.4.36 EP0041: DDI Study – Ethanol (Phase 1)

Study Report#	EP0041
Title	A double-blind, randomized, placebo-controlled, three-way crossover study to investigate the drug-drug interactions of brivaracetam and ethanol in healthy male subjects
Objectives	<u>Primary:</u> Assess if BRV alters the psychomotor and cognitive impairment effects of ethanol <u>Secondary:</u> 1. Assess PK interactions between BRV and ethanol 2. Assess safety and tolerability of BRV when co-administered with ethanol
Study Design	single-center, double-blind, randomized, placebo-controlled, 3-way crossover study
Duration	11 weeks (21 days screening, 44 days treatment [including up to 21 days between treatment periods], and follow-up 21 days after Day1 in Period 3)
Dosage and Administration	N=18 healthy male subjects were randomized to receive the following 3 treatments in a randomized order: <i>Treatment A:</i> Ethanol iv infusion+BRV tablets <i>Treatment B:</i> Ethanol PBO iv infusion+BRV tablets <i>Treatment C:</i> Ethanol iv infusion+BRV PBO tablets N=3 subjects were randomized in each of the following 6 treatment sequences: ABC, CAB, BCA, ACB, BAC, and CBA. Brivaracetam was administered as a single oral dose of 200mg as 4 x 50 mg film-coated tablets. Matching placebo film-coated tablets were utilized for Treatment C. Ethanol or ethanol PBO (5% glucose solution) was administered as a 5.5-hour iv clamp (0.5 hours loading phase followed by 5 hours at a steady-state level of 0.6g/L). Ethanol doses of approximately 60g/h for the first 5 minutes and 45g/h during the second 5 minutes. Subsequently, the infusion rate was adjusted based on breath ethanol measurements to maintain breath ethanol levels (and by extension, blood ethanol levels) of 0.6g/L. The legal driving limit is 0.5 g/L in many European countries (et Beek, 2012). Following administration of BRV/BRV PBO, the subjects were observed for approximately 36 hours. There was a washout of 7 to 21 days between treatment periods.
PK Assessment	<u>Plasma Samples - BRV:</u> Pre-dose, 15, 30, 60 minutes, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 36 hours post-dose <u>Plasma Samples - EtOH:</u> same as BRV, but sample is at 10 hours post-dose. <u>PK Analyses:</u> <i>BRV:</i> Cmax, tmax, λz, t1/2, AUC0-t, AUC0-∞. <i>Ethanol:</i> serum ethanol concentrations, breath ethanol concentrations, ethanol total infused dose <i>Ethanol Effect on BRV PK:</i> Sponsor utilized an ANOVA model to assess the effect of ethanol on log-transformed values of BRV Cmax, AUC0-t, and AUC0-∞. Bioequivalence of Treatment A (Ethanol iv infusion+BRV tablets) and Treatment B (Ethanol PBO iv infusion+BRV tablets) was concluded if the 90% CI was contained

<p>Bioanalytical Methods</p>	<p>within the standard 80-125% no-effect boundaries for all 3 PK parameters.</p> <p>Sponsor utilized a commercially-available breathalyzer device for measuring ethanol breath concentration.</p> <p>HPLC-MS/MS Analytical Methods for Plasma Concentrations</p> <table border="1" data-bbox="365 367 1372 793"> <tr> <td>Analyte Name</td> <td>Brivaracetam</td> </tr> <tr> <td>Analyte ID</td> <td>ucb 34714</td> </tr> <tr> <td>Internal Standard (IS)</td> <td>(b) (4)</td> </tr> <tr> <td>Standard curve concentrations</td> <td>10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL</td> </tr> <tr> <td>Standards accuracy</td> <td>-8.5 to 8.0%</td> </tr> <tr> <td>Standards precision</td> <td>3.9 to 6.25%</td> </tr> <tr> <td>QC concentrations</td> <td>25, 150, 1800 ng/mL</td> </tr> <tr> <td>QC Accuracy</td> <td>-7.78% to 2.67%</td> </tr> <tr> <td>QC Precision</td> <td>3.72 to 8.25%</td> </tr> <tr> <td>LLOQ</td> <td>10.0 ng/mL</td> </tr> </table> <p>[Reviewer comment: The assay for brivaracetam is acceptable.]</p>	Analyte Name	Brivaracetam	Analyte ID	ucb 34714	Internal Standard (IS)	(b) (4)	Standard curve concentrations	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL	Standards accuracy	-8.5 to 8.0%	Standards precision	3.9 to 6.25%	QC concentrations	25, 150, 1800 ng/mL	QC Accuracy	-7.78% to 2.67%	QC Precision	3.72 to 8.25%	LLOQ	10.0 ng/mL
Analyte Name	Brivaracetam																				
Analyte ID	ucb 34714																				
Internal Standard (IS)	(b) (4)																				
Standard curve concentrations	10, 20, 45, 100, 200, 450, 1000, 2000 ng/mL																				
Standards accuracy	-8.5 to 8.0%																				
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QC concentrations	25, 150, 1800 ng/mL																				
QC Accuracy	-7.78% to 2.67%																				
QC Precision	3.72 to 8.25%																				
LLOQ	10.0 ng/mL																				
<p>Population/ Demographics</p>	<p>N=18 health male subjects were enrolled, n=17 finished (1 subject withdrew consent)</p> <p><u>Key inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Male subjects age 18 to 55 years of age in good health 2. Cardiovascular assessments (BP, HR, ECG) are free of clinical relevant abnormalities. 3. normal renal and hepatic function as assessed by clinical laboratory test results 4. If having sexual intercourse with female of childbearing potential, both partners must use adequate birth control <p><u>Key exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Subject had received treatment with any prescribed or over-the-counter medications (including herbal medicines such as St John's Wort) within 7 days or 5 half-lives (whichever was longer) prior to Screening. Note: Use of paracetamol (acetaminophen) within this period prior to Screening may have been acceptable, subject to approval by the Investigator. 2. Subject had a history of an average alcohol consumption of more than 21 units of alcohol per week or an average daily intake of greater than 3 units, within 6 months of the study. One unit was equivalent to a half-pint (220mL) of beer or 1 measure (25mL) of spirits or 1 glass (125mL) of wine. 3. Ethanol intolerance 4. History of smoking within 3 months prior to screening consumed any grapefruit, grapefruit juice, grapefruit-containing products, or star fruit within 14 days prior to dosing or was not able to refrain from these products during the course of the study. 5. Presence of disease and/or existence of any surgical or medical condition that, in the opinion of the Investigator, might have interfered with the absorption, distribution, metabolism, or excretion of BRV or ethanol <p><u>Prohibited concomitant medications:</u> With the exception of paracetamol, all prescription or nonprescription medicines, including over-the-counter remedies,</p>																				

vitamins, herbal and dietary supplements (including St. John's Wort) were prohibited within 7 days or 5 half-lives (whichever was longer) before Screening and during the clinical part of the study, unless required to treat an AE.

PK Results

Figure EP0041-1: Geometric Mean (95% CI of Mean) BRV Plasma Concentration Profile With and Without Concomitant Ethanol Administration

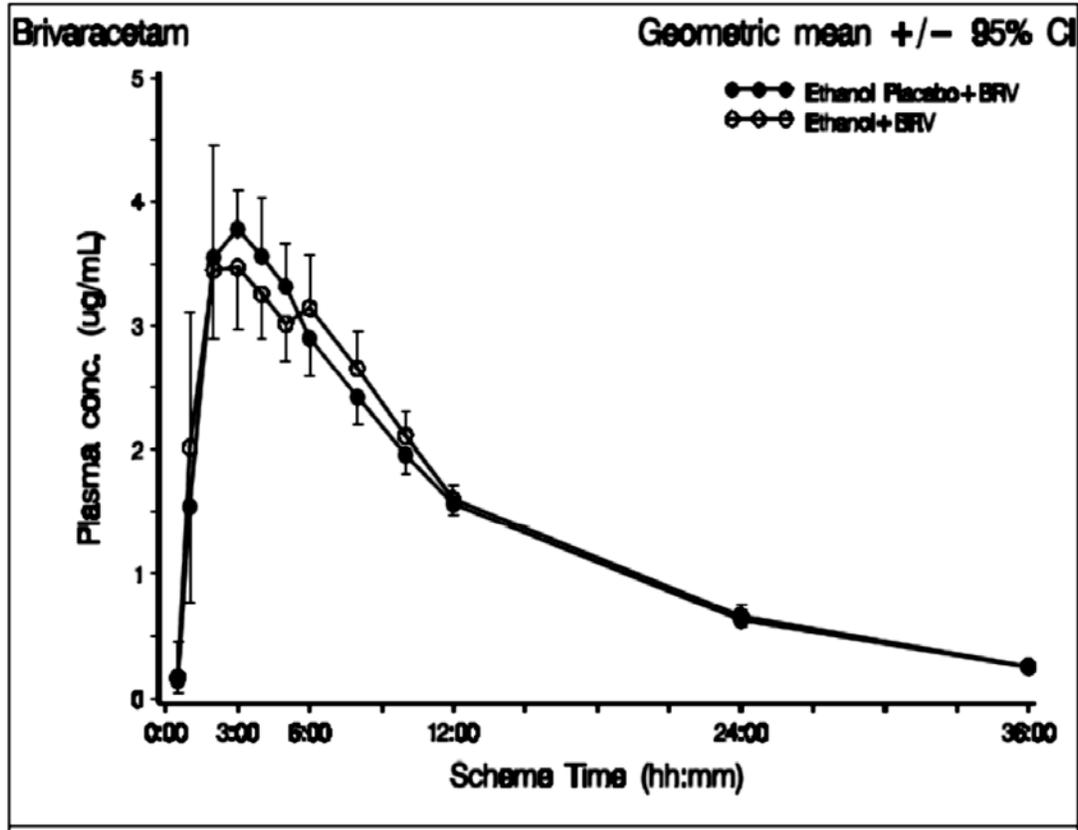


Table EP0041-1: Geometric Mean (%CV) BRV PK Parameters With and Without Concomitant Ethanol Administration

Parameter	BRV N=17	Ethanol + BRV N=16
	Geometric mean (CV%)	
C _{max} (µg/mL)	4.9075 (20.4)	4.3086 (25.9)
t _{max} ^a (h)	2.0000 (1.000 – 6.000)	2.0000 (0.5000 – 8.000)
AUC _(0-∞) (µg.h/mL)	50.435 (9.2)	51.208 (10.9)
AUC (µg.h/mL)	53.805 (10.4)	54.596 (11.2)
CL/F (L/h)	3.7170 (10.4)	3.6633 (11.2)
t _{1/2} (h)	8.9243 (15.1)	8.8315 (13.5)
λ _z (h ⁻¹)	0.077669 (15.1)	0.078488 (13.5)

AUC=area under the plasma concentration-time curve; BRV=brivaracetam; CL/F=clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation; Geo=geometric; λ_z=terminal disposition rate constant; PK=pharmacokinetic; PK-PPS=Pharmacokinetic Per-Protocol Set; t_{1/2}=terminal half-life; t_{max}=time to reach C_{max}
^a T_{max} is reported as median (range).

Table EP0041-2: Bioequivalence Assessment of BRV Exposure With and Without Ethanol

	Back-transformed LSM Test	Back-transformed LSM Reference	Point estimate of ratio (T/R) (%)	90% CI	
				Lower (%)	Upper (%)
AUC (µg.h/mL)	54.8216	53.9676	101.58	98.41	104.85
AUC _(0-∞) (µg.h/mL)	51.5086	50.6324	101.73	98.69	104.86
C _{max} (µg/mL)	4.3689	4.9404	88.4330	78.60	99.50

ANOVA=analysis of variance; AUC=area under the plasma concentration-time curve; BRV=brivaracetam; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; LSM=least squares mean; PK=pharmacokinetic; PK-PPS=Pharmacokinetic Per-Protocol Set; T=test; R=reference

Figure EP0041-2: Bioequivalence Assessment of BRV Exposure With and Without Ethanol

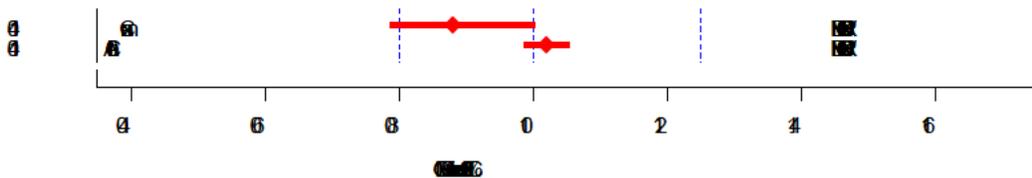


Figure EP0041-3: Geometric Mean (95% CI of Mean) Ethanol Breath Concentration Profile With and Without Concomitant Brivaracetam Administration

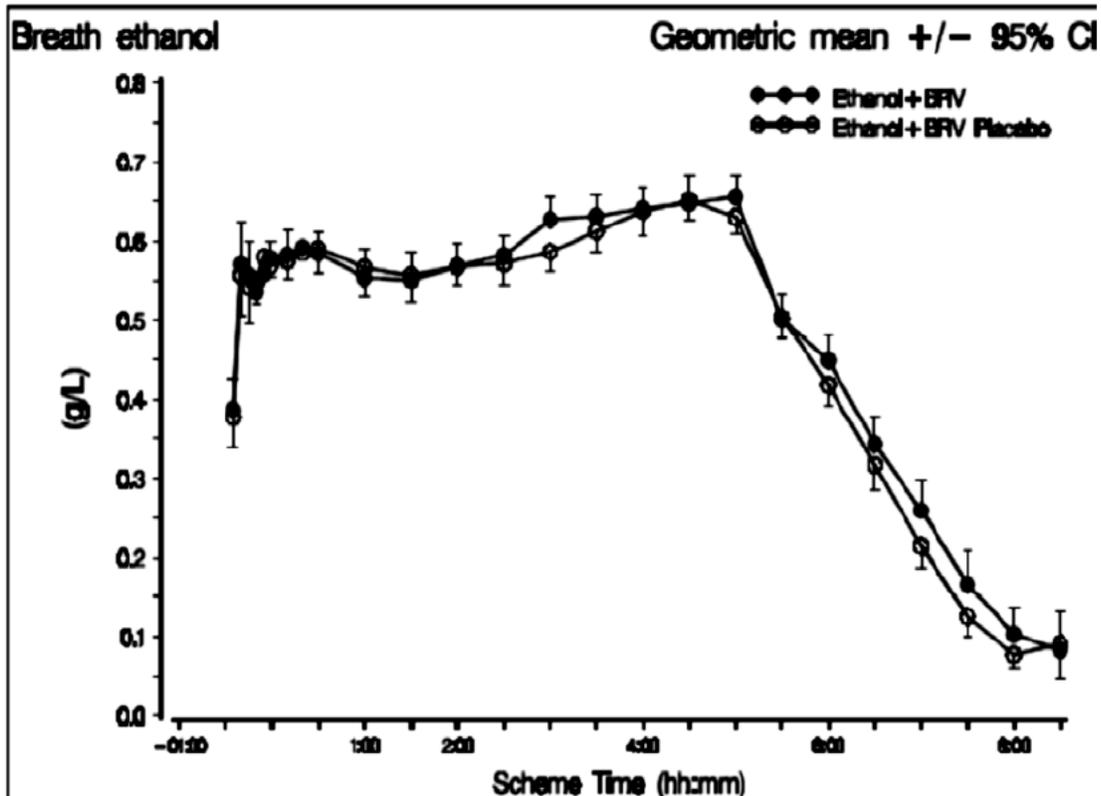


Table EP0041-3: Bioequivalence Assessment of Ethanol Breath Exposure With and Without Brivaracetam					
	Back-transformed LSM Test	Back-transformed LSM Reference	Point estimate of treatment ratio (T/R) (%)	90% CI	
				Lower (%)	Upper (%)
Total ethanol exposure (g)	69.8448	69.5693	100.40	97.75	103.12

Safety	<ul style="list-style-type: none"> The proposition of subjects that reported TEAEs in each arm were: <ul style="list-style-type: none"> 94% in the Ethanol + BRV group, 100% in the Ethanol+ BRV PBO group, 88% in the Ethanol PBO + BRV group The most common TEAEs were somnolence (72%), dizziness (61%), and feeling drunk (56%). The majority of TEAEs were mild, and none were severe
Sponsor's Conclusions	<ul style="list-style-type: none"> Overall tolerability was good and no new safety findings were identified. BRV increases the inebriating effects of ethanol. This increase appears to be additive for all of the measured variables, except for the impairment of adaptive tracking performance which seemed to be supra-additive Brivaracetam did not modify serum or breath ethanol levels nor the total ethanol exposure. Administration of BRV, during constant iv infusion of ethanol compared with administration during constant infusion of saline, did not change the AUC(0-t) and AUC_{0-∞} of BRV (point estimate of the mean ratios: 101.7% and 101.6%, respectively), but a 12% decrease of BRV Cmax was observed.
Reviewer Comment	<ul style="list-style-type: none"> <i>The data suggest that ethanol does not affect single-dose BRV PK, and BRV does not affect single-dose alcohol PK.</i> <i>With the exception of "feeling drunk", the AE profile is comparable with prior BRV studies.</i> <i>Please refer to the review of the medical officer and safety officer for information regarding the interpretation of the psychomotor effects of co-administering BRV with ethanol.</i>

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/s/

MICHAEL A BEWERNITZ
08/07/2015

XINNING YANG
08/18/2015
reviewed in vitro studies

YUXIN MEN
08/31/2015

MEMORANDUM OF CONSULTATION

FROM: Jihong Shon, M.D., Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3 (DCP3), Office of Clinical Pharmacology (OCP)
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, DCP3, OCP

TO: Billy Dunn, MD, Director, Division of Neurology Products
Office of Drug Evaluation I, Office of New Drugs (OND)

SUBJECT: Consultation on the labeling information (Section 12 Pharmacokinetics) regarding the exposure change of hormonal contraceptives following co-administration of brivaracetam

1. BACKGROUND

Brivaracetam is a novel class of anticonvulsant. The proposed indication is the treatment of partial onset seizures in patients 16 years of age and older with epilepsy as an adjunctive therapy (NDA 205836, submission date of November 22, 2014).

The Sponsor proposed the labeling information in the section 12.3 - Pharmacokinetics as follows:

Oral Contraceptives:

Coadministration of TRADENAME (b) (4) (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23%, respectively, without impact on suppression of ovulation.

On May 7, 2015, the Division of Neurology Products (DNP) requested the Division of Bone, Reproductive and Urologic Products (DBRUP) to provide a consultation on whether the decreased exposure of estrogen and progestin in the anticipated dose range (50 to 200mg/day) create a risk for the failure of oral hormonal contraceptive and it would warrant entry of potential risk into labeling.

2. EXECUTIVE SUMMARY

Study N01080 evaluated the effects of multiple dose administration of brivaracetam 400 mg per day (given as 200 mg twice daily) on the multiple dose administration of an oral contraceptive containing ethinyl estradiol (EE) 0.03 mg and levonorgestrel (LNG) 0.15 mg. Coadministration of brivaracetam 200 mg twice daily for 20 days decreased the AUC values of EE and LNG by 27% and 23%, respectively. The C_{max} values of EE and LNG were decreased by 14% and 10%, respectively. There was no ovulation case during the study. Study N021282 evaluated the effects of multiple dose administration of brivaracetam 100 mg per day (given as 50 mg twice daily) on the multiple dose

administration of an oral contraceptive containing EE 0.03 mg and LNG 0.15 mg. Coadministration of brivaracetam 50 mg twice daily for 20 days decreased the AUC values of EE and LNG by 10% and 8%, respectively. The C_{max} values of EE and LNG were decreased slightly (by around 5%). This study did not include a PD evaluation. Based on the results from these two drug-drug interaction (DDI) studies, coadministration of the proposed maximum dose of brivaracetam 200mg with an oral contraceptive containing EE and LNG is anticipated to decrease the exposure of both components less than what was observed with brivaracetam 400 mg per day.

In the integrated summary of safety (ISS), 36 pregnancy cases were reported in the population treated with brivaracetam. Out of them, 11 pregnancy cases used a hormonal contraceptive method. Seven subjects on oral or implant hormone contraceptives also had concomitant treatments with the other antiepileptic drugs which have a metabolic induction potential on hormonal contraceptives. One subject on oral contraceptive did not have any concomitant medication which has an induction potential except for brivaracetam. This result suggests that one may not rule out the possibility that brivaracetam contributes to an efficacy failure of hormonal contraceptives especially when treated concomitantly with other drugs of metabolic enzyme inducers. However, it is difficult to interpret the pregnancy outcome findings as detailed information of these pregnancy cases was not available.

Therefore, the labeling recommendations for section of 12.3 Pharmacokinetics are based on the currently available information and they are:

- 1) Add a brief study design (treatment duration and study population) and include the PK data of C_{max} changes,
- 2) Use a proper name of drug in the description of study (i.e., instead of (b) (4)", state "brivaracetam 200mg twice daily"),
- 3) State that the effect of brivaracetam on hormonal contraceptives containing other progestins has not been evaluated.

Refer to the section 4 in this review for the detailed labeling recommendations.

3. SUMMARY OF THE SUPPORTING MATERIALS

1) DDI studies between brivaracetam and oral contraceptive

(1) The effect of 400 mg brivaracetam per day on the PK and PD of oral contraceptive containing EE and LNG

Title	Randomized, monocenter, open label, two-way crossover, multiple oral dose interaction study between ucb 34714, 200 mg (oral capsule (b) (4) twice daily and oral contraceptive (EE 30 µg and LNG 150 µg) once daily in 24 healthy female volunteers
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Study design	<ul style="list-style-type: none"> 24 healthy premenopausal women (Subjects withdrawn were replaced) Treatments: <ul style="list-style-type: none"> Brivaracetam: 200mg (capsule (b) (4)) at 1 hour after a light breakfast and a standard evening meal for 20 days (400mg per day) EE (30 µg)+LNG (150 µg): one tablet daily at the same hour between 7 AM and 8 AM during 21 days of each menstrual cycle During concomitant treatment period, it was taken together with brivaracetam PK: PK parameters of EE and LNG and brivaracetam on Day 20 CYP3A4 activity using urinary 6β-hydroxycortisol/cortisol ratio PD: luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone (PG) and estradiol (E2) Sex hormone binding globulin (SHBG) Safety: adverse event including bleeding pattern, vital sign, physical exam, laboratory, ECG, etc. 																																																																																				
Results	<p>PK</p> <p>1) EE</p> <table border="1" data-bbox="483 789 1377 1024"> <thead> <tr> <th rowspan="2">Parameter</th> <th rowspan="2">Reference^(a): Oral Contraceptive</th> <th rowspan="2">Test^(a): 200 mg ucb 34714 + Oral Contraceptive</th> <th rowspan="2">CV^(b) (%)</th> <th colspan="2">Test versus Reference^(c)</th> </tr> <tr> <th>Point estimate</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td>C_{max} (pg/mL)</td> <td>102.85 (90.73 - 116.58)</td> <td>88.63 (78.19 - 100.47)</td> <td>17.5</td> <td>86.2</td> <td>78.9 -94.1</td> </tr> <tr> <td>AUCτ (pg*h/mL)</td> <td>1077.13 (948.99 - 1222.58)</td> <td>789.71 (695.76 - 896.35)</td> <td>12.5</td> <td>73.3</td> <td>68.8 - 78.1</td> </tr> <tr> <td>t_{max} (h)</td> <td>2.00 (1.00 - 3.25)</td> <td>1.50 (1.00 - 3.05)</td> <td>NA</td> <td>-0.23</td> <td>-0.50 - 0.25</td> </tr> </tbody> </table> <p>(a) Values are geometric LS means (95% CI), for t_{max}: median (range), (b) Intra-individual coefficient of variation (%), and (c) Point estimate and 90% CI</p> <p>2) LNG</p> <table border="1" data-bbox="461 1129 1365 1365"> <thead> <tr> <th rowspan="2">Parameter</th> <th rowspan="2">Reference^(a): Oral Contraceptive</th> <th rowspan="2">Test^(a): 200 mg ucb 34714 + Oral Contraceptive</th> <th rowspan="2">CV^(b) (%)</th> <th colspan="2">Test versus Reference^(c)</th> </tr> <tr> <th>Point estimate</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td>C_{max} (pg/mL)</td> <td>5896.38 (5234.56 - 6641.87)</td> <td>5294.05 (4699.85 - 5963.39)</td> <td>10.1</td> <td>89.8</td> <td>85.3 - 94.5</td> </tr> <tr> <td>AUCτ (pg*h/mL)</td> <td>71206.9 (61575.4 - 82344.9)</td> <td>55189.2 (47724.3 - 63821.7)</td> <td>13.9</td> <td>77.5</td> <td>72.2 - 83.2</td> </tr> <tr> <td>t_{max} (h)</td> <td>1.47 (0.97 - 2.02)</td> <td>1.50 (0.50 - 3.05)</td> <td>NA</td> <td>0.25</td> <td>-0.01 - 0.28</td> </tr> </tbody> </table> <p>3) Cortisol metabolic ratio: 6.38 (4.2~9.67) → 10.48 (6.44~17.04) (1.6-fold change).</p> <p>PD</p> <p>Table 11:9 Possible Interaction Effect on Hormone Concentrations by ucb 34714 by Comparison of the Maximum Hormone Concentration - PP Population</p> <table border="1" data-bbox="472 1602 1365 1793"> <thead> <tr> <th rowspan="2">Parameter</th> <th rowspan="2">Reference^(a): Oral Contraceptive</th> <th rowspan="2">Test^(a): 200 mg ucb 34714 + Oral Contraceptive</th> <th rowspan="2">CV^(b) (%)</th> <th colspan="2">Test versus Reference^(c)</th> </tr> <tr> <th>Point estimate</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td>ES (pg/mL)</td> <td>21.81 (16.22 - 29.33)</td> <td>19.64 (11.26 - 34.27)</td> <td>39</td> <td>90.90</td> <td>75.09 - 110.06</td> </tr> <tr> <td>PROG (ng/mL)</td> <td>2.23 (1.70 - 2.94)</td> <td>1.97 (1.49 - 2.59)</td> <td>17</td> <td>88.13</td> <td>80.77 - 96.16</td> </tr> <tr> <td>LH (mIU/mL)</td> <td>4.36 (1.82 - 10.41)</td> <td>3.50 (1.62 - 7.56)</td> <td>36</td> <td>81.68</td> <td>68.33 - 97.64</td> </tr> <tr> <td>FSH (mIU/mL)</td> <td>3.25 (2.51 - 4.21)</td> <td>3.43 (2.66 - 4.42)</td> <td>22</td> <td>105.36</td> <td>94.44 - 117.55</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Follicular activity based on the level of FSH was suppressed except for one subject (No. 12) following concomitant medication. No luteal activity based on the level of LH 	Parameter	Reference ^(a) : Oral Contraceptive	Test ^(a) : 200 mg ucb 34714 + Oral Contraceptive	CV ^(b) (%)	Test versus Reference ^(c)		Point estimate	90% CI	C _{max} (pg/mL)	102.85 (90.73 - 116.58)	88.63 (78.19 - 100.47)	17.5	86.2	78.9 -94.1	AUCτ (pg*h/mL)	1077.13 (948.99 - 1222.58)	789.71 (695.76 - 896.35)	12.5	73.3	68.8 - 78.1	t _{max} (h)	2.00 (1.00 - 3.25)	1.50 (1.00 - 3.05)	NA	-0.23	-0.50 - 0.25	Parameter	Reference ^(a) : Oral Contraceptive	Test ^(a) : 200 mg ucb 34714 + Oral Contraceptive	CV ^(b) (%)	Test versus Reference ^(c)		Point estimate	90% CI	C _{max} (pg/mL)	5896.38 (5234.56 - 6641.87)	5294.05 (4699.85 - 5963.39)	10.1	89.8	85.3 - 94.5	AUCτ (pg*h/mL)	71206.9 (61575.4 - 82344.9)	55189.2 (47724.3 - 63821.7)	13.9	77.5	72.2 - 83.2	t _{max} (h)	1.47 (0.97 - 2.02)	1.50 (0.50 - 3.05)	NA	0.25	-0.01 - 0.28	Parameter	Reference ^(a) : Oral Contraceptive	Test ^(a) : 200 mg ucb 34714 + Oral Contraceptive	CV ^(b) (%)	Test versus Reference ^(c)		Point estimate	90% CI	ES (pg/mL)	21.81 (16.22 - 29.33)	19.64 (11.26 - 34.27)	39	90.90	75.09 - 110.06	PROG (ng/mL)	2.23 (1.70 - 2.94)	1.97 (1.49 - 2.59)	17	88.13	80.77 - 96.16	LH (mIU/mL)	4.36 (1.82 - 10.41)	3.50 (1.62 - 7.56)	36	81.68	68.33 - 97.64	FSH (mIU/mL)	3.25 (2.51 - 4.21)	3.43 (2.66 - 4.42)	22	105.36	94.44 - 117.55
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	<ul style="list-style-type: none"> - No ovulation at any time during the study · Bleeding pattern - Occurrence of intra-cyclic bleeding was similar between the two arms. - 1 case: abnormal bleeding pattern “possible relationship” ➤ Spotting between D10 and Day 21 and light to moderate bleeding on D11, D12, D17, D18 and D21. ➤ The AUC of EE and LNG decreased by 49% and 47% in the concomitant treatment period when compared without brivaracetam. This subject showed the largest decreased pattern in the exposure of EE as well as LNG in the group (Mean values in the group: EE = 26%(±13%) and LNG = 20%(±16%)) ➤ No ovulation case
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(2) The effect of 100 mg brivaracetam per day on the PK of oral contraceptive containing EE and LNG

Title	Interaction study between brivaracetam 50mg twice daily and a combined oral contraceptive containing 30µg EE and 150µg LNG in healthy female subjects																																																				
Study design	<ul style="list-style-type: none"> · 28 healthy premenopausal women · Treatments: <ul style="list-style-type: none"> - Brivaracetam: daily 50mg (two 25mg tablets with excipient) twice for 20 days - EE (30 µg)+LNG (150 µg): one tablet daily for 21 days of each menstrual cycle - During concomitant treatment period, it was taken together with brivaracetam. From day 1 to day 17, there was no restriction with regards to meals and how much time after meal or before meal. From day 18 onwards subjects took the medication, at least 1 hour after a standard breakfast and 1 hour after a standard evening meal. The subjects were fasting before the day of PK study. · Safety: adverse event including bleeding pattern, vital sign, physical exam, laboratory, ECG, etc. 																																																				
Results	<ul style="list-style-type: none"> · Twenty two subjects completed the study. · PK <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">Oral contraceptive</th> <th rowspan="2">Parameters (units)</th> <th rowspan="2">Reference^(a) OC with PBO</th> <th rowspan="2">Test^(a) OC with BRV</th> <th rowspan="2">CV^(b) (%)</th> <th colspan="2">Reference versus Test^(c)</th> </tr> <tr> <th>Point Estimate</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Ethinylestradiol</td> <td>AUC_τ (pg*h/mL)</td> <td>989 (889; 1100)</td> <td>893 (803; 994)</td> <td>9.95</td> <td>90.3</td> <td>85.9; 95.0</td> </tr> <tr> <td>C_{max} (pg/mL)</td> <td>110 (98.4; 123)</td> <td>105 (94.3; 118)</td> <td>16.1</td> <td>95.8</td> <td>88.4; 104</td> </tr> <tr> <td>t_{max} (h)</td> <td>1.50 (1.00; 2.00)</td> <td>1.00 (0.50; 2.00)</td> <td>NA</td> <td>-0.29</td> <td>-0.50; -0.25</td> </tr> <tr> <td rowspan="3">Levonorgestrel</td> <td>AUC_τ (ng*h/mL)</td> <td>70.8 (61.8; 81.0)</td> <td>65.3 (57.1; 74.7)</td> <td>9.91</td> <td>92.3</td> <td>87.8; 97.0</td> </tr> <tr> <td>C_{max} (ng/mL)</td> <td>6.53 (5.86; 7.29)</td> <td>6.20 (5.56; 6.92)</td> <td>9.06</td> <td>94.9</td> <td>90.7; 99.4</td> </tr> <tr> <td>t_{max} (h)</td> <td>1.00 (0.50; 2.00)</td> <td>1.00 (0.50; 3.00)</td> <td>NA</td> <td>0.00</td> <td>-0.25; 0.00</td> </tr> </tbody> </table>						Oral contraceptive	Parameters (units)	Reference ^(a) OC with PBO	Test ^(a) OC with BRV	CV ^(b) (%)	Reference versus Test ^(c)		Point Estimate	90% CI	Ethinylestradiol	AUC _τ (pg*h/mL)	989 (889; 1100)	893 (803; 994)	9.95	90.3	85.9; 95.0	C _{max} (pg/mL)	110 (98.4; 123)	105 (94.3; 118)	16.1	95.8	88.4; 104	t _{max} (h)	1.50 (1.00; 2.00)	1.00 (0.50; 2.00)	NA	-0.29	-0.50; -0.25	Levonorgestrel	AUC _τ (ng*h/mL)	70.8 (61.8; 81.0)	65.3 (57.1; 74.7)	9.91	92.3	87.8; 97.0	C _{max} (ng/mL)	6.53 (5.86; 7.29)	6.20 (5.56; 6.92)	9.06	94.9	90.7; 99.4	t _{max} (h)	1.00 (0.50; 2.00)	1.00 (0.50; 3.00)	NA	0.00	-0.25; 0.00
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	<ul style="list-style-type: none"> · Bleeding pattern - No difference in the incidence of spotting and bleeding between the two treatment arms.
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Reviewer’s comments:

- The study design of two DDI studies is acceptable to evaluate the effect of brivaracetam on the PK and PD of oral contraceptive.
- The brivaracetam 400mg daily dose for 20 days decreased the AUCt of EE and LNG by 27% and 23%, respectively. It also decreased the C_{max} of EE and LNG by 14% and 10%, respectively. There was no ovulation case in the study. The brivaracetam 100mg daily dose for 20 days decreased the AUCt of EE and LNG by 10% and 8%, respectively. It decreased the C_{max} of EE and LNG by around 5%.
- These results suggest that brivaracetam has a dose (exposure)-dependent effect (decreased pattern) on the exposure of EE and LNG. Coadministration of the proposed maximum dose of brivaracetam 200mg is anticipated to decrease the exposure of EE and LNG less than what was observed with brivaracetam 400 mg.
- In the study with 400mg brivaracetam, one subject with an abnormal bleeding pattern showed the largest exposure decrease of EE and LNG in the study group. The significantly decreased exposure of hormonal contraceptives likely triggered an intra-cyclic bleeding event. However, the ovulation was not detected in this case based on the PG levels.
- The mean cortisol metabolic ratio measured as a marker of CYP3A4 enzyme induction increased by 1.6 fold in the study with 400mg brivaracetam. This finding shows that multiple treatment of daily 400mg brivaracetam induced CYP3A4 activity mildly when compared to carbamazepine (3-fold) (Desoky et al. 2005).
- Given that brivaracetam has a dose(exposure)-dependent effect on the exposure change of LNG, it may have a different effect on other progestins which have a different metabolic profile. It implies that the current findings of LNG likely have limited generalizability to other progestins.

2) The PK characteristics of brivaracetam

- Brivaracetam is primarily metabolized by hydrolysis and secondarily by hydroxylation via CYP2C19.
- Fourteen days treatment of brivaracetam did not significantly affect CYP3A4 activity as measured by using a cortisol metabolic ratio.

Treatment	Placebo	200mg	400mg	800mg
Mean change of 6-β-hydroxycortisol/cortisol ratio (CI)	0.83 (0.62, 1.11)	0.87 (0.62, 1.21)	1.18 (0.88, 1.57)	1.23 (0.90, 1.69)

- Two weeks treatment with brivaracetam up to 150mg per day had no significant effect on the CYP3A activity as measured by using a midazolam metabolic ratio.
- No major DDI potential was found with other antiepileptics including carbamazepine, phenytoin, lamotrigine and topiramate.

Reviewer's comments:

- *The known PK characteristics of brivaracetam indicate that the clinical dosage (up to 200mg/d) may result a lesser degree of clinically significant reduction in systemic exposure of EE and LNG than that from brivaracetam 400 mg/d dose.*

3) The exposure-response relationship of hormonal contraceptives

In a combined hormonal contraceptive, progestin is likely the main driving force of contraceptive efficacy, while estrogen is mainly responsible for bleeding/cycle control but also suppresses FSH secretion. The exposure-response relationship for efficacy of hormonal contraceptives has been not established well.

4) Pregnancy outcome from clinical trials of brivaracetam

In the ISS submitted by the Sponsor, 36 pregnancy cases were reported in the population treated with brivaracetam from the clinical trials. Out of 36 cases, 11 were found to be on hormonal contraceptives at the time of the pregnancy. The history related with pregnancy of 11 subjects is summarized as follows:

Table 2. Eleven cases of pregnancy while on hormonal contraceptives

Case No.	Brivaracetam dose	Method of Contraceptives	Pregnancy outcome	Discontinuation of brivaracetam	Concomitant medication
N01125-623-0004	120	Intrauterine device (Mirena)	Elective termination	Yes	<u>Carbamazepine</u> and lactulose
N01193-245-0347	50	Combined oral contraceptive 30 µg	Elective termination	Yes	<u>Clobazam</u> and <u>carbamazepine</u>
N01193-203-0229 N01199-1003-0009	40	Combined oral contraceptive 50 µg + condom	Spontaneous abortion - Fetal death	Yes	<u>Carbamazepine</u>
N01253-329-D143 N01199-1029-0002	50	Injectable hormonal contraceptive (Mesigyna once a month)	Full term healthy baby	Yes	<u>Forgot to take Mesigyna</u>
N01254-264-K026 N01199-1264-0004	150	Combined oral contraceptive 50 µg	Full term healthy baby	Yes	Clobazam Valproate
N01253-355-B317	60	Hormonal IUS - Mirena	Spontaneous abortion	No	Zonisamide, iron, multivitamins,

N01199-1055-0007					pseudoephedrine, salbutamol, and fluticasone
N01254-264-L018 N01199-1264-0001	150	Combined oral contraceptive – strength not reported	Full term healthy baby	Yes	<u>Carbamazepine</u>
N01253-392-A223 N01199-1392-0002	80	Combined oral contraceptive – strength not reported	Spontaneous abortion	Yes	<u>Carbamazepine</u> , ibuprofen, lacosamide, and paracetamol
N01193-203-0261 N01199-1003-0010	200 (off for 18 days)	Subdermal implant (18 months)	Ongoing	Yes	<u>Phenytoin</u> and valproic acid
N01114-044-0553 N01125-745-0001	150	Progesterone only oral contraceptive 75 µg (desogestrel)	Full term healthy baby	Yes	<u>Carbamazepine</u>
N01254-023-A222 N01125-518-2004	150	Combined oral contraceptive 35 µg with barrier method	Premature (35 weeks) healthy baby	Yes	<u>Carbamazepine</u> , Cilest, and levetiracetam

The DBRUP requested additional information on the dataset related with pregnancy prevalence to the DNP. The response from the DNP is as follows:

We had our safety reviewer exam this issue. Based upon her evaluation we concluded the following

Using the number of subjects in Pool S3, which constitutes control period reporting during double blind period, the incidence of pregnancies in BRV subjects (0.2% or 4/1717) is double that of placebo subjects (0.1% or 1/686). This represents roughly 1 in 1000 for placebo Vs 2 in 1000 incidence for patients on drug, which I think is unlikely statistically significant. It includes all pregnancy, of which 3 represent the use of a condom with spermicide (all on BRV), one oral contraceptive (on BRV), one abstinence (placebo). Admittedly the placebo patient was practicing abstinence, but considering the low numbers, I am not sure we can conclude anything. It also provides no information on hormonal interactions.

In the entire safety database, out of a total of 41 pregnancies in BRV subjects, there were 9 pregnancies in subjects taking oral contraceptives, 2 in subjects with IUDs, 2 in subjects on injectable hormonal contraception, 1 in a subject with a subdermal implant, 3 using abstinence and 7 presumed sexually inactive. The remainder used other birth control methods. The total BRV exposure for the database (males and females) as of the 120-day Safety Update = 7195.6 subject-years. If we assume that 41 patients became pregnant in the full data base, and estimate the patient years for fertile female patients¹ we come up with 41 pregnancies in 2,518 patient-years, which calculates to 16 pregnancies per 1000 patient-years. This is close to the expected failure rate of BCPs, but we also know that patients who became pregnant used a variety of birth control, some of which are very ineffective¹. Thus, 26% of patients who became pregnant were practicing “abstinence” or thought to be sexually inactive. So we do not think the numbers are dramatically greater than that expected, but acknowledge that this is a very rough estimation. Considering the study records, we believe this is the best we can do.

Reviewer’s comments:

- *In the initial ISS report, seven pregnancy cases on oral (6) and implant (1) hormonal contraceptives were found to have concomitant treatments with the other antiepileptic drugs including those with a metabolic induction potential on hormonal contraceptives such as carbamazepine and phenytoin.*
- *One subject (N01254-264-K026) on oral contraceptive did not take any CYP inducers while on brivaracetam and did not have any relevant clinical history that may have affected the pregnancy event.*
- *At the time of the pregnancy, two subjects (N01125-623-0004 and N01253-355-B317) had a hormonal intrauterine system (Mirena®) which had been placed before the diagnosis of pregnancy. Of these, one subject had concomitant treatment with carbamazepine.*
- *One subject (N01253-329-D143) missed a cycle of regular injectable contraceptive.*
- *The specific information of pregnancy cases was not provided therefore, only the limited information was available (e.g. the dose and duration of the used hormonal contraceptives)*
- *The causal relationship in the pregnancy cases of women who were on oral or implant contraceptives may provide a clue that treatment of brivaracetam may contribute to an efficacy failure of hormonal contraceptives, particularly when women get treated with other CYP3A4 inducers.*
- *In the updated information from the DNP, a total of 41 pregnancy cases were reported. Five pregnancies were added to the number reported in the ISS. Although, the DBRUP requested additional information on these cases to facilitate the consult review, no such information was provided. Given that available information for clinical interpretation of pregnancy outcome is quite limited, the role of brivaracetam related with an efficacy failure of hormonal contraceptives is inconclusive up to this point.*

4. LABELLING RECOMMENDATION

The labeling recommendations for section of 12.3 Pharmacokinetics based on the currently available information are as follows:

Recommendation	Rationale
Add a brief study design	It needs to provide relevant information of study design (treatment duration and study population) for proper interpretation of the study results.
Add the data of C _{max}	The data of C _{max} should be included as basic PK information.
Use a proper name of drug	(b) (4) should be described as “ <u>brivaracetam</u> 200mg twice daily for 20 days” because this regimen is not proposed for the marketing and the formulation (capsule (b) (4)) used in this

	study is different from the to-be-marketed (tablet) formulation.
State the uncertainty of effect of brivaracetam on other progestins	The current findings on the PK of LNG have limited generalizability to other progestins when considering a possible different effect on other progestins which have a different metabolic profile.

Based on above recommendations, the proposed label in the section 12.3 can be reconstructed as follows:

Proposal from the sponsor	Recommendation
<p>12.3 Pharmacokinetics</p> <p><i>Drug Interactions</i></p> <ul style="list-style-type: none"> • <i>Oral contraceptives</i> <p>(b) (4)</p> <p>Coadministration of (b) (4) (b) (4) (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23%, respectively, without impact on suppression of ovulation.</p> <p>(b) (4)</p>	<ul style="list-style-type: none"> • <i>Oral contraceptives</i> <p>(b) (4)</p> <p>Coadministration of brivaracetam 200 mg twice daily for 20 days (twice the recommended maximum daily dose) with an oral contraceptive containing ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23% and C_{max} by 14% and 10%, respectively, without impact on suppression of ovulation in 24 healthy premenopausal women.</p> <p>(b) (4)</p>

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/s/

JIHONG SHON
08/17/2015

MYONG JIN KIM
08/17/2015

Clinical Pharmacology Review

PRODUCT (Generic Name): Brivaracetam

NDA: 205,836 (0000)
205,837 (0000)
205,838 (0000)

PRODUCT (Brand Name): (b) (4) TM

DOSAGE FORM: Tablet / IV Solution / Oral Solution

INDICATION: adjunctive therapy in the treatment of partial onset seizures in adults 16 years of age and older with epilepsy

NDA TYPE: New Molecular Entity

SPONSOR: UCB Inc.

IND : 070205, (b) (4) 103908, 110606

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1. EXECUTIVE SUMMARY

Sponsor is seeking approval of (b) (4) (brivaracetam) for the proposed indication of “adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy”. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is considered to be the primary mechanism for brivaracetam anticonvulsant activity. The proposed formulations are film-coated oral tablets (10, 25, 50, 75, and 100 mg), oral solution (10 mg/mL), and a solution for IV injection (50 mg / 5 mL). (b) (4) should be taken twice daily. The recommended starting dose is 50 mg bid (100 mg/day). The dose may be adjusted to 25 mg bid (50 mg/day) or 100 mg bid (200 mg/day) depending as needed.

To support approval, Sponsor conducted three pivotal, placebo-controlled, Phase 3 trials to assess the safety and efficacy of brivaracetam. The clinical pharmacology program consisted of single- and multiple-dose studies assessing the pharmacokinetics of brivaracetam, a mass balance and metabolic profiling study, pharmacokinetics in Japanese healthy subjects, absolute and relative bioavailability, effect of food, pharmacokinetics in specific populations (hepatic impairment, renal impairment, and elderly), in-vivo drug interaction trials, and bridging of the to-be-marketed formulations with the formulation used in clinical development. Sponsor also conducted exposure-response analyses using efficacy data from the phase 3 trials. Population pharmacokinetic analyses were conducted using phase 2 and phase 3 pharmacokinetic data to assess the effects of common covariates on the pharmacokinetics of brivaracetam in patients with epilepsy.

1.1 Recommendations

The NDA is acceptable from a clinical pharmacology perspective. The labeling recommendations should be conveyed to the Sponsor.

Comments to the Medical Officer:

- 1) Based on subgroup analysis and exposure-response analyses of patients with and without concomitant levetiracetam, no additional benefit of brivaracetam was observed for subjects already on levetiracetam. Therefore, brivaracetam should not be used in patients already on levetiracetam.
- 2) Co-administration carbamazepine may increase the concentration of the active metabolite, carbamazepine-epoxide, by 157%. If tolerability issues arise, a carbamazepine dose reduction should be considered.
- 3) Co-administration with phenytoin may increase phenytoin concentration by 20%. As phenytoin is a narrow therapeutic product, its levels should be monitored when initiating BRV with existing phenytoin or initiating phenytoin with existing brivaracetam.
- 4) No dose adjustment is required for patients with hepatic impairment.

1.2 Phase IV Commitment/Requirement

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Exposure-Response for Effectiveness:

An Emax model was used to describe the relationship between the primary endpoint (28-day/one-week adjusted partial-onset seizure frequency) and steady-state average brivaracetam concentration ($C_{av,ss}$). Exposure-response results show that 50 mg/day demonstrated substantially better efficacy than placebo, and the exposure-response curve is reaching its plateau at 100 mg/day and 200 mg/day doses.

Since levetiracetam and brivaracetam have the same target and mechanism of action, it is hypothesized that patients whose seizures are not well controlled by levetiracetam are not likely to benefit from the concomitant use of brivaracetam. Exposure-response analyses for two subgroups stratified by levetiracetam use at the time of study entry confirmed no additional benefit of brivaracetam would be expected for subjects already on levetiracetam.

Exposure-Response for Safety: Relatively flat dose/exposure-safety relationships at the proposed dose levels were observed for brivaracetam for the common adverse events (somnolence, dizziness, and fatigue).

Pharmacokinetics:

Absorption:

- Brivaracetam is highly permeable and is rapidly and nearly completely absorbed after oral administration.
- Median T_{max} for tablets without food is 1 hour (range 0.25 to 3 hours)

Distribution:

- Brivaracetam is $\leq 20\%$ bound to plasma proteins.
- Volume of distribution is 0.5 L/kg, close to the value of total body water.
- Brivaracetam is distributed into most tissues.
- In rodents, the brain-to-plasma concentration ratio is 0.8.

Metabolism:

- Primary metabolic route is hydrolysis of the amide group by hepatic and extra hepatic amidase into the carboxylic acid metabolite
- Secondary metabolic route is hydroxylation of the propyl side chain by CYP2C19 into the hydroxy metabolite.
- A third metabolite is created by hydrolysis by amidase of the hydroxy metabolite into the hydroxy acid metabolite. The hydroxy metabolite is also created via hydroxylation by 2C9 of the carboxylic acid metabolite.
- None of the 3 metabolites are active.

Elimination:

- In the mass balance study, 90% of the radioactivity was excreted into the urine after 48 hours and fecal excretion accounted for <1% of the dose. Over 48 hours, 8.7% of the dose was excreted into the urine at brivaracetam, 34.2% was the carboxylic acid metabolite (M9, or ucb 42145), 15.9% was the hydroxy metabolite (M1b, or ucb 100406-1), and 15.2% was the hydroxyacid metabolite (M4b, or ucb-107029-1), and 18.3% was other metabolites. Brivaracetam was the main radioactive compound in the plasma for up to 24 hours (representing 80% of the circulating radioactivity).
- Brivaracetam renal CL is 4 mL/min. The renal CI is significantly less than what would be expected based GFR for a drug with $f_u=0.8$ ($GFR \cdot f_u = 125 \text{ mL/min} \cdot 0.8 = 100 \text{ mL/min}$), suggesting tubular resorption is taking place.
- Total brivaracetam CL is 58 mL/min which is far less than hepatic blood flow (1100 mL/min). This suggests that BRV has a low extraction ratio.
- Half-life is 7-9 hours.

Single-Dose and Multiple Dose Pharmacokinetics:

- Single dose pharmacokinetics was assessed on single ascending doses of 10, 20, 40, 80, 150, 300, 600, 1000, or 1400 mg.
- Steady state was achieved after 4-5 days of bid dosing

Time-dependency:

Brivaracetam pharmacokinetics does not vary significantly with time.

Dose proportionality:

The C_{max} is proportional from 10 to 1400 mg. The AUC is proportional from 10 to 600 mg. The AUC is 24% to 28% greater than proportional at doses > 600 mg.

Pharmacokinetics in patients:

In patients with epilepsy, BRV mean CL_{ss}/F was 3.58 L/h (CV 24.7%). In healthy subjects receiving 100 mg/day (50 mg bid) and 200 mg/day (100 mg bid) for 14 days, CL_{ss}/F on Day 14 was 3.572 L/h (CV 20.68%) and 3.611 L/h (16.48%).

Intrinsic Factors:

Renal Impairment: BRV $AUC_{0-\infty}$ was 21% greater in subjects with severe renal impairment compared to healthy controls. Due to the relatively flat exposure-safety relationship, the 21% BRV increase is not expected to result in tolerability issues. The carboxylic acid, hydroxy, and hydroxy-acid metabolite $AUC_{0-\infty}$ were increased 3-fold, 4-fold, and 21-fold, respectively, in subjects with severe renal impairment compared with healthy controls. The elevated metabolite exposures exceeded those tested in the thorough QT study. However, Sponsor conducted non-clinical toxicology studies 4 to 13 weeks in duration with $AUC_{0-24 \text{ hours}}$ at steady state that were 8.5-fold, 10.7-fold, and 25-fold greater than the predicted 24-hour AUC at steady state in subjects with severe renal impairment. In light of these safety margins, no dose adjustment is required in subjects with renal impairment.

Hepatic Impairment: BRV AUC_{0-∞} increased 50-58% in subjects with Child-Pugh Grade A, B, and C compared to health controls.

The hydroxy metabolite (hydroxy metabolite (ucb-100406-1) exposure was lower in Child-Pugh A, B, and C and hydroxy-acid metabolite (ucb-107092-1) exposure was lower in Child-Pugh C, compared to healthy controls. However, these decreases are not expected to result in an efficacy results as these metabolites are not active.

Carboxylic acid metabolite (ucb 42145) exposures increased in Child-Pugh A, B, and C and hydroxy-acid exposures increased in Child-Pugh A and B compared to healthy subjects. However, these metabolite exposure increases are not expected to result in safety or tolerability issues.

No dose adjustment is required for patients with hepatic impairment.

Age:

Elderly: Subjects age 40-80 years have 17.6% lower BRV CL than subjects < 40 years (corresponding to a 23% increase in C_{ss}). The BRV exposure-safety relationship for the common adverse events (e.g. somnolence, dizziness, and fatigue) indicates a modest increase of adverse event risk with increasing BRV exposures (see the Pharmacometrics section of this review for details). A dose adjustment is not necessary for elderly subjects.

Pediatrics: Preliminary PK data indicate that patients age < 8 years have greater CL (per kg) than pediatric patients age 8 to 16 years. Efficacy has not been evaluated at this time in patients < 16 years of age.

Gender: Females have 13% greater C_{av,ss}. No dose adjustment is required.

Race: Brivaracetam PK is not significantly affected by race (Black/African American, American Indian / Alaska Native, other races).

Ethnicity: Hispanic / Latino subjects have 9% greater C_{av,ss}. No dose adjustment is necessary.

Extrinsic Factors:

Drug-drug interactions:

- Brivaracetam is a substrate of CYP2C19 as well as hepatic and extra-hepatic amidases
- Brivaracetam inhibits epoxide hydrolase
- Brivaracetam does not significantly inhibit CYP enzymes

- Brivaracetam does not significantly induce CYP enzymes nor phase 2 enzymes
- Brivaracetam is not a substrate of major transporters
- Brivaracetam does not inhibit major transporters

Concomitant AED	Influence of AED on (b) (4)	Influence of (b) (4) on AED
Carbamazepine	30% decrease in plasma concentration. No dose adjustment required.	None Consider dose reduction, if tolerability issues arise (due to Increase of carbamazepine epoxide. See below.)
Lacosamide	No data	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None (monohydroxy derivative, MHD)
Phenobarbital	24% decrease in plasma concentration. No dose adjustment required.	None
Phenytoin	27% decrease in plasma concentration. No dose adjustment required.	20% increase in plasma concentration. Consider a dose reduction if tolerability issues arise.
Pregabalin	No data	None
Topiramate	None	None
Valproic Acid	None	None
Zonisamide	No data	None

Rifampicin: Concomitant rifampicin decrease brivaracetam plasma concentrations by 45%. The brivaracetam dose should be doubled when using concomitant rifampicin.

Carbamazepine: Co-administration carbamazepine increased the concentration of the active metabolite, carbamazepine-epoxide, by 157%. If tolerability issues arise, a carbamazepine dose reduction should be considered.

Phenytoin: Co-administration with phenytoin may increase phenytoin concentration by 20%. Phenytoin levels should be monitored when initiating BRV with existing phenytoin or initiating phenytoin with existing brivaracetam.

Oral Contraceptive: Coadministration of brivaracetam 400 mg/day (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and

levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23%. However, brivaracetam 100 mg/day co-administered with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) did not significantly influence the pharmacokinetics of either substance. No dose adjustment to the oral contraceptives is required.

Biopharmaceutics:

Formulations: The 25, 50, 75, and 100 mg formulations (b) (4)

The solution for IV injection contains brivaracetam, sodium acetate trihydrate, glacial acetic acid, sodium chloride, and water.

The solution for oral administration contains brivaracetam, methylparaben, Citric acid, Sodium citrate (b) (4), carboxymethylcellulose sodium, sucralose, sorbitol solution, glycerin, raspberry flavor (b) (4), and water.

BCS class: Brivaracetam is BCS class 1.

Bioequivalence/Relative Bioavailability:

- A 50 mg dose of the to-be-marketed oral solution is bioequivalent to the 50 mg tablet used in clinical development.
- A 100 mg dose administered as a 2-minute IV-bolus of the to-be-marketed solution for IV injection was bioequivalent to 2 x 50 mg tablet used in clinical development.
- A 12-second IV bolus or 15-minute IV-infusion of 10 mg of the to-be-marketed solution of IV injection had comparable bioavailability to the 10 mg to-be-marketed tablet.

Dose Strength Equivalence:

The 10 mg, 25 mg, 50 mg 75 mg, and 100 mg to-be-marketed tablets are bioequivalent to the 50 mg tablet used in clinical development.

Food effect:

Food reduces C_{max} by 37%, reduces AUC by 5%, and delays T_{max} by 3 hours. Brivaracetam can be administered without regard to meals.

2. QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1. What are therapeutic indication(s) and the proposed mechanisms of action?

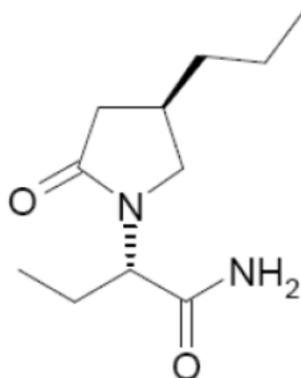
Brivaracetam is proposed for use as adjunctive therapy in the treatment of partial onset seizures in adults 16 years of age and older with epilepsy.

Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is considered to be the primary mechanism for BRV anticonvulsant activity.

2.1.2. What are the highlights of physico-chemical properties of the drug substance?

Brivaracetam is a 2-pyrrolidone derivative. The empirical formula is $C_{11}H_{20}N_2O_2$ and the molecular weight is 212.29.

Figure 1: Chemical Structure of Brivaracetam



(b) (4)™ brivaracetam tablets colored, debossed film-coated tablets available in 10 mg (white), 25 mg (grey), 50 mg (yellow), 75 mg (purple), and 100 mg (green-grey). (b) (4)

(b) (4)™ brivaracetam solution for intravenous injection contains 10 mg BRV/mL. In addition, the solution contains sodium acetate trihydrate (b) (4)%, glacial acetic acid (b) (4) to achieve pH 5.5), sodium chloride (b) (4)%, and water 9 (b) (4)% (b) (4)

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)

(b) (4) TM brivaracetam oral solution contains 10 mg BRV/mL. In addition, the solution contains BRV (b) (4)%, methylparaben (b) (4)%, citric acid (b) (4)%, sodium citrate (b) (4)%, Carboxymethylcellulose sodium (b) (4)%, sucralose (b) (4)%, sorbitol solution (b) (4)%, glycerin (b) (4)%, raspberry flavor (b) (4)%, and purified water (b) (4)%.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed starting dose is 100 mg/day (50 mg twice daily) of brivaracetam oral tablets. Based on individual patient response, the dose may be adjusted between 50 mg/day (25 mg twice daily) and 200 mg/day (100 mg twice daily). The oral solution and solution for injection use the same dose and dose regimen as the oral tablets.

- 10 mg tablets are white to off white, round, film-coated, and debossed with "u10" on one side.
- 25 mg tablets are grey, oval, film-coated, and debossed with "u25" on one side.
- 50 mg tablets are yellow, oval, film-coated, and debossed with "u50" on one side.
- 75 mg tablets are purple, oval, film-coated, and debossed with "u75" on one side.
- 100 mg tablets are green-grey, oval, film-coated, and debossed with "u100" on one side.
- 10 mg/mL oral solution is a slightly viscous, clear, colorless to yellowish, raspberry-flavored liquid.
- Solution for injection contains 50 mg brivaracetam (50 mg/5 mL) in one vial. It is a clear, colorless, sterile solution.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The brivaracetam clinical development program consisted of 28 phase I studies in health subjects or special populations. Design features of the clinical pharmacology trials are summarized in the table below.

Table 1: Brivaracetam Clinical Pharmacology Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	
N01066/ United Kingdom	Randomized, monocenter, double-blind, placebo-controlled, 3-alternating panel, 3-period rising single oral dose (10 to 1400mg), safety, tolerability, pharmacokinetic and pharmacodynamic study of ucb 34714 (capsule without excipient) in 27 healthy male volunteers
N01067/ United Kingdom	Randomized, mono-center, double blind, placebo-controlled, parallel group, 2 weeks repeated oral dose, safety, tolerability, pharmacokinetic and pharmacodynamic study of ucb 34714 100mg, 200mg and 400mg (100 and 200mg capsules (b) (4)) (b) (4) twice daily in 36 healthy male volunteers
N01068/ Belgium	Open label, monocenter, excretion balance, pharmacokinetics and metabolism of [¹⁴ C]-labeled ucb 34714 after single 150mg oral dose administration in 6 healthy male volunteers
N01075/ United Kingdom	Randomized, monocenter, open label, two-way cross-over, food interaction pilot study of a single dose (150 mg) of ucb 34714 (oral capsule (b) (4)) in 8 healthy male volunteers
5.3.3.4 – Extrinsic Factor PK Study Reports	
EP0041/ The Netherlands	A double-blind, randomized, placebo-controlled, three-way crossover study to investigate the drug-drug interactions of brivaracetam and ethanol in healthy male subjects
N01080/ United Kingdom	Randomized, monocenter, open label, two-way crossover, multiple oral dose interaction study between ucb 34714, 200mg (oral capsule (b) (4)) twice daily and oral contraceptive (ethinylestradiol 30µg and levonorgestrel 150 µg) once daily in 24 healthy female volunteers
N01081/ United Kingdom	Monocenter, open label, bilateral pharmacokinetic interaction study of ucb 34714 (200mg oral capsules bid) and carbamazepine (100mg oral tablets/300mg bid) during single and multiple oral administrations in 14 healthy male subjects
N01082/ United Kingdom	Monocenter, open label, interaction study between ucb 34714 at steady state (200mg oral capsules, twice daily) and single dose phenytoin 600mg (2x300mg oral capsules) in 20 healthy male volunteers
N01133/ United Kingdom	Monocenter, open label, unilateral metabolic interaction study of ucb 34714 (100, 200 and 400mg daily) on carbamazepine (≥600mg daily) during a four-week bid administration period in 9 adult male subjects suffering from epilepsy
N01135/ United Kingdom, Poland	Multicenter, open label, unilateral metabolic interaction study of ucb 34714 (100, 200 and 400mg daily) on carbamazepine (≥600mg daily) during a four-week bid administration period in 9 adult subjects suffering from epilepsy and treated with carbamazepine and valproate (≥500mg daily)
N01170/ Belgium	Monocenter, open label, unilateral interaction study of brivaracetam at steady-state (200mg twice daily) on topiramate (200mg single dose) in 14 healthy volunteers
N01171/ France	Monocenter, open label, unilateral interaction study of ucb 34714 at steady-state (200mg twice daily) on lamotrigine (25mg single dose) in 14 healthy male volunteers
N01172/ USA	A multicenter, open-label, unilateral interaction study of ucb 34714 (400mg daily) on stable phenytoin monotherapy during a 45 day bid administration period in 15 adult subjects suffering from epilepsy
N01259/ Belgium	Monocenter, open-label, randomized, 2x2-way cross-over study to assess the effects of gemfibrozil and rifampicin on the pharmacokinetics of brivaracetam, a CYP2C8 substrate, in healthy male subjects
N01261/ Belgium	Single-centre, open-label Phase I study to assess the effects of a repeated administration of brivaracetam on CYP3A4 activity in healthy male subjects using midazolam as a probe
N01282/ France	Interaction study between brivaracetam 50mg twice daily and a combined oral contraceptive containing 30µg ethinylestradiol and 150µg levonorgestrel in healthy female subjects

(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

5.3.3.3 – Intrinsic Factor PK Study Reports	
N01109/ Poland	Monocenter, open-label, parallel group, not randomized, pharmacokinetic study of a single oral administration of 200mg capsule of ucb 34714, in subjects with normal renal function and with renal function impairment
N01111/ Belgium	Open label, parallel group, not randomized, pharmacokinetics study of a single oral administration of 100mg ucb 34714 (50mg capsules) in healthy subjects and patients with impaired liver function (Child-Pugh classes A, B and C)
N01118/ France	Multicenter, open-label, pharmacokinetic, safety and tolerability study of a single dose followed by a 10 day bid dosing regimen of ucb 34714 administered twice a day orally as 200mg capsules in healthy elderly volunteers
N01209 Part A/ Japan	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects
N01209 Part B/ Japan	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects
5.3.1.1 Bioavailability (BA) Study Reports	
N01185/ United Kingdom	Pharmacoscintigraphic investigation of the regional drug absorption of ucb 34714 (200mg) delivered using the Enterion™ capsule in 3 different sites of the GI tract in comparison with the 200mg immediate release oral capsule: open-label, randomized, four-way cross-over, single dose study, in 9 healthy adult male volunteers
N01256A (Part A)/ Belgium	A randomized, monocenter, open-label, three-way crossover, dose availability study of three different formulations of brivaracetam (Part A), followed by a non-randomized, monocenter, open-label safety assessment via two formulations (Part B), on healthy volunteers
N01256B (Part B)/ Belgium	A randomized, monocenter, open-label, three-way cross-over, dose availability study of three different formulations of brivaracetam (Part A), followed by a non-randomized, monocenter, open-label safety assessment study of four escalating doses of brivaracetam (BRV) administered via two formulations (Part B), on healthy volunteers
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	
EP0007/ The Netherlands	A randomized, single-center, open-label, 5-way crossover, single-dose bioavailability/bioequivalence comparison of brivaracetam oral tablets (10mg, 50mg, 75mg, and 100mg) and brivaracetam intravenous bolus injection (100mg) in healthy volunteers
N01287/ France	Monocenter, open label, randomized, five-way cross-over relative bioavailability/bioequivalence study of brivaracetam solid oral formulations (capsule and tablet) using as reference brivaracetam oral solution with assessment of food effect on brivaracetam oral tablet formulation
N01296/ France	Randomized, monocenter, open-label, two-way cross-over, single dose bioequivalence study of two different formulations of brivaracetam in healthy fasting subjects
5.3.4.1 – Healthy Subject PD and PK/PD Study Reports	
N01233/ France	Randomized, placebo- and moxifloxacin-controlled study of the effect of brivaracetam on cardiac repolarization in four parallel groups of healthy male and female subjects

Sponsor conducted 3 phase II studies, and 5 phase III studies. Design features of the clinical pharmacology trials are summarized in the table below.

(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

Table 2: Brivaracetam Phase 2 and Phase 3 Trials

5.3.3.2 – Patient PK and Initial Tolerability Study Reports	
N01263/ Belgium, Czech Republic, Mexico, Poland, Spain, USA	Open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of brivaracetam in subjects from ≥ 1 month to < 16 years old with epilepsy
5.3.5.1 – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication POS	
N01114/ Belgium, Czech Republic, Finland, France, Germany, The Netherlands, Poland, Spain, United Kingdom	A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 used as adjunctive treatment at doses of 50 and 150mg/day in bid administration (oral capsules of 25mg) for a maximum of 12 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized
N01193/ Brazil, India, Mexico, USA	A multicenter, double-blind, randomized, placebo-controlled, 4 parallel groups, dose-ranging trial evaluating the efficacy and safety of brivaracetam used as adjunctive treatment at doses of 5, 20 and 50mg/day in bid administration (oral tablets of 2.5 or 10mg) for a maximum of 7 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized
N01252/ Belgium, Switzerland, Germany, Finland, France, Hungary, India, Italy, The Netherlands, Poland, Spain, United Kingdom	A multi-center, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with partial onset seizures
N01253/ Australia, Brazil, Canada, Mexico, USA	An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with partial onset seizures
N01254/ Austria, Belgium, Czech Republic, Germany, Hong Kong, India, Italy, South Korea, Norway, South Africa, Russia, Singapore, Sweden, Taiwan, Ukraine	An international, randomized, double-blind, parallel-group, placebo-controlled, flexible dose study: evaluation of the safety and efficacy of brivaracetam in subjects (≥ 16 to 70 years old) suffering from localization-related or generalized epilepsy
N01358/ Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Hungary, India, Italy, Japan, Latvia, Lithuania, Mexico, Poland, Russia, South Korea, Spain, Sweden, Taiwan, The Netherlands, United Kingdom, USA, US territory of Puerto Rico	A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of brivaracetam in subjects (≥ 16 to 80 years old) with partial onset seizures
5.3.5.2 – Study Reports of Uncontrolled Clinical Studies	
N01258/ Czech Republic, Germany, Poland, USA	A multicenter, open-label, four-arm, randomized trial evaluating the safety and tolerability of brivaracetam intravenous infusion and bolus, administered in bid regimen as an adjunctive antiepileptic treatment in subjects from 16 to 70 years suffering from epilepsy

In addition, there were 4 population PK reports: CL0027, CL0028, and CL0178 which were based on 5 studies (3 were pivotal), as well as CL0187 which was based on 1 study.

Pivotal Clinical Trials:

Studies N01252, N01253, and N01358 were multi-center, double-blind, parallel-group, placebo-controlled randomized trials of brivaracetam in age 16 to 70 years (N01252, and N01253) or 16 to 80 years (N01358) with partial onset seizures. The trials required subjects to be receiving 1-2 concomitant AEDs. Trials N01252 and N01253 permitted use of concomitant levetiracetam but trial N01358 did not permit the use of concomitant levetiracetam. Key design features are demonstrated in the figures below.

Figure 2: Study Design Diagram for Study N01252

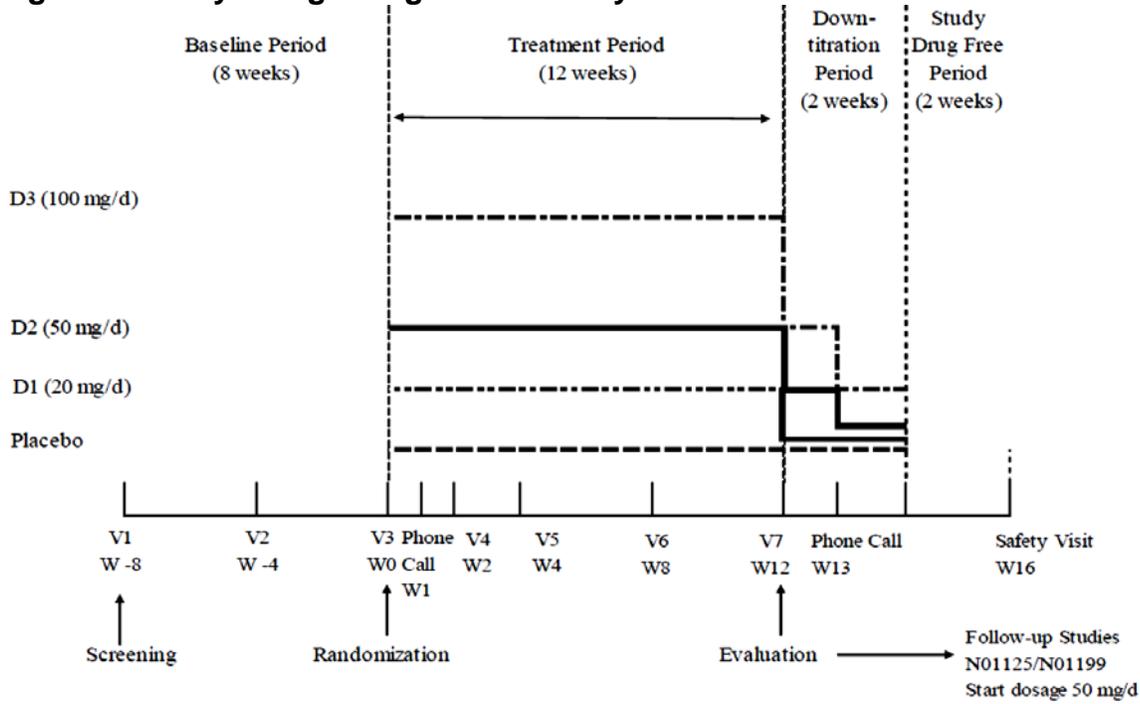


Figure 3: Study Design Diagram for Study N01253

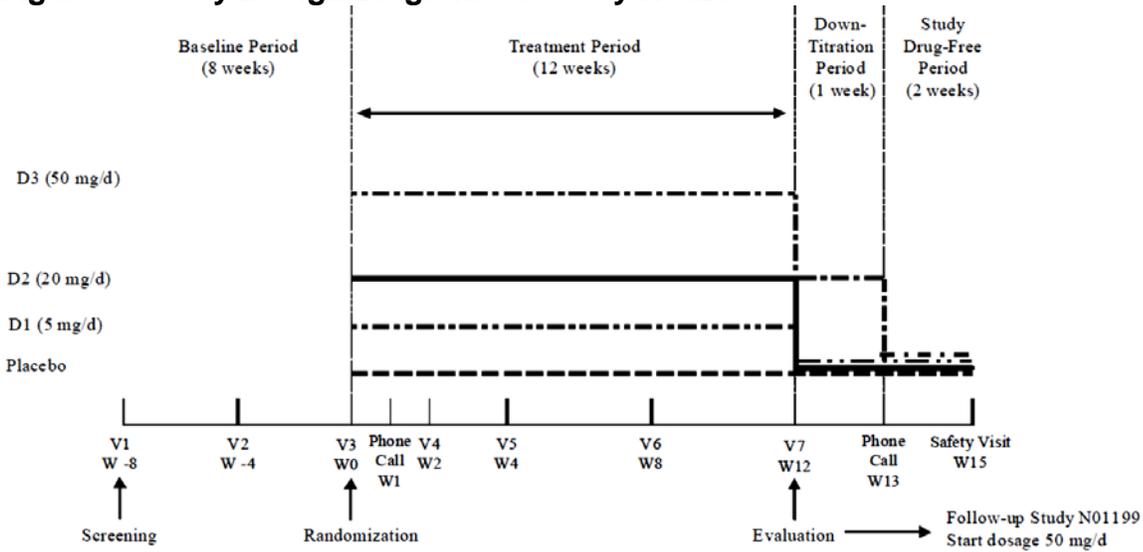
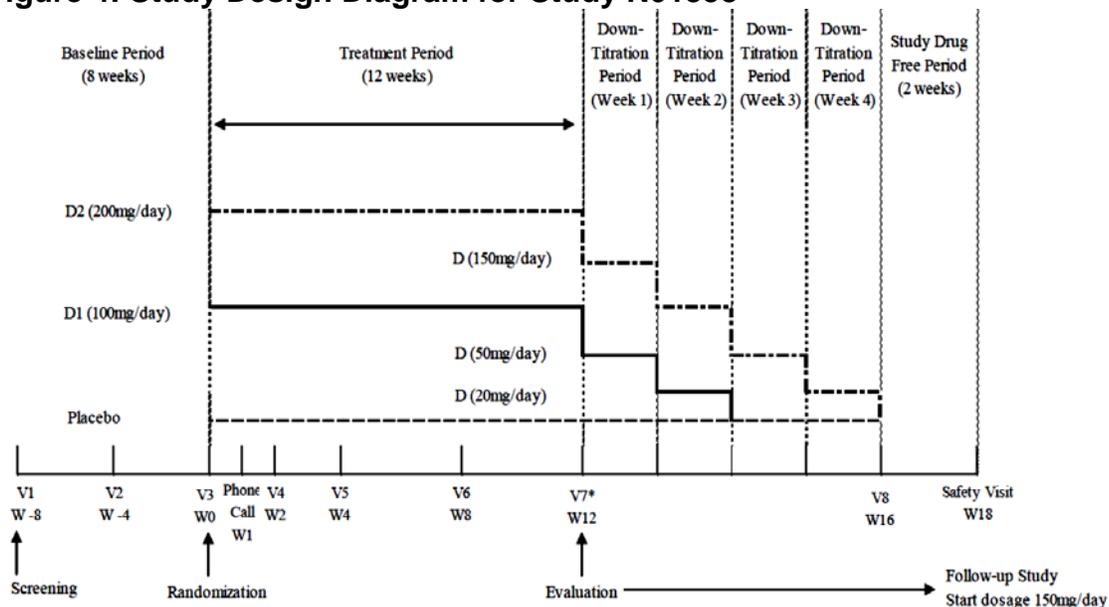


Figure 4: Study Design Diagram for Study N01358



EDV=Early Discontinuation Visit; D=dose; V=visit; W=week

* Subjects with an EDV at any time during the Treatment Period should have proceeded through the 4-week Down-Titration Period and 2-week Study Drug-Free Period.

In Trial N01252, n=399 patients with epilepsy were randomized 1:1:1:1 to placebo, BRV 20, 50, or 100 mg/day as oral tablets administered BID (2 equal intakes, morning and evening) for 12 weeks. Subjects were stratified for use of levetiracetam (using levetiracetam or not using levetiracetam). After the Treatment Period, subjects entered the long-term follow-up study (N01125 or N01199) at the recommended starting dose of BRV 50 mg/day, or down-titrated over 2 weeks followed by a 2-week study drug-free period.

In Trial N01253, n=400 patients with epilepsy were randomized 1:1:1:1 to placebo, BRV 5, 20, or 50 mg/day as oral tablets administered BID (2 equal intakes, morning and evening). Subjects were randomized to the full dose without a titration and were treated for 12 weeks. After the Treatment Period, subjects entered the LTFU study at the recommended starting dose of 50 mg/day or down-titrated over 1 week followed by a 2-week study-drug-free period.

In Trial N01358, n=768 patients with epilepsy were randomized 1:1:1 to placebo, BRV 100, or 200 mg/day as oral tablets administered BID (2 equal intakes administered twice daily). Subjects were randomized to the full dose without a titration and were treated for 12 weeks. Subjects underwent a 4-week down-titration after the 12-week treatment period. Subjects were stratified by country, previous LEV use (never used levetiracetam vs. prior use of levetiracetam), and number of AEDs previously used but discontinued prior to study entry (≤ 2 versus > 2 AEDs).

2.2.2. What is the basis for selecting the clinical endpoints or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint was POS (Type I) frequency per week over the Treatment Period in trials N01253 and N01254. In trial N01358, the primary efficacy variable was the POS (Type I) frequency per 28 days over the Treatment Period. The log-transformed POS frequency per week over the Treatment Period was analyzed applying an ANCOVA model, including treatment and a stratification effect combining study region as factors and the log-transformed Baseline seizure frequency per week as covariate. In studies N01252 and N01253, current concomitant levetiracetam use was included in the model. In trial N01358, prior levetiracetam use was included in the model.

The key secondary efficacy endpoints were Responder Rate (the proportion of subjects who had a $\geq 50\%$ reduction in seizure frequency per week from Baseline for POS over the Treatment Period; N01253 and N01254) and Percent reduction for POS frequency per week from Baseline Period to the Treatment Period (all three pivotal trials).

2.2.3. Exposure Response

2.2.3.1 Is there any significant exposure-response relationship? And does the relationship support the proposed dosing regimen?

An Emax model was used to describe the relationship between average steady state brivaracetam plasma concentration ($C_{av,ss}$) and % change from baseline in POS frequency. There was a flat relationship between common adverse events (dizziness, fatigue, somnolence) and $C_{av,ss}$.

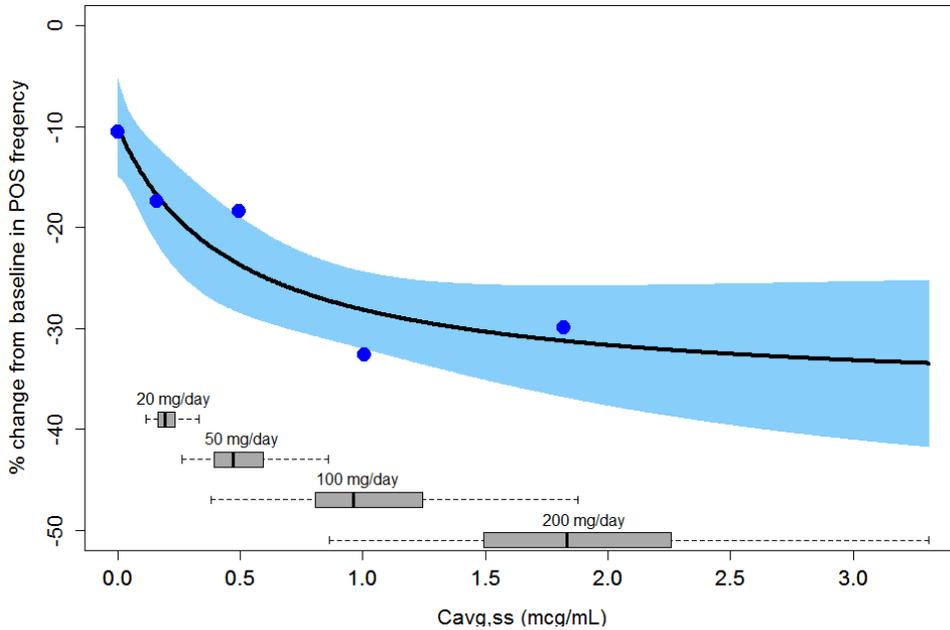
Exposure response - Efficacy:

From the efficacy point of view, all 3 proposed doses (50, 100, and 200 mg/day) are acceptable. All three dose levels demonstrated a statistically significant improvement in the primary efficacy endpoint (percent reduction over PBO for 28-day/one-week adjusted POS frequency) compared to placebo. For 50 mg/day, although it was evaluated in two pivotal studies, N01252 and N01253, only study N01253 demonstrated statistically significant reduction over PBO in POS frequency ($p=0.004$), whereas study N01252 showed statistically insignificant results ($p=0.274$).

Exposure-response analysis was performed using data pooled from all 3 pivotal phase 3 studies. The exposure-response results show that 50 mg/day demonstrated substantially better efficacy than placebo, and the exposure-response curve is reaching its plateau at 100 mg/day and 200 mg/day doses. A pooled analysis conducted by the sponsor using data from the 3 phase 3 studies excluding subjects on concomitant LEV showed statistically significant

efficacy results for all 3 doses, as shown in Table 33. Therefore, the efficacy of all 3 doses is considered adequate.

Figure 5 Results of Exposure Response Analysis for Efficacy

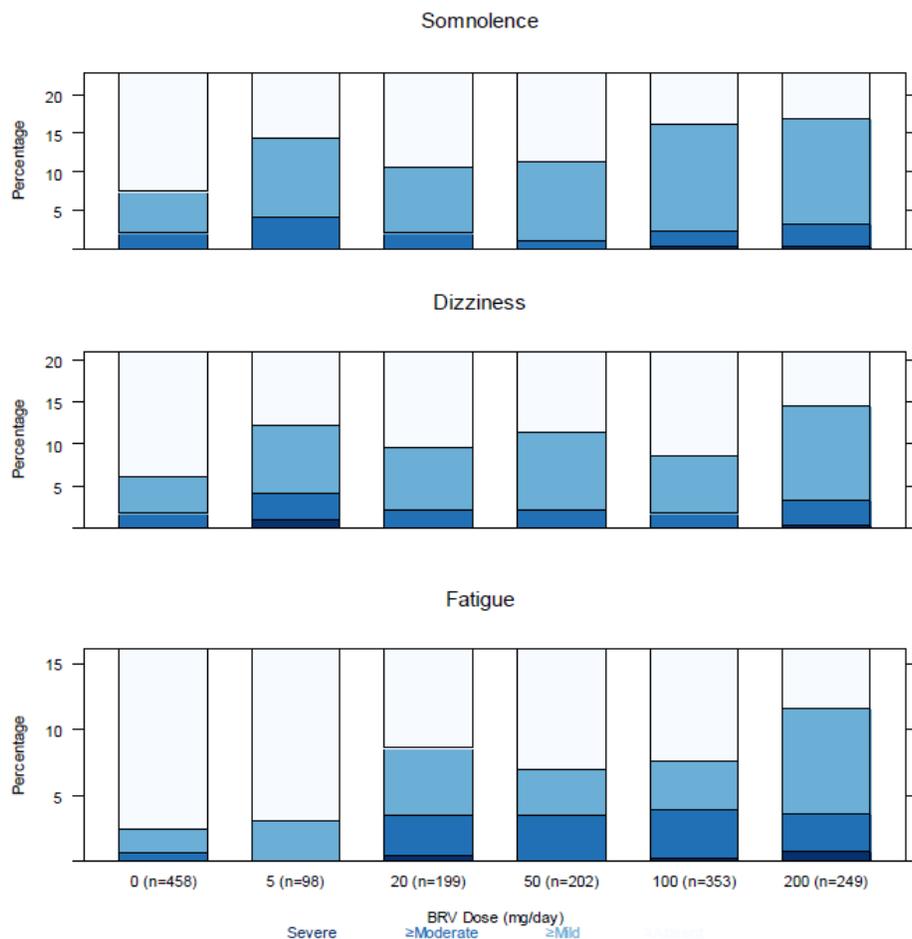


Note: the blue circles represent observed mean % change from baseline in POS frequency in the placebo group (first circle) and the 4 steady-state average concentration quartiles; the solid line represents exposure-response model fit; the blue shaded area represents the 95% CI for the model fit; the grey boxplots represent the exposure distributions for 20, 50, 100, and 200 mg/day dose levels.

Exposure response - Safety:

In the pooled safety data from the pivotal clinical trials, there was relatively flat dose/exposure-safety relationships at the proposed dose levels were observed for BRV for the common adverse events (somnolence, dizziness, and fatigue).

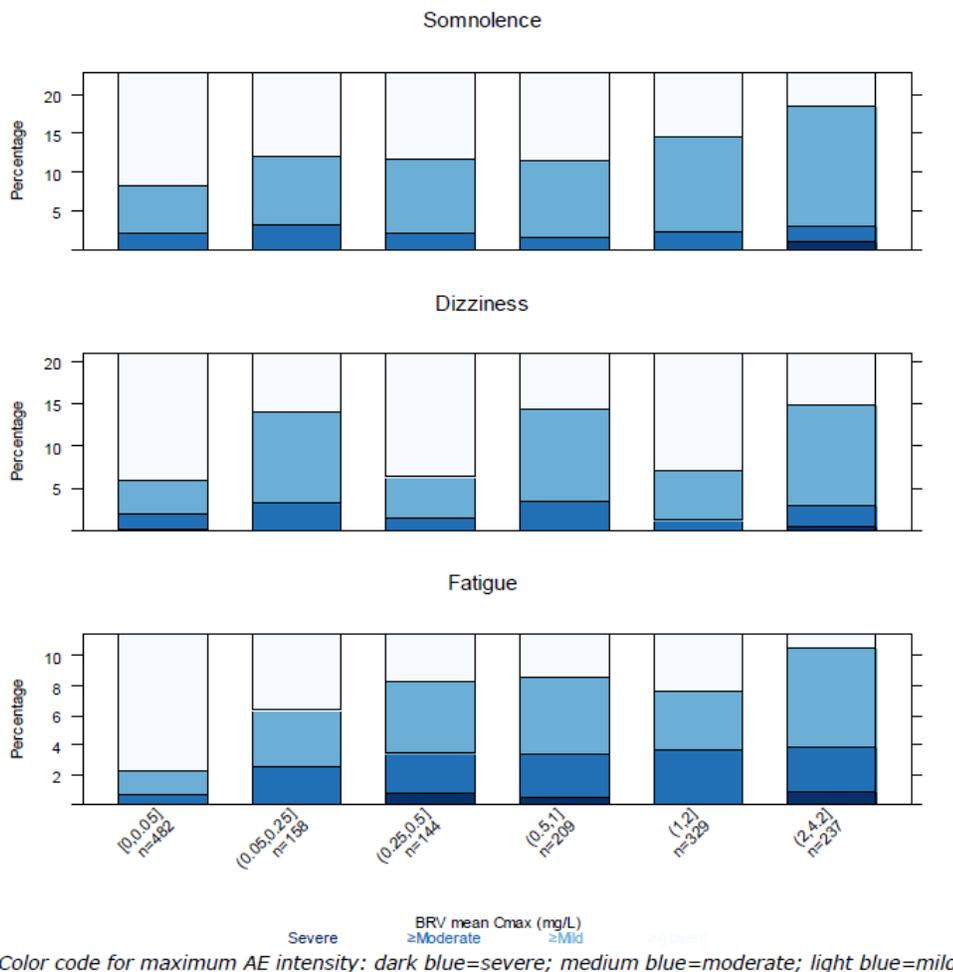
Figure 3 Relationship between fraction of subjects with their maximum AE intensity during treatment and randomized dose



Color code for maximum AE intensity: dark blue=severe; medium blue=moderate; light blue=mild

Source: study report CL0027 page 299

Figure 4 Relationship between fraction of subjects with their maximum AE intensity during treatment and popPK model-predicted BRV Cmax



Due to the relatively flat dose/exposure-safety relationships that were observed in phase 3 studies and the plateau in the dose/exposure-efficacy relationship, the case for providing a range of doses is not as clear as for other anti-epileptic drugs.

According to the Keppra label, the incidence of somnolence and dizziness were comparable in adults experiencing partial onset seizures in pooled, placebo-controlled studies with levetiracetam were comparable with brivaracetam. However, Keppra use was associated with other toxicities (asthenia, headache, infection occurred with > 10% of subjects receiving levetiracetam) that were not as common with brivaracetam in this patient population.

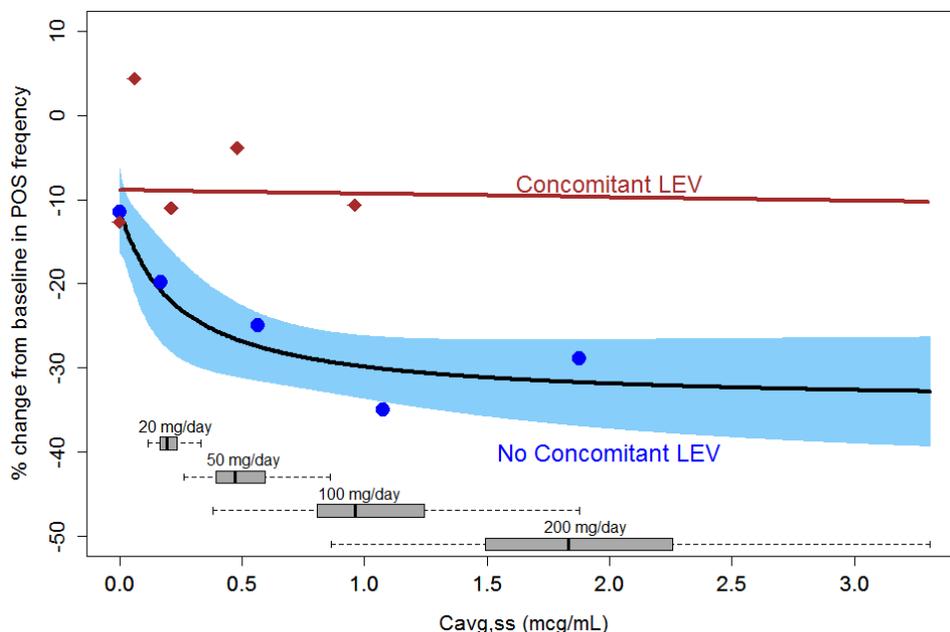
Subgroup Analysis by LEV use:

Exposure-response analyses were conducted for efficacy stratified by concomitant levetiracetam use. In trials N01252 and N01253, 20% of randomized subjects were receiving concomitant levetiracetam. In trial N01358, concomitant levetiracetam use was prohibited.

As levetiracetam and brivaracetam have the same target site and thus the same mechanism of action, it was hypothesized that no additional benefit would be achieved by co-administering brivaracetam to patients already treated with levetiracetam.

The exposure-response analyses stratified by concomitant levetiracetam use confirm this hypothesis (see the figure below).

Figure 5: Exposure Response Analysis Results Stratified by LEV Use



Note: the blue circles represent observed mean % change from baseline in POS frequency in the placebo group and the 4 steady-state average concentration quartiles in subjects taking no concomitant LEV/Keppra; the red squares represent observed mean % change from baseline in POS frequency in the placebo group and the 4 steady-state average concentration quartiles in subjects taking concomitant LEV; the solid lines represent exposure-response model fits; the blue shaded area represents the 95% CI for the model fit for subjects taking no concomitant LEV; the grey boxplots represent the exposure distributions for 20, 50, 100, and 200 mg/day dose levels.

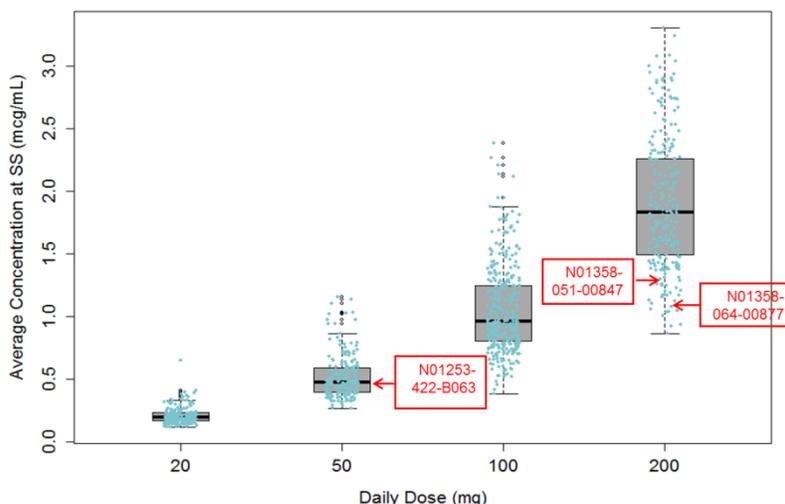
The results suggest that no additional benefit of BRV would be expected for subjects already on levetiracetam. **Therefore, BRV should not be used in patients already on LEV.**

Sudden Unexpected Death in Epilepsy (SUDEP):

Due to the elevated SUDEP rate observed in the brivaracetam arm compared to the placebo arm, a comparison of exposures in patients with SUDEP versus the remaining patients. There were 13 SUDEP cases but only 4 occurred during the double-blind treatment period. Only 3 subjects out of these 4 had PK data. The three subjects were receiving the 50 mg/day, 200 mg/day and 200 mg dose levels, respectively. The $C_{av,ss}$ level in the patients with SUDEP during the double-blind treatment period was compared with the rest of the $C_{av,ss}$ data. The

result shows that the steady-state exposures of all 3 subjects are within normal range of exposures at corresponding dose levels (see the figure below).

Figure 6: BRV Concentrations in Subjects with SUDEP versus Concentration Distribution of All Subjects



Note: Boxplots with jitters represent the distribution of average concentration at SS from all subjects; Red box with arrows indicate the steady-state average concentration levels of the 3 subjects experiencing SUDEP events.

Based on these results, it cannot be concluded that SUDEP events were related to insufficient BRV exposures.

2.2.4. Does brivaracetam prolong the QT or QTc interval?

No significant QT prolongation was observed from administration of up to 400 BRV bid oral capsules from Day 1 to Day 7 morning compared to a single 400 mg oral tablet of moxifloxacin in study N01233. The largest upper limit of the two-sided 90% CI for the mean difference between BRV (75 mg and 400 mg doses) and placebo was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The results of the FDA analysis are shown in the figure below. See the review of IND 070205 / IND (b) (4) signed on 03/05/2009 for details.

Table 7: Brivaracetam and Moxifloxacin Effect on $\Delta\Delta QTcSS$

Treatment	Time (h)	$\Delta\Delta QTcSS$ (ms)	90% CI (ms)
Brivaracetam 75 mg bid	4	0.9	-3.2, 5.0
Brivaracetam 400 mg bid	9	-1.4	-5.6, 2.7
Moxifloxacin 400 mg	4	13.2	9.3, 17.0

* The results presented here for moxifloxacin in the table are not multiple endpoints adjusted. If Bonferroni adjustment is applied, the largest lower bound will be 7.2 ms.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single and multiple dose PK parameters?

Sponsor conducted a single-dose PK study (N01066) and a multiple dose PK study (n01067).

Figure 6: Mean PK Profile for BRV for 48 Hours after Single Doses (N01066)

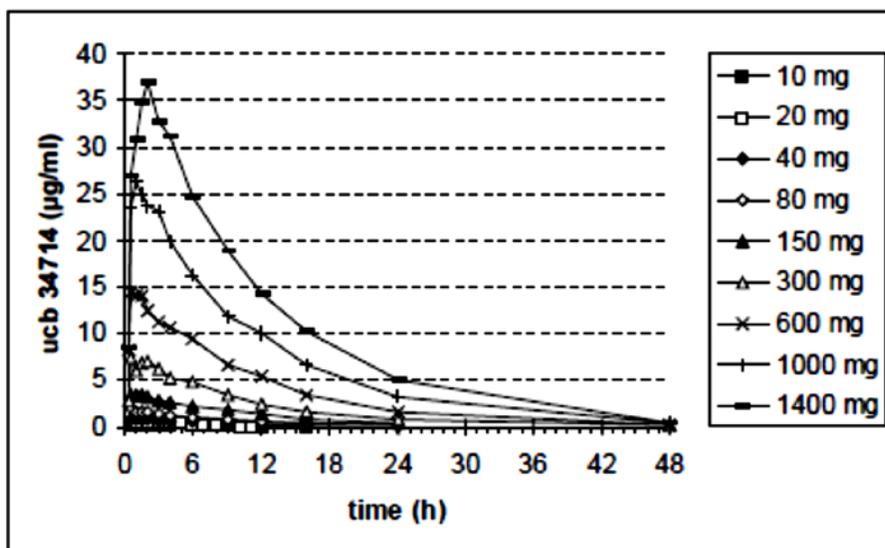


Table 8: Mean ± SD BRV Plasma PK Parameters After Single Oral Capsule Administration (N01066)

Parameter (unit)	BRV dose (mg)				
	10	20	40	80	150
C _{max} (µg/mL)	0.305 (38.8)	0.429 (16.7)	0.945 (24.1)	2.18 (16.9)	4.24 (19.9)
t _{max} ^a (h)	0.5 (0.5–2)	1 (0.5–3)	1.26 (0.5–2)	0.5 (0.5–1.5)	0.75 (0.5–3)
AUC(0-t) (µg.h/mL)	1.79 (22.2)	3.65 (32.9)	8.35 (12.5)	17.3 (12.0)	37.2 (11.0)
AUC (µg.h/mL)	2.54 (14.9)	4.50 (32.9)	9.74 (16.6)	19.7 (13.0)	43.1 (14.0)
t _{1/2} (h)	8.06 (10.7)	8.18 (19.1)	8.05 (17.1)	7.71 (12.4)	8.04 (12.9)
CL/F (mL/min/kg)	0.88 (9.84)	1.07 (29.4)	0.95 (17.1)	0.95 (8.49)	0.82 (10.7)
V _z /F (L/kg)	0.61 (13.0)	0.73 (15.4)	0.65 (3.84)	0.63 (10.4)	0.57 (11.2)
	300	600	1000	1400	
C _{max} (µg/mL)	8.58 (15.9)	16.15 (12.5)	28.46 (16.3)	41.28 (24.1)	
t _{max} ^a (h)	1 (0.25–2)	0.75 (0.25–1.5)	1.27 (0.5–4)	1.75 (1–4)	
AUC(0-t) (µg.h/mL)	81.2 (20.0)	165 (19.8)	313 (15.8)	432 (13.5)	
AUC (µg.h/mL)	84.3 (18.0)	170 (17.6)	317 (16.4)	465 (18.8)	
t _{1/2} (h)	7.43 (14.7)	7.26 (14.1)	7.41 (16.9)	7.31 (17.1)	
CL/F (mL/min/kg)	0.86 (11.3)	0.83 (12.3)	0.73 (8.88)	0.70 (21.7)	
V _z /F (L/kg)	0.54 (5.15)	0.52 (12.0)	0.46 (12.6)	0.44 (20.7)	

The following figure illustrates the mean ± SD plasma concentration profile of brivaracetam after two weeks of 100 mg bid (200 mg/day) administration.

Figure 7: Mean ± SD PK Profile for BRV On Days 1, 7, and 14 of Repeat 100 mg bid Administration (N01067)

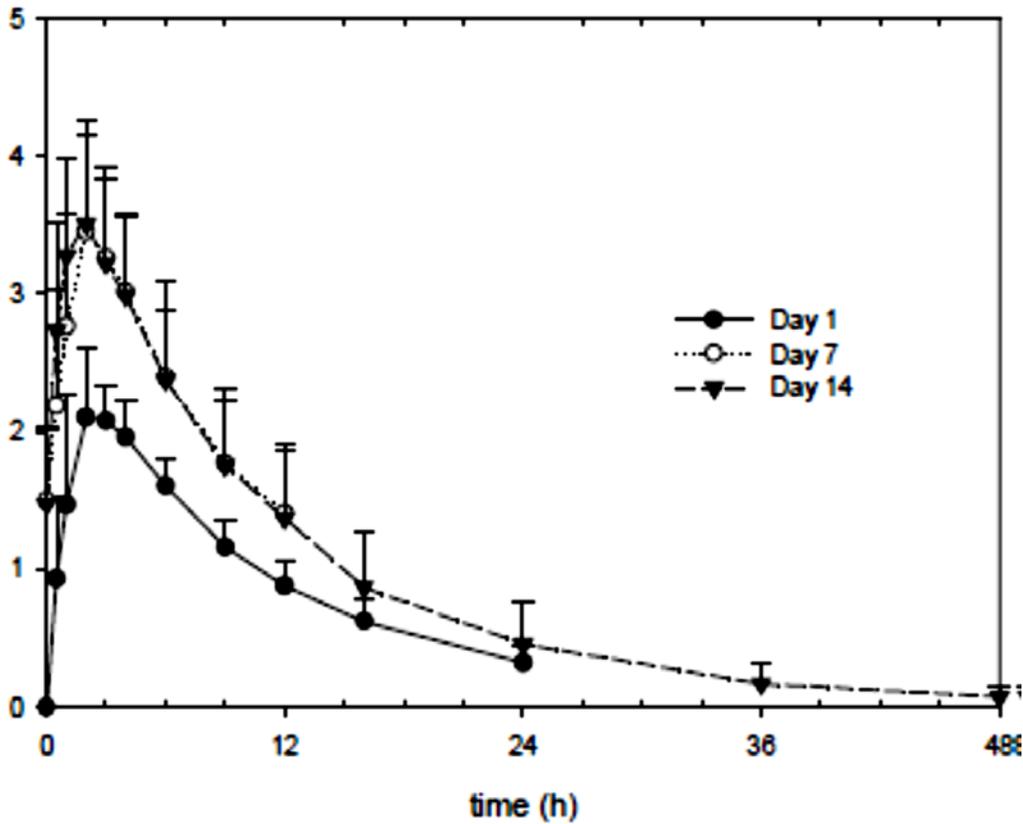


Table 9: Mean ± SD BRV Plasma PK Parameters After Single and Multiple Administration of 100 mg BID BRV Oral Capsules (N01067)

Parameter (unit)	BRV 100mg bid		
	Day 1	Day 7	Day 14
C_{max} (µg/mL)	2.23 (14.1)	3.50 (21.5)	3.54 (19.6)
t_{max}^a (h)	2 (1-4)	2 (1-3)	2 (1-2)
AUC ^b (µg.h/mL)	27.5 (22.8)	27.7 (21.1)	28.0 (24.1)
$t_{1/2}$ (h)	7.67 (19.9)	NC	7.33 (25.7)
CL/F (mL/min/kg)	0.83 (20.5)	0.83 (21.3)	0.82 (22.6)
V_z/F (L/kg)	0.55 (8.67)	NC	0.52 (11.3)

PK Parameters

The terminal elimination half-life is 7-8 hours in phase 1 trials. Results of population PK analyses from phase 3 trials in epilepsy patients receiving 1-2 concomitant AED medications are shown in the table below.

Table 10: Results of Brivaracetam Population PK analyses (Report CL0028)

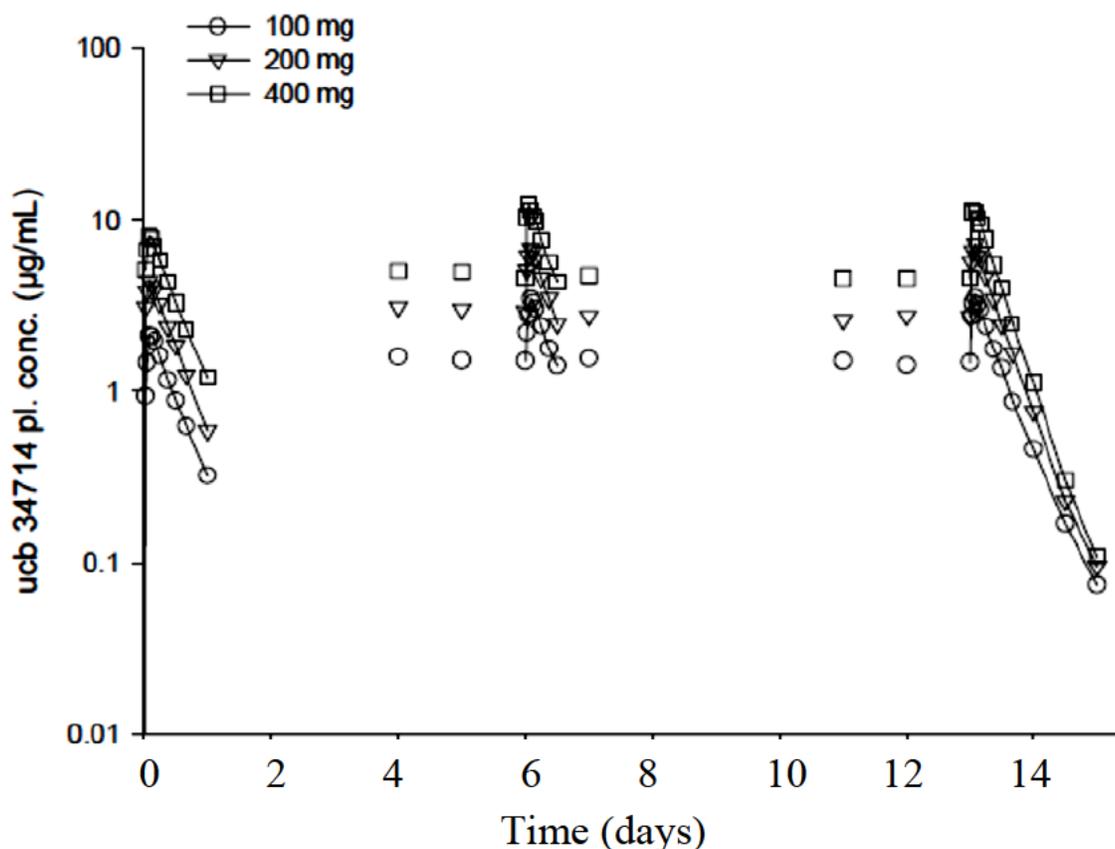
Parameter	Estimate (95% CI¹)	SE² (%CV)	IIV³	Shrinkage⁴
CL (L/h)	3.58 (3.50/3.66)	1.1%	24.7%	17.2%
V (L)	48.1 (45.8/50.4)	2.4%	30.5%	56.0%
Ka (1/h)	1.42 (1.26/1.57)	5.5%	101.2%	53.9%
Exponent for WT on CL	0.565 (0.499/0.631)	6.0%		
Exponent for WT on V	0.639 (0.483/0.795)	12.5%		
Effects on CL:				
CBZ ⁵	34.8% (30.5%/39.2%)	5.5%		
PHT ⁵	26.8% (20.0%/33.9%)	11.8%		
PB ⁵	23.9% (15.0%/33.4%)	17.6%		
Residual error:				
Proportional residual error (CV, %)	20.7 (19.7/21.7)	2.4%		14.0%

Steady State

Time to reach steady state:

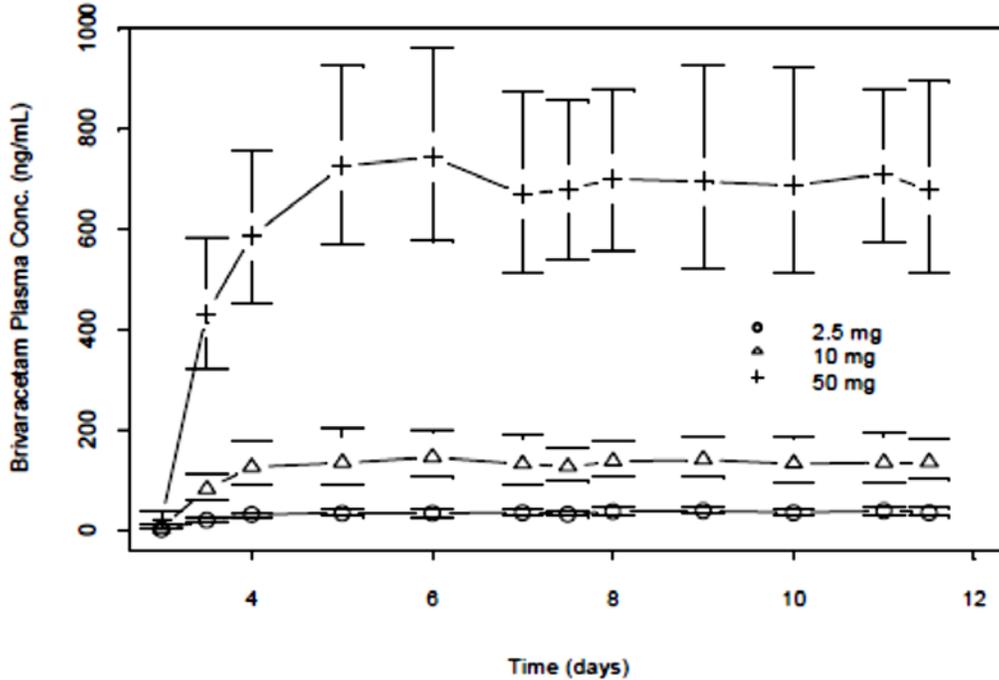
Based on available samples in the multiple dose PK study N01067, steady state was achieved by 4 days of 100 mg bid, 200 mg bid, or 400 mg bid dosing (see the figure below).

Figure 8: Mean BRV Plasma Concentration Profile over 14 Days of 100 mg bid, 200 mg bid, and 400 mg bid BRV Oral Capsules (N01067)



In study N01209, multiple doses of brivaracetam oral capsules were administered to healthy Japanese adult males. Based on trough concentrations, steady-state was achieved by approximately 5 days for the 50 mg bid group and approximately 4 days for the 2.5 mg bid and 10 mg bid groups.

Figure 9: Geometric Mean \pm SD Trough BRV Profile for 2.5 mg bid, 10 mg bid, and 50 mg bid BRV Oral Capsules from Days 1 to 12 (N01209B)

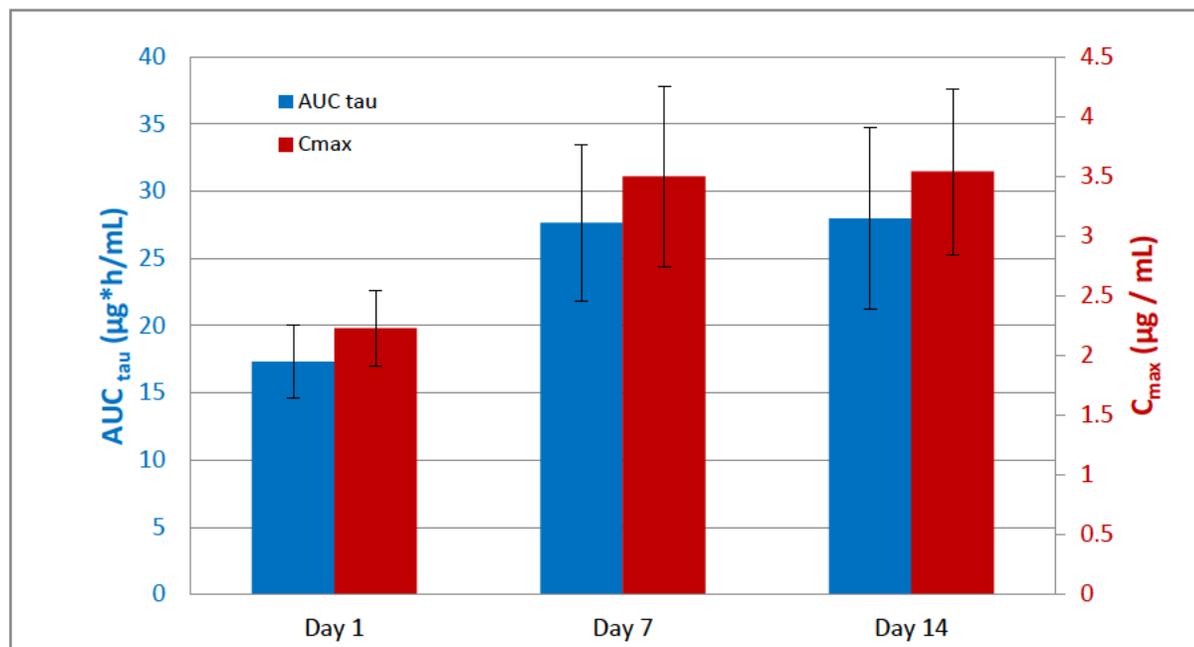


Overall, brivaracetam is likely to reach steady state after 4-5 days of 50 mg bid, 100 mg bid, or 200 mg bid administration.

Accumulation:

In study N01067, BRV accumulation, based on AUC_{τ} , was 1.62 to 1.60 (Days 7 and 14) for the 100 mg bid group, 1.52 to 1.51 (Days 7 and 14) for the 200 mg bid arm, and 1.39 to 1.42 (Days 7 to 14) for the 400 mg bid arm.

Figure 11: BRV C_{max} and AUC_{tau} (Mean ± SD) Over 14-Days of 100 mg bid (200 mg/day) Oral Administration



Fluctuation:

In study N01067, the peak-trough-fluctuation ($100\% \cdot [c_{max,ss} - c_{min,ss}] / c_{av,ss}$) was 92.34%, 104.31%, and 105.86% after 7 days of 100 mg bid, 200 mg bid, and 400 mg bid brivaracetam oral capsules. On Day 14, the PTF was 92.79%, 112.80%, and 120.16% for the 100 mg bid, 200 mg bid, and 400 mg bid groups.

Time-dependency of PK:

In study N01067, the overall BRV CL/F for the 100 mg bid group was not significantly changed after 14-days of administration.

Table 12: Geometric Mean (%CV) Plasma PK Parameters BRV On Days 1, 7, and 14 of Repeat 100 mg bid Administration

		ucb 34714 100 mg bid		
		Day 1	Day 7	Day 14
t_{max} (h)	Median	2.00	2.00	2.00
	Range	(1.02-4.03)	(0.98-3.00)	(1.00-2.00)
C_{max} (μ g/mL)	G. mean	2.23	3.50	3.54
	CV%	14.1	21.5	19.6
$t_{1/2}$ (h)	G. mean	7.67	-	7.33
	CV%	19.9	-	25.7
CL/F ^(b) (mL/min/kg)	G. mean	0.833	0.827	0.817
	CV%	20.5	21.3	22.6
V_z/F (L/kg)	G. mean	0.551	-	0.518
	CV%	8.7	-	11.3

The renal CL of brivaracetam increased from 0.038 mL/min/kg on Day 1 to 0.047 mL/min/kg. While the reason for this increase in renal CL is not clear, the change in renal CL does not warrant a dose adjustment as the renal route accounts for < 10% of BRV CL.

Table 13: Geometric Mean (%CV) Urinary PK Parameters BRV On Days 1, 7, and 14 of Repeat 100 mg bid Administration

Dose level: 100 mg bid				
Parameter	Units	Day 1	Day 7	Day 14
CL _R	mL/min/kg	0.038 (0.303)	0.042 (0.421)	0.047 (0.389)
CL _{NR}	mL/min/kg	0.790 (0.209)	0.780 (0.234)	0.765 (0.242)

The 200 mg bid group also demonstrated comparable BRV CL over 14 days. However, the 400 mg bid group demonstrated a 11% to 14% increase in BRV CL on Days 7 to 14, respectively, compared to Day 1. The reason for the increased CL in the 400 mg bid dose is not clear. However, the highest dose recommended for approval in this submission is 100 mg bid.

2.2.4.2 What are the characteristics of drug absorption?

Administration in fasted subjects, the median t_{max} was 1 hours (range 0.3 to 3 hours) in study EP0007. Oral tablet bioavailability is nearly 100% based AUC comparison with IV administration. The relative bioavailability between different formulations of brivaracetam is nearly 100%. Administration with a high-fat meal decreases C_{max} by 37%, delays t_{max} by 37%, and increases AUC by 5%.

2.2.4.3 What are the characteristics of drug distribution?

The protein binding of brivaracetam to human plasma was constant in the range of 0.5-100 µg/mL, with an average value of 20.7%.

The volume of distribution is 0.5 to 0.6 L/kg across 25 mg to 400 mg repeat doses of IV, oral capsule, and oral tablet formulations. The volume of distribution is comparable to total body water for a 70 kg adult (40 L).

Table 14: Comparison of Brivaracetam Volume of Distribution after Single and Repeat Doses of IV and Oral Formulations

BRV dose	Geometric mean (geometric CV%)			
	N01256B	N01067		N01287
	V _z	V _z /F		V _z /F
	iv infusion single dose N=6 (3M/3F)	capsule single dose N=9 (M only)	capsule bid (Day 14) N=9 (M only)	tablet single dose N=24 (14M/10F)
25mg	0.55 (8.53)	ND.	ND.	ND.
50mg	0.59 (12.2)	ND.	ND.	0.62 (14.3)
100mg	0.56 (13.2)	0.55 (8.67)	0.52 (11.33)	ND.
150mg	0.52 (11.8)	ND.	ND.	ND.
200mg	ND.	0.52 (7.65)	0.49 (6.07)	ND.
400mg	ND.	0.56 (8.89)	0.52 (10.36)	ND.

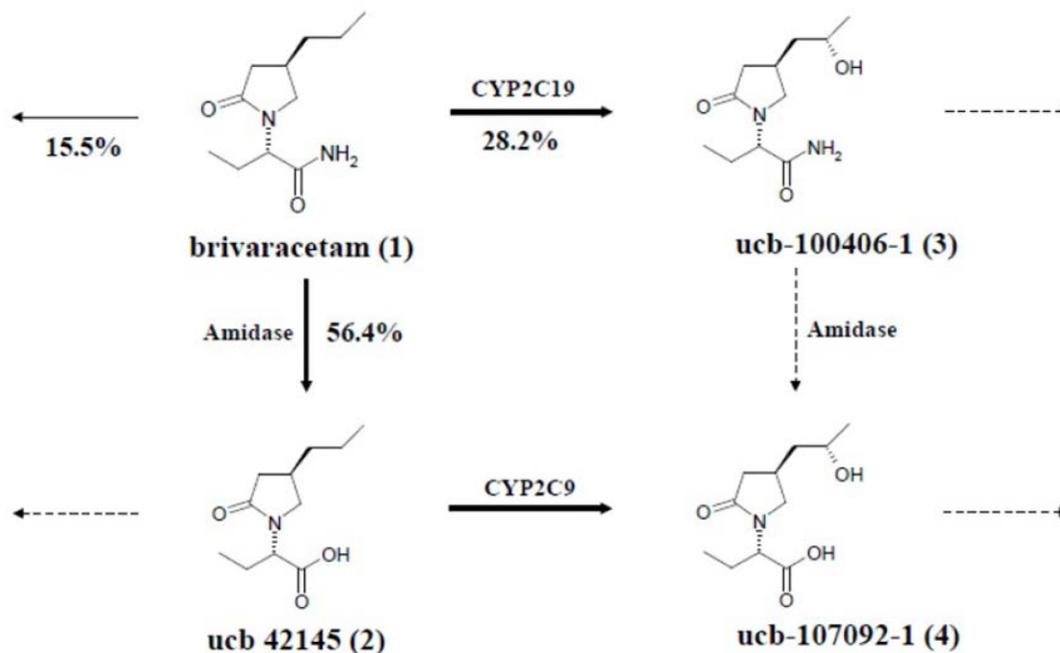
The mean V_d was 48.1 L in epilepsy patients receiving 25 mg bid, 50 mg bid, and 100 mg bid brivaracetam oral tablets in the phase 2 and phase 3 trials. The blood to plasma ratio of brivaracetam was 0.83 to 0.9 over a concentration range of 1 and 100 µg/mL.

2.2.4.4 What are the characteristics of drug metabolism?

Brivaracetam is extensively metabolized and excreted renally. The main metabolic pathway is hydrolysis of the acetamide group via hepatic and extra-hepatic amidase. This forms the carboxylic acid metabolite (ucb 42145). A secondary pathway is omega-1 hydroxylation by 2C19 into the hydroxy metabolite (ucb-100406-1).

The carboxylic acid metabolite (ucb 42145) can undergo hydroxylation by 2C9 to form the hydroxy acid metabolite (ucb-107092-1). In addition, the hydroxy metabolite (ucb-100406-1) can undergo hydrolysis of the acetamide group to form the hydroxy acid metabolite (ucb-107092-1).

Figure 15: Main Metabolic Pathways for BRV in Humans



None of the three metabolites are active. The table below shows a comparison of plasma exposures for brivaracetam and metabolites following IV and oral administration.

Table 16: Plasma exposures ($\mu\text{g}\cdot\text{h}/\text{mL}$) to BRV and metabolites following iv and oral dosing

Study and treatment (N)	BRV dose	Geometric mean AUC (geometric CV%)			
		BRV	ucb-100406-1 (hydroxy metabolite)	ucb 42145 (carboxylic acid metabolite)	ucb-107092-1 (hydroxyacid metabolite)
N01259 oral, gemfibrozil control (N=25)	150mg	41.4 (14.8)	4.18 (44.6)	3.29 (22.5)	0.966 (21.8)
oral, rifampicin control (N=26)		41.2 (14.7)	3.77 (62.1)	3.23 (22.9)	1.04 (17.3)
Mean oral ^b (N=51)		41.30	3.98	3.26	1.00
Percent of sum4 ^a		83.4%	8.0%	6.6%	2.0%
N01256B iv (N=6)	150mg	52.844 (27.2)	3.481 (35.9)	3.453 (6.07)	1.060 (16.6)
Percent of sum4 ^a		86.9%	5.7%	5.7%	1.7%

Mutations leading to ineffective CYP2C19 lead to 10-fold decrease in hydroxylation metabolite and 22% or 44% increase in BRV (for one or both mutated alleles, respectively).

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Hepatic and extrahepatic metabolism represent the major route of elimination with <10% of dose in unchanged in urine). Fecal excretion accounts for < 1% of dose. Please refer to section 2.2.2.

2.2.4.6 What are the characteristics of drug elimination?

Mass-Balance: The parent drug represented ~80% of the circulating radioactivity for up to 24 hours. By 48 hours, 90% of the radioactivity was excreted into the urine and < 1% of the dose was excreted into the feces. The 48 hour cumulative urinary excretion of parent compound brivaracetam was 8.7%, carboxylic acid (ucb 42145, M9) was 34.2%, hydroxy metabolite (ucb 100406-1, M1b) was 15.9%, and hydroxy acid metabolite (ucb-107029-1, M4b) was 15.2% of the dose, respectively. The renal CL of brivaracetam represented 5 to 15% of total body brivaracetam CL (suggesting tubular resorption is taking place).

In Study N01256B after iv administration of BRV 150mg, cumulative urinary excretions (fe_{0-72h}) were 12.6% for BRV, 29.6% for the carboxylic acid metabolite (ucb 42145), 10.8% for the hydroxy metabolite (ucb-100406-1), and 16.1% for the hydroxy-acid metabolite (ucb-107092-1).

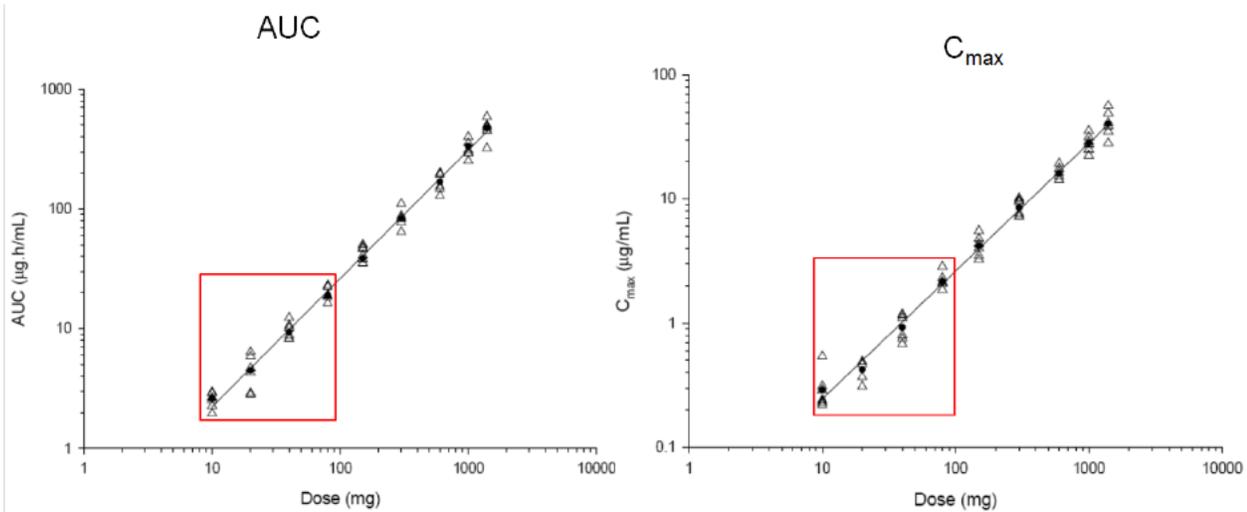
In study N01259 (in the control group without concomitant gemfibrozil or rifampicin), cumulative urinary excretions (fe_{0-72h}) were 8.33% for BRV, 27.2% for the carboxylic acid metabolite (ucb 42145), 12.9% for the hydroxy metabolite (ucb-100406-1), and 14.2% for the hydroxy-acid metabolite (ucb-107092-1).

Brivaracetam terminal plasma $t_{1/2}$ is 7-9 hours in patients and healthy subjects.

2.2.4.7 Based on PK parameters, what is the degree of linearity in the dose concentration relationship?

Single-Dose: Proportionality was assessed in study N01066. C_{max} is dose-proportional from 10 to 1400 mg. AUC is dose-proportional from 10 to 600 mg. At doses greater than 600 mg, AUC is 24-28% greater than proportional. The proposed to-be-marketed oral tablet strengths, 10, 25, 50, 75, and 100 mg are contained within the dose range that is proportional for C_{max} and AUC.

Figure 17: Dose-Exposure Relationship for Single BRV Oral Capsules



*The red boxes indicate the strengths that are being included in the commercial tablets

Multiple Dose: In study N01067, the $AUC_{0-\infty}$ increases in a dose-proportional manner for the 100 mg bid and 200 mg bid groups on Days 1, 7, and 14. For the 400 mg bid group, the AUC_{τ} increased less than proportionally (15-19% less) on Days 7 and 14.

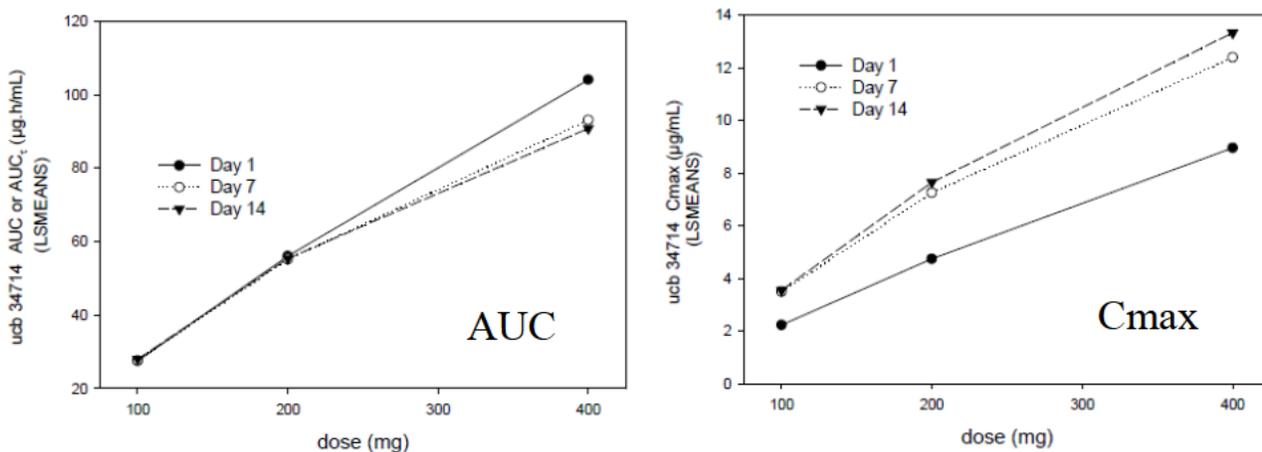
Table 18: Statistical Comparison of Dose-Normalized PK Parameters after 100, 200, and 400 mg bid Brivaracetam Oral Capsules Administered for 14 days (N01067).

		200/100 mg bid Ratio (90% CI)		400/100 mg bid Ratio (90% CI)		400/200 mg bid Ratio (90% CI)	
AUC	Day 1	1.018	(0.880; 1.178)	0.945	(0.817; 1.094)	0.928	(0.802; 1.075)
AUC τ	Day 7	0.998	(0.858; 1.161)	0.842	(0.724; 0.979)	0.843	(0.725; 0.981)
[µg \cdot h/mL]	Day 14	0.989	(0.845; 1.158)	0.811	(0.693; 0.950)	0.820	(0.700; 0.959)
C $_{max}$	Day 1	1.062	(0.930; 1.212)	1.003	(0.879; 1.145)	0.945	(0.828; 1.078)
[µg/mL]	Day 7	1.038	(0.900; 1.196)	0.886	(0.768; 1.021)	0.854	(0.740; 0.984)
	Day 14	1.079	(0.908; 1.282)	0.940	(0.792; 1.117)	0.871	(0.733; 1.035)

Clearance was analyzed without dose normalization.

AUC is $AUC_{0-\infty}$

Figure 19: Least-Squares Mean AUC and Cmax of BRV after 100, 200, and 400 mg bid Brivaracetam Oral Capsules Administered for 14 days (N01067).



Similarly, the C_{max} increased proportionally for the 100 mg bid and 200 mg bid groups from Day 1, 7, and 14 (though the upper limit of the 90% CI was 1.282 on Day 14 for the 200/100 mg comparison). The C_{max} increased less than proportionally (6-14% less) for the 400 mg group compared to the two other dose groups on Days 7 and 14.

2.2.4.8 How does the PK of the drug and its major metabolites in healthy subjects compare to that in patients?

The population PK analyses (CL0028) estimated the brivaracetam clearance in patients with epilepsy receiving brivaracetam 50 mg/day (25 mg bid), or 100 mg/day (50 mg bid), or 200 mg/day (100 mg bid) as well as 1-2 concomitant AEDs in the phase 2 and phase 3 trials. The mean BRV CL_{ss}/F was 3.58 L/h (CV 24.7%).

In study N01067, healthy subjects receiving brivaracetam 100 mg/day (50 mg bid) and 200 mg/day (100 mg bid) for 14 days, demonstrated a brivaracetam Cl_{ss}/F of 3.572 L/h (CV 20.68%) and 3.611 L/h (16.48%), respectively.

The brivaracetam CL is comparable in healthy volunteers compared to patients with epilepsy receiving 1-2 concomitant AEDs.

2.2.4.9 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The %CV of BRV CL_{ss}/F was 24.7% in *epilepsy* patients receiving 50 mg/day (25 mg bid), or 100 mg/day (50 mg bid), or 200 mg/day (100 mg bid) in phase 2 and phase 3 trials.

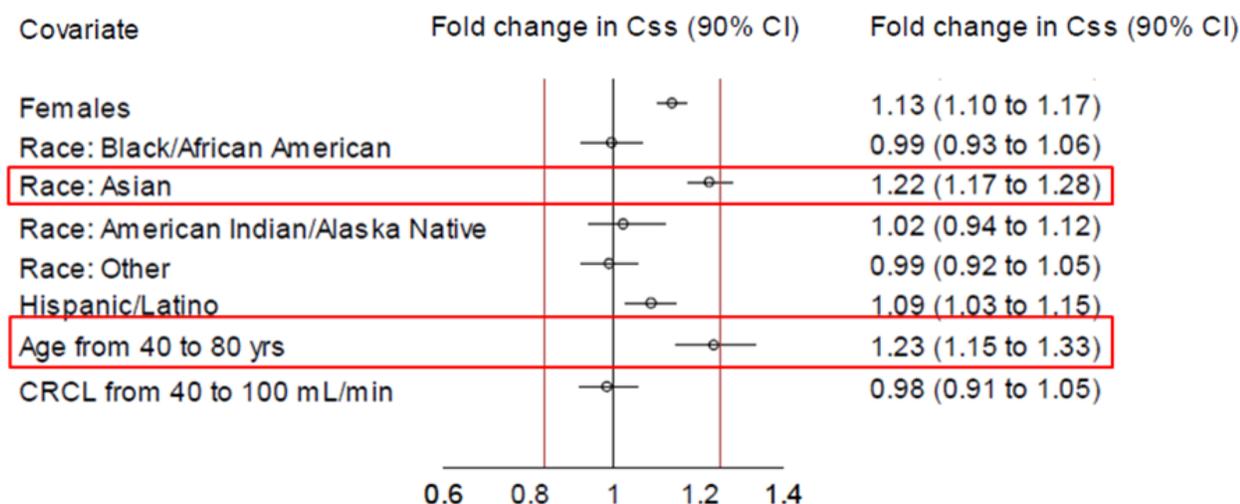
The %CV of %CV of BRV CL_{ss}/F was 20.68% and 16.48% in *healthy subjects* receiving 100 mg/day (50 mg bid) and 200 mg/day (100 mg bid) for 14 days in study N01067.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Sponsor conducted a population PK analyses based on C_{ss} PK data obtained from trials N01114, N01193, N01252, N01253, N01358. The follow figure presents key intrinsic factors affecting BRV PK.

Figure 20: Forest Plot of Intrinsic Factors Affecting BRV C_{ss} Based on Pop PK



The results of the population PK study as well as clinical pharmacology studies in special populations will be discussed below.

2.3.1.1 Elderly

Study N01118 was an open-label, pharmacokinetic, safety and tolerability study of a single dose followed by a 10 day b.i.d. dosing regimen of BRV administered twice a day orally as 200 mg capsules in healthy elderly volunteers (65-75 years). The following

- AUC_{tau} accumulation was comparable in elderly adults (R_{AUC,tau} = 1.47 in study N01118) and non-elderly adults (R_{AUC,tau} = 1.5 in study N01067)
- C_{max} was 14% greater after multiple 200 mg bid doses to elderly subjects (Day 12 mean C_{max} 8.751 [19.9%] µg/mL) compared to multiple 200 mg bid doses to healthy non-elderly subjects (Day 14 mean C_{max} 7.65 [26.2%] µg/mL in study N01067). Considering the safety profile in the current study, no dose reduction is required based on the C_{max} elevations.
- AUC_{tau} was 15% greater after multiple 200 mg bid doses to elderly subjects (Day 12 mean AUC_{tau} 63.59 [15.0%] µg*h/mL) compared to multiple 200 mg bid doses to healthy non-elderly subjects (Day 14 mean AUC_{tau} 55.38 [18.3%] µg/mL in study N01067). Considering the safety profile in the current study, no dose reduction is required based on the AUC elevations.

Reviewer Comment:

The elderly PK study N01118 was conducting using a 400 mg/day (200 mg bid) dose level, which is double the maximum dose the Sponsor proposed for approval (200 mg/day, 100 mg bid). Despite this high dose, 15 out of 16 randomized the elderly subjects were able to complete the study. In addition, the TEAE rate for dizziness, headache, and somnolence (43.7%, 37.5%, and 56.2%) in elderly subjects receiving 400 mg/day (200 mg bid) were lower than to the values reported for the 400 mg/day (200 mg bid) group in trial N01067 (66.7%,

44.4%, and 44.4%). In addition, exposure-response analyses for safety demonstrated a flat relationship between brivaracetam exposure and common adverse events (dizziness, headache, and somnolence)

For these reasons, no BRV dose adjustment is necessary in elderly subjects.

2.3.1.2 Gender

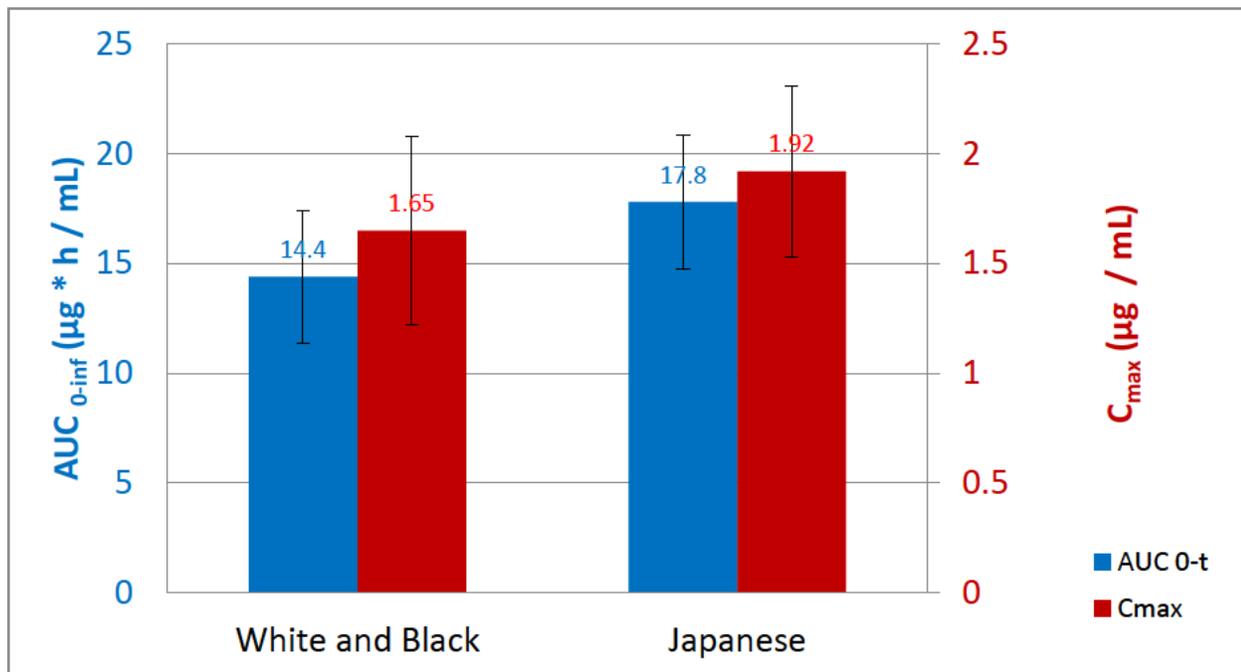
There is no significant change in BRV C_{ss} in Females.

2.3.1.3 Race

Asian:

The population PK analyses indicate a 22% increase in C_{ss} for the Asian racial group. In addition to the Asian subjects analyzed in the population PK analyses, Sponsor conducted a study where BRV was assessed in Japanese subjects (N01209). Study N01209 was an open-label, randomized, five-way cross-over relative bioavailability/bioequivalence study of 50 mg brivaracetam solid oral formulations (capsule and tablet) using as reference brivaracetam 50 mg oral solution in Japanese subjects. Sponsor provide a comparison of the exposures in n=8 Japanese subjects (study N01209) was made with n=13 Caucasian (n=13) and n=1 black subjects (study N01287).

Figure 21: BRV PK (Mean ± Std) in Japanese (N01209) Versus White and Black (N01287) After a Single 50 mg Tablet



Reviewer Comment:

*The 16% increase in C_{max} and 23% increase AUC_{0-t} in Japanese compared to Black and White subjects, and the overall 22% increase in C_{ss} in Asians compared to non-Asians indicates that **a dose adjustment is not necessary for people of the Asian race.***

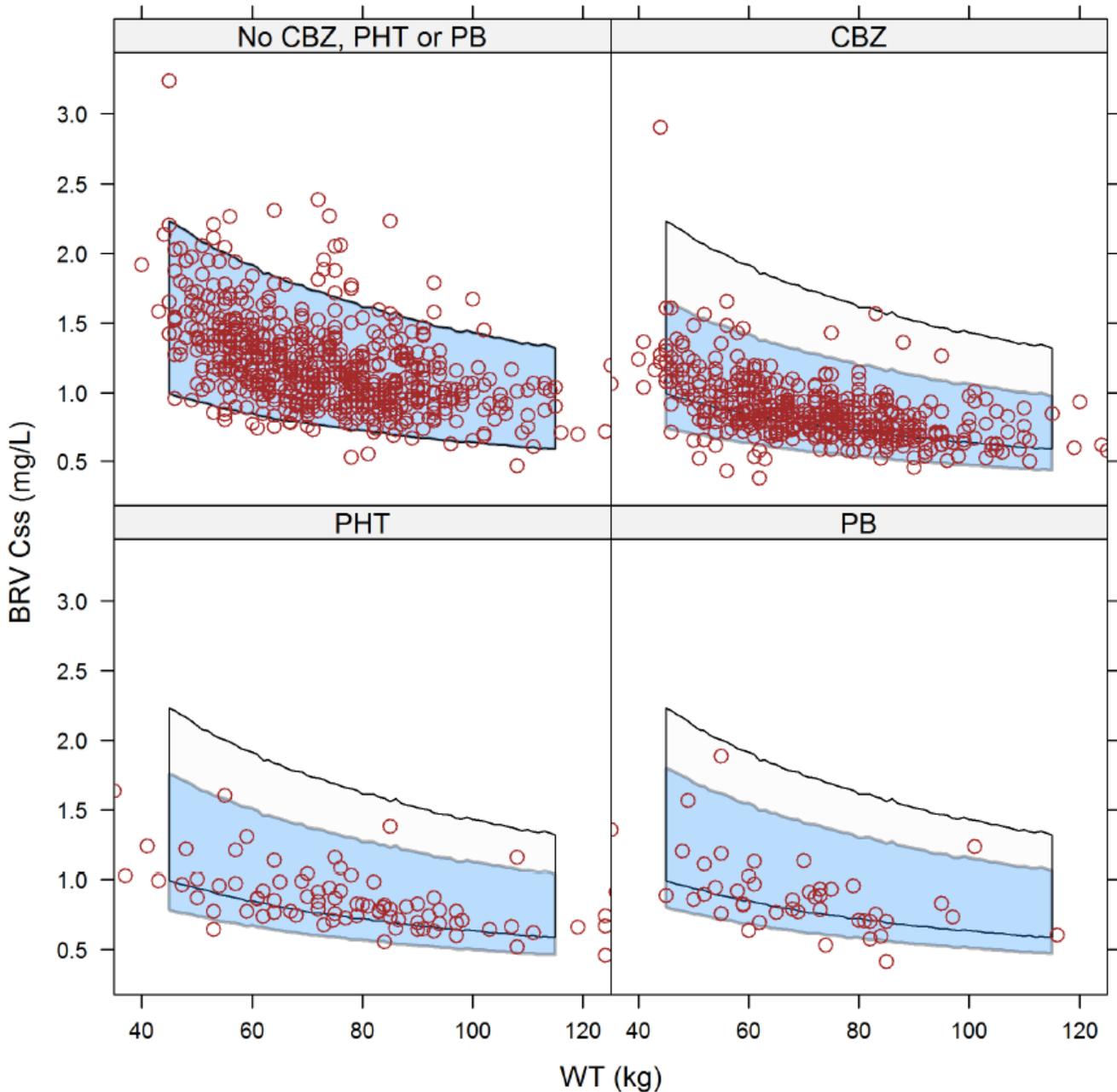
Other Races / Ethnicities: There is no significant change in BRV C_{ss} in Black/African American, American Indian / Alaska Native, other races, Hispanic / Latino on BRV PK.

2.3.1.4 Weight

Sponsor determined that body weight (allometrically scaled to a 70 kg body weight) is a covariate on brivaracetam CL and V. Overall, the brivaracetam population CL varied from 2.82 to 4.74 mL/min (a 68% increase) across a weight range from 46 to 115 kg (which encompasses 95% of the weights on the patient population).

Sponsor conducted PK simulations to determine the effect of weight on brivaracetam C_{ss} . In addition to weight Sponsor included the effects of carbamazepine, phenytoin, and phenobarbital (co-medications which were demonstrated the largest effect on brivaracetam pharmacokinetics).

Figure 22: Predicted C_{ss} for 50 mg BRV BID as a function of WT and co-administration of CBZ, PHT, or PB



The blue area encompasses 90% of predicted C_{ss} values for patients in either the absence of CBZ, PHT, and PB co-administration, or the presence of CBZ or PHT or PB co-administration. The black solid line is identical for all graphs and is added as reference encompassing 90% of predicted C_{ss} values in the absence of CBZ, PHT, and PB co-administration. The red circles are the predicted C_{ss} values for patients in the analysis that have only one of CBZ, PHT, or PB co-administered or none of these three AEDs.

*Reviewer comment: Though there is a trend towards decreasing $C_{av,ss}$ in patients with greater body weight, the plateau of the exposure-response analyses suggest that a **dose increase based on body weight is not necessary.***

2.3.1.5 Pediatrics

Sponsor conducted study N01263, an open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive brivaracetam in subjects from ≥ 1 month to < 16 years old with epilepsy. Brivaracetam oral solution was administered at weekly increasing doses:

subjects ≥ 8 years of age: 0.4mg/kg, 0.8mg/kg, and 1.6mg/kg bid,

subjects < 8 years of age: 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg bid

(b) (4)

Reviewer Comment:

This reviewer concurs with the Sponsor that, based on the lower exposures observed in patients < 8 years, a dose increase may be required in subjects < 8 years of age old.

Sponsor submitted a waiver request for subject's age < 1 month, and a deferral request for subject's age 1 month to < 16 years.

(b) (4)

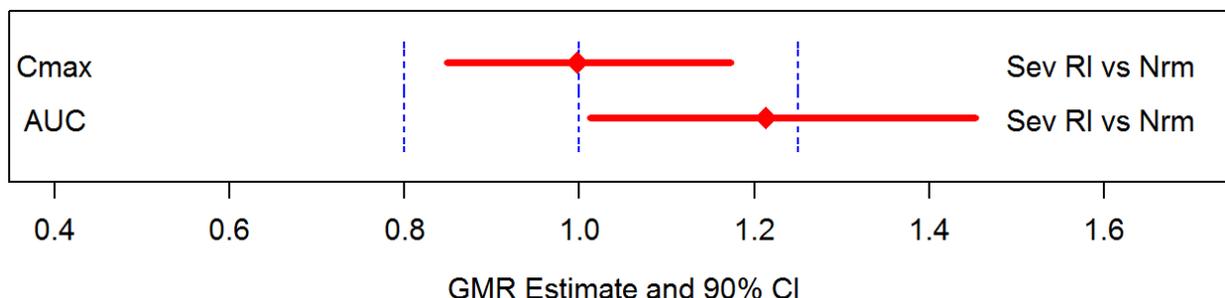
2.3.1.6 Renal Impairment

Sponsor conducted study N01109, Phase 1, open-label, parallel-group, not randomized, PK study in healthy subjects with normal renal function or subjects with severe renal impairment.

Table 23: Geometric Mean (CI) of AUC_{0-∞} for BRV and Metabolites after a single 200 mg administration to health (Group A) and Severe RI (Group D) (PP population)

Parameter	Healthy Subjects (Group A) – n=9 AUC _{0-∞} (µg*h/mL)	Severe Renally Impaired Subjects (Group D) – n=9 AUC _{0-∞} (µg*h/mL)	Ratio Group D / Group A % (90% CI)
Brivaracetam (ucb 34714)	63.1 (54.0 – 73.7)	76.5 (58.5 – 100.1)	121.25% (101.19% – 145.29%)
Carboxylic acid metabolite (ucb 42145)	3.51 (2.71 – 4.55)	11.4 (7.97 – 16.3)	324.0% (250.7% – 418.5%)
Hydroxy metabolite (ucb-100406-1)	14.1 (8.78 – 22.7)	57.5 (39.1 – 84.8)	407.7% (285.3% – 582.6%)
Hydroxy-Acid metabolite (ucb-107092-1)	1.67 (1.31 – 2.13)	35.8 (23.8 – 54.0)	2148% (1627% - 2836%)

Figure 24: Effect of Severe Renal Impairment on BRV Exposure (Study N01109)



Severe renal impairment was associated with a 21% increase in BRV AUC_{0-∞} and a < 1% decrease in BRV C_{max}. Patients with a severe renal impairment demonstrated increases of 3.2-fold, 4.1-fold, and 21.5-fold in AUC_{0-∞} of the carboxylic acid metabolite (ucb 42145), hydroxy metabolite (ucb-100406-1), and hydroxyacid metabolite (ucb-107092-1), respectively.

Sponsor made the following conclusions:

- Dose adjustments are not required for patients with impaired renal function.
- Non-clinical studies were performed to characterize the safety of the hydroxyacid metabolite, and they did not reveal any safety issues.
- Brivaracetam is not recommended in patients with end-stage renal disease that are undergoing dialysis due to a lack of data.

Reviewer Comments: None of the three metabolites (carboxylic acid metabolite [ucb 42145], hydroxy metabolite [ucb-100406-1], or hydroxyacid metabolite [ucb-107092-1]) are active. However, concern was raised in the TQT review regarding the elevated exposures observed in subjects with renal impairment. IN particular, though BRV exposures achieved after 6.5 days of 400 mg BRV bid dosing (800 mg/day) did not result in a significant QT effect, the

reviewer raised a concern that the exposures observed in severe RI may not be covered by the metabolite exposures in the TQT study (see the review of IND 70205 signed on 03/05/2009 for details)

In order to help assess risk of metabolites exposures such as those observed in severe RI patients, the human PK in the renal impairment study N01109 were compared with non-clinical PK. The $AUC_{0-\infty}$ single dose was used as an estimate of $AUC_{\tau,ss}$ for each metabolite. However, as the non-clinical toxicology studies reported $AUC_{0-24\text{hour}}$, the $AUC_{\tau,ss}$ for metabolites in humans was multiplied by 2 (as the tau is 12 hours) before comparison with the non-clinical $AUC_{0-24\text{hour}}$.

Though metabolite exposures in severe RI patients were over 3-, 4-, and 21-fold greater than in healthy volunteers, the Sponsor has conducted in-vivo non-clinical studies 4 to 13 weeks in duration which achieved metabolite exposures in 8.5 -, 10.7-, and 25-fold excess of predicted SS metabolite exposures in patients with severe renal impairment (see the table below).

Table 25: Comparison of Metabolite Exposures in Patients with Severe RI, Healthy Patients in TQT Study, and Animals:

Study	TQT (N01233)	Renal Impairment (N01109)			Animal Studies	
Name	AUC_{τ} in healthy Volunteers receiving 6.5 days 400 mg BID	$AUC_{0-\infty}$ in Healthy Volunteer after single oral 200 mg dose	$AUC_{0-\infty}$ in severe RI after single oral 200 mg dose	Predicted AUC_{0-24h} at SS in Severe RI Patients ($AUC_{\tau,ss} = AUC_{0-\infty, \text{single dose}}$, $AUC_{0-24h,ss} = 2 \times AUC_{\tau,ss}$)	AUC_{0-24h} at SS in animal studies	Fold-Increase in animal AUC at SS compared to severe RI predicted AUC SS
BRV (Ucb 34714)	123 $\mu\text{g}^*\text{h}/\text{mL}$	63.1 $\mu\text{g}^*\text{hr}/\text{mL}$	76.5 $\mu\text{g}^*\text{hr}/\text{mL}$	153 $\mu\text{g}^*\text{hr}/\text{mL}$	6795 $\mu\text{g}^*\text{hr}/\text{mL}$ (4-week rat study)	44-fold
carboxylic acid metabolite (ucb 42145)	7.52 $\mu\text{g}^*\text{hr}/\text{mL}$	3.51 $\mu\text{g}^*\text{hr}/\text{mL}$	11.4 $\mu\text{g}^*\text{hr}/\text{mL}$	22.8 $\mu\text{g}^*\text{hr}/\text{mL}$	195 $\mu\text{g}^*\text{hr}/\text{mL}$ (4-week rat study)	8.5-fold
hydroxy metabolite (ucb-100406-1)	10.8 $\mu\text{g}^*\text{hr}/\text{mL}$	14.1 $\mu\text{g}^*\text{hr}/\text{mL}$	57.5 $\mu\text{g}^*\text{h}/\text{mL}$	115 $\mu\text{g}^*\text{hr}/\text{mL}$	1231 $\mu\text{g}^*\text{hr}/\text{mL}$ (4-week monkey study)	10.7-fold
Hydroxy-acid metabolite (ucb-107092-1)	2.54 $\mu\text{g}^*\text{hr}/\text{mL}$	1.67 $\mu\text{g}^*\text{hr}/\text{mL}$	35.8 $\mu\text{g}^*\text{h}/\text{mL}$	71.6 $\mu\text{g}^*\text{hr}/\text{mL}$	1818 $\mu\text{g}^*\text{hr}/\text{mL}$ (13-week rat study)	25-fold

As there were no cardiovascular safety signals in these 4 to 13 week non-clinical toxicology studies, the actual clinical dose (100 mg bid, or 200 mg/day) will be half of the single 200 mg

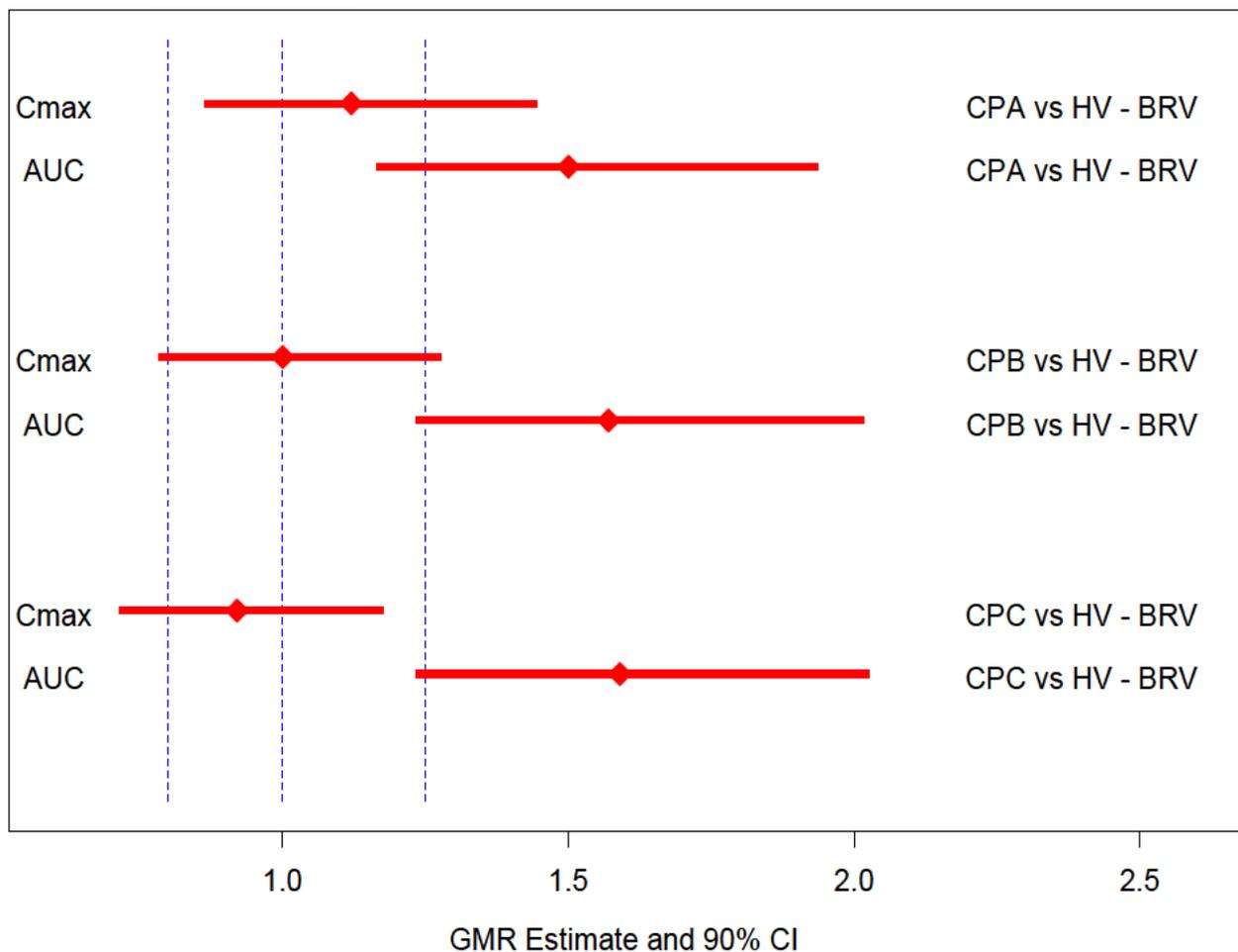
dose administered in this study, and since their exposures exceed the predicted steady-state exposures in patients with severe RI by 50-, 9.6, 6.3-, and 15-fold for BRV and metabolites, then **no dose adjustment is required for patients with renal impairment.**

2.3.1.7 Hepatic Impairment

Sponsor conducted study N01111 where a single oral administration of 100 mg BRV (2 x 50 mg capsules) was administered to healthy subjects and patients with impaired liver function (Child-Pugh classes A, B, and C).

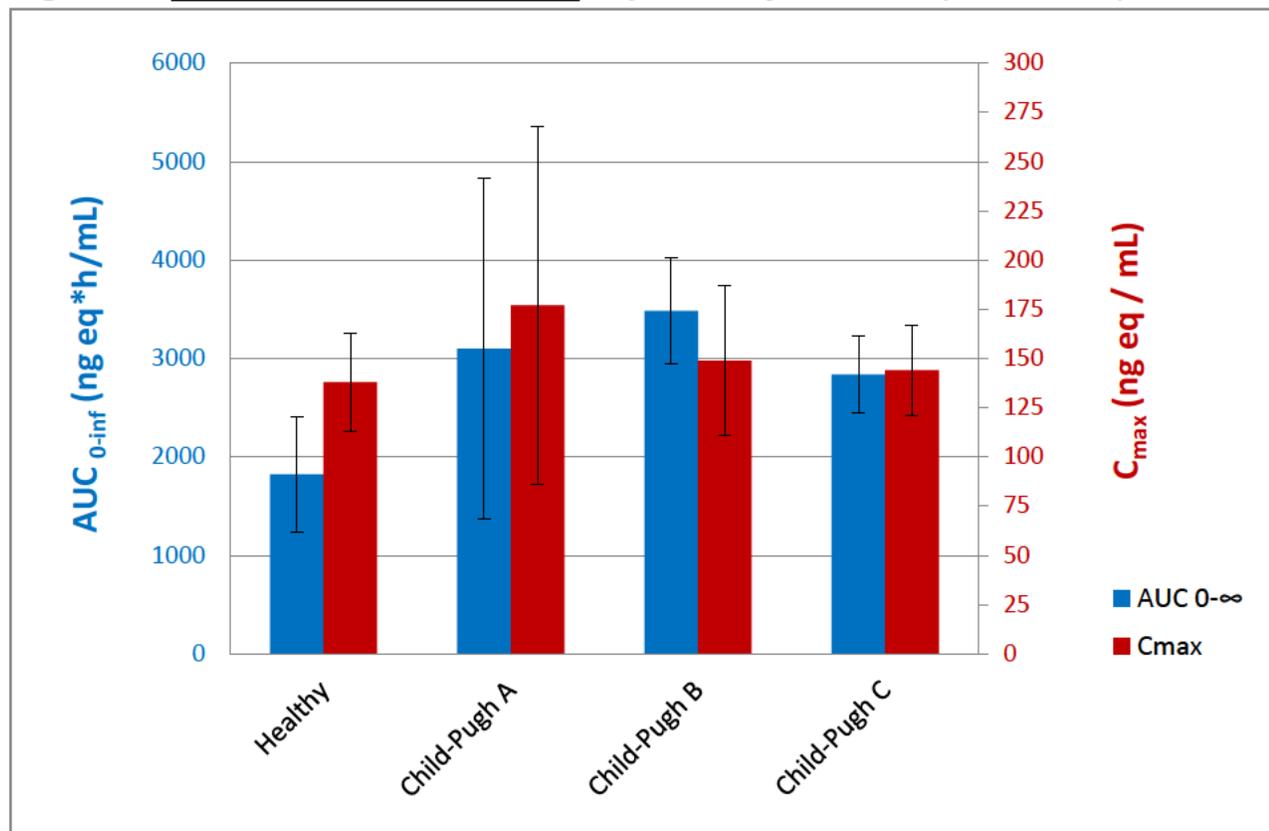
There was no consistent change in BRV C_{max} with regard to hepatic impairment severity. The $AUC_{0-\infty}$ increased by 50%, 57%, and 58% in subjects with Child-Pugh A, B, and C grades of hepatic impairment.

Figure 26: Brivaracetam Exposure by Hepatic Impairment Status (Study N01111)



The carboxylic acid metabolite (ucb 42145) C_{max} and $AUC_{0-\infty}$ increased up to 28% and 91%, respectively, in subjects with hepatic impairment.

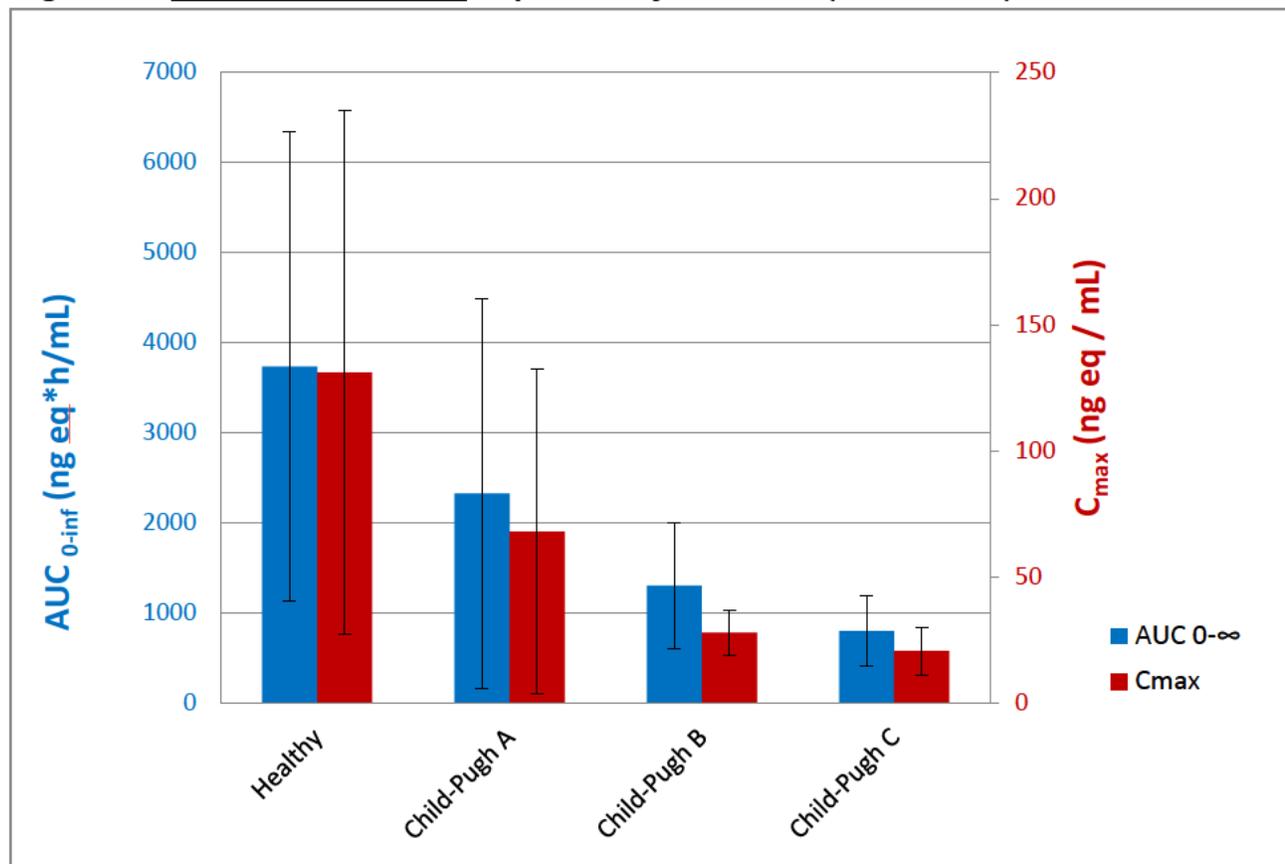
Figure 27: Carboxylic Acid Metabolite Exposure By HI Status (Mean ± Std)



*carboxylic acid metabolite = ucb 42145

The hydroxy metabolite (ucb-100406-1) C_{max} and AUC_{0-∞} decreased by up to 84% and 78%, respectively, in subjects with hepatic impairment.

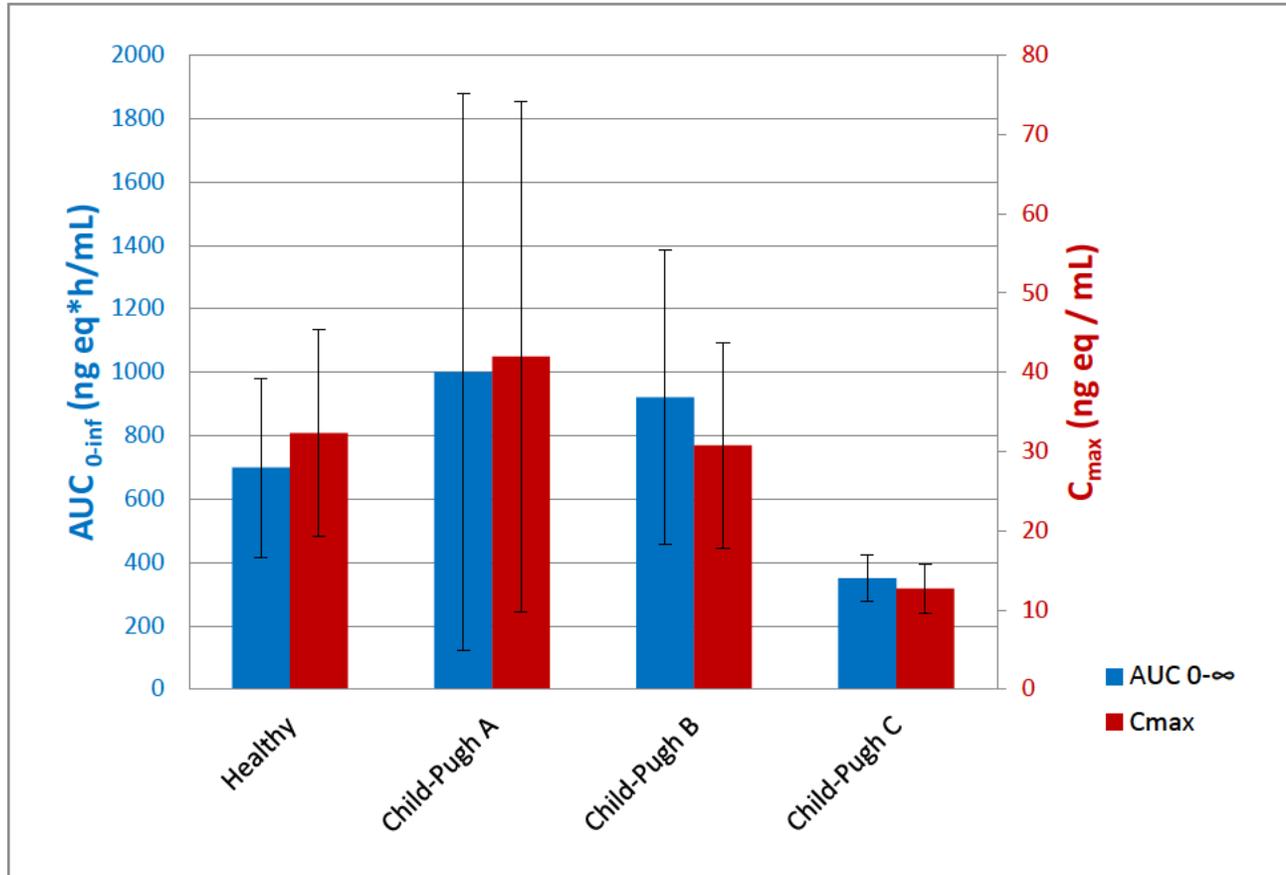
Figure 28: Hydroxy Metabolite Exposure By HI Status (Mean ± Std)



*hydroxy metabolite = ucb-100406-1

The hydroxy-acid metabolite (ucb-107092-1) C_{max} and AUC_{0-∞} increased in Child-Pugh Class A (up to 30% and 43% increase, respectively) and decreased in Child-Pugh Class C (50% and 60% reduction).

Figure 29: Hydroxyacid Metabolite Exposure By HI Status (Mean ± Std)



* hydroxyacid metabolite = ucb-107092-1

Sponsor proposes the following labeling actions based on the results of the HI study.

- A 25 mg twice daily (50 mg per day) starting dose should be considered.
- A maximum dose of 75 mg twice daily (150 mg per day) is recommended for all stages of hepatic impairment

Reviewer Comments:

As the 3 metabolites are not active, then reductions in the hydroxy metabolite and hydroxyacid metabolite are not likely to result in reduced efficacy. Based on the analyses conducted for the metabolite exposure increase observed in severe renal impairment (see section 2.3.1), the increase in hydroxy acid metabolite exposure is not expected to result in tolerability issues.

(b) (4)
the Sponsor (b) (4) in the current submission proposes a dose reduction.

The Sponsor's upper dose limit of 75 mg bid (150 mg/day) for patients with hepatic impairment seems unnecessary for the following reasons:

- *TEAE rates in study N01111 (hepatic impairment study) were comparable or lower in the hepatic impairment arms compared to the healthy subject arm,*
- *the BRV exposure-safety relationship for the common adverse events (e.g. somnolence, dizziness, and fatigue) indicates a modest increase of adverse event risk with increasing BRV exposures (see the Pharmacometrics section of this review for details),*
- *metabolites are not active (and reduced metabolite exposures not likely to reduce efficacy),*
- *safety of metabolite exposure increases are supported by available non-clinical data (see section 2.3.1), and*

*For the same reasons, the reduced starting dose is also unnecessary. **Overall, no dose adjustment is required for hepatic impairment.***

2.3.1.8 CYP2C19 Polymorphisms

Sponsor conducted study N01209, a double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects. The study conducted an assessment of 2C19 genotype (extensive metabolizers and poor metabolizers) on brivaracetam pharmacokinetics. Poor metabolizer subjects had approximately 44% higher exposure (AUC_{0-∞}) as compared to homozygous EM subjects.

Reviewer Comments:

*The BRV exposure-safety relationship for the common adverse events (e.g. somnolence, dizziness, and fatigue) indicates a modest increase of adverse event risk with increasing BRV exposures (see the Pharmacometrics section of this review for details). As such, default starting dose of 50 mg bid (100 mg/day) is acceptable and a reduction of the maximum dose, 100 mg bid (200 mg/day) is unnecessary. **For these reasons, it is not necessary to assess the CYP2C19 genotype of patients receiving brivaracetam.***

2.4 Extrinsic Factors

2.4.1 Is the drug and/or the major metabolite a substrate, inhibitor or inducer of CYP enzymes on an in vitro basis?

Metabolism: The biotransformation of brivaracetam included the hydrolysis of the amide group into the carboxylic acid metabolite ucb 42145, ω-1 hydroxylation into the hydroxy metabolite ucb-100406-1, and the combination of the 2 pathways into the hydroxyacid metabolite ucb-107092-1. The hydrolytic reactions are mediated by hepatic and extra-hepatic

amidase and serine esterase, not by acetylcholinesterase, butyrylcholinesterase, or carboxylesterase 1/2. The formation of ucb-100406-1 involves multiple CYPs: CYP2C19, 2C9, 3A4 and limited role by CYP2C8. The affinity of brivaracetam for CYP2C19 (K_m) was about 70 μM , whereas its affinity for CYP2B6, 2C8, 2C9 and 3A4 was much less ($K_m \geq 900 \mu\text{M}$). The oxidation of ucb 42145 into ucb-107092-1 was primarily mediated by CYP2C9.

Inhibition potential: Brivaracetam at the concentration of 200 μM (42 $\mu\text{g}/\text{mL}$) was shown to act as a reversible inhibitor of CYP2C19 (46% inhibition). Brivaracetam did not significantly inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6 or 3A4. Brivaracetam did not produce any metabolism-dependent inhibition for these CYP isoforms.

The IC_{50} of ucb 34714 for CYP2C19 was estimated to be about 230 μM . Thus, the approximate K_i value could be 115 μM if the mechanism of inhibition was competitive. The ratio of steady-state C_{max} of brivaracetam after 100 mg bid dosing divided by its K_i for CYP2C19 is estimated to be about 0.14, just marginally above a cut-off of 0.1, suggesting that brivaracetam is less likely to cause significant DDI mediated by CYP2C19 inhibition *in vivo*.

The carboxylic acid metabolite ucb 42145 and the hydroxy metabolite ucb-100406-1 did not have significant inhibition effect on CYP2C9 and 2C19.

Brivaracetam was an inhibitor of epoxide hydroxylase ($\text{IC}_{50} = 8.2 \mu\text{M}$ in hepatocytes), suggesting that brivaracetam can inhibit the enzyme in vivo.

Induction Potential: Brivaracetam at concentrations up to 10 μM caused little or no change of mRNA expression of CYP1A2, 2B6, 2C9, 2C19, 3A4, and microsomal epoxide hydrolase. Brivaracetam at concentrations up to 500 μM did not induce CYP1A2 measured by enzyme activity. Brivaracetam at concentrations up to 100 μM slightly induced CYP2B6 activity. However, the effect was small (up to 2.6-fold) and less than (< 40%) the effect of positive control. Brivaracetam at concentrations up to 100 μM did not increase CYP3A activity. Though at higher concentrations (up to 500 μM), brivaracetam showed some induction of CYP3A activity, the effect was small (at most 3-fold) and less than (<40%) of the effect of positive control.

Overall, brivaracetam is not expected to have induction effect on CYP1A2, 2B6, 2C9, 2C19, and 3A in vivo at its therapeutic doses.

2.4.2 Is the drug and/or the major metabolite a substrate and/or an inhibitor of P-glycoprotein transport processes or any other transporter system?

Transporter Substrate: Brivaracetam was not a substrate of P-gp, MRP1 or MRP2. It has not been tested as substrate for other major transporters. Since brivaracetam absorption is high (95%) and it is eliminated mainly by metabolism, inhibition of efflux transporter such as BCRP is not expected to have significant effect on its PK. Since renal clearance of brivaracetam is a minor pathway, renal transporters OAT1, OAT3, and OCT2 are not expected to play an important role in brivaracetam PK. Permeability of brivaracetam measured in Caco-2 monolayer cells was similar between apical to basolateral and basolateral to apical directions and was comparable to that of the high permeability marker antipyrine. Considering its high

passive permeability, OATP1B1/3 may not contribute significantly to its uptake into hepatocytes.

Overall, these transporters are not expected to play a significant role in PK of brivaracetam.

Transporter Inhibitor: Brivaracetam (200 µM) and its metabolites ucb 42145 (10µM), ucb-100406-1 (10µM) and ucb-107092-1 (2µM) were tested for their ability to inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, P-gp or BSEP. Brivaracetam showed inhibition of OAT3 (18.1%), OATP1B1 (29.6%), and OCT1 (21.7%), suggesting that its IC₅₀ on these transporters would be more than 200 µM. Thus, the ratios of total C_{max}/IC₅₀ (for P-gp and BCRP), (Dose/250 mL)/IC₅₀ (for P-gp and BCRP), free C_{max}/IC₅₀ (for OATs and OCT2), or free liver inlet C_{max}/IC₅₀ (for OATP1B1/3) are less than the cut-off values of 0.1, 10, 0.1, or 0.25, **suggesting that at therapeutic doses brivaracetam will not inhibit these transporters in vivo.**

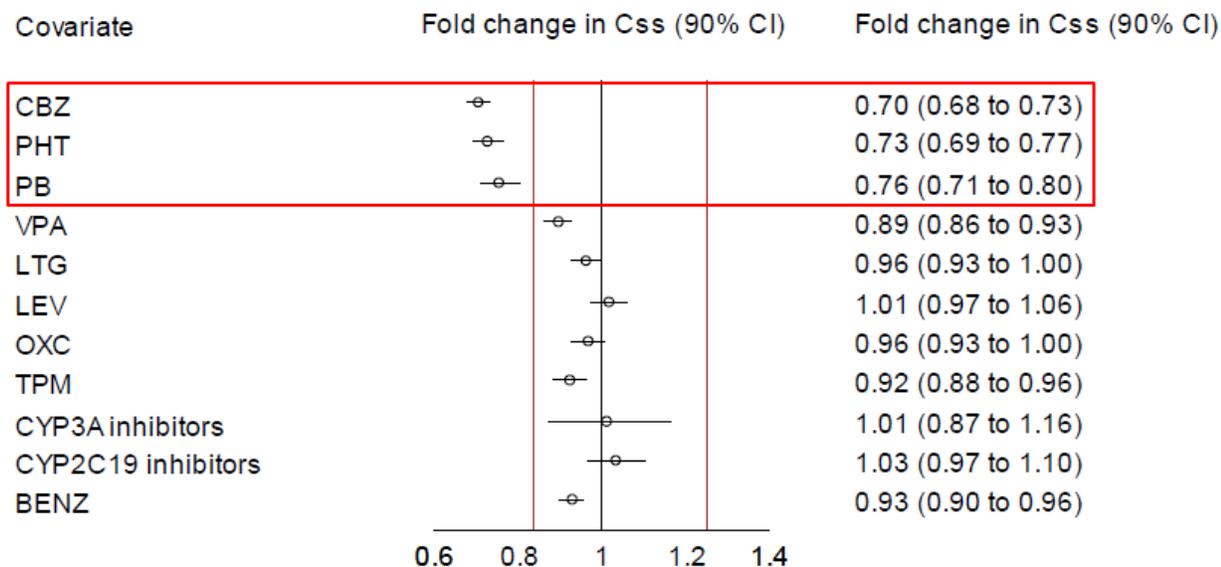
None of the brivaracetam metabolites had systemic exposure exceeding 25% of the parent drug. Thus, there is no need to evaluate their drug-interaction potential *in vitro*. Nevertheless, the weak inhibitory effects of the metabolites tested above on transporters suggested that they are unlikely to inhibit those transporters *in vivo*.

2.4.3 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

2.4.3.1. Effect of co-administered drugs on brivaracetam

Sponsor conducted a population PK analysis assessing the effect of concomitant anti-epileptic drugs administered in clinical trials on BRV PK.

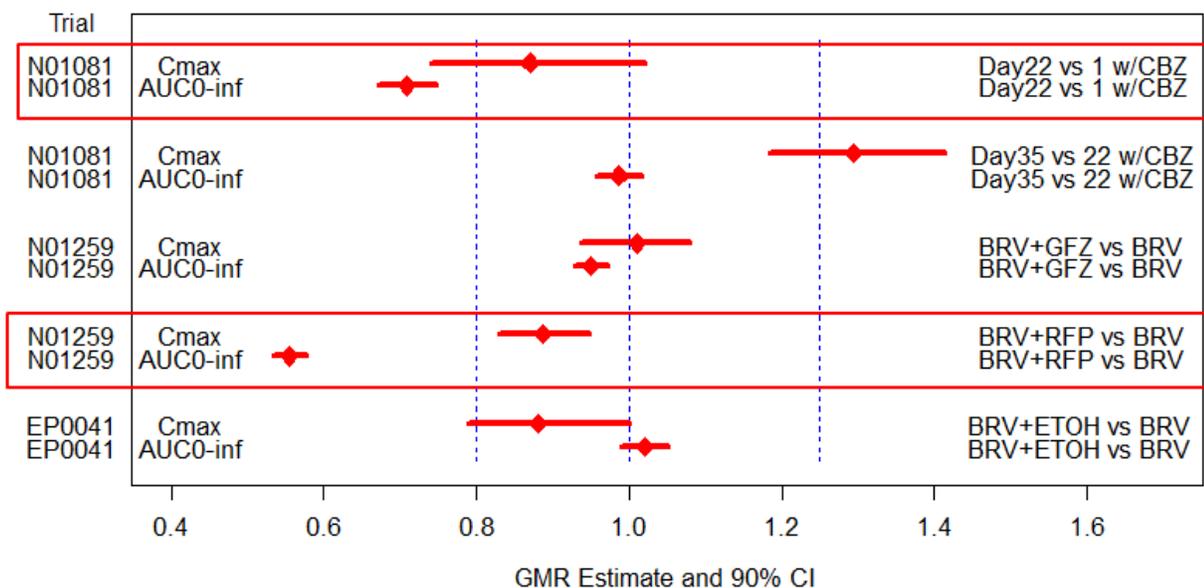
Figure 30: Results of Population PK Analyses of The Effect Concomitant Anti-Epileptic Drug Use on BRV Exposures



The population PK results indicate a 30%, 27%, and 24% reduction in BRV C_{ss} with concomitant carbamazepine, phenytoin, and phenobarbital use. Sponsor proposes no dose BRV adjustment when used with carbamazepine, phenytoin, or phenobarbital.

Sponsor also conducted in-vivo drug interaction studies where the effects of carbamazepine, gemfibrozil, rifampicin, ethanol on BRV PK were assessed.

Figure 31: Forest Plot of In-Vivo Drug Interaction Study Results of the Effect of Other Drugs on Brivaracetam PK



BRV AUC_{0-∞} was reduced by 29% by carbamazepine (Study N01081) and BRV AUC_{0-∞} was reduced 45% by rifampicin (Study N01259).

Sponsor indicates that no BRV dose adjustment is required with concomitant carbamazepine. Sponsor suggests that the BRV should be increased when using concomitant rifampicin.

Reviewer Comments:

Based on population PK analyses and in-vivo studies, this reviewer assessed the need for BRV dose adjustments due to concomitant use of carbamazepine, phenytoin, phenobarbital, and rifampicin.

Carbamazepine: Concomitant carbamazepine use was associated with a 29 % reduction in BRV AUC_{0-∞} on Day 22 in Study N01081. This decrease in BRV exposure was comparable at Day 35. The population PK analyses indicate that concomitant carbamazepine use was responsible for a 30% decrease in BRV C_{ss}.

Phenytoin: *The population PK analyses indicate that concomitant phenytoin use was responsible for a 27% decrease in BRV C_{ss} .*

Phenobarbital: *The population PK analyses indicate that concomitant phenytoin use was responsible for a 24% decrease in BRV C_{ss} .*

*Based on the “flat” exposure-response analysis for efficacy, a **BRV dose adjustment is not necessary when considered when co-administered with carbamazepine, phenytoin, or phenobarbital.***

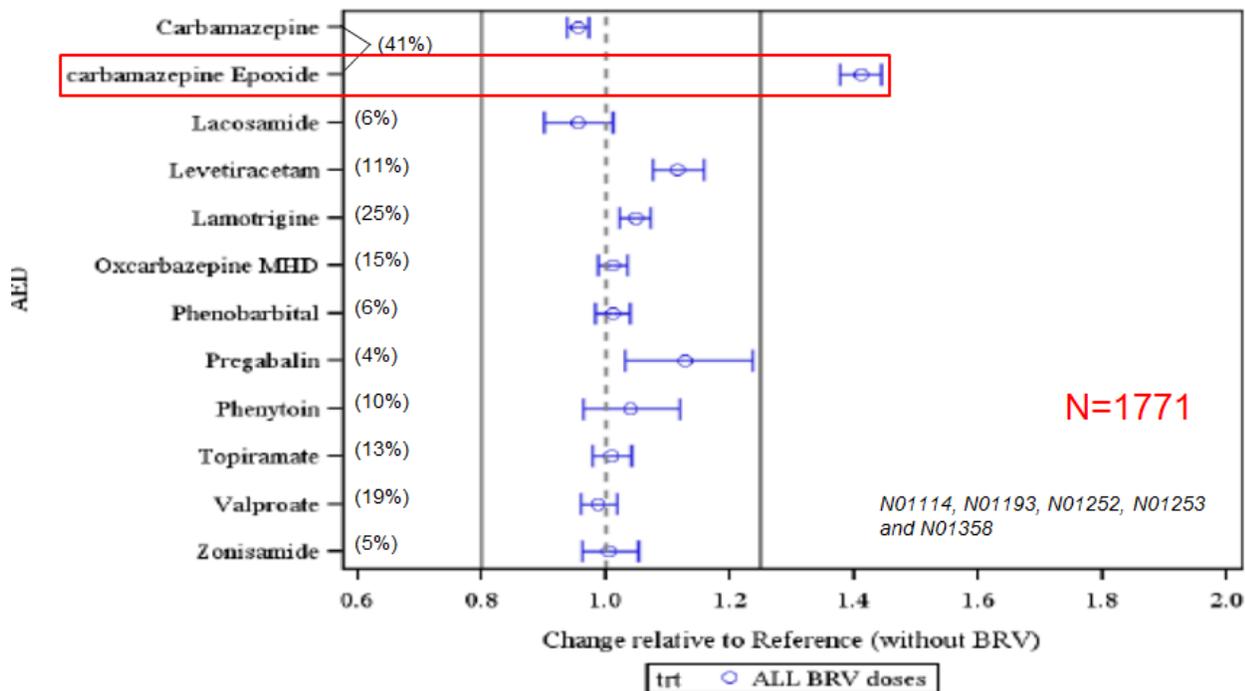
Rifampicin: *The BRV reduction was accompanied by an increase in hydroxy metabolite (ucb-100406-1) exposure (C_{max} : 3 fold \uparrow , AUC: 2 fold \uparrow , $Ae(0-72)$: 2 fold \uparrow). Since the conversion of BRV to the hydroxy metabolite (ucb-100406-1) is catalyzed by 2C19, and since rifampicin is a 2C19 inducer, then 2C19 induction is likely the mechanism causing reduced BRV exposures with concomitant rifampicin.*

*Brivaracetam $AUC_{0-\infty}$ was reduced 45% with concomitant rifampicin. **The BRV dose should be doubled while receiving concomitant rifampicin.***

2.4.3.2. Effect of brivaracetam on co-administered drugs

Sponsor conducted a population PK analysis assessing the effect of BRV on the exposures of commonly-used concomitant anti-epileptic drugs in the clinical trials (population PK report CL0028).

Figure 32: Forest Plot of Population PK Analysis Results (CL0178) of BRV effect on Concomitant Medication C_{trough} Levels



The drug interaction analysis (CL0178) utilized concomitant AED PK data from studies N01114, N01193, N01252, N01253 and N01358. BRV doses ranged from 5 mg/day to 200 mg/day. The percentage in parentheses represents the proportion of patients receiving the particular co-medication.

Sponsor conducted numerous in-vivo drug interaction studies.

Figure 33: Results of In-vivo Interaction Studies of BRV on Carbamazepine, Valproic Acid, and Lamictal

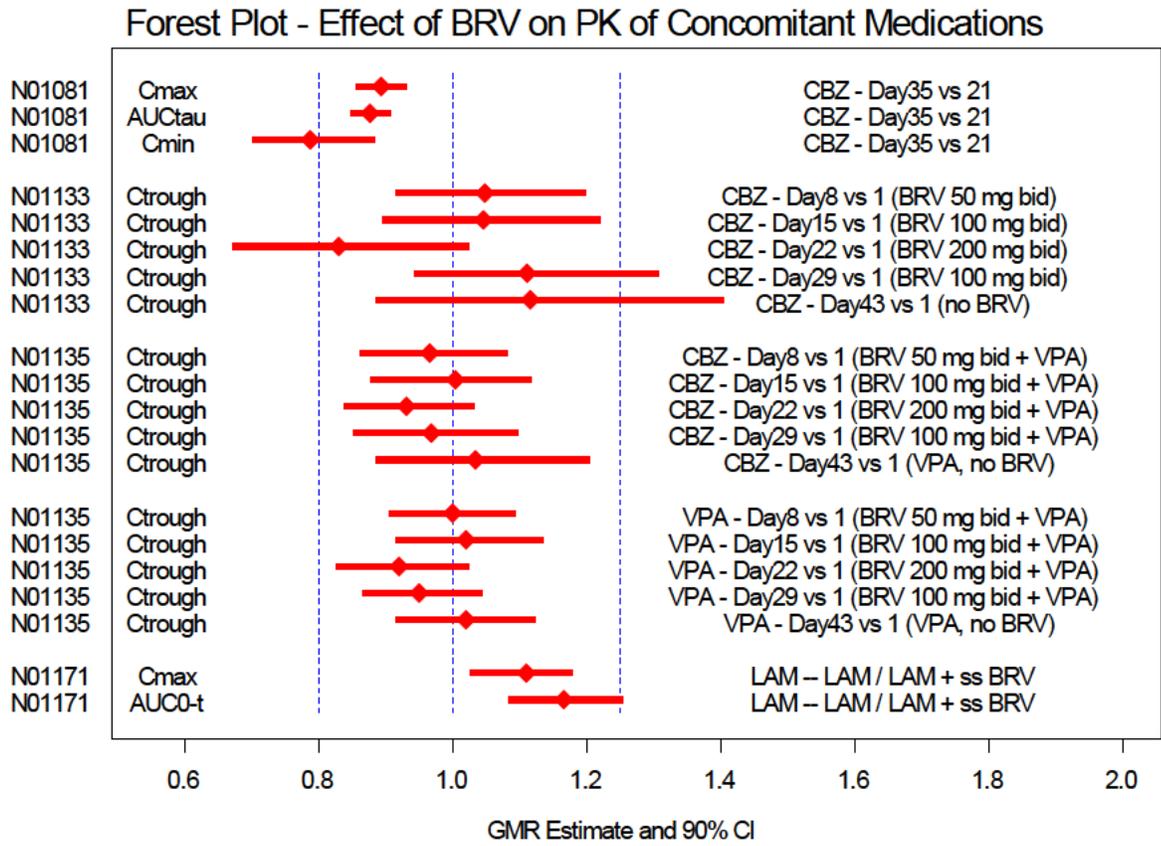
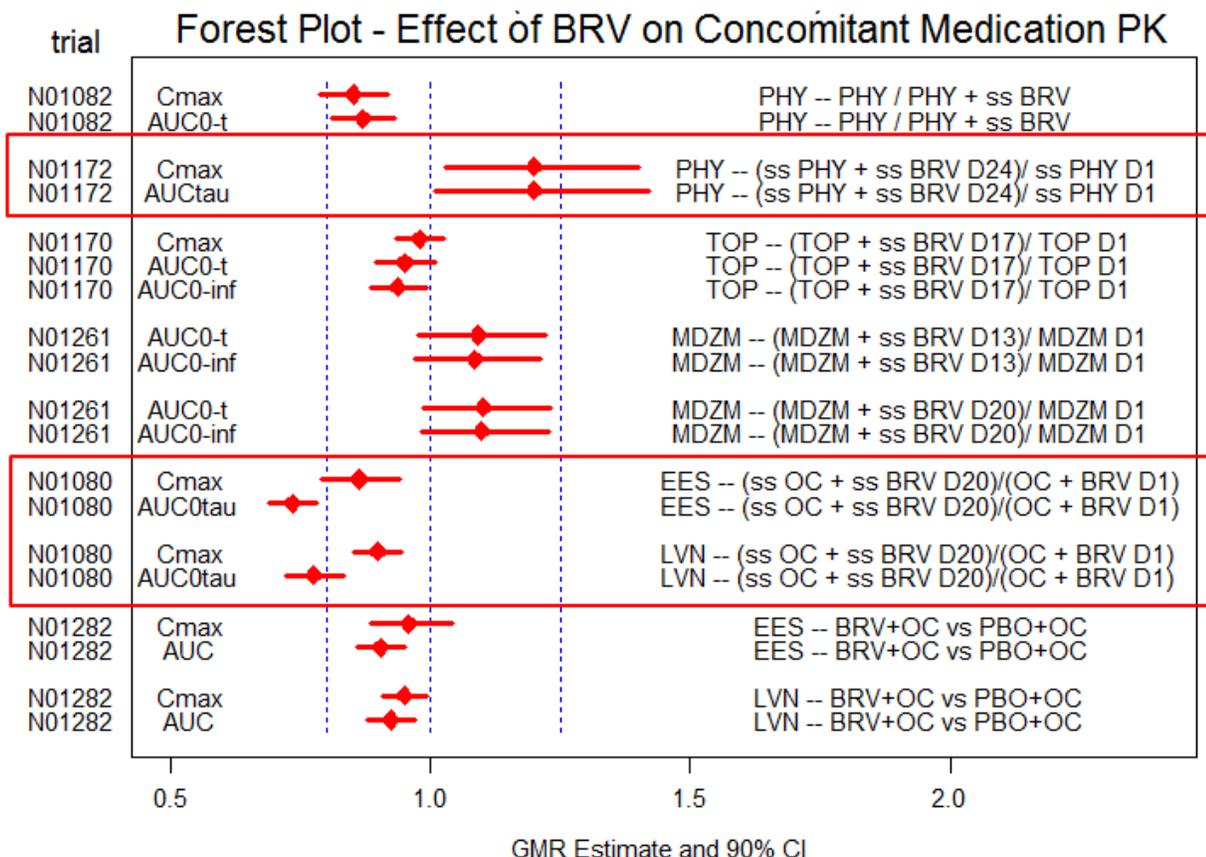


Figure 34: Results of In-vivo Interaction Studies of BRV on Phenytoin, Topiramate, Midazolam, and Combined Oral Contraceptives (EES + LVN)



Sponsor indicates that no dose adjustment of concomitant phenytoin, topiramate, midazolam, or combined oral contraceptive (30 µg ethinylestradiol [EES] and 150 µg levonorgestrel [LVN]) is necessary.

Reviewer comment:

Carbamazepine: Based on the results of in-vivo drug interaction studies (N01081, N01133, and N01135), there was no consistent effect of BRV on carbamazepine. In addition, the population PK analyses demonstrated that BRV had a minor effect on carbamazepine C_{trough} . Overall, BRV is not likely to cause a clinically significant change in carbamazepine exposures.

However, the exposure of carbamazepine-epoxide, the active metabolite of carbamazepine, increased substantially with BRV. The increase in carbamazepine-epoxide is likely due to the inhibition of epoxide-hydrolase by BRV.

While the population PK analysis indicated a 1.4-fold increase in the active metabolite carbamazepine-epoxide, the in-vivo trial indicated a 2.5-fold increase in carbamazepine-epoxide C_{min}. The reason for this difference is not clear.

While the potential for increased toxicity is possible with increased carbamazepine-epoxide, it may also result in increased efficacy.

A carbamazepine dose should be considered if tolerability issues arise.

Phenytoin: *While the in-vivo phenytoin interaction study N01172 demonstrated a 20% increase in phenytoin due to BRV, the population PK analyses suggest BRV increases phenytoin C_{ss} by 4% increase. The reason for this difference is not clear.*

*According to the phenytoin label, phenytoin concentrations should be monitored when changing from one dosage form to another, during a loading dose, or during enteral feeding. Thus, due to the increase of up to 20% in phenytoin exposures with BRV, and due to the practice of monitoring phenytoin concentrations during dose adjustments or changing dosage forms, **phenytoin concentrations should be monitored when used concomitantly with BRV.***

Combined Oral Contraceptives: *Study N01082 indicated a 26% and 22% decrease in EES and LVN, respectively, from BRV 200 mg bid (400 mg/day). However, study N01282 demonstrated a 10% and 7% AUC decrease in EES and LVN, respectively from BRV 50 mg bid (100 mg/day). This finding suggests that the reduction in EES and LVN exposure may increase with increasing BRV dose. It should be noted that the 200 mg bid dose utilized in study N01082 2-fold greater than the highest proposed dose for the label, 100 mg bid. It is not clear what the change in EES and LVN exposure is at the BRV 100 mg bid.*

At the time of this review, there is no exposure-response data to assess the effect these reductions in EES + LVN on oral contraceptive efficacy. As such, from a PK/PD standpoint, it is not clear whether a dose increase in combined oral contraceptive products is required when used with concomitant BRV.

*The medical officers have reviewed the safety data from the brivaracetam clinical trials and concluded that **a dose adjustment of combined oral contraceptives is not necessary.***

2.5. General Biopharmaceutics

An inspection was requested to inspect the clinical and analytical sites for study EP0007 as well as study N01296. Study EP0007 compares the bioavailability of the IV injection route with the oral tablet (filed under NDA 205837). Study N01296 assessed the bioequivalence of the oral solution with the oral tablet (filed under NDA 205838). At the time of this review, the inspections were not yet complete. If issues arise with inspections, a subsequent review report will be written to address the issues.

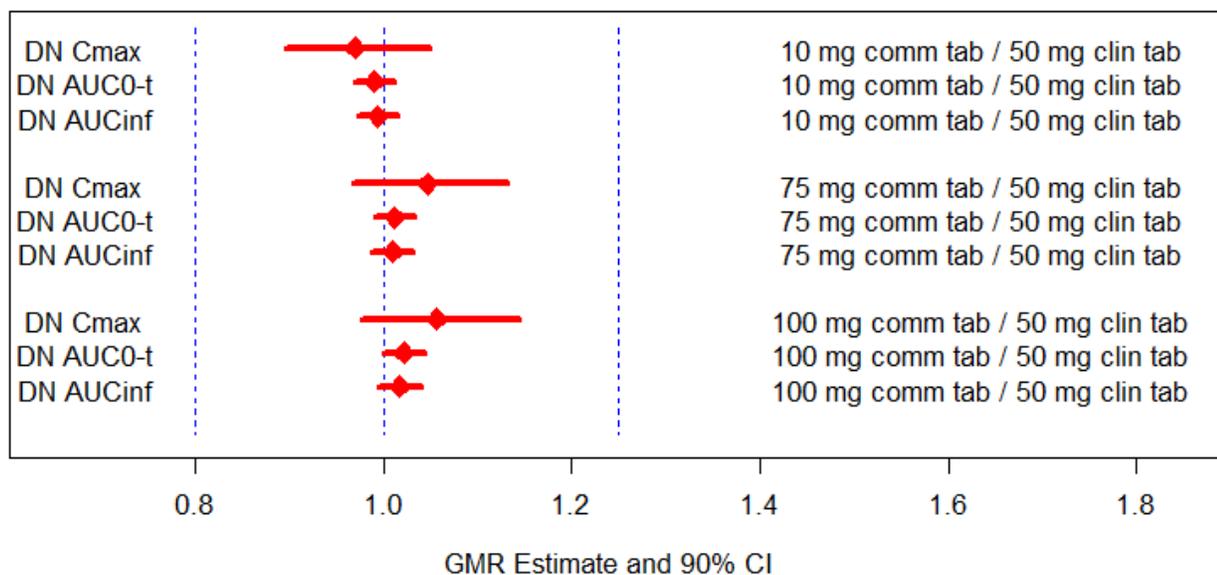
2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

Brivaracetam was granted BCS class 1 designation in 2007.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

In trial EP0007, one of the objectives was to assess the bioequivalence of the commercial tablet with the tablet used in clinical development. Study EP0007 was a randomized, single-center, open-label, 5-way crossover, single-dose bioavailability/bioequivalence comparison of brivaracetam oral tablets (10 mg, 50 mg, 75 mg, and 100 mg) and brivaracetam intravenous bolus injection (100 mg) in healthy volunteers.

Figure 35: Forest Plot of Bioequivalence Assessments of Colored, Debossed, Commercial Tablets with Clinical Development Tablets (Trial EP0007)



The Sponsor's conclusions were

1. The 3 commercial BRV tablets (10, 74, and 100 mg) were BE to the 50 mg BRV clinical development tablet.
2. The 100 mg IV bolus had comparable bioavailability to with the 50 mg and 100 mg tablets in terms of AUC_{norm} (dose-normalized AUC) but had 20% greater $C_{max, norm}$ compared to 50 mg and 100 mg tablets.

Reviewer Comment: *These results support the bioequivalence of the tablets used in clinical development with the colored, debossed, commercial tablets.*

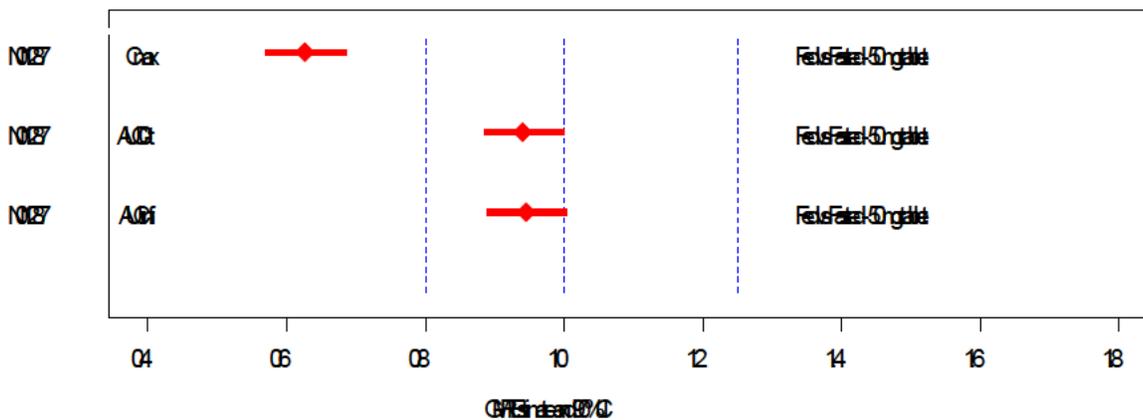
2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Sponsor assessed the effects of food on BRV tablet bioavailability in trial N01287. Trial N01287 was an open-label, randomized, five-way cross-over relative bioavailability / bioequivalence study. One of the aims in this study was to assess the food effect on the BRV tablet formulation.

Table 36: Effect of Food on T_{max} of After Administration of 50 mg BRV Tablets in Study N01287

	T _{max} 50 mg BRV <u>tablet</u> [median (min – max)]
Fed	3 (0.25 – 3) hours
Fasted	0.5 (0.25-3) hours

Figure 37: Forest Plot of the Effect of Food on PK of a BRV 50 mg Tablet in Study N01287



Sponsor’s conclusions:

1. Food intake reduced C_{max} by 37% and delayed t_{max} by 3.0 hours.
2. Food intake did not significantly affect AUC_{0-∞}, AUC_{0-t}, or other PK parameters

Reviewer comment: Food does not have a substantial impact on the extent of brivaracetam absorption. The reduction in C_{max} is not likely to result in a reduction of efficacy. Brivaracetam tablets can be administered without regard to food.

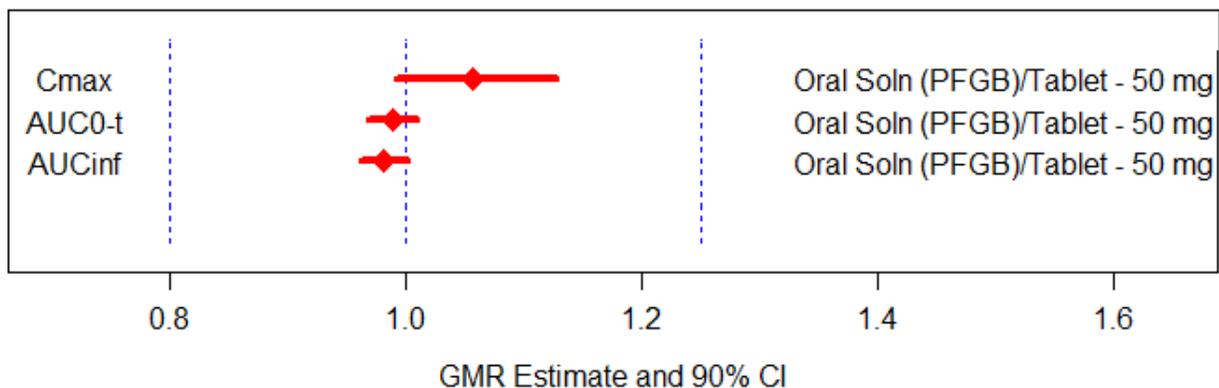
2.5.4 What is the effect of timing of drug administration on the bioavailability (BA) of the drug from the dosage form?

2.5.5 What is the relative bioavailability of other formulations?

2.5.5.1 Oral Solution

Sponsor conducted study N01296 to assess the bioequivalence of the oral solution and commercial tablet. Study N01296 was a randomized, open-label, two-way cross-over, single dose bioequivalence study of 50 mg commercial oral solution (pre-filled glass bottles) with 50 mg of film-coated tablets used in clinical development.

Figure 38: Forest Plot of Bioequivalence Assessments of Commercial Oral Solution with Clinical Development Tablets (Trial N01296)



*PFGB = pre-filled glass bottles

Reviewer Comment: The data support the bioequivalence of the commercial oral solution to the tablets from clinical development.

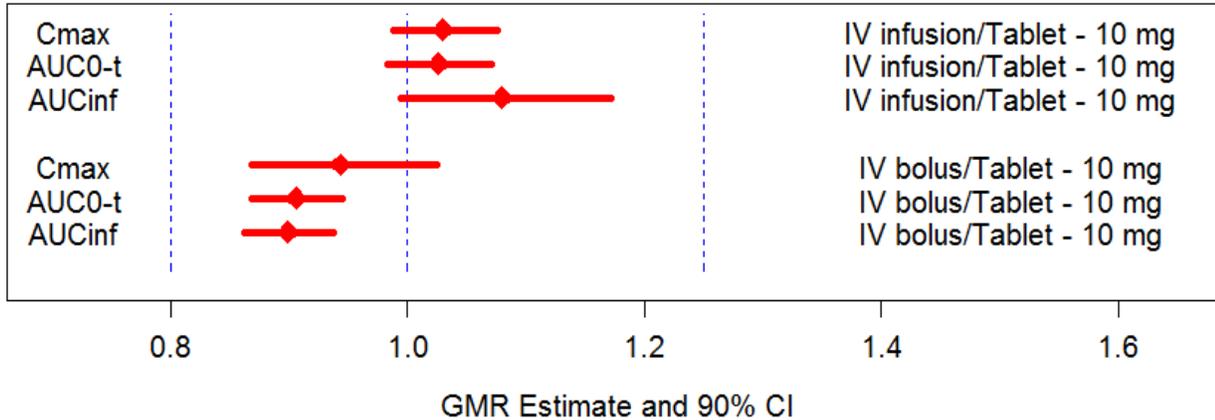
2.5.5.2. Solution for Intravenous Injection

Sponsor conducted two studies comparing the bioavailability of the solution for injection to the oral tablets.

Study N01256(A) was a randomized, monocenter, open-label, three-way crossover, dose availability study in healthy volunteers. In this study, Sponsor compared the bioavailability of the 10 mg IV solution (administered as a 12-second bolus or 15-minute infusion) with 10 mg

oral tablets. The 10 mg oral tablets are the same formulation as was used in clinical development; however, the 10 mg oral tablet strength was not used in clinical development.

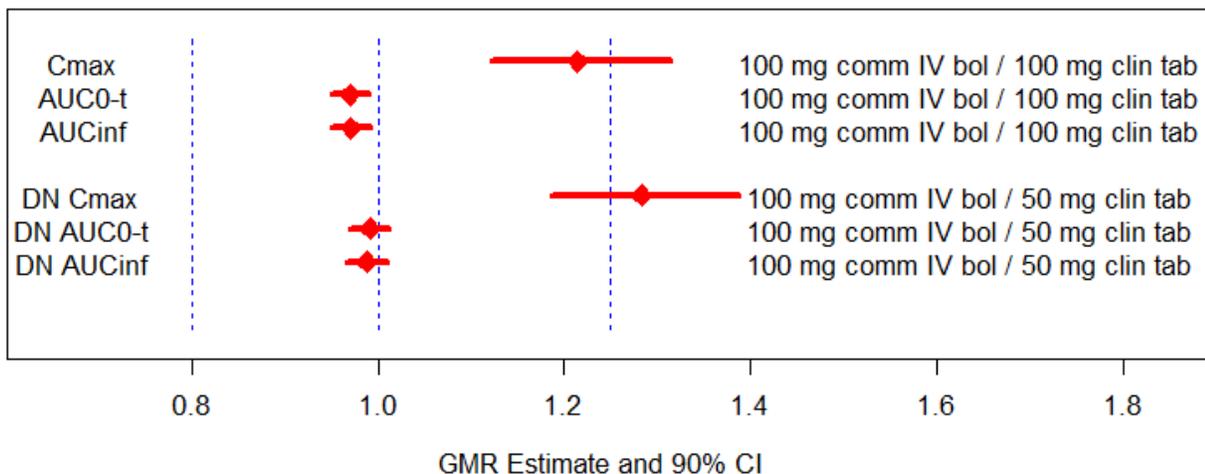
Figure 39: Forest Plot of Bioavailability Comparisons Between of Commercial Solution for IV Injection with Clinical Development Tablets (Trial N01296)



Reviewer comment: The data from trial N01296 support the bioequivalence of 10 mg of the clinical-development oral tablet with 10 mg of the commercial IV solution (whether administered as a 12-second bolus or a 15-minute infusion).

In trial EP0007, one of the objectives was to compare the bioavailability of the commercial IV solution with the tablet used in clinical development. Trial EP0007 was a randomized, single-center, open-label, 5-way crossover, single-dose bioavailability/bioequivalence comparison of brivaracetam oral tablets (10 mg, 50 mg, 75 mg, and 100 mg) and brivaracetam intravenous bolus injection (100 mg) in healthy volunteers. Sponsor compared the exposures of single 100 mg IV bolus injections with the exposures a single 100 mg dose and dose-normalized exposures of single doses less than 100 mg.

Figure 40: Forest Plot of Bioavailability Comparisons of Commercial Solution for IV Injection with Clinical Development Tablets (Trial EP0007)



Sponsor made the following conclusions:

1. The 3 commercial BRV tablets (10, 74, and 100 mg) were BE to the 50 mg BRV clinical development tablet.
2. The 100 mg IV bolus had comparable bioavailability to with the 50 mg and 100 mg tablets in terms of AUC_{norm} (dose-normalized AUC) but had 20% greater C_{max, norm} compared to 50 mg and 100 mg tablets.

Reviewer comments: *The study demonstrates that the commercial solution for injection has comparable bioavailability in terms of AUC to the oral tablet used in clinical development. This also held true for lower doses of the clinical tablet (based on dose-normalized AUC values).*

The IV formulations have 30-40% greater C_{max} than the C_{max} after oral tablet administration. As IV brivaracetam will be used in an in-patient setting, and as the adverse events are dizziness/fatigue/headache, and as the concentrations from IV are only higher than the oral exposure for about 1.5 hours (see Figure EP0007-2 in the ISR for study EP0007), a dose adjustment when switching to IV administration is not necessary.

BRV can be administered as an IV infusion or IV bolus at the same dose level as oral tablets.

2.6. Analytical

2.6.1. Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Sponsor submitted 16 bioanalytical validation reports of methods to quantify brivaracetam and 3 metabolites in plasma and urine. Methods included:

- achiral reversed-phase liquid chromatography (LC) in the gradient mode with electrospray ionization tandem mass spectrometry (ESI/MS/MS), aka LC-ESI/MS/MS
- achiral reversed phase ultra high pressure liquid chromatography (UPLC) in gradient mode with electrospray ionization (ESI) tandem mass spectrometry (MS/MS), aka UPLC-ESI/MS/MS

The assays are considered adequately validated under the FDA's Bioanalytical Guidance.

Sponsor tested for interference of AEDs with brivaracetam. No significant interference of other AEDs with brivaracetam was observed.

The method used to quantify the ¹⁴C-brivaracetam in the plasma in study N01068 is adequately validated. The method used for metabolic profiling is not considered validated but served the purpose of the study. Sponsor utilized radio-HPLC-MS for quantitative metabolic profiling. In addition radio-HPLC-MS(/MS) was utilized for metabolite structure elucidation.

The table below lists details for 4 plasma assays for brivaracetam and metabolites and 2 urine assays for brivaracetam and metabolites that were used to analyze the plasma samples in most of the clinical trials.

(b) (4) TM (Brivaracetam oral tablet / IV solution / oral solution)

Table 41: Bioanalytical Methods for the Determination of Brivaracetam and Metabolites in Plasma Samples Obtained in Clinical Studies

Report Title	Validation of an Analytical Assay for the Determination of ucb 34714, ucb-100406-1, ucb 42145 and ucb-107092-1 in Plasma and Urine Samples by LC-ESI/MS/MS Using an Automated Sample Preparation	Validation Update of an Analytical Assay for the Determination of ucb 34714, ucb-100406-1, ucb 42145 and ucb-107092-1 in Plasma by UPLC-ESI/MS/MS –	Method validation for the determination of UCB 34714 in human plasma by LC-MS/MS (AM MS0096NL)	Validation of an analytical assay for the determination of ucb 34714 in plasma samples by LC/ESI/MS
Used in Clinical Trial	N01109, N01111, N01133, N01172, N01233,	N01209, N01259, N01282, N01287, N01296	N01114, N01193, N01252, N01253, N01254	N01066, N01067, N01068, N01075, N01080, N01081, N01082, N01118, N01170, N01171
Lab Code	V2.0, V2.1	V3.0, V3.1, V3.2	4032041101	TA0668 / RPLE00F2103
Analyte	ucb 34714, ucb-100406-1, ucb 42145 and ucb-107092-1	ucb 34714, ucb-100406-1, ucb 42145 and ucb-107092-1	UCB 34714	UCB 34714
Internal standard (IS)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Analytical Method	LC-ESI/MS/MS	UPLC-ESI/MS/MS	LC-MS/MS	LC/ESI/MS
Stock Solution Solvent	acetonitrile	Acetonitrile and methanol	methanol	Methanol, acetonitrile
Extraction Method	Solid Phase Extraction	Solid Phase Extraction	Solid Phase Extraction	Solid Phase Extraction
Linear Range	100 to 20000 ng/mL for BRV 20 to 20000 ng/mL for 3 metabolites	2.00 to 2000 ng/mL for ucb 34714 and ucb-107092-1 2.00 to 500 ng/mL for ucb-100406-1 and ucb 42145	0.010 - 4.00 mg/L (10-4000 ng/mL)	50 to 2000 ng/ml
Drug Recovery	97.7% for BRV, 95.8% to 102.0% for 3 metabolites	91.8% to 102% for BRV 93.4% to 107.6% for 3 metabolites	86.7 to 108%	72.5% to 74.6%
Average recovery of IS	Not mentioned	Not mentioned	Not mentioned	75.1%
QC Concentrations	10, 25, 35, 150, 1800 ng/mL for BRV 2, 6, 10, 75, 1800 ng/mL for 3 metabolites	2, 6, 75, 1600 ng/mL for BRV and ucb-107092-1 2, 6, 30, 400 for ucb-100406-1 and ucb 42145	0.01, 0.03, 0.3, 0.9 mg/L	150, 600, 1750 ng/ml
QC Intra-assay precision	≤ 3.9% for BRV ≤ 3.7% for 3 metabolites	≤ 11.2% for BRV ≤ 10.2% for 3 metabolites	≤ 5.8%	≤ 3.2%
QC Intra-assay accuracy	≤ ± 3.4% for BRV ≤ ± 7.2% for 3 metabolites	≤ ± 10.0% for BRV ≤ ± 11.6% for 3 metabolites	Not mentioned	Not mentioned
QC Inter-assay precision	≤ 3.9% for BRV ≤ 6.0% for 3 metabolites	≤ 12.0% for BRV ≤ 11.0% for 3 metabolites	≤ 5.4%	≤ 12.8%
QC Inter-assay accuracy	≤ ± 2.3% for BRV ≤ ± 4.2% for 3 metabolites	≤ ± 8.2% for BRV ≤ ± 7.6% for 3 metabolites	88.2 to 102%	≤ ± 4.4%
Stock solution Storage Stability	518 days at -20°C	395 days at ca -20°C	24 hours at -20°C	31 days at -20°C
QC sample long term storage stability	299 days for ucb-100406-1 and ucb 42145 at -20°C.	517 days at ca -20°C	3 days at refrigerator temperature	91 days at -20°C
QC sample bench-top stability	24 h at room temperature	24 hours in room temperature	3 days at room temperature, 120 hours at 50°C	24 hours at room temperature
Processed sample stability	144 hours at ca 15°C	179 hours on the autosampler at 15°C	Stable for 96 plasma cycles	72 hours on the injector tray at room temperature
Freeze-thaw stability (cycles)	6 freeze-thaw cycles	6 freeze-thaw cycles	3 freeze-thaw cycles	3 freeze/thaw cycles
Dilution integrity	500-fold dilution	500-fold dilution	6-fold	1000-fold
Specificity	No relevant interfering peaks	No relevant interfering peaks	No significant interference	No interfering peaks

BRV = ucb 34714, ucb 42145 = carboxylic acid metabolite, ucb-100406-1 = hydroxy metabolite, and ucb-107092-1 = hydroxyacid metabolite

(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

Table 42: Bioanalytical Methods for the Determination of Brivaracetam and Metabolites in Urine Samples Obtained in Clinical Studies

Report Title	Validation of an Analytical Assay for the Determination of ucb 34714, ucb-100406-1, ucb 42145 and ucb-107092-1 in Plasma and Urine Samples by LC-ESI/MS/MS Using an Automated Sample Preparation	Validation of an analytical assay for the determination of ucb 34714 in urine samples by LC/ESI/MS
Used in Clinical Trial	N01172, N01111, N01109	N01075, N01066 N01067, N01118
Lab Code	V2.0, V2.1	TA0667 / RPLE00F2102
Analyte	ucb 34714, ucb-100406-1, ucb 42145 and ucb-107092-1	ucb 34714
Internal standard (IS)	(b) (4)	(b) (4)
Analytical Method	LC-ESI/MS/MS following 10-fold dilution with human plasma	LC/ESI/MS following 10-fold dilution with internal standard
Stock Solution Solvent	acetonitrile	Methanol and acetonitrile
Extraction Method	Solid Phase Extraction	Mobile phase
Linear Range	10 to 2000 ng/mL for BRV 2 to 2000 ng/mL for 3 metabolites	0.25 to 50 µg/ml
Drug Recovery	97.7% for BRV, 95.8% to 102.0% for 3 metabolites	97.1% to 100.0%
Average recovery of IS (%)	Not mentioned	Not mentioned
QC Concentrations	10, 25, 35, 150, 1800 ng/mL for BRV 2, 6, 10, 75, 1800 ng/mL for 3 metabolites	0.25, 0.75, 7.5 and 40 µg/ml
QC Intra-assay precision	≤ 3.9% for BRV ≤ 3.7% for 3 metabolites	≤ 4.3%
QC Intra-assay accuracy	≤ ± 3.4% for BRV ≤ ± 7.2% for 3 metabolites	Not mentioned
QC Inter-assay precision	≤ 3.9% for BRV ≤ 6.0% for 3 metabolites	≤ 3.6%
QC Inter-assay accuracy	≤ ± 2.3% for BRV ≤ ± 4.2% for 3 metabolites	≤ ± 5.4%
Stock solution Storage Stability	At least 518 days at -20°C	31 days at -20°C
QC sample long term storage stability	74 days at ca -20°C	31 days at -20°C
QC sample bench-top stability	24 hours at room temperature	24 hours at room temperature
Processed sample stability	144 hours at ca 15°C on the injector tray followed by 120 hours at ca 4°C	96 hours on the injector tray at room temperature
Freeze-thaw stability (cycles)	Not mentioned	Three freeze/thaw cycles
Dilution integrity	500-fold dilution	400-fold
specificity	No relevant interfering peaks	No significant interfering peaks

BRV = ucb 34714, ucb 42145 = carboxylic acid metabolite, ucb-100406-1 = hydroxy metabolite, and ucb-107092-1 = hydroxyacid metabolite

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for (b)(4)® (brivaracetam) immediate release oral tablets and found it acceptable provided that the recommended revisions are made to the labeling language.

Labeling recommendation to be sent to the Sponsor:

The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~Strikethrough~~ text is recommendation for deletion from the perspective of OCP.

4. Appendices

4.1. Labeling Recommendations

(b)(4)
(b)(4)

7 DRUG INTERACTIONS

7.1 Rifampicin

(b)(4)
-Prescribers should (b)(4) (b)(4)
dose in patients (b)(4) treatment with rifampin [see *Clinical Pharmacology* (12.3)].

7.2 Carbamazepine

(b)(4)
-If tolerability issues arise when co-administrated, a carbamazepine dose reduction should be considered.

7.3 Phenytoin

(b)(4) -Phenytoin (b)(4)
levels should be monitored (b)(4)

8.7 Renal Impairment

Dose adjustments are not required for patients with impaired renal function. (b) (4)
(b) (4) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

(b) (4)
(b) (4)

12.3 Pharmacokinetics

The tablets, oral solution, and injection (b) (4) (b) (4) exhibits linear and time-independent pharmacokinetics at the approved doses (b) (4)
(b) (4)

Absorption

(b) (4) is highly permeable and is rapidly and almost completely absorbed after oral administration. Pharmacokinetics is dose-proportional from 10 to 600 mg. The median t_{max} for tablets taken without food is 1 hour (b) (4) range (b) (4) 0.25 to 3 h). Co-administration with a high-fat meal slowed down the absorption (b) (4) the extent of absorption remained unchanged. When (b) (4) (50 mg tablet) (b) (4) decreased by 37% and T_{max} (b) (4) delayed by 3 hours (b) (4) AUC (b) (4) decreased by 5%

Distribution

(b) (4) is weakly bound ($\leq 20\%$) to plasma proteins. The volume of distribution is 0.5 L/kg, a value close to that of the total body water. (b) (4)
(b) (4) is rapidly and evenly distributed in most tissues. (b) (4)

Metabolism

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid, and secondarily by hydroxylation on the propyl side chain. The hydrolysis (b) (4)
(b) (4) the hydroxylation pathway is mediated primarily by CYP2C19. In vivo, in human subjects possessing ineffective mutations of CYP2C19, (b) (4)

(b) (4)
The 3 metabolites are not pharmacologically active.

Elimination

Brivaracetam is eliminated primarily by metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in the urine within 72 hours after intake. Fecal excretion accounts for less than 1% of the dose. Less than 10% of the dose is excreted unchanged in the urine. The terminal plasma half-life ($t_{1/2}$) is approximately 9 hours

Specific Populations

(b) (4)
In a study in elderly subjects (65 to 79 years old; with creatinine clearance 53 to 98 mL/min/1.73 m²) receiving (b) (4) (b) (4) (200 mg twice daily), the plasma half-life of (b) (4) was 7.9 hours and 9.3 hours in the 65 to 75 and >75 years groups, respectively. The steady-state plasma clearance of (b) (4) was slightly lower (0.76 mL/min/kg) than in young healthy controls (0.83 mL/min/kg)

(b) (4)
There are no differences in the pharmacokinetics of (b) (4) (b) (4)

Race

A population pharmacokinetic analysis comparing Caucasian and non-Caucasian patients showed no significant pharmacokinetic difference.

Renal Impairment

A study in subjects with severe renal impairment (creatinine clearance <30 mL/min/1.73m² and not requiring dialysis) revealed that the plasma AUC of (b) (4) was moderately increased (b) (4) 21%) relative to healthy controls, while the AUC of the acid, hydroxy and hydroxyacid metabolites were increased 3-, 4-, and 21-fold, respectively. The renal clearance of these non-active metabolites was decreased 10-fold. (b) (4)

(b) (4) RADENAME has not been studied in patients undergoing hemodialysis

Hepatic Impairment

A pharmacokinetic study in subjects with hepatic cirrhosis (Child-Pugh grades A, B, and C) showed (b) (4) (50%, 57% and 59%), compared to matched healthy controls

Drug Interactions

Drug Interaction Studies with AEDs

Potential interactions between (b) (4) and other AEDs were investigated in a pooled analysis of plasma drug concentrations from all phase 2-3 studies and in a population exposure-response analysis of placebo-controlled phase-3 studies in adjunctive therapy in the treatment of partial onset seizures. The interactions are summarized in Table 3.

Table 3: Drug Interactions Between (b) (4) and Concomitant Antiepileptic Drugs

Concomitant AED	Influence of AED on (b) (4)	Influence of (b) (4) on AED
Carbamazepine	26 (b) (4) % decrease in plasma concentration. (b) (4)	None (b) (4) Increase of carbamazepine epoxide. (b) (4)
Lacosamide	No data	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None (monohydroxy derivative, MHD)
Phenobarbital	49 (b) (4) % decrease in plasma concentration. (b) (4)	None
Phenytoin	24 (b) (4) % decrease in plasma concentration. (b) (4)	(b) (4) 20% increase in plasma concentration. (b) (4)
Pregabalin	No data	None
Topiramate	None	None
Valproic Acid	None	None
Zonisamide	No data	None

(b) (4) is (b) (4) reversible inhibitor of epoxide hydrolase resulting in an increased concentration of carbamazepine epoxide, an active metabolite of carbamazepine. The carbamazepine epoxide plasma concentration increased (b) (4)

Drug Interaction Studies with Other Drugs

Effect of Other Drugs on (b) (4)

(b) (4)
 Co-administration with CYP inhibitors is unlikely to significantly affect brivaracetam exposure

Co-administration with (b) (4) rifampicin, (b) (4) decrease (b) (4) plasma concentrations by 45%



Oral contraceptives

Co-administration of TRADENAME (b) (4) (twice the recommended maximum daily dose) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) reduced estrogen and progestin AUCs by 27% and 23%. However, c
Co-administration of (b) (4) (b) (4) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg) did not significantly influence the pharmacokinetics of either substance. (b) (4)

4.2 Pharmacometric Review

4.1.1 Summary of Findings

4.1.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

4.1.1.1.1 Are the sponsor's proposed doses (50, 100, and 200 mg/day) supported by the data?

Yes.

Three pivotal phase 3 studies, N01252, N01253, and N01358, were included in this submission to support the use of brivaracetam (BRV) for adjunctive therapy in adults with partial onset seizures (POS). These 3 studies were similar in design. They were all multicenter, randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of BRV 5 mg/day (N01253), 20 mg/day (N01252 and N01253) and 50 mg/day (N01252 and N01253), 100 mg/day (N01252 and N01358), and 200 mg/day (N01358) as adjunctive treatment without up-titration in adult patients with refractory POS taking 1 to 2 antiepileptic drugs (AEDs) with or without secondary generalization. The primary efficacy endpoint was percent reduction over PBO for 28-day/one-week adjusted POS frequency. The primary efficacy results are summarized in Table 43.

From the efficacy point of view, all 3 proposed doses (50, 100, and 200 mg/day) are acceptable. The recommended starting dose of 100 mg/day was demonstrated to be able to significantly reduce POS frequency over PBO in study N01358 ($p < 0.001$). In addition, 100 mg/day was statistically significant at the 0.05 level without control for multiplicity in study N01252. For 50 mg/day, although it was evaluated in two pivotal studies, N01252 and N01253, only study N01253 demonstrated statistically significant reduction over PBO in POS frequency ($p = 0.004$), whereas study N01252 showed statistically insignificant results ($p = 0.274$). For the 200 mg/day dose, it was evaluated in one study, N01358, as recommended by the agency to obtain data at the upper end of the dose-response curve based on the efficacy results from N01252 and N01253. The result showed statistically and clinically significant reduction over PBO in POS frequency ($p < 0.001$).

Given the facts above, independent exposure-response analysis was performed by the pharmacometrics reviewer to further evaluate the adequacy of the 3 doses. Data from all 3 studies were pooled for the exposure-response analysis. The relationship between percent change from baseline in POS frequency and model-predicted steady-state average BRV concentrations was best described by an E_{max} model, as shown in Figure 44. Our exposure-response results show that 50 mg/day demonstrated substantially better efficacy than placebo, and the exposure-response curve is reaching its plateau at 100 mg/day and 200 mg/day doses. Additional benefit could be expected by increasing the dose from 50 mg/day to 100 mg/day or 200 mg/day, which is consistent with the primary efficacy results. Moreover, a pooled analysis conducted by the sponsor using data from the 3 phase 3 studies excluding subjects on concomitant LEV showed statistically significant efficacy results for all 3 doses, as shown in Table 43. Therefore, the efficacy of all 3 doses is considered adequate.

For safety, although significant dose/exposure-safety relationships are commonly seen in drugs for the same indication, relatively flat dose/exposure-safety relationships at the proposed dose levels were observed for BRV for the common adverse events (somnolence, dizziness, and fatigue).

Due to the relatively flat dose/exposure-safety relationships that were observed in phase 3 studies and the plateau in the dose/exposure-efficacy relationship, the case for providing a range of doses is not as clear as for other anti-epileptic drugs. It might be sufficient to have one dose on the plateau of the exposure-efficacy relationship for all patients.

Table 43: Primary Efficacy Study Results

Statistics	PBO	BRV (mg/day)			
		20	50	100	200
N01252 (ITT Population)^{a, b}					
n	100	99	99	100	---
Percent reduction over PBO	--	10.2	9.2	20.5	--
95% CI	--	-6.8, 24.5	-8.0, 23.7	5.4, 33.1	--
p-value	--	0.222	0.274	0.010 ^e	--
N01253 (mITT Population)^{a, b}					
n	96	99	101	--	--
Percent reduction over PBO	--	8.7	22.0	--	--
95% CI	--	-8.2, 22.9	7.7, 34.2	--	--
p-value	--	0.292	0.004 ^f	--	--
N01358 (ITT Population)^{a, c}					
n	259	--	--	252	249
Percent reduction over PBO	--	--	--	22.8	23.2
95% CI	--	--	--	13.3, 31.2	13.8, 31.6
p-value	--	--	--	<0.001 ^f	<0.001 ^f
Pool E1^d					
n	418	161	161	332	249
Percent reduction over PBO	--	11.7	19.5	24.4	24.0
95% CI	--	-0.9, 22.7	8.0, 29.6	16.8, 31.2	15.3, 31.8
p-value	--	0.06741	0.00148	<0.00001	<0.00001

BRV=brivaracetam; CI=confidence interval; ITT=Intent-to-Treat; mITT=modified Intent-to-Treat; PBO=placebo; POS=partial-onset seizure.

^a Parametric effect estimates and treatment group comparisons were based on ANCOVA for log-transformed Treatment Period 28-day adjusted POS frequency with effects for treatment and stratification effects (as defined for each study), and log-transformed Baseline POS frequency as a continuous covariate.

^b In order to control the Type I error, testing was performed in sequence starting with 50mg/day, then 100mg/day, and finally 20mg/day for N01252 and in sequence starting 50mg/day, then 20mg/day, and finally 5mg/day for N01253, only moving to the next test if the previous one was significant at the 0.050 level.

^c Type I error rate controlled using a Hochberg procedure.

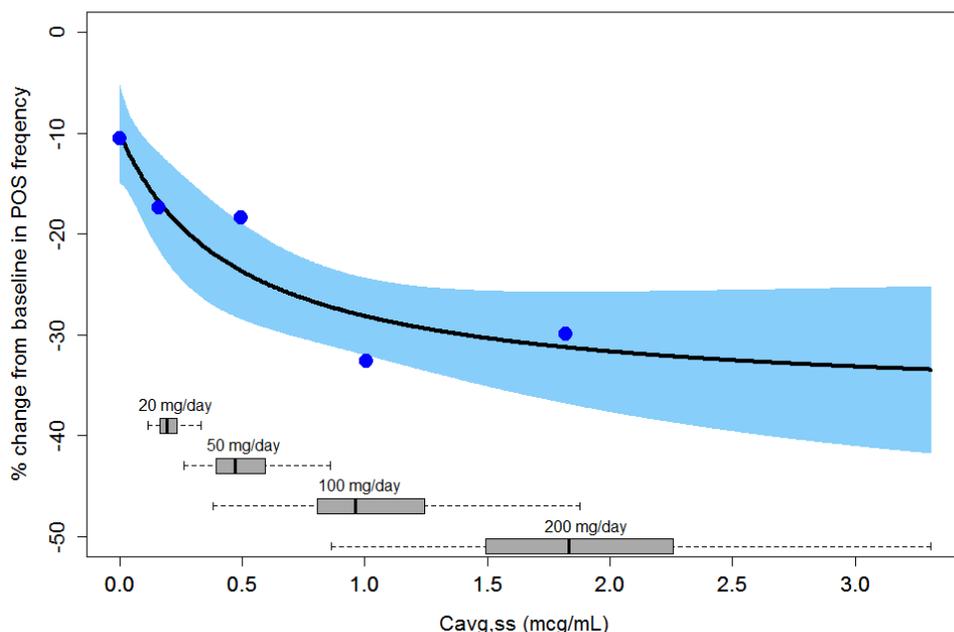
^d Parametric effect estimates and treatment group comparisons were based on ANCOVA for log-transformed Treatment Period 28-day adjusted POS frequency with effects for treatment and study, and log-transformed Baseline POS frequency as a continuous covariate.

^e Statistically significant at the 0.050 significance level without control for multiplicity (individual studies only).

^f Statistically significant with control for multiplicity.

Source: Clinical overview page 22

Figure 44 Exposure Response Analysis Results



Note: the blue circles represent observed mean % change from baseline in POS frequency in the placebo group (first circle) and the 4 steady-state average concentration quartiles; the solid line represents exposure-response model fit; the blue shaded area represents the 95% CI for the model fit; the grey boxplots represent the exposure distributions for 20, 50, 100, and 200 mg/day dose levels.

4.1.1.1.2 Should labeling restrict the use of BRV in patients on concomitant levetiracetam (LEV)?

Yes, labeling should restrict the use of BRV in patients on LEV.

In N01252 and N01253, patients on concomitant LEV were included in the studies and the number of subjects on concomitant LEV at the time of study entry was limited to 20% of randomized subjects. A pooled analysis (E2) combining data from N01252 and N01253 was conducted by the sponsor to evaluate the subgroup effects for subjects taking and not taking LEV at the time of study entry. The results from the pooled analysis showed no observed benefit versus PBO when BRV was added to LEV, as shown in Table 45. For N01358, subjects receiving concomitant LEV were excluded from the study. Since LEV and BRV have the same target and mechanism of action, it is hypothesized that patients whose seizures are not well controlled by LEV are not likely to benefit from the use of BRV. And our exposure-response analyses for two subgroups stratified by LEV use at the time of study entry confirmed our hypothesis. The results show that no additional benefit of BRV would be expected for subjects already on LEV (Figure 46). Therefore, BRV should not be used in patients already on LEV.

Table 45: Percent Reduction in POS Frequency from Baseline by LEV use at Study Entry (Pool E2)

Statistics	PBO	BRV (mg/day)		
		20	50	100
LEV at core study entry				
n	37	37	39	20
Median	22.1	16.2	12.7	4.7
Q1, Q3	-0.9, 35.0	-14.9, 43.1	-13.0, 41.2	-7.8, 29.9
Median difference vs PBO	--	-4.9	-4.7	-8.7
No LEV at core study entry				
N	158	161	161	80
Median	16.2	28.3	34.7	38.3
Q1, Q3	-10.2, 37.8	2.9, 57.5	7.0, 62.4	6.4, 75.4
Median difference vs PBO	--	12.6	18.1	24.3
95% CI (LL, UL)	--	3.8, 21.9	8.9, 27.3	12.1, 36.5
p-value	--	0.00538	0.00014	0.00009

BRV=brivaracetam; CI=confidence interval; ISE=Integrated Summary of Efficacy; LEV=levetiracetam; LL=lower limit; PBO=placebo; POS=partial-onset seizure; Q1=25th percentile; Q3=75th percentile; UL=upper limit

Note: Hodges-Lehmann nonparametric effect estimates and corresponding 2-sided 95% CIs are provided for the effect difference between each BRV treatment group and PBO. Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test.

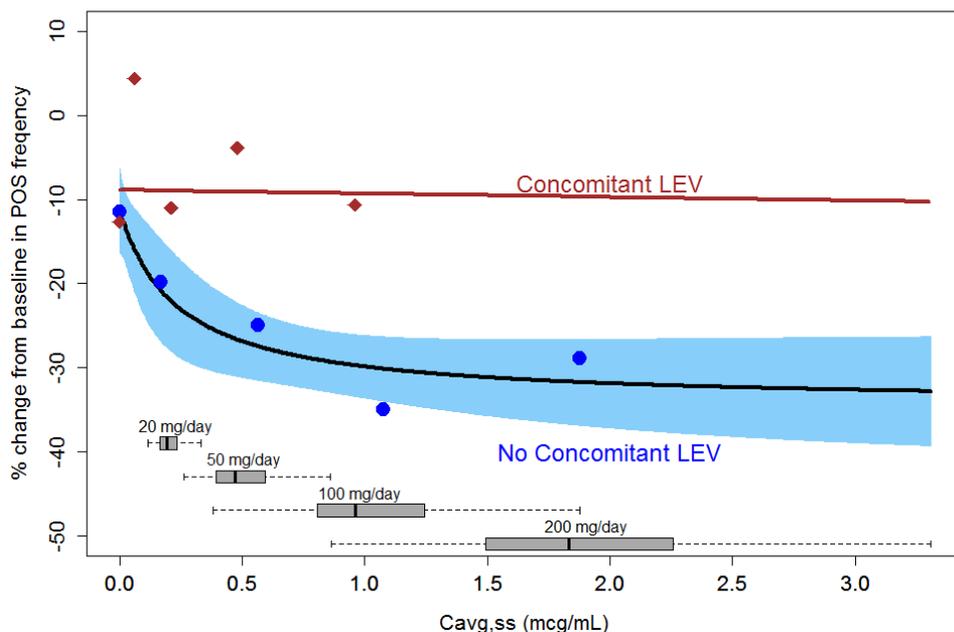
Note: Confidence intervals are provided only for subjects who were not using LEV at core study entry.

Note: Antiepileptic drug use within the 5 years prior to study entry was collected in N01252 and N01253.

Note: No LEV at core study entry includes subjects who never used LEV and subjects with previous LEV use only.

Source: ISE page 130 of 184

Figure 46: Exposure Response Analysis Results Stratified by LEV Use

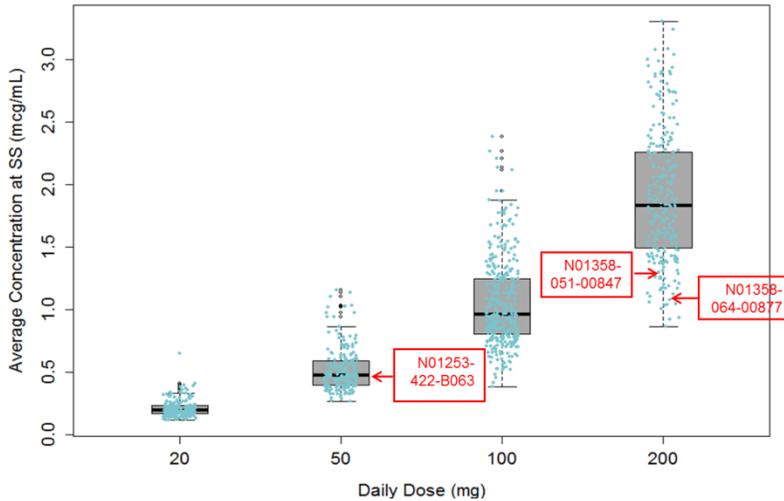


Note: the blue circles represent observed mean % change from baseline in POS frequency in the placebo group and the 4 steady-state average concentration quartiles in subjects taking no concomitant LEV/Keppra; the red squares represent observed mean % change from baseline in POS frequency in the placebo group and the 4 steady-state average concentration quartiles in subjects taking concomitant LEV; the solid lines represent exposure-response model fits; the blue shaded area represents the 95% CI for the model fit for subjects taking no concomitant LEV; the grey boxplots represent the exposure distributions for 20, 50, 100, and 200 mg/day dose levels.

4.1.1.1.3 Are Sudden Unexpected Death in Epilepsy (SUDEP) events related to BRV exposures?

A higher SUDEP rate has been observed in the BRV treatment arm than that in the placebo arm. 13 SUDEP cases were observed in the submission, of which 4 cases occurred during the double-blind treatment phase. And only 3 out of these 4 SUDEP events occurred during the fixed dose pivotal phase 3 studies (N01252, N01253, and N01358) and have PK measurements. Of these 3 subjects, subject N01253-422-B063 was on 50 mg/day dose level and subjects N01358-051-00847 and N01358-064-00877 were on 200 mg/day dose level. The average steady-state concentrations of these 3 subjects experiencing SUDEP were compared with the exposure distribution of all subjects at different dose levels. The result shows that the steady-state exposures of all 3 subjects are within normal range of exposures at corresponding dose levels, as shown in Figure 47. Based on these results, it cannot be concluded that SUDEP events were related to insufficient BRV exposures.

Figure 47: BRV Concentrations in Subjects with SUDEP versus Concentration Distribution of All Subjects



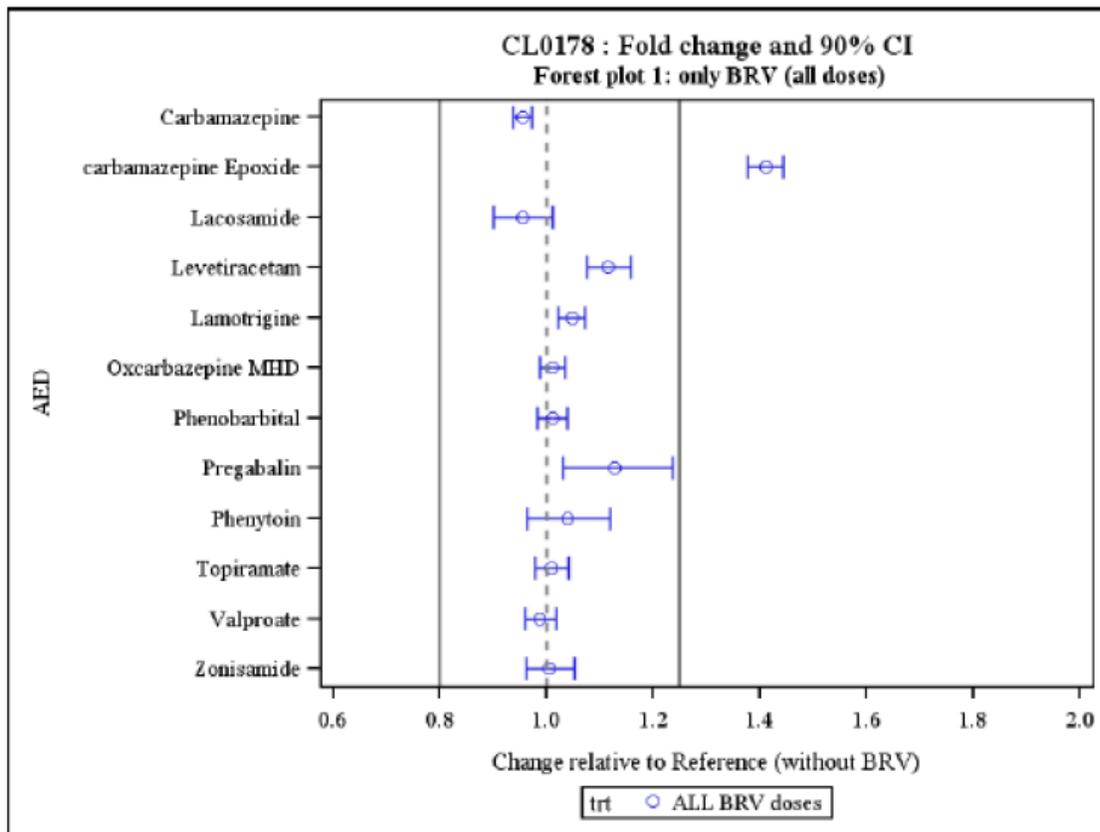
Note: Boxplots with jitters represent the distribution of average concentration at SS from all subjects; Red box with arrows indicate the steady-state average concentration levels of the 3 subjects experiencing SUDEP events.

4.1.1.1.4 Are there significant effects of BRV on the plasma concentrations of other concomitant AEDs?

No significant effect of BRV was demonstrated on the plasma concentrations of carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine MHD, phenobarbital, phenytoin, pregabalin, topiramate, valproate and zonisamide. However, BRV could increase the plasma concentrations of carbamazepine-epoxide in a dose-dependent manner.

A retrospective meta-analysis was conducted by the sponsor to evaluate the effect of BRV on the plasma concentrations of other AEDs in an epileptic population with partial onset seizures using data from 2 Phase 2 (N01114 and N01193) and 3 Phase 3 studies (N01252, N01253 and N01358). The result is shown in the figure below, demonstrating significant effect of BRV only on carbamazepine-epoxide, but not on other AEDs. (Please see Section 3.6 for details about the meta-analysis.)

Figure 48: Forest plot of the fold change in AED plasma concentrations at steady state by AED name



Source: study report CL0178 page 38

4.1.1.2 Recommendations

All proposed doses including 50, 100, and 200 mg/day are considered adequate. However, it is recommended to restrict the use BRV in subjects on concomitant LEV.

4.1.1.3 Label Statements

The pharmacometrics reviewer recommends restricting the use of BRV in patients receiving concomitant levetiracetam in the label.

4.1.2 Pertinent regulatory background

Brivaracetam is a new molecular entity that has been studied for the adjunctive therapy in the treatment of POS in patients older than 16 years of age with epilepsy.

4.1.3 Results of Sponsor's Analysis

4.1.3.1 Summary of clinical study report N01252

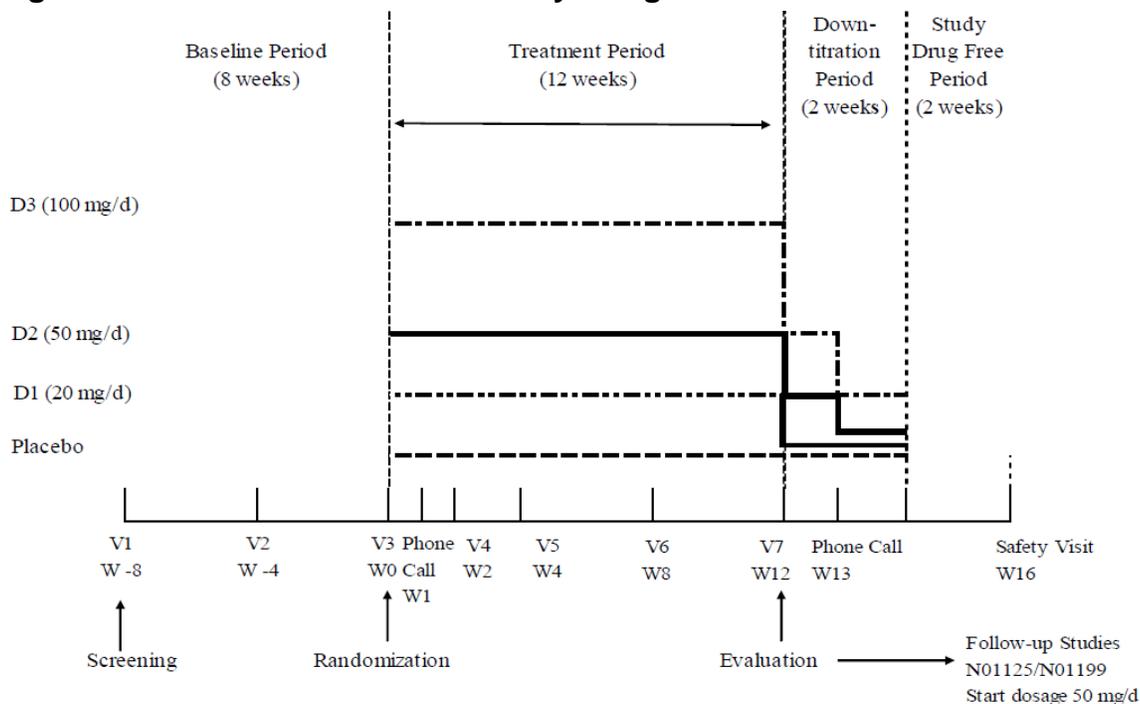
Study N01252 was a Phase 3, randomized, multi-center, double-blind, parallel-group, PBO-controlled study to evaluate efficacy and safety of BRV oral tablets in subjects 16 to 70 years

of age with refractory POS whether or not secondarily generalized. After completing the 8-week baseline period, eligible subjects were randomized in a 1:1:1:1 ratio to receive PBO, BRV 20mg/day, BRV 50mg/day, or BRV 100mg/day during the 12-week double-blind treatment period. Central randomization was stratified by geographical region and by concomitant LEV use. The number of subjects taking LEV at the time of study entry was limited to 20% of randomized subjects. During the treatment period, the dose could be reduced once for tolerability reasons using a fallback option. The study design is shown in Figure 49.

A total of 399 subjects were randomized to receive PBO or BRV (20mg/day, 50mg/day, or 100mg/day). Of the 398 subjects who received study drug 367 subjects (92.2%) completed the study; completion rates were similar across all treatment groups. A total of 31 subjects (7.8%) discontinued the study. The most common reason for discontinuation was AE for all treatment groups (4 subjects [4.0%] in the PBO group, 4 subjects [4.0%] in the BRV 20mg/day group, 6 subjects [6.1%] in the BRV 50mg/day group, and 5 subjects [5.0%] in the BRV 100mg/day group).

The primary efficacy variable was the POS frequency per week over the treatment period. This variable was transformed prior to being analyzed using the logarithmic transformation $\log_e[x+1]$ (where x is the seizure frequency per week). The log-transformed POS frequency per week over the treatment period was analyzed applying an analysis of covariance (ANCOVA) model, including treatment and a stratification effect combining study region and concomitant LEV use as factors and the log-transformed baseline seizure frequency per week as covariate. Results of the primary efficacy analysis are summarized in Table 50. The percent reductions over PBO in the POS frequency per week over the treatment period were 6.8%, 6.5%, and 11.7% in the BRV 20mg/day, BRV 50mg/day, and BRV 100mg/day groups, respectively. The primary outcome for study N01252 did not achieve statistical significance based on the pre-specified sequential testing procedure, which required statistical significance at the 0.05 level for BRV 50mg/day vs PBO prior to the testing of BRV 100mg/day and BRV 20mg/day in sequence. The comparison of BRV 100mg/day vs PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome ($p=0.037$).

Figure 49 Schematic of N01252 study design



Source: clinical study report N01252 page 33

Table 50 Primary efficacy analysis: treatment comparison of the log-transformed POS frequency per week over the treatment period using an ANCOVA model in N01252 (ITT Population)

Statistics	PBO (N=100)	BRV		
		20mg (N=99)	50mg (N=99)	100mg (N=100)
n	100	99	99	100
LS means (log-transformed) (SE)	1.167 (0.042)	1.096 (0.042)	1.099 (0.042)	1.042 (0.042)
LS means (back-transformed)	2.211	1.993	2.002	1.836
Treatment comparison vs PBO				
% reduction over PBO	--	6.8	6.5	11.7
95% CI	--	-4.8, 17.1	-5.2, 16.9	0.7, 21.4
p-value ^a	--	0.239	0.261	0.037 ^b

ANCOVA=analysis of covariance; BRV=brivaracetam; CI=confidence interval; ITT=Intent-to-Treat;

LS means=least square means; PBO=placebo; SE=standard error

^a In order to control the Type I error, testing was performed in sequence starting with 50mg, then 100mg, and finally 20mg, only moving to the next test if the previous one was significant at the 0.050 level.

ANCOVA on log-transformed partial seizure frequency per week over the Treatment Period, with log-transformed Baseline seizure frequency per week as covariate, and including terms for treatment and stratification factors.

^b Nominally statistically significant.

Source: clinical study report N01252 page 90

4.1.3.2 Summary of clinical study report N01253

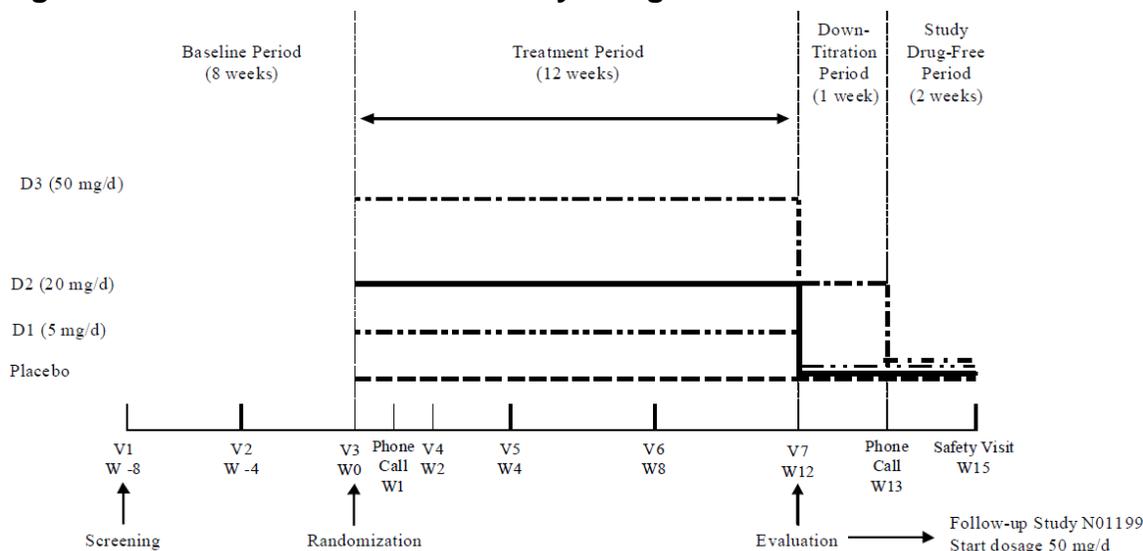
N01253 was a Phase 3, randomized, multi-center, double-blind, parallel-group, PBO-controlled study to evaluate the efficacy and safety of BRV oral tablets in subjects 16 to 70 years of age with POS. The primary objective of the study was to evaluate the efficacy of BRV at doses of 5, 20, and 50mg/day in reducing seizure frequency in subjects with POS not fully controlled despite optimal treatment with 1 to 2 concomitant antiepileptic drugs (AEDs), compared with placebo.

After completing the 8-week baseline period, eligible subjects were randomized in a 1:1:1:1 ratio to receive PBO, BRV 5mg/day, BRV 20mg/day, or BRV 50mg/day during the 12-week treatment period. Central randomization (random permuted blocks) was stratified by geographical region and by concomitant LEV use. The number of subjects taking LEV at the time of study entry was limited to 20% of randomized subjects. Subjects were randomized to the full dose, without up-titration. During the Treatment Period, the fallback option could only be exercised once, if the Investigator deemed it necessary for tolerability reasons. After exercising the fallback option, the study drug dose was kept stable for the rest of the treatment period. At the end of the Treatment Period, the subject either entered a long-term follow up (LTFU) study at a recommended starting dose of BRV 50mg/day (N01199), or entered a down-titration period of 1 week, followed by a 2-week study drug-free period. The study design is shown in Figure 51.

A total of 400 subjects were randomized to receive PBO or BRV (5mg/day, 20mg/day or 50mg/day) and 396 subjects were included in the ITT Population. Of these 396 subjects, 361 subjects (91.2%) completed the study; completion rates were generally similar across all treatment groups. Of the subjects who completed the study, 347 subjects (87.6%) completed the treatment period and entered LTFU. A total of 35 subjects (8.8%) discontinued the study. The most common reason for discontinuation was AE.

The primary efficacy variable was the POS frequency per week over the treatment period, which was transformed prior to being analyzed using the logarithmic transformation $\log_e[x+1]$ (where x is the seizure frequency per week). The log-transformed POS frequency per week over the treatment period was analyzed using an analysis of covariance (ANCOVA) model, including treatment and a stratification effect combining study region and concomitant LEV use as factors and the log-transformed baseline seizure frequency per week as covariate. The percent reductions over PBO in the POS frequency per week over the treatment period were -0.9%, 4.1%, and 12.8% in the BRV 5mg/day, BRV 20mg/day, and BRV 50mg/day groups, respectively. The primary outcome for study N01253 achieved statistical significance for BRV 50mg/day versus PBO ($p=0.025$). However, neither BRV 20mg/day versus PBO nor BRV 5mg/day versus PBO reached statistical significance based on the sequential testing procedure (Table 52).

Figure 51 Schematic of N01253 study design



Source: clinical study report N01253 page 32

Table 52 Primary efficacy analysis: treatment comparison of the log-transformed POS frequency per week over the treatment period using an ANCOVA model in N01253 (mITT Population)

Statistics	PBO (N=96)	BRV		
		5mg (N=96)	20mg (N=99)	50mg (N=101)
n	96	96	99	101
LS means (log-transformed) (SE)	1.418 (0.044)	1.427 (0.044)	1.376 (0.044)	1.282 (0.043)
LS means (back transformed)	3.131	3.168	2.961	2.602
Treatment comparison vs PBO				
% reduction over PBO	–	-0.9	4.1	12.8
95% CI	–	-13.9, 10.6	-8.1, 15.0	1.7, 22.6
p-value ^a	–	0.885	0.492	0.025

ANCOVA=analysis of covariance; BRV=brivaracetam; CI=confidence interval; LS means=least square means; mITT=Modified Intent-to-Treat; PBO=placebo; POS=partial onset seizures; SE=standard error

^a In order to control the Type I error, testing was performed in sequence starting with 50mg, then 20mg, and finally 5mg, only moving to the next test if the previous one was significant at the 5% level. Analysis of covariance on log-transformed POS frequency per week over the Treatment Period, with log-transformed Baseline seizure frequency per week as covariate, and including terms for treatment and stratification factors.

Source: clinical study report N01253 page 90

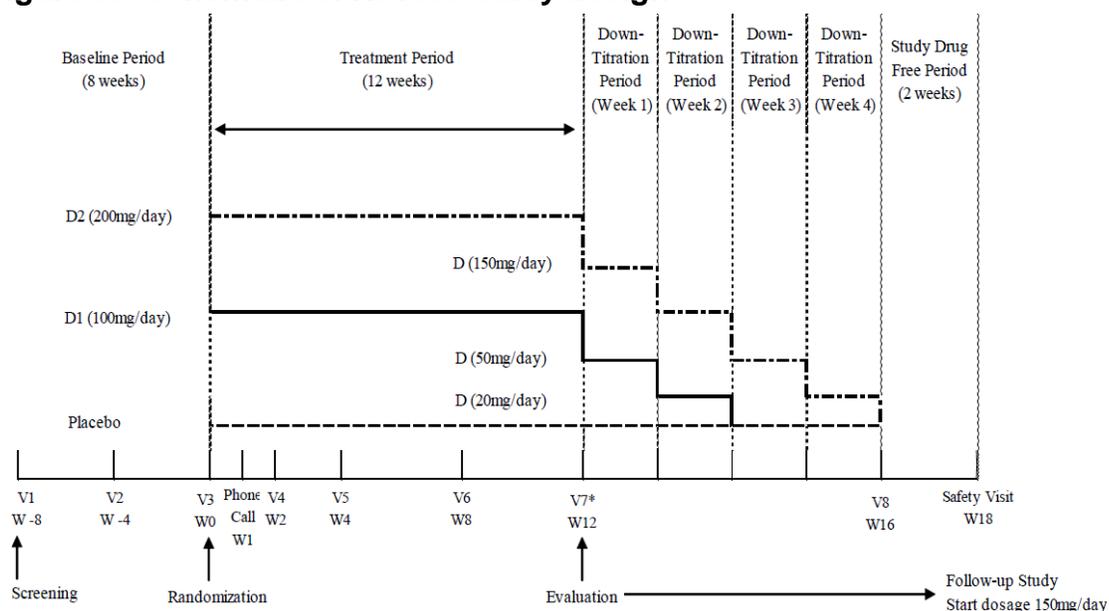
4.1.3.3 Summary of clinical study report N01358

Study N01358 was a Phase 3, multi-center, randomized, double-blind, PBO-controlled study to evaluate the efficacy and safety of BRV as adjunctive therapy in subjects (16 to 80 years old) with POS. The primary objective of this study was to evaluate the efficacy of BRV at doses of 100 and 200mg/day compared with placebo as adjunctive treatment in adult subjects with POS not fully controlled by current treatment with 1 or 2 concomitant AEDs. The secondary objective of this study was to assess the safety and tolerability of BRV.

After completing the 8-week baseline period, eligible subjects were randomized in a 1:1:1 ratio to PBO, BRV 100mg/day, or BRV 200mg/day. A central randomization with stratification for country, LEV status (never used LEV vs prior LEV use only), and number of AEDs previously used, but discontinued prior to study entry (≤ 2 vs > 2 AEDs) was used to ensure the balance across treatment groups (PBO, BRV 100mg/day, and BRV 200mg/day) within each combination of stratification levels. The study excluded subjects receiving concomitant LEV. Furthermore, LEV use within 90 days prior to study entry was not allowed. Seven hundred sixty-eight subjects were randomized to receive PBO or BRV (100mg/day or 200mg/day). The study design is shown in Figure 53.

A total of 1045 subjects were screened and 277 of these subjects were screen failures. 768 subjects were randomized to receive PBO or BRV (100mg/day or 200mg/day). A total of 72 subjects (9.4%) discontinued the study; 17 subjects (6.5%) in the PBO group, 29 subjects (11.4%) in the BRV 100mg/day group, and 26 subjects (10.4%) in the BRV 200mg/day group. The most common reason for discontinuation was AE (10 subjects [3.8%] in the PBO group, 21 subjects [8.3%] in the BRV 100mg/day group, and 17 subjects [6.8%] in the BRV 200mg/day group). The primary efficacy variable was the POS frequency per 28 days during the 12-week treatment period. The primary efficacy outcome for the USA was the percent reduction in POS frequency over PBO based on analysis of covariance (ANCOVA). The reduction in POS frequency over PBO in both BRV groups were statistically significant ($p < 0.001$) and clinically relevant. In addition, the percent reduction in the 28-day adjusted POS frequency over PBO in the BRV 100mg/day and 200mg/day groups was similar (22.8% and 23.2%, respectively) with no dose response. Table 54 summarizes the primary efficacy analysis results.

Figure 53 Schematic of N01358 study design



EDV=Early Discontinuation Visit; D=dose; V=visit; W=week

* Subjects with an EDV at any time during the Treatment Period should have proceeded through the 4-week Down-Titration Period and 2-week Study Drug-Free Period.

Source: clinical study report N01358 page 38

Table 54 Primary efficacy analysis results of N01358: percent reduction over PBO in the 28-day adjusted POS frequency (ITT Population)

Statistics	PBO N=259	BRV 100mg/day N=252	BRV 200mg/day N=249
Number of subjects analyzed	259	252	249
Back-transformed LS means	9.2	6.9	6.8
Percent reduction over PBO	-	22.8	23.2
95% CI (LL, UL)	-	(13.3, 31.2)	(13.8, 31.6)
p-value ^a	-	<0.001*	<0.001*
p-value ^b	-	<0.001*	<0.001*

ANCOVA=analysis of covariance; AED=antiepileptic drug; BRV=brivaracetam; CI=confidence interval; ITT=Intent-to-Treat; LEV=levetiracetam; LL=lower limit; LS=least square; PBO=placebo; POS=partial-onset seizure; UL=upper limit

*Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

Note: Parametric effect estimates and treatment group comparisons were based on an ANCOVA with log-transformed (log[x+1]) Treatment Period 28-day adjusted POS frequency as the outcome and an effect for treatment, an effect for pooled country, and an effect for the 4 combinations of stratification levels for number of previous AEDs and LEV status, and log-transformed Baseline POS frequency as a continuous covariate.

^a p-values were not adjusted for multiplicity.

^b Multiplicity-adjusted p-values were based on a Hochberg multiple comparison procedure.

Source: clinical study report N01358 page 100

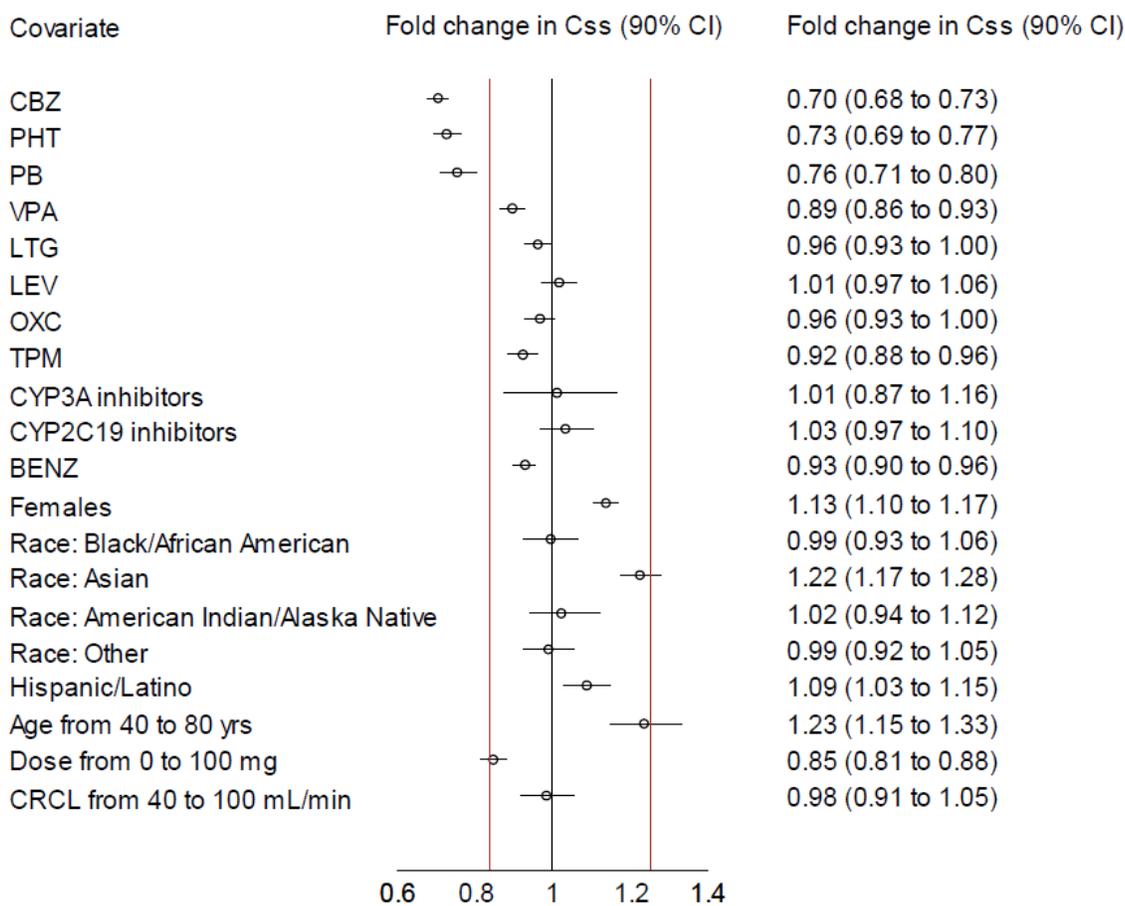
4.1.3.4 Summary of population PK study report CL0028

A population PK model was developed to characterize BRV PK in adults POS patients, to evaluate the relationship of BRV PK with demographic and other covariates, and to perform simulations to demonstrate dose-exposure relationships for the recommended BRV doses.

Data from two Phase 2 studies (N01114 and N01193) and three Phase 3 studies (N01252, N01253, and N01358) were included in the analysis. Study N01114 was a Phase 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study evaluating the efficacy and safety of BRV used as adjunctive treatment at doses of 50 and 150 mg/day in European Caucasian epileptic subjects. BRV was administered twice daily for a maximum of 12 weeks in patients aged from 16 to 65 years. The trial consisted of a baseline period of 4 weeks followed by a 10-week double-blind add-on treatment period with BRV or placebo. The treatment period consisted of a 3-week up-titration period followed by a 7-week maintenance period with a stable drug dose. Finally, a down-titration period of 2 weeks was included. Patients were uncontrolled while treated by one or two concomitant AEDs and had at least 4 POS during the 4-week baseline period. Study N01193 was a Phase 2 multi-center, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study evaluating the efficacy and safety of BRV used as adjunctive treatment at doses of 5, 20, and 50 mg/day in Caucasian, Hispanic, African-American and Indian-Pakistani epileptic subjects. BRV was administered twice daily for a maximum of 7 weeks in patients aged from 16 to 65 years with POS. The study consisted of a baseline period of 4 weeks followed by a 7-week double-blind add-on treatment period with BRV or placebo. No up-titration or down titration was included in this study and the dose of BRV was maintained throughout the treatment period. Patients were uncontrolled when treated by one or two concomitant AEDs and had at least 4 POS during the 4 week baseline period. Information for studies N01252, N01253, and N01358 are summarized in section 3.1 to 3.3.

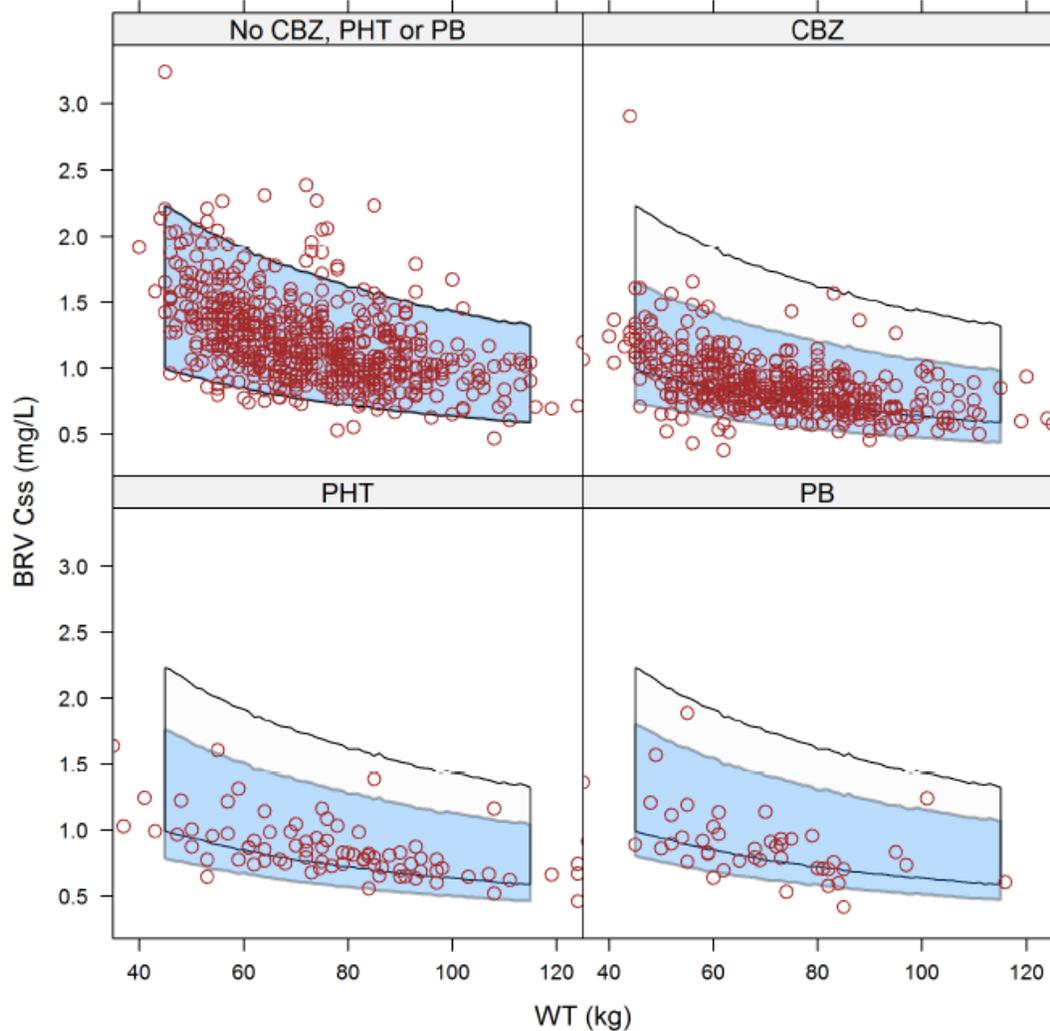
A total of 5820 BRV PK samples from 1248 patients on active BRV treatment were included in the analysis. The results show that a one-compartment model with first order absorption and first order elimination best fitted the data. The effect of body weight on CL and V was implemented using allometric scaling where exponents were estimated. The influence of a number of covariates on BRV CL was assessed in the model and the results were summarized using a forest plot with 90% confidence interval (CI) as shown in Figure 55. A subsequent automated structured covariate search was performed resulting in the statistically significant factors, Carbamazepine (CBZ), Phenytoin (PHT), Phenobarbital (PB), Valproate (VPA), race, sex, age and dose. And then after applying a clinical significance criterion requiring a CL change of at least 20%, only the co-administration of CBZ, PHT and PB remained as significant covariates. The percentage increase in CL (with 95% CI) for co-administration with the enzyme inducers CBZ, PHT and PB was estimated to be 34.8% (30.5% -39.2%), 26.8% (20.0%-33.9%) and 23.9% (15.0%-33.4%) respectively. The influence of these 3 significant covariates was demonstrated using the simulation results in Figure 56. The final model parameter estimates were summarized in Table 57. Diagnostic plots were used for final model evaluation and the results are shown in Figure 58 and Figure 59. In addition, visual predictive check (VPC) stratified by dose was conducted to assess the predictive performance of the final model and the results are shown in Figure 60 .

Figure 55 Forest plot for covariate effects on fold change in BRV C_{ss} with 90% CI. Red lines indicate the fold change limits associated with 20% change in CL.



Source: population PK study report CL0028 page 41

Figure 56 Predicted C_{ss} for 50 mg BRV BID as a function of WT and co-administration of CBZ, PHT, or PB



The blue area encompasses 90% of predicted C_{ss} values for patients in either the absence of CBZ, PHT, and PB co-administration, or the presence of CBZ or PHT or PB co-administration. The black solid line is identical for all graphs and is added as reference encompassing 90% of predicted C_{ss} values in the absence of CBZ, PHT, and PB co-administration. The red circles are the predicted C_{ss} values for patients in the analysis that have only one of CBZ, PHT, or PB co-administered or none of these three AEDs.

Source: population PK study report CL0028 page 23

Table 57 Final population PK model parameter estimates

Parameter	Estimate (95% CI¹)	SE² (%CV)	IIV³	Shrinkage⁴
CL (L/h)	3.58 (3.50/3.66)	1.1%	24.7%	17.2%
V (L)	48.1 (45.8/50.4)	2.4%	30.5%	56.0%
Ka (1/h)	1.42 (1.26/1.57)	5.5%	101.2%	53.9%
Exponent for WT on Cl	0.565 (0.499/0.631)	6.0%		
Exponent for WT on V	0.639 (0.483/0.795)	12.5%		
Effects on CL:				
CBZ ⁵	34.8% (30.5%/39.2%)	5.5%		
PHT ⁵	26.8% (20.0%/33.9%)	11.8%		
PB ⁵	23.9% (15.0%/33.4%)	17.6%		
Residual error:				
Proportional residual error (CV, %)	20.7 (19.7/21.7)	2.4%		14.0%

¹95%CI is estimate±1.96*the standard error for the estimate

²Standard errors of the estimate are reported as %CV: 100*(standard error for the estimate)/estimate

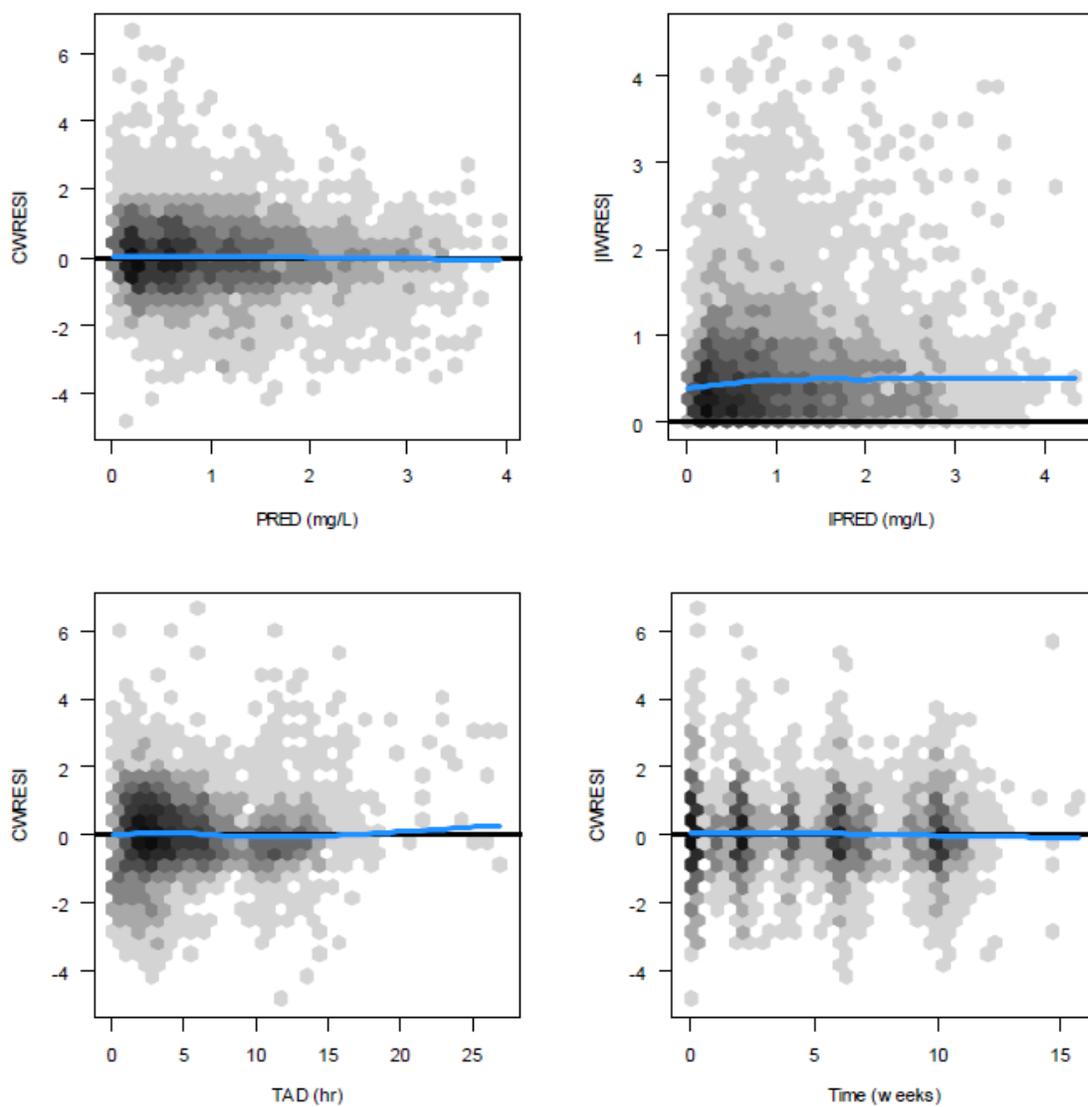
³IIV is the CV of the inter-individual variability calculated as the square root of the diagonal element in the omega matrix

⁴Shrinkage values as reported by NONMEM

⁵effects are back-transformed log-estimates, changed from a factor to a percentage change

Source: population PK study report CL0028 page 46

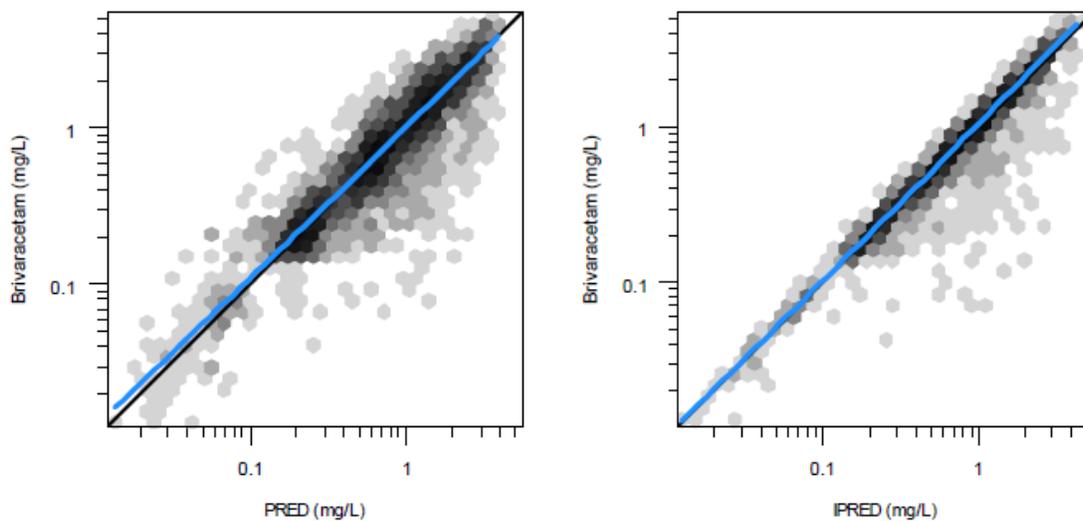
Figure 58 Goodness of fit plots using conditional weighted residuals (CWRESI)



The horizontal black lines are zero lines, the blue lines are smoothes through the data.

Source: population PK study report CL0028 page 52

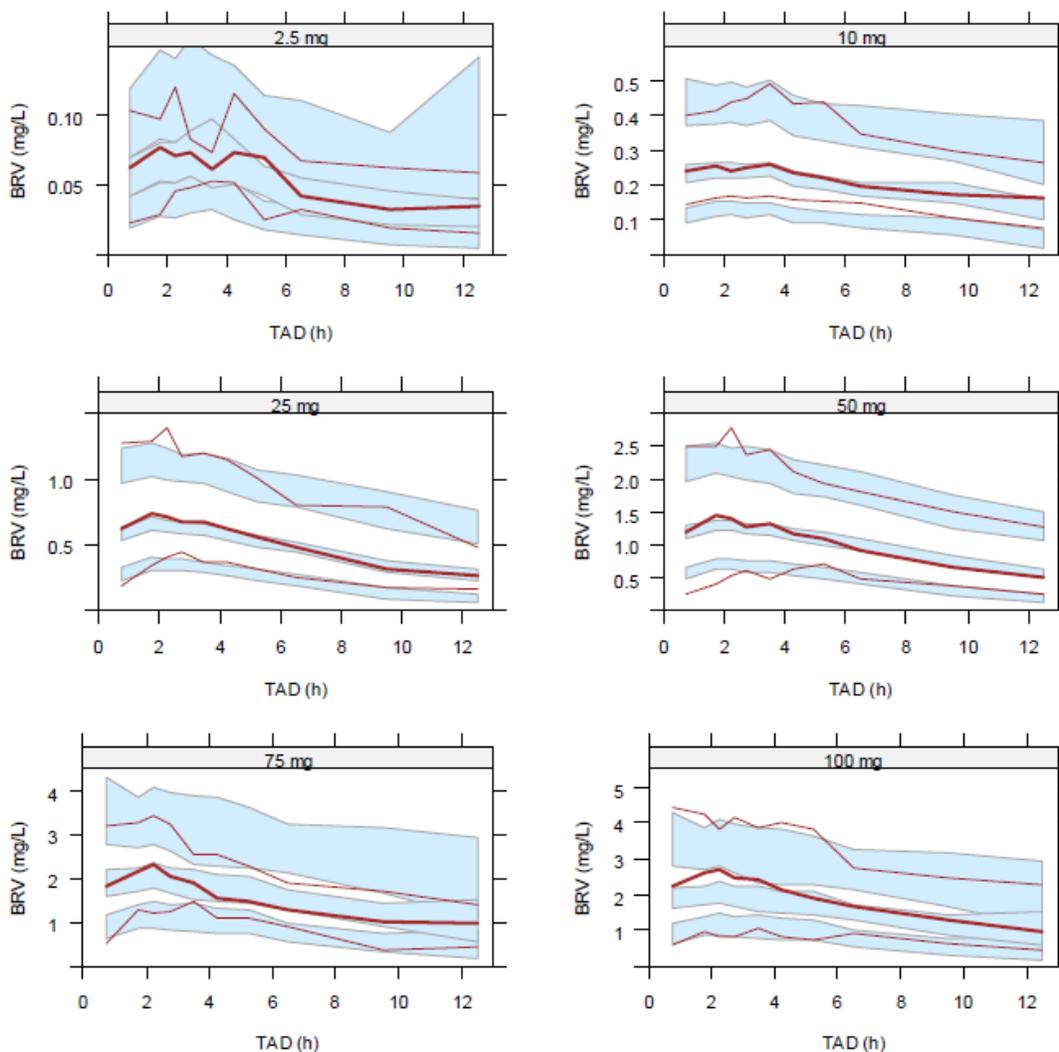
Figure 59 Goodness of fit plots in Log scale



The black lines are lines of identity, the blue lines are smoothes through the data.

Source: population PK study report CL0028 page 54

Figure 60 VPC results



Red lines are the 5th, 50th (median), and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles.

Source: population PK study report CL0028 page 55

Reviewer's comments:

The sponsor's population PK model adequately described BRV concentration-time data from two Phase 2 studies (N01114 and N01193) and three Phase 3 studies (N01252, N01253, and N01358). The covariate effect on BRV CL was reasonably investigated with the established model. The sponsor's analysis results show that co-administration with enzyme-inducing AEDs carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB) could result in 34.8%, 26.8%, and 23.9% increase in mean BRV clearance and correspondingly 26%, 21%, and 19% decrease in BRV plasma concentration, respectively. The influence of concomitant CBZ on BRV exposure was evaluated in a phase 1 study (N01081), which showed that steady-state CBZ at 300 mg bid increased BRV clearance resulting in 29% decrease in BRV exposure. The result of this dedicated study is consistent with the result from the population PK analysis. The effects of concomitant PHT and PB on BRV exposure were not evaluated in dedicated studies. Based on the findings, the sponsor's proposal of no dose adjustment for these three concomitant AEDs is considered acceptable since the

changes in BRV exposure when co-administrated with CBZ, PHT, or PB are all less than 30%.

4.1.3.5 Summary of exposure-response analysis study report CL0027

4.1.3.5 .1 Exposure-efficacy analysis

A model-based exposure-response analysis of BRV was conducted in adult patients with POS. The objective of the analysis was to determine the population exposure-response relationship between BRV concentration and daily seizure counts in two Phase II studies (N01114, N01193) and three Phase III studies (N01252, N01253, N01358) in the treatment of epilepsy as adjunctive therapy in POS, and to assess the influence of covariates on BRV effect.

The final dataset included 251278 seizure counts from 1912 subjects. The exposure-response model, based on estimated daily average BRV concentrations (C_{av}) and daily seizure counts, was developed using a count model to describe daily seizures where seizure rates are a function of both placebo and drug effects. A covariate analysis was also conducted to evaluate if exposure-response relationship was influenced by demographic covariates and co-medication. Daily C_{av} values were derived by simulating a concentration profile for every individual on every day for which a seizure count was recorded using the population PK model in analysis CL0028. The analyses were performed using NONMEM Version 7.2.0 and R Version 3.0.2 softwares.

The results show that a mixture model with two populations separating the subjects into a mixture-model responder population and a mixture-model placebo-like population best described the data. Daily seizure rates were described using a negative binomial statistical distribution with inter-individual variability in the over-dispersion factor. The seizure rate on a given day was assumed to be influenced by the number of seizures on the preceding day. A Box-Cox transformation was used to transform the baseline daily seizure rates improving the description of the baseline seizure rate distribution. And an E_{max} model was used to describe the relationship between C_{av} and daily seizure rate. The covariate analysis revealed that only LEV co-administration and baseline seizure frequency significantly influenced the response to BRV treatment. The final model parameter estimates are shown in Table 61. EC_{50} of BRV was estimated to be 0.572 mg/L, which is slightly above the median exposure obtained after BRV doses of 50 mg/day. Further seizure frequency reduction is obtained by increasing the dose to 100 mg/day and 200 mg/day and a plateau seems to be reached. The percentage of subjects in the mixture-model responder population was estimated to be 29.3% with a median baseline seizure frequency of 0.32 seizures/day and without LEV co-administration. Covariate analysis indicated that LEV co-administration effectively reduced the fraction of mixture-model responder subjects to close to 0%. Covariate analysis also indicated that subjects with high baseline seizure rates had a much lower probability of ending up in the mixture-model responder population.

VPCs for median % change in daily seizure frequency from baseline and fraction of subjects with more than 50% change in daily seizure frequency from baseline (50% responders) were performed to evaluate the predictive performance of the exposure-response model. The results are shown in Figure 62. Simulations were conducted to visualize the effect of specific BRV concentrations on seizure counts. Figure 63 provides predicted individual percent changes from baseline for the final mixture model, without distinguishing between the

mixture-model placebo-like population and the mixture-model responder population. Figure 64 shows the simulated BRV effect by BRV concentrations split by mixture-model population.

Table 61 NONMEM parameter estimates for the final exposure-response model

Parameter	Estimate (95% CI)	SE ¹ (%CV)	IIV ²	Shrinkage Responders (%) ³	Shrinkage Placebo (%) ³
S ₀ (day ⁻¹) (θ1)	0.311 (0.297/0.325)	2.0%	72.2%	41.3%	13.8%
ES ₅₀ (seizures) (θ2)	1.98 (1.87/2.10)	3.0%			
S _{max} (% increase) (θ3) ⁴	102.7% (85.7%/121.3%)	6.3%	128.0%	38.8%	22.3%
Placebo (% change) (θ4) ⁴	-18.6% (-21.0%/-16.1%)	7.5%	34.8%	52.3%	29.2%
E _{max} (% change) (θ5) ⁴	-89.2% (-95.0%/-76.8%)	17.5%	58.4%	47.5%	100.0%
EC ₅₀ (mg/L) (θ6)	0.572 (0.288/1.14)	62.7%			
Over-dispersion α (θ7)	0.143 (0.122/0.166)	4.0%	257.7%	29.8%	21.8%
Box-Cox parameter on S ₀ (θ8)	0.606 (0.466/0.746)	11.8%			
Mixture fraction (% of subjects in the mixture- model responder population) (θ9)	29.3 (21.4/37.2)	13.7%			
Log baseline on mixture fraction (odds ratio)	0.00706 (0.00181/0.0276)	14.0%			
LEV on mixture fraction (odds ratio)	0.101 (0.00923/1.12)	53.5%			

¹Standard errors of the estimate are reported as %CV: 100* standard error for the estimate /estimate

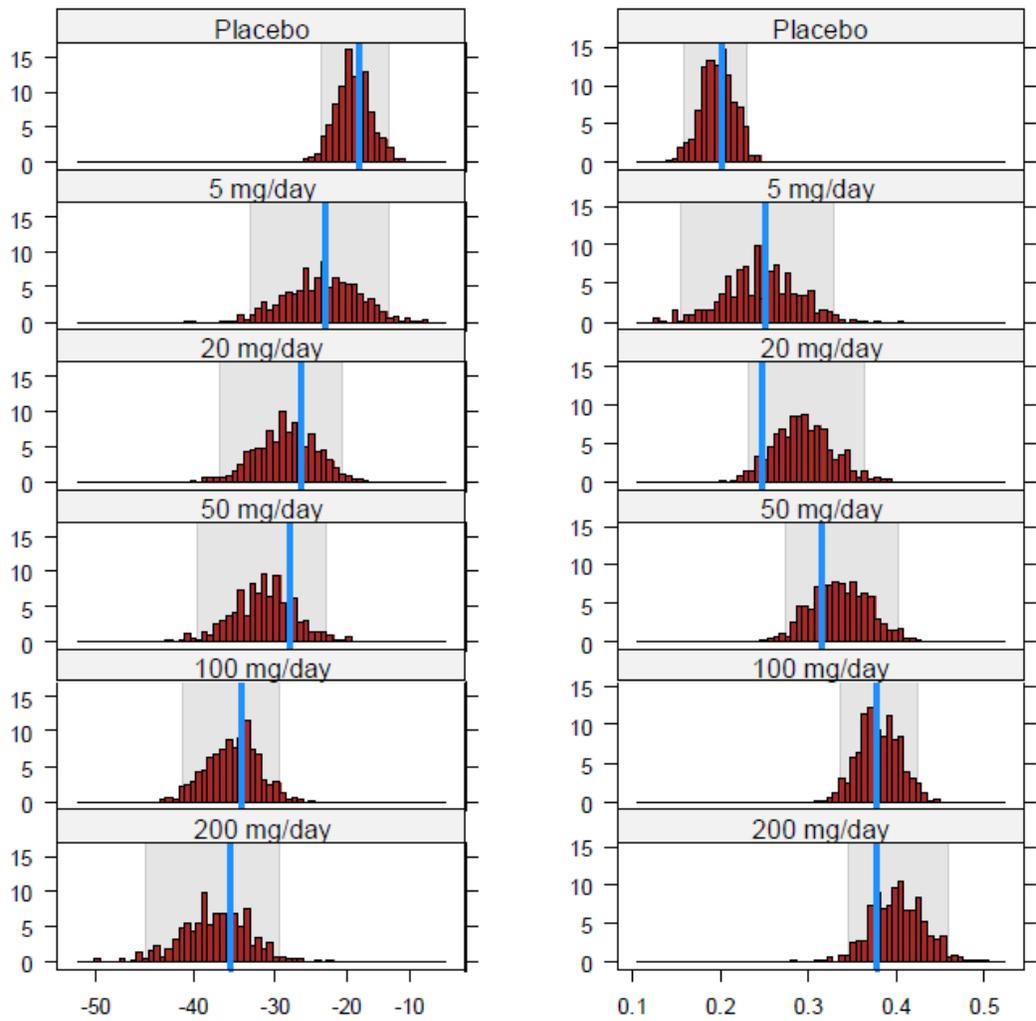
²IIV is the CV of the inter-individual variability calculated as the square root of the diagonal element in the omega matrix

³Shrinkage values as reported by NONMEM

⁴Parameters are back-transformed log-estimates, changed from a factor to a percent change

Source: PKPD study report CL0027 page 63

Figure 62 VPC for the final model by dose for median percent change from baseline (left) and fraction of 50% responders (right)



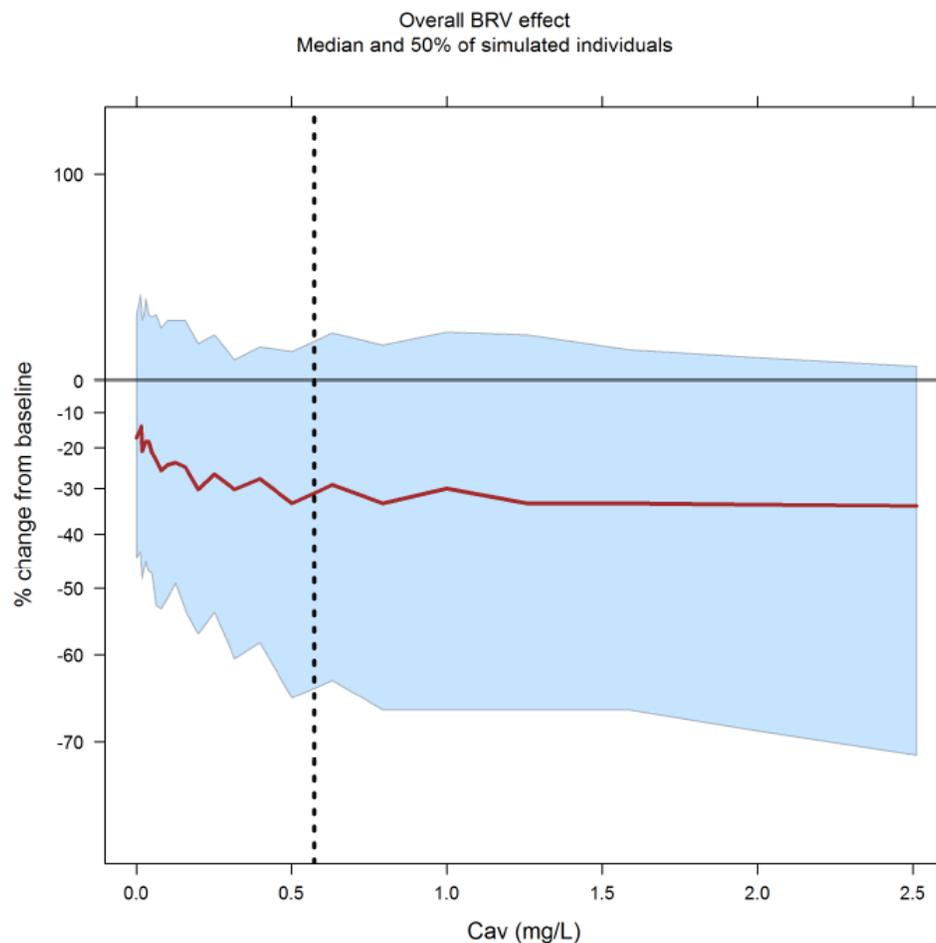
Median % change from baseline

Fraction responders (decrease >50%)

Histograms provide the distribution of outcomes for 500 simulated trials, the blue vertical line displays the result for the observed data.

Source: PKPD study report CL0027 page 24

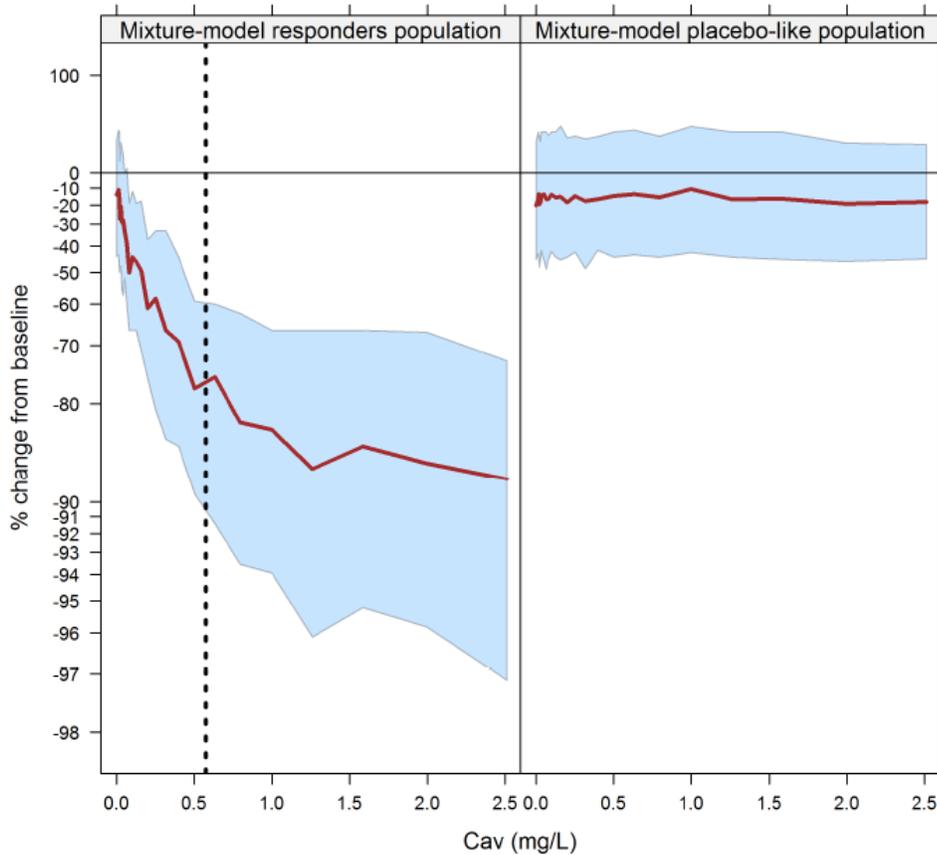
Figure 63 Overall simulated BRV effect by BRV concentration



Median and 50% of simulated individuals. Vertical dotted line: EC_{50} .

Source: PKPD study report CL0027 page 64

Figure 64 Simulated BRV effect by BRV concentrations split by mixture-model population



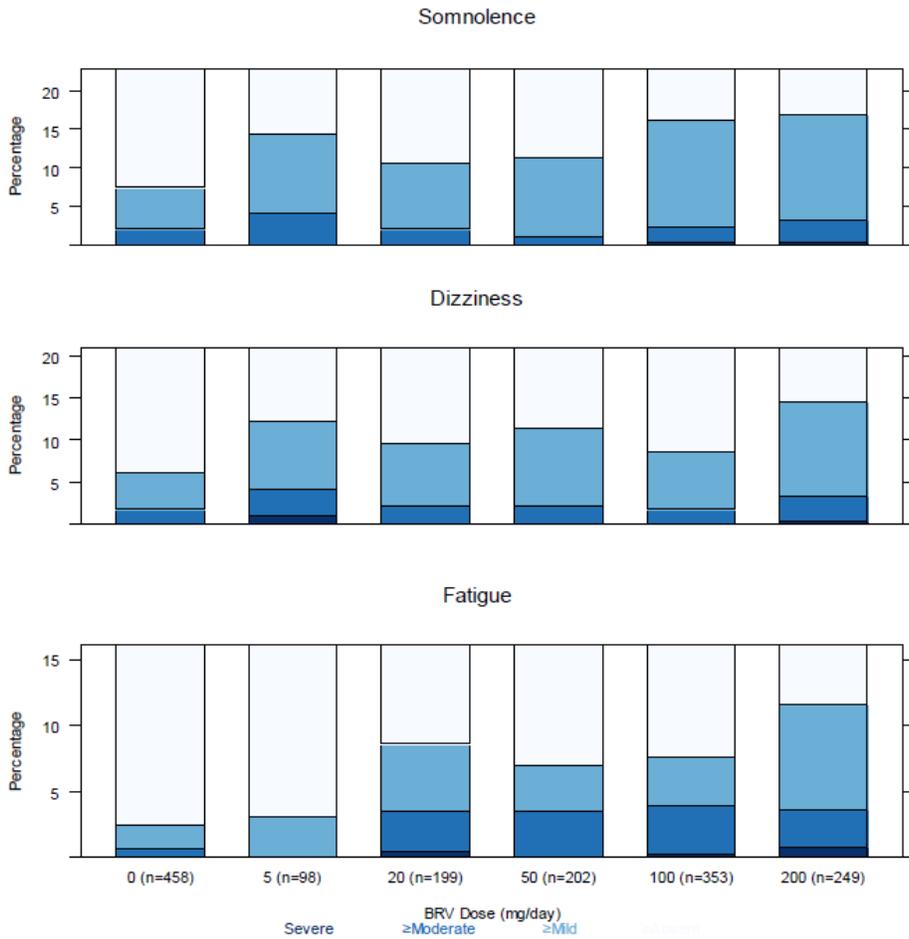
Median and 50% of simulated individuals. Vertical dotted line: EC₅₀.

Source: PKPD study report CL0027 page 65

4.1.3.5.2 Dose/exposure-safety analysis

Exploratory dose/exposure-safety analyses were conducted using data from 3 Phase 3 studies N01252, N01253, and N01358. The most common adverse events, including somnolence, dizziness, and fatigue, were selected for this analysis. Population PK model-predicted BRV C_{max} value was selected as the exposure parameter. Relatively flat dose/exposure-safety relationships at the proposed dose levels were observed, as shown in the figures below.

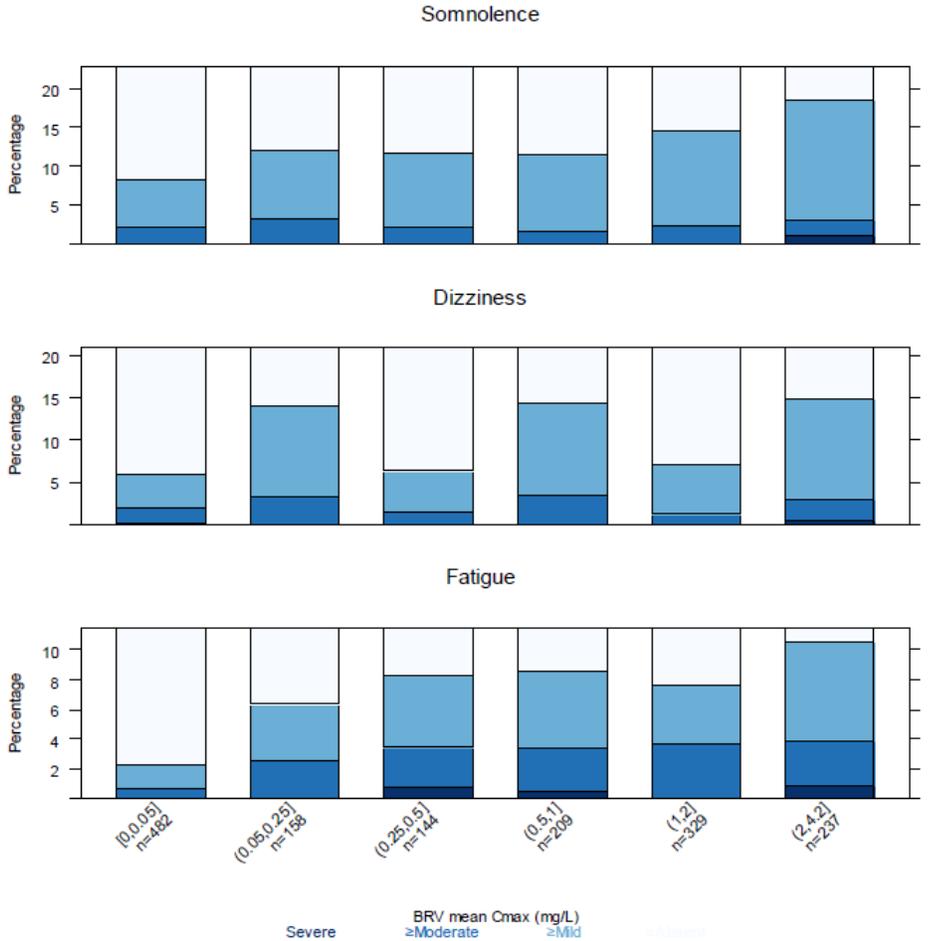
Figure 65 Relationship between fraction of subjects with their maximum AE intensity during treatment and randomized dose



Color code for maximum AE intensity: dark blue=severe; medium blue=moderate; light blue=mild

Source: study report CL0027 page 299

Figure 66 Relationship between fraction of subjects with their maximum AE intensity during treatment and popPK model-predicted BRV Cmax



Source: study report CL0027 page 297

Reviewer’s comments:

The sponsor’s population exposure-response model seems to adequately describe relationship between predicted Cav and daily seizure count in two Phase 2 studies (N01114 and N01193) and three Phase 3 studies (N01252, N01253, and N01358).

The EC50 was estimated to be 0.572 mg/L from the sponsor’s final model. However, it is the EC50 only for the mixture-model responder population, but not the entire population. Our independent exposure-response analysis fitted an Emax model to all subjects from the three Phase 3 studies N01252, N01253, and N0135, which reasonably captures the observed data. Our model-estimated EC50 of 0.48 mg/L is generally consistent with the sponsor’s result.

4.1.3.6 Summary of pharmacokinetic interaction study report CL0178

A retrospective meta-analysis was conducted to evaluate the effect of BRV on the plasma concentrations of other AEDs in an epileptic population with partial onset seizures. The AEDs investigated in this analysis included: carbamazepine (CBZ) and its main metabolite (CBZ-E,

(b) (4)™ (Brivaracetam oral tablet / IV solution / oral solution)

carbamazepine-10,11epoxide), lacosamide (LCM), levetiracetam (LEV), lamotrigine (LTG), MHD (10-hydroxyoxcarbazepine, circulating metabolite of oxcarbazepine), phenytoin (PHT), phenobarbital (PB), pregabalin (PGN), primidone (PRM, and its circulating metabolite phenobarbital), topiramate (TPM), valproate (VPA), and zonisamide (ZNS).

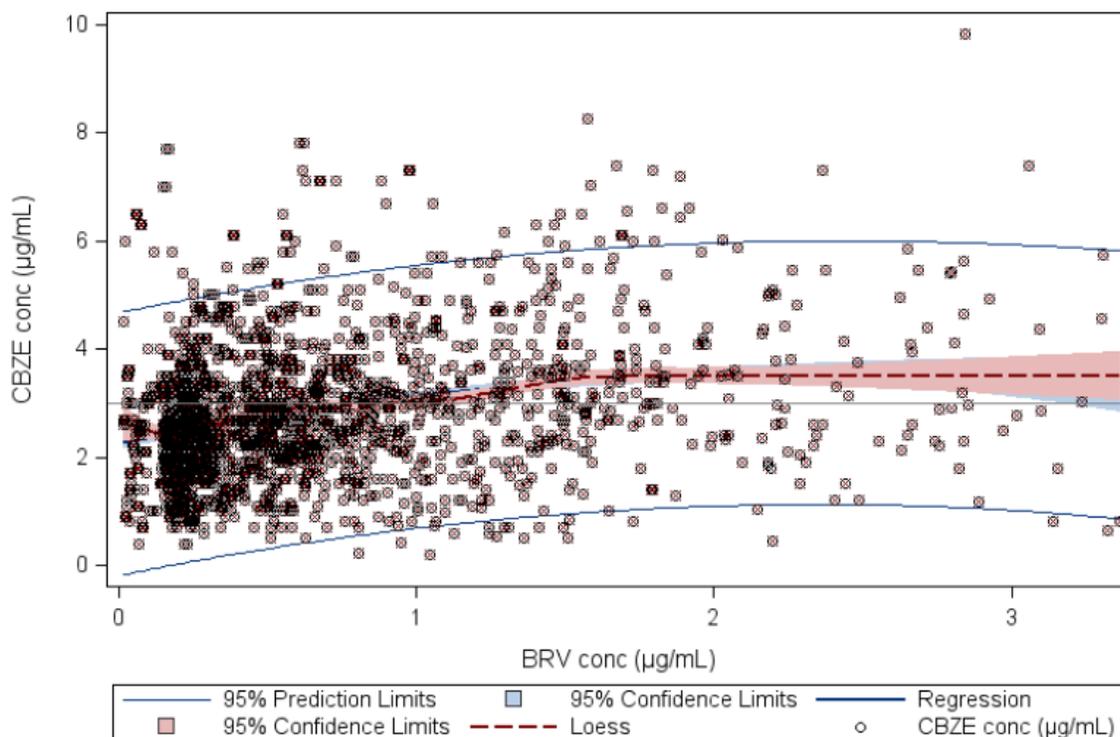
Data from two Phase 2 studies (N01114 and N01193) and three Phase 3 studies (N01252, N01253, and N01358) were used in this analysis. The analysis population included all evaluable subjects, i.e. with at least one AED measure at baseline and at least one AED assessment during the treatment period, who was treated during at least one week with constant dose of BRV/placebo, who received constant dose of AED during at least 2 weeks during the treatment period. The effect on AEDs was assessed in the treatment groups (Placebo/BRV) as well as in BRV dose groups (0, 5, 20, 50, 100, 150, 200mg/day). In all studies, AED plasma concentrations were measured at least once during baseline and at least once under co-administration of BRV or placebo. The primary variable was the AED plasma concentration. The primary parameter was defined as the ratio of geometric means of AED plasma concentrations between the evaluation visit and the baseline period. Possible interaction of BRV on other AEDs administered concomitantly was investigated based on repeated measurements of AED plasma concentrations over time (visit). From the covariance analysis, least squares (LS) means of the primary parameter were calculated together with 90% CI for each fixed effect. A clinically significant AED concentration change was excluded if both limits of 90% CI of the geometric LS means ratio were within the predefined 0.8-1.25 boundaries.

A total of 1771 subjects (70% received BRV, 30% received PBO) were included in the final analysis. Carbamazepine (41% of subjects) was the most common AED co-medication, followed by lamotrigine (25%), valproate (19%), oxcarbazepine (15%) and topiramate (13%), levetiracetam (11%), phenytoin (10%), phenobarbital (6%), lacosamide (6%), pregabalin (4%), zonisamide (5%) and primidone (1%). Benzodiazepines (eg, clonazepam) were not counted because they were not measured in all studies.

Geometric mean steady state plasma concentrations varied from baseline to BRV treatment period (all doses considered) for CBZ: 8.85 to 8.66µg/mL; CBZ-E: 1.72 to 2.45µg/mL; VPA: 66.2 to 65.9µg/mL; LTG: 6.00 to 6.54µg/mL, LEV: 27.4 to 30.1µg/mL, TPM: 6.07 to 6.25µg/mL, MHD: 20.6 to 21.1µg/mL, PHT: 10.3 to 11.0µg/mL; PB: 21.0 to 21.3µg/mL, PGN: 3.80 to 4.48µg/mL, PRM: 9.42 to 10.4µg/mL, ZNS: 20.2 to 21.4µg/mL. A forest plot summarizing the fold change in AED plasma concentrations at steady state by AED name is shown in Figure 48. The results demonstrate that the 90% CI of LS geometric mean ratios between BRV evaluation and baseline periods was within 0.80-1.25 limits for CBZ, LCM, LEV, LTG, MHD, PB, PHT, TPM, VPA, and ZNS; and the ratio and its 90% CI were fully outside the 0.8-1.25 boundaries for CBZ-E and the mean percentage increase from baseline reached a value of 47% with 90% CI of 44-51%. Dose effect was observed for CBZ-E as with a mean increase of 37% for 50mg/day BRV, 62% for 100mg/day BRV, 77% for 150mg BRV and 98% for 200mg/day BRV and the Figure 67 depicts the relationship between CBZ-E and BRV plasma concentrations.

The sponsor concluded that no significant effect of brivaracetam was demonstrated on the plasma concentrations of carbamazepine, lacosamide, lamotrigine, levetiracetam, MHD, phenobarbital, phenytoin, pregabalin, topiramate, valproate and zonisamide. Therefore, no dose adjustment is required when BRV 5 to 200mg/day is added to carbamazepine, lacosamide, levetiracetam, lamotrigine, oxcarbazepine (monitored as MHD), phenobarbital, phenytoin, pregabalin, topiramate, valproate, and zonisamide.

Figure 67 Relationship between CBZ-E and BRV plasma concentration



Source: study report CL0178 page 42

Reviewer's comments:

In general, the sponsor's meta-analysis was conducted adequately to evaluate the effect of BRV exposure on the plasma concentrations of concomitant AEDs. No significant effect of BRV was found on AEDs except CBZ-E. The results show BRV could increase CBZ-E concentrations in a dose-dependent manner when BRV is co-administrated with CBZ. The mean increase in CBZ-E concentrations from baseline was 37 % for 50mg BRV, 62% for 100mg BRV, and 98% for 200mg BRV. Such effect of BRV on CBZ-E exposure is expected due to the inhibitory effect of BRV on epoxide hydrolase.

4.1.4 Reviewer's Analysis

4.1.4.1 Introduction

Exposure-response analyses were conducted to evaluate the appropriateness of 50 mg/day and 200 mg/day, and to evaluate the subgroup effect of concomitant LEV use. An exposure comparison analysis was performed to assess the relationship between BRV exposure and SUDEP events. The analysis served as a quality control to the sponsor's analysis and an opportunity to develop an independent scientific opinion on the key questions.

4.1.4.2 Objectives

Analysis objectives are:

To evaluate the appropriateness of 50 mg/day and 200 mg/day

To evaluate the effect of concomitant LEV use on BRV efficacy

To evaluate the relationship between BRV exposure and SUDEP events

4.1.4.3 Methods

Independent exposure-response analyses were conducted. Population PK model-predicted steady-state average concentrations were used as the predictor variable in the exposure-response analysis. The primary efficacy variable, POS frequency over the treatment period, was used in the exposure-response analysis. Particularly, change from baseline in POS frequency over the treatment period was selected as the response variable.

4.1.4.3.1 Data Sets

Data sets used are summarized in Table 68.

Table 68 Analysis Data Sets

Study Number	Name	Link to Sharedrive
N01252,	EFFSZP.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brivaracetam_NDA205836_205837_205838_XW\ER Analyses\Study N01252
N01253	EFFSZP.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brivaracetam_NDA205836_205837_205838_XW\ER Analyses\Study N01253
N01358	ADSZP.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brivaracetam_NDA205836_205837_205838_XW\ER Analyses\Study N01358

4.1.4.3.2 Software

NONMEM (version 7.2) and R (version 3.1.2) were used for dataset construction, analyses, and graphics generation.

4.1.4.3.3 Models

The sponsor's population PK model was used to generate model-predicted BRV steady-state average concentrations. Emax models were used to describe the relationship between model-predicted BRV steady-state average concentrations and the efficacy endpoint. A total of 1533 subjects were included in the analysis from 3 Phase 3 studies (N01252, N01253, and N01358). 34 subjects were excluded from the analysis due to lack of predicted BRV average steady state exposures. For the overall exposure-response model, all subjects including subjects taking or not taking concomitant LEV were included in the analysis. For the subgroup analysis regarding to concomitant LEV use, the whole study population was split into two subpopulations by concomitant LEV use and two exposure models were developed for the two subpopulations separately.

4.1.4.4 Results

See Section 1 (Summary of Findings) of this report.

4.1.5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER model for all.r	Exposure-response model for all subjects from N01252, N01253, and N01358	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brivaracetam_NDA205836_205837_205838_XW\ER Analyses\Reviewer's analysis\For Emax Model
ER model for nonLEV and LEV.r	Subgroup exposure-response models for subjects taking and not taking concomitant LEV	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Brivaracetam_NDA205836_205837_205838_XW\ER Analyses\Reviewer's analysis\For Emax Model

4.3 Pharmacogenomics Review

EXECUTIVE SUMMARY

The sponsor provided a study report for study N01209, a double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects. This study report contained CYP2C19 genotype information on a subset of subjects from this study and comparisons between extensive and poor metabolizers. The sponsor's classification of subjects as homozygous or heterozygous Extensive (EM) or Poor (PM) metabolizers based on the haplotype of the genotype alleles is acceptable. Concordance of metabolizer status between the sponsor's assignments and the reviewer's assignments was 100%. PM subjects had approximately 40% higher exposure ($AUC_{0-\infty}$) as compared to homozygous EM subjects. Small numbers of subjects, data only in Japanese subjects, and inconsistency with very limited impact of CYP2C19 inhibitors on exposure make the results difficult to rely upon for dose adjustments or expected differences in exposure in the population at large.

4.2.1 Background

Brivaracetam is being developed in 3 different formulations: a tablet with strengths between 10 and 100 mg, an oral solution, and an IV solution (both at 10 mg/mL). Brivaracetam is a small molecule modulator that displays a high and selective affinity for brain-specific binding site synaptic vesicle protein 2A (SV2A), which appears to be the primary target for its pharmacological activity. Brivaracetam is pharmacologically similar to the AED levetiracetam (LEV). The sponsor claims however, compared to LEV, that BRV displays a markedly higher selectivity and affinity for SV2A.

Based on the information the sponsor provided in the Summary of Clinical Pharmacology, brivaracetam is primarily metabolized by two biotransformation pathways (amidase and CYP2C19 hydrolysis) in humans. The enzymes responsible for the two biotransformation pathways in humans were determined by in vitro metabolism studies with recombinant human cytochrome P450 isoforms and human liver microsomes. Metabolism of brivaracetam lead to three primary inactive metabolites (*ucb 42145*, *ucb-100406-1*, and *ucb-107092-1*) driven by amidases (*ucb 42145*), CYP2C19 (*ucb-100406-1*), or both amidase and CYP2C19 hydrolysis (*ucb-107092-1*).

The sponsor has not proposed dosing recommendations for CYP2C19 PMs. The sponsor's analysis of the single (SD) and multiple (MD) dose parts of study N01209 showed PMs have AUC values 42%-47% higher than homozygous EMs (*Study Report N01209A/B, Tables 11:13 and 11:9*).

The purpose of this review is to evaluate the CYP2C19 genotype information submitted by the sponsor and comment on the reliability and generalizability of exposure differences seen between EMs and PMs in Japanese subjects.

4.2.2 Submission Contents Related to Genomics

The sponsor submitted the following reports and datasets related to the pharmacogenetic (PGx) analysis of brivaracetam:

Table 69: Reports and Datasets Pertaining to PGx Analyses of Brivaracetam

<i>ID</i>	<i>Report Description</i>	<i>Datasets</i>
N01209A	Clinical study report for a double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) of brivaracetam (BRV) in Japanese healthy adult male subjects	---
N01209B	Clinical study report for a double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects	---

Study N01209 enrolled 80 subjects, 79 of which completed the study; 50 subjects in Part A and 29 subjects in Part B. DNA samples were collected from subjects who consented to optional participation in PGx research during the study. Of the 79 subjects who completed the study, 69 subjects (87%) also had listed genotypes in the study reports (43 Part A & 26 Part B).

Table 70: Clinical Trials Utilized for PopPK Analyses

<i>Study</i>	<i>Description</i>	<i>Number of Subjects Completed (Part A/B)</i>	<i>Number of Subjects with Genotype (Part A/B)</i>
N01209	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects	79 (50/29)	69 (43/26)

Source: Study reports (N01209A/N01209B), study synopses.

DNA samples were analyzed for genetic variants in the genes encoding CYP2C19 using Invader Assay technology and genotyped by the (b) (4). The following table lists the variants investigated, methods utilized, and functional consequences of these variants.

Table 71: Polymorphisms Tested and Genotyping Methods Utilized for 2C19

<i>Polymorphism</i>	<i>Identifier</i>	<i>Genotyping Method</i>	<i>CYP2C19 Enzymatic Activity</i>
CYP2C19*2	rs4244285	Invader Assay	None
CYP2C19*3	rs4986893	Invader Assay	None

Source: Study reports (N01209A/N01209B), Section 6.5, 9.8.1.2.2, and 9.8.1.2.3. <http://www.cypalleles.ki.se>

4.2.3 Key Questions and Summary of Findings

3.1 Is the sponsor's predicted metabolizer status classification accurate based on reported genotype data?

Yes. While the sponsor genotyped only the 2 most common alleles associated with lack of functional CYP2C19, the assigned metabolizer status categories were completely concordant with the reviewer’s assignments. Additionally, other non-functional variants that effect CYP2C19 function occur at very low frequencies within Asian and Caucasian populations.

Sponsor’s Analyses:

Subjects were classified as homozygous Extensive (homEM), heterozygous Extensive (hetEM), or Poor (PM) metabolizers based on haplotype of the genotyped variants. Subjects were classified as PMs if they possessed 2 non-functioning alleles, heterozygous EMs if they had one non-functioning allele and one normal functioning allele, or homozygous EMs if neither allele was non-functional. A summary of the sponsor’s assigned metabolizer status for all subjects in the study are provided in the following table.

Table 72: Sponsor’s Assignment of CYP2C19 Metabolizer Status

Metabolizer Status	Number of Subjects (Part A/B)	Percentage of PopPK Subjects (N=79) (Part A/B)
<i>Homozygous Extensive</i>	22 (12/10)	28% (24%/35%)
<i>Heterozygous Extensive</i>	31 (19/12)	39% (38%/41%)
<i>Poor</i>	16 (12/4)	20% (24%/14%)
<i>Not Genotyped</i>	10 (7/3)	13% (14%/10%)

Source: Study reports (N01209A/N01209B), Section 11.2.1.1.

Reviewer’s Analyses:

Subjects were re-classified using identical methodologies as listed above using the sponsor’s provided subject level genotype dataset. The reviewer notes that all sponsor calls were concordant with the reviewer’s calls. It should be noted that the sponsor only genotyped the two most common of alleles in order to classify subjects as EMs or PMs and that these alleles all abolish function of CYP2C19 gene activity. There are several known variants (e.g. *4, *5, *6) that lead to abolishment of activity for CYP2C19 that the sponsor did not genotype which could lead to some subjects currently classified as EMs to be reclassified as PMs if these other variants were genotyped. The reviewer does not anticipate that the failure to genotype for other non-functional variants will impact the sponsor’s analysis given that these additional variants are exceedingly rare.

In additional analyses, the sponsor classified subjects in Part A based on % urinary excretion of the CYP2C19 generated metabolite *ucb-100406-1* and compared these groups to the genotype derived metabolizer status calls. Overall correlation was good, with PMs 100% concordant but with some overlap between heterozygous and homozygous EMS (N01209A study report, Figure 11:15).

3.2 Should dosing adjustment recommendations be made for CYP2C19 PMs based on the observed differences in exposure seen in the sponsor’s analysis?

No. While the sponsor’s analysis suggests there is a ~40% increase in exposure ($AUC_{0-\infty}$) in PMs as compared to homozygous EMs, these analyses are based on small numbers of Japanese subjects and drug-drug interaction (DDI) data using a CYP2C19 inhibitor did not affect exposure (see Pharmacometrics review by Xiaofeng Wang). Additionally, the sponsor reports that doses of up to 800 mg daily were well tolerated in Phase 2 studies, that the MTD may be ≥ 800 mg/day, and that the exposure-response relationship with safety is flat (see Pharmacometrics review by Xiaofeng Wang).

Sponsor’s Analyses:

Study N01209 consisted of single and multiple dose parts (A/B) and as such analyses on the effect of CYP2C19 metabolizer status were done separately on each part (A/B) which led to fairly small numbers of subjects with each metabolizer status. Results from Part A (SD) and Part B (MD) showed consistent effects on exposure ($AUC_{0-\infty}$), with PMs having increased exposure over homozygous EMs of 42% and 47%, respectively (see the following tables).

Table 73: Effect of CYP2C19 Metabolizer Status on BRV PK Parameters in Part A

Parameter	homEM	hetEM	PM	PMs vs. homEMs	PMs vs. hetEMs
C_{max} [$\mu\text{g.mL}^{-1}/\text{mg.kg}^{-1}$]	2.17 (1.89-2.49)	2.08 (1.87-2.32)	2.31 (1.99-2.67)	1.06	1.11
AUC_{0-t} [$\mu\text{g.mL}^{-1}.\text{h}/\text{mg.kg}^{-1}$]	16.6 (15.6-17.7)	20.0 (19.1-21.0)	23.1 (21.6-24.7)	1.39	1.15
AUC [$\mu\text{g.mL}^{-1}.\text{h}/\text{mg.kg}^{-1}$]	16.9 (15.8-18.0)	20.6 (19.6-21.7)	24.0 (22.4-25.7)	1.42	1.16

homEM: homozygous extensive metabolizer; hetEM: heterozygous extensive metabolizer

Source: Study report N01209A, Table 11:13. Numbers in () are 95% confidence intervals

Table 74: Effect of CYP2C19 Metabolizer Status on BRV PK Parameters in Part B

<i>Parameter</i>	<i>homEM</i>	<i>hetEM</i>	<i>PM</i>	<i>PMs vs. homEMs</i>	<i>PMs vs. hetEMs</i>
Day 1					
C_{max} [$\mu\text{g}\cdot\text{mL}^{-1}/\text{mg}\cdot\text{kg}^{-1}$]	1747 (18.9)	2174 (30.9)	2026.7	1.16	0.93
AUC [$\mu\text{g}\cdot\text{mL}^{-1}\cdot\text{h}/\text{mg}\cdot\text{kg}^{-1}$]	14386 (12.1)	18159 (10.2)	21103.3	1.47	1.16
Day 12					
C_{max} [$\mu\text{g}\cdot\text{mL}^{-1}/\text{mg}\cdot\text{kg}^{-1}$]	2556 (16.3)	3052 (16.3)	4778.5	1.87	1.57
AUC _T [$\mu\text{g}\cdot\text{mL}^{-1}\cdot\text{h}/\text{mg}\cdot\text{kg}^{-1}$]	14653 (13.7)	18617 (9.06)	20430.5	1.39	1.10

homEM: homozygous extensive metabolizer; hetEM: heterozygous extensive metabolizer

Source: Study report N01209B, Table 11:9. Numbers in () are coefficient of variation (CV) estimates

Reviewer’s Comments: Comparisons between PMs and homozygous EMs involved small subject numbers. For the single ascending dose part (A), the comparison was 9 PMs versus 10 homozygous EMs and in the multiple dose part (B), the comparison was 3 PMs versus 8 homozygous EMs. Small sample sizes such as these combined with inconsistent effects on exposure between these genetic analyses and the dedicated DDI data using a CYP2C19 inhibitor (see Pharmacometrics review by Xiaofeng Wang), make interpreting the effect of CYP2C19 on exposure difficult.

4.2.4 Summary and Conclusions

Overall, the sponsor’s classification of subjects as homozygous EM, heterozygous EM, or PM based on the haplotype of the genotyped CYP2C19 alleles (*2 and *3) is acceptable. All the subject’s genotype based metabolizer status assignments were confirmed by the reviewer and concordance between the sponsor’s assignments and the reviewer’s was 100%. Information provided in the Summary of Clinical Safety shows that doses of up to 800 mg daily were well tolerated in the clinical development program, so an increase in AUC of ~40% on doses of up to 200 mg daily (the max recommended dose) should not be clinically meaningful as to warrant dose adjustments.

4.2.5 Recommendations

None.

4.2.5.1 Post-marketing studies

None.

4.2.5.2 Label Recommendations

None.

The individual study reviews (appendices 4.3 and 4.4) are located in a separate document.

4.6 Filing Review

Office of Clinical Pharmacology			
<i>New Drug Application Filing and Review Form</i>			
General Information About the Submission			
	Information		Information
NDA Number	205,836-0000 205,837-0000 205,838-0000	Brand Name	Briviact
OCP Division (I, II, III)	DCP-I	Generic Name	brivaracetam
Medical Division	DNP	Drug Class	Antiepileptic agent
OCP Reviewer	Michael Bewernitz, Ph.D. Xinning Yang, Ph.D.	Indication(s)	Adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy.
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Tablet Oral solution Solution for IV
Pharmacometrics Reviewer	Xiaofeng Wang, Ph.D.	Pharmacogenomics Reviewer	Jeffery Kraft, Ph.D.
Pharmacometrics Team Leader	Kevin Krudys, Ph.D.	Pharmacometrics Team Leader	Christian Grimstein, Ph.D.
Date of Submission	11/202014	Route of Administration	Oral / IV
Estimated Due Date of OCP Review	7/24/15	Sponsor	UCB Inc.
Division Due Date	8/15/15	Priority Classification	S
PDUFA Due Date	11/20/15		

Clin. Pharm. and Biopharm. Information

The Sponsor has submitted 3 NDAs based on a single new molecular entity: NDA 205836-0000 (brivaracetam tablets), NDA 205837-0000 (brivaracetam injection) and NDA 205838-0000 (brivaracetam oral solution). NDA 205836-0000 (brivaracetam tablets), an original submission, was submitted under section 505(b)(1) of the FDCA. The proposed indication is "Adjunctive therapy in the treatment of partial onset seizures (POS) in patients 16 years of age and older with epilepsy". The recommended starting dose is 50 mg twice daily. Based on individual patient response, the dose may be adjusted between 25 mg twice daily and 100 mg twice daily

Proposed tablet strengths are 10, 25, 50, 75, and 100 mg. Solution for IV injection (50mg/5ml single use vial) as well as oral solution are both 10 mg/mL strength. Brivaracetam injection may be used when oral administration is temporarily not feasible. When switching to or from oral to intravenous administration, the total daily dose and frequency of administration should be maintained. It may be administered as a bolus injection or as a 15-minute IV infusion. The clinical study experience of intravenous brivaracetam is limited to 4 days of consecutive treatment. Brivaracetam was granted BCS Class I status by FDA in December 2007. There are 36 study reports containing information that is relevant to the clinical pharmacology review.

Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	-			Bioanalytical reports are embedded within each CSR.
I. Clinical Pharmacology				
Mass balance:	X	1	1	N01068
Isozyme characterization:	X	5	5	TA0686, NCD1998, NCD2232, NCD1674 NCD2195
Blood/plasma ratio:	X	1	1	PSM0937
Plasma protein binding:	X	(included as part of B/P ratio study above)		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	2	N01066, N01185
multiple dose:	X	5	2	N01067 (MAD), N01233 (TQT), will be reviewed. (b) (4) will not be reviewed.
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting / non-fasting single dose:	(assessed in SAD study 1066 and in BA study 1256A)			
fasting / non-fasting multiple dose:	(assessed in MAD study 1067)			
Drug-drug interaction studies -				

In-vivo effects on primary drug:	X	12	12	N01080, N01081, N01082, N01133, N01135, N01170, N01171, N01172, N01259, N01261, N01282, EP0041
In-vitro:	X	18	18	NCD1663 PSM0937 TA0686 NCD1998 NCD2232 NCD1674 NCD2195 TA0776 NCD1677 NCD1678 PSM1033 NCD2328 PSM0815 NCD1710 NCD2207 NCD2061 PSM1175 NCD2050
Subpopulation studies -				
ethnicity:	-			Addressed in population PK analyses
sex:	-			
pediatrics:	X	1	1	N01263
Elderly:	X	1	1	N01118
Renal impairment:	X	1	1	N01109
Hepatic impairment:	X	1	1	N01111
PD:				
Phase 2:	X	2	0	(b) (4) (b) (4) will not be reviewed.
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2	2	N01114, N01193
Phase 3 clinical trial:	X	4	4	N01252, N01258 , N01253 N01358
Population Analyses -				
Data rich:	X			CL0028 (Population PK Report):

Data sparse:	X	4		CL0028 (Population PK Report): CL0187 (Population PK Report in Pediatrics): CL0178 (Assessment of PK Drug Interaction of BRV on AED Plasma Conc.): CL0027 (PKPD Report):
II. Biopharmaceutics				
Absolute bioavailability:	X	(performed as part of BE study EP0007, see below)		
Relative bioavailability -				
solution as reference:	X	4	4	N01256A N01256B N01287, N01296
alternate formulation as reference:	-			
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	EP0007
replicate design; single / multi dose:	-			
Food-drug interaction studies:	X	2	2	N01075 (food effect also evaluated as part of BA study N01287)
Dissolution:	-			
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	X	1	1	The influence of CYP2C19 genetic polymorphism on brivaracetam PK was assessed in study N01209A and N01209B and will be reviewed by PG.
Chronopharmacokinetics	-			

Pediatric development plan	X	1	1	Sponsor is requesting a deferral for pediatric patients (b) (4)
Literature References	-			
Total Number of Studies		69	60	
Filability and QBR comments				
	“X” if yes	Comments		
Application filable?	X			
Comments sent to firm?	-			
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. The selected dose is acceptable? 2. Have the analytical methods been sufficiently validated? 3. Is the commercial tablet bioequivalent to the tablet utilized in clinical trials? 4. Is the oral solution bioequivalent to the oral tablet? 5. Is the IV solution bioequivalent to the oral tablet? 6. Are the label statements acceptable? 7. Dose adjustment needed for the specific population? 8. Dose adjustment needed due to DDI? 			
Other comments or information not included above	---			
Primary reviewer Signature and Date	Michael Bewernitz / Xiaofeng Wang / Jeff Kraft / Xinning Yang			
Secondary reviewer Signature and Date	Angela Yuxin Men , Kevin Krudys, Christian Grimstein			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		X		Adequate assay information could not be found for 3 clinical study reports. An information request will be sent.
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant	X			

	to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			Sponsor has submitted deferrals for pediatrics age 16 years and under (b) (4)
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	No translations required based on preliminary view of CSRs.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

A DSI inspection will be requested for the clinical and bioanalytical portions of study EP0007 and study N01296.

The following information request will be submitted to the Sponsor:

Please direct us to the location of the following documents within the respective NDA submission:

1. Report for UCB Study Number TA0668 (validation report referenced in the clinical study report for Study 01171, NDA 205836). If this validation report is not present in the current submission, please submit the report.
2. Report(s) of calibration and performance for bioanalytical assay utilized in Study EP0007 as well as Study N01258 (NDA 205837)

If any of the aforementioned documents are not present in the current submissions, please submit them.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Table 75: Brivaracetam Clinical Pharmacology Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	
N01066/ United Kingdom	Randomized, monocenter, double-blind, placebo-controlled, 3-alternating panel, 3-period rising single oral dose (10 to 1400mg), safety, tolerability, pharmacokinetic and pharmacodynamic study of ucb 34714 (capsule without excipient) in 27 healthy male volunteers
N01067/ United Kingdom	Randomized, mono-center, double blind, placebo-controlled, parallel group, 2 weeks repeated oral dose, safety, tolerability, pharmacokinetic and pharmacodynamic study of ucb 34714 100mg, 200mg and 400mg (100 and 200mg capsules (b) (4) twice daily in 36 healthy male volunteers
N01068/ Belgium	Open label, monocenter, excretion balance, pharmacokinetics and metabolism of [¹⁴ C]-labeled ucb 34714 after single 150mg oral dose administration in 6 healthy male volunteers
N01075/ United Kingdom	Randomized, monocenter, open label, two-way cross-over, food interaction pilot study of a single dose (150 mg) of ucb 34714 (oral capsule (b) (4) in 8 healthy male volunteers
5.3.3.4 – Extrinsic Factor PK Study Reports	
EP0041/ The Netherlands	A double-blind, randomized, placebo-controlled, three-way crossover study to investigate the drug-drug interactions of brivaracetam and ethanol in healthy male subjects
N01080/ United Kingdom	Randomized, monocenter, open label, two-way crossover, multiple oral dose interaction study between ucb 34714, 200mg (oral capsule (b) (4) twice daily and oral contraceptive (ethinylestradiol 30µg and levonorgestrel 150 µg) once daily in 24 healthy female volunteers
N01081/ United Kingdom	Monocenter, open label, bilateral pharmacokinetic interaction study of ucb 34714 (200mg oral capsules bid) and carbamazepine (100mg oral tablets/300mg bid) during single and multiple oral administrations in 14 healthy male subjects
N01082/ United Kingdom	Monocenter, open label, interaction study between ucb 34714 at steady state (200mg oral capsules, twice daily) and single dose phenytoin 600mg (2x300mg oral capsules) in 20 healthy male volunteers
N01133/ United Kingdom	Monocenter, open label, unilateral metabolic interaction study of ucb 34714 (100, 200 and 400mg daily) on carbamazepine (≥600mg daily) during a four-week bid administration period in 9 adult male subjects suffering from epilepsy
N01135/ United Kingdom, Poland	Multicenter, open label, unilateral metabolic interaction study of ucb 34714 (100, 200 and 400mg daily) on carbamazepine (≥600mg daily) during a four-week bid administration period in 9 adult subjects suffering from epilepsy and treated with carbamazepine and valproate (≥500mg daily)
N01170/ Belgium	Monocenter, open label, unilateral interaction study of brivaracetam at steady-state (200mg twice daily) on topiramate (200mg single dose) in 14 healthy volunteers
N01171/ France	Monocenter, open label, unilateral interaction study of ucb 34714 at steady-state (200mg twice daily) on lamotrigine (25mg single dose) in 14 healthy male volunteers
N01172/ USA	A multicenter, open-label, unilateral interaction study of ucb 34714 (400mg daily) on stable phenytoin monotherapy during a 45 day bid administration period in 15 adult subjects suffering from epilepsy
N01259/ Belgium	Monocenter, open-label, randomized, 2x2-way cross-over study to assess the effects of gemfibrozil and rifampicin on the pharmacokinetics of brivaracetam, a CYP2C8 substrate, in healthy male subjects
N01261/ Belgium	Single-centre, open-label Phase I study to assess the effects of a repeated administration of brivaracetam on CYP3A4 activity in healthy male subjects using midazolam as a probe
N01282/ France	Interaction study between brivaracetam 50mg twice daily and a combined oral contraceptive containing 30µg ethinylestradiol and 150µg levonorgestrel in healthy female subjects
5.3.3.3 – Intrinsic Factor PK Study Reports	
N01109/ Poland	Monocenter, open-label, parallel group, not randomized, pharmacokinetic study of a single oral administration of 200mg capsule of ucb 34714, in subjects with normal renal function and with renal function impairment
N01111/ Belgium	Open label, parallel group, not randomized, pharmacokinetics study of a single oral administration of 100mg ucb 34714 (50mg capsules) in healthy subjects and patients with impaired liver function (Child-Pugh classes A, B and C)
N01118/ France	Multicenter, open-label, pharmacokinetic, safety and tolerability study of a single dose followed by a 10 day bid dosing regimen of ucb 34714 administered twice a day orally as 200mg capsules in healthy elderly volunteers
N01209 Part A/ Japan	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects
N01209 Part B/ Japan	A double-blind, randomized, placebo-controlled study to evaluate the safety and pharmacokinetics of single oral dose (Part A) and repeated oral doses (Part B) of brivaracetam (BRV) in Japanese healthy adult male subjects
5.3.1.1 Bioavailability (BA) Study Reports	
N01185/ United Kingdom	Pharmacoscintigraphic investigation of the regional drug absorption of ucb 34714 (200mg) delivered using the Enterion™ capsule in 3 different sites of the GI tract in comparison with the 200mg immediate release oral capsule: open-label, randomized, four-way cross-over, single dose study, in 9 healthy adult male volunteers
N01256A (Part A)/ Belgium	A randomized, monocenter, open-label, three-way crossover, dose availability study of three different formulations of brivaracetam (Part A), followed by a non-randomized, monocenter, open-label safety assessment via two formulations (Part B), on healthy volunteers
N01256B (Part B)/ Belgium	A randomized, monocenter, open-label, three-way cross-over, dose availability study of three different formulations of brivaracetam (Part A), followed by a non-randomized, monocenter, open-label safety assessment study of four escalating doses of brivaracetam (BRV) administered via two formulations (Part B), on healthy volunteers

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	
EP0007/ The Netherlands	A randomized, single-center, open-label, 5-way crossover, single-dose bioavailability/bioequivalence comparison of brivaracetam oral tablets (10mg, 50mg, 75mg, and 100mg) and brivaracetam intravenous bolus injection (100mg) in healthy volunteers
N01287/ France	Monocenter, open label, randomized, five-way cross-over relative bioavailability/bioequivalence study of brivaracetam solid oral formulations (capsule and tablet) using as reference brivaracetam oral solution with assessment of food effect on brivaracetam oral tablet formulation
N01296/ France	Randomized, monocenter, open-label, two-way cross-over, single dose bioequivalence study of two different formulations of brivaracetam in healthy fasting subjects

5.3.4.1 – Healthy Subject PD and PK/PD Study Reports	
N01233/ France	Randomized, placebo- and moxifloxacin-controlled study of the effect of brivaracetam on cardiac repolarization in four parallel groups of healthy male and female subjects

Sponsor conducted 3 phase II studies, and 5 phase III studies. Design features of the clinical pharmacology trials are summarized in the table below.

Table 76: Brivaracetam Phase 2 and Phase 3 Trials

5.3.3.2 – Patient PK and Initial Tolerability Study Reports	
N01263/ Belgium, Czech Republic, Mexico, Poland, Spain, USA	Open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of brivaracetam in subjects from ≥1 month to <16 years old with epilepsy

5.3.5.1 – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication POS

N01114/ Belgium, Czech Republic, Finland, France, Germany, The Netherlands, Poland, Spain, United Kingdom	A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 used as adjunctive treatment at doses of 50 and 150mg/day in bid administration (oral capsules of 25mg) for a maximum of 12 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized
N01193/ Brazil, India, Mexico, USA	A multicenter, double-blind, randomized, placebo-controlled, 4 parallel groups, dose-ranging trial evaluating the efficacy and safety of brivaracetam used as adjunctive treatment at doses of 5, 20 and 50mg/day in bid administration (oral tablets of 2.5 or 10mg) for a maximum of 7 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized
N01252/ Belgium, Switzerland, Germany, Finland, France, Hungary, India, Italy, The Netherlands, Poland, Spain, United Kingdom	A multi-center, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥16 to 70 years old) with partial onset seizures
N01253/ Australia, Brazil, Canada, Mexico, USA	An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥16 to 70 years old) with partial onset seizures
N01254/ Austria, Belgium, Czech Republic, Germany, Hong Kong, India, Italy, South Korea, Norway, South Africa, Russia, Singapore, Sweden, Taiwan, Ukraine	An international, randomized, double-blind, parallel-group, placebo-controlled, flexible dose study: evaluation of the safety and efficacy of brivaracetam in subjects (≥16 to 70 years old) suffering from localization-related or generalized epilepsy

N01358/ Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Hungary, India, Italy, Japan, Latvia, Lithuania, Mexico, Poland, Russia, South Korea, Spain, Sweden, Taiwan, The Netherlands, United Kingdom, USA, US territory of Puerto Rico	A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of brivaracetam in subjects (≥16 to 80 years old) with partial onset seizures
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5.3.5.2 – Study Reports of Uncontrolled Clinical Studies

N01258/ Czech Republic, Germany, Poland, USA	A multicenter, open-label, four-arm, randomized trial evaluating the safety and tolerability of brivaracetam intravenous infusion and bolus, administered in bid regimen as an adjunctive antiepileptic treatment in subjects from 16 to 70 years suffering from epilepsy
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/s/

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